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## **Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): a phase II, open-label, randomised, multicentre, controlled clinical trial.**

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# Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): a phase II, open-label, randomised, multicentre, controlled controlled clinical trial.

Rafael León-López<sup>1</sup>, Sheila Cárcel-Fernández<sup>1</sup>, Laura Limia-Pérez<sup>2</sup>, Alberto Romero-Palacios<sup>3</sup>, María Concepción Fernández Roldán<sup>4</sup>, Eduardo Aguilar-Alonso<sup>5</sup>, Inés Pérez-Camacho<sup>6</sup>, Jesús Rodríguez-Baño<sup>7,8</sup>, Nicolás Merchant<sup>9</sup>, Julián Olalla<sup>10</sup>, María Ángeles Esteban<sup>11</sup>, Marta Santos<sup>12</sup>, Antonio Luque-Pineda<sup>13</sup>, Julián Torre-Cisneros<sup>13,14,15</sup>

<sup>1</sup>Intensive Care Unit, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/Reina Sofía University Hospital/University of Córdoba, Córdoba, Spain.

<sup>2</sup>Internal Medicine Unit, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/Reina Sofía University Hospital/University of Córdoba, Córdoba, Spain. CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain.

<sup>3</sup>Infectious Diseases Unit, Puerto Real University Hospital, Puerto Real, Spain.

<sup>4</sup>Infectious Diseases Unit, Virgen de las Nieves University Hospital, Granada, Spain.

<sup>5</sup>Intensive Care Unit, Infanta Margarita Hospital, Cabra, Spain.

<sup>6</sup>Infectious Diseases Unit, Málaga Regional University Hospital, Málaga, Spain.

<sup>7</sup>Infectious Diseases Unit, Virgen Macarena University Hospital, Sevilla, Spain.

<sup>8</sup>Spanish Network for Research in Infectious Diseases (REIPI, RD16/0016/0001), Instituto de Salud Carlos III, Madrid, Spain.

<sup>9</sup>Infectious Diseases and Microbiology Unit, Virgen de Valme University Hospital, Sevilla, Spain.

<sup>10</sup>Internal Medicine Service, Costa del Sol University Hospital, Marbella, Spain

<sup>11</sup>Infectious Diseases Unit, Torrecárdenas University Hospital, Almería, Spain.

<sup>12</sup>Infectious Diseases Unit, Jerez de la Frontera University Hospital, Jerez de la Frontera, Spain.

<sup>13</sup>Clinical Trials Unit, Instituto Maimonides de Investigación Biomédica de Córdoba (IMIBIC)/Reina Sofia University Hospital/University of Córdoba (SCReN PT17/0017/0032), Córdoba, Spain.

<sup>14</sup>Infectious Diseases Unit, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/Reina Sofía University Hospital/University of Córdoba, Córdoba, Spain

<sup>15</sup>Spanish Network for Research in Infectious Diseases (REIPI, RD16/0016/0008), Instituto de Salud Carlos III, Madrid, Spain

**\*Author for correspondence:** Antonio Luque-Pineda [antonio.luque@imibic.org](mailto:antonio.luque@imibic.org)

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## ABSTRACT

**Introduction** About 25% of patients with COVID-19 develop acute respiratory distress syndrome (ARDS) associated with a high release of pro-inflammatory cytokines such as interleukin-6 (IL-6). The aim of the SARICOR study is to demonstrate that early administration of sarilumab (an IL-6 receptor inhibitor) in hospitalised patients with COVID-19, pulmonary infiltrates and a high IL-6 or D-Dimer (DD) serum level could reduce the progression of ARDS requiring high-flow nasal oxygen or mechanical ventilation (non-invasive or invasive).

**Methods and analysis** Phase II, open-label, randomised, multicentre, controlled clinical trial to study the efficacy and safety of the administration of two doses of sarilumab (200 and 400 mg) plus best available therapy (BAT) in hospitalised adults with COVID-19 presenting cytokine release syndrome. This strategy will be compared with a BAT control group. The efficacy and safety will be monitored up to 28 days post-administration. A total of 120 patients will be recruited (40 patients in each arm).

**Ethics and public dissemination** The clinical trial has been approved by the Research Ethics Committee of the coordinating centre and authorised by the Spanish Agency of Medicines and Medical Products (AEMPS). If the hypothesis is verified, the dissemination of the results could change clinical practice by increasing early administration of sarilumab in adult patients with COVID-19 presenting cytokine release syndrome, thus reducing ICU admissions.

**Trial registration number** NCT04357860

### Strengths and limitations of this study

- Early use of sarilumab can reduce the progression of respiratory failure and prevent the saturation of ICUs.
- The trial will study two doses of the drug. One could be selected for phase III trials with a larger sample.
- Limitations include not being a blind trial and having a limited sample size.
- The stock of sarilumab is limited in Spain. The government distributes the drug to ensure treatment of patients with rheumatoid arthritis. Pharmacies must request authorisation for dispensation of the drug on a case-by-case basis.
- The incidence of new cases is decreasing in Spain.

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the newly discovered SARS-CoV-2 coronavirus. Data on the severity of confirmed cases have varied over time. Subjects with severe acute respiratory syndrome (SARS) and high levels of pro-inflammatory cytokines and chemokine are associated with T-cell depletion, pulmonary inflammation and extensive lung damage. The levels of these cytokines negatively correlate with absolute lymphocyte counts, thus inducing T-cell exhaustion and apoptosis and causing acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).<sup>[1]</sup>

A similar phenomenon is observed in the case of cytokine release syndrome (CRS) associated with chimeric antigen receptor T-cell (CAR-T) therapy. One of the key mediators of

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3 autoimmunity, inflammation, viral cytokine storms and CRS-induced damage is interleukin-6 (IL-  
4 6). Patients with SARS-CoV-2 infection have high plasma IL-6 levels, especially those with a more  
5 severe presentation and high C-reactive protein (CRP) levels.<sup>[2]</sup>  
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7

8 It has been suggested that IL-6 blockade may constitute a novel therapeutic strategy for  
9 cytokine storm and systemic inflammatory response syndrome in sepsis, macrophage activation  
10 syndrome and haemophagocytic lymphohistiocytosis.<sup>[3]</sup> Remarkable beneficial effects of IL-6  
11 blockade therapy using an IL-6 receptor inhibitor have been described in patients with severe  
12 SARS-CoV-2 pneumonia in a retrospective case series from China.<sup>[4]</sup>  
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15 Sarilumab is a human monoclonal antibody against the IL-6 receptor that is currently  
16 licensed for rheumatoid arthritis. It is safe and well tolerated.<sup>[5]</sup> The most common side effects  
17 are upper respiratory tract infections, headache, hypertension and abnormal liver function tests.  
18 The most serious side effects are infections, such as diverticulitis, and hypersensitivity  
19 reactions.<sup>[6]</sup>  
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22 It is hypothesised that IL-6 might play a key role in the cytokine storm in SARS-CoV-2  
23 patients with pneumonia, and that blockade of IL-6 would be a suitable therapeutic target for  
24 these patients. This study investigates the efficacy and safety of early treatment with sarilumab  
25 compared to standard of care in patients with severe SARS-CoV-2 pneumonia.  
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## 30 METHODS AND ANALYSIS

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### 33 Design

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35 This is a phase II, open-label, randomised, multicentre, controlled clinical trial. The  
36 patients will be assigned to three treatment groups (Figure 1):  
37

- 38 1. Control group: 40 patients will receive the best available therapy (BAT) for a maximum of 14  
39 days.
  - 40 2. Treatment group 1 (T1): 40 patients will receive BAT for a maximum of 14 days + 200 mg of  
41 sarilumab subcutaneously (single dose)
  - 42 3. Treatment group 2 (T2): 40 patients will receive BAT for a maximum of 14 days + 400 mg of  
43 sarilumab subcutaneously (single dose)
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### 47 Study population and setting

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50 Ten university hospitals located in Andalusia, Spain, will participate in the trial. The trial  
51 will include hospitalised patients with confirmed SARS-CoV-2 infection causing respiratory  
52 disease and presenting high serum levels of IL-6 or D-Dimer (DD). Patients who meet all the  
53 inclusion criteria and have no exclusion criteria will be prospectively included in the study. The  
54 inclusion and exclusion criteria for the trial are described in Box 1.  
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**Box 1 Study selection criteria***Inclusion criteria*

- 1. Age ≥18 years and <75 years**
- 2. Hospitalisation for COVID-19 based on a positive PCR in a respiratory tract sample in the absence of respiratory distress requiring high-flow nasal oxygen or mechanical ventilation**
- 3. Interstitial pneumonia confirmed by chest radiography or CT scan**
- 4. IL-6 levels >40 pg/ml. In the absence of IL-6, D-Dimer (DD) >1500 or >1000 if progressive increments are documented**
- 5. In women of childbearing age, a negative pregnancy test**
- 6. Signed informed consent**

*Exclusion criteria*

- 1. SOFA score >6 points**
- 2. Patient who, in the researcher's opinion, is not subsidiary of invasive mechanical ventilation.**
- 3. Neutrophil count <2 x 10<sup>3</sup>/µL**
- 4. Platelet count <100 x 10<sup>3</sup>/µL**
- 5. ALT or AST levels >5 times the upper limit of normal**
- 6. Severe renal failure (CrCl <30 ml/min)**
- 7. Active bacterial infection**
- 8. Active tuberculosis or history of not completing treatment against tuberculosis**
- 9. Antecedents of diverticulitis**
- 10. Hypersensitivity to sarilumab or its excipients**
- 11. Treatment with TNF antagonists**
- 12. Treatment with anti-IL6 in the previous 30 days**
- 13. Chronic treatment with corticosteroids at doses >0.5 mg/kg /day of prednisone or equivalent. Topical and inhaled corticosteroids are acceptable.**
- 14. Concomitant treatment with immunomodulators, including vitamin D or statins. Macrolides such as azithromycin are acceptable.**

- 15. Patients on immunosuppressive treatment for any cause**
  - 16. HIV-infected patients with CD4 <200/mm<sup>3</sup>**
  - 17. Past or current history of autoimmune disease**
  - 18. Patients receiving immunomodulatory antibody therapy, including immunoglobulins**
  - 19. Participation in any clinical trial that evaluated any investigational product in the last 3 months or less than 5 half-lives of the product under investigation**
  - 20. Pregnancy**
  - 21. Any other condition that, in clinical judgement, prevents the patient's adherence to the protocol**

**Abbreviations:** SOFA, sequential organ failure assessment. PCR, polymerase chain reaction. CT scan, computed tomography scan. ALT, alanine transaminase. AST, aspartate transaminase. CrCl, creatinine clearance. TNF, tumour necrosis factor. HIV, human immunodeficiency viruses.

## Withdrawal criteria

Patients may withdraw from the study at any time, for any reason and without prejudice to future medical treatment. Patients who do not comply with the study procedure or have not been followed up will be considered a study "withdrawal". The reasons for withdrawal will be examined in full accordance with bioethical principles regarding the guarantee of patients' rights. The criteria for withdrawal from the study are described below.

1. Patient request
  2. Violation or deviation from the protocol (e.g. breach of administration of treatment, need for prohibited treatment).
  3. Researchers decision, based on clinical reasons
  4. Administrative decision of the investigators, promoter or regulatory authorities
  5. Loss to follow-up
  6. Suspected unexpected serious adverse reaction (SUSAR)
  7. Serious adverse event (SAE) that at the discretion of the promoter or investigator is not acceptable.
  8. Any adverse event considered intolerable by either the patient or the investigator
  9. Pregnancy

## **Study variables**

## ***Outcome variables***

The primary outcome variable is the development of adult respiratory distress syndrome requiring high-flow nasal oxygenation (HFNO) or mechanical ventilation, both non-invasive and invasive.

The secondary outcome variables are: all-cause (crude) mortality at day 28, time (in days) to clinical improvement, time (in days) until oxygenation improvement for at least 48

hours, proportion of patients who require invasive mechanical ventilation, negativisation of PCR to SARS-CoV-2, cytokine kinetics and side effects.

Clinical improvement will be assessed on a seven-category ordinal scale consisting of the following categories: 1, not hospitalised with resumption of normal activities; 2, not hospitalised, but unable to resume normal activities; 3, hospitalised, not requiring supplemental oxygen; 4, hospitalised, requiring supplemental oxygen; 5, hospitalised, requiring high-flow oxygen therapy; 6, hospitalised requiring ECMO, invasive mechanical ventilation or both; and 7, death.

### **Other variables**

The following demographics and clinical information will be collected from all patients: age, sex, weight, height, body mass index (BMI), comorbidities, previous treatment, history of the current disease, respiratory rate (bpm), basal oxygen saturation (%), arterial pO<sub>2</sub> (mm Hg), pO<sub>2</sub>/FiO<sub>2</sub> rate, oxygen saturation/FiO<sub>2</sub> rate, blood pressure (mmHg), heart rate (bpm), consciousness level, temperature (°C), clinical improvement, organ failure assessment score (SOFA), microbiological test, analytical parameters (haematimetry, glucose, creatinine, AST, ALT, C-reactive protein, albumin, LDH, ferritin, troponin I, protein kinase, procalcitonin, lipid profile, IL-6, D-dimer, prothrombin time, INR). All concomitant medication and adverse events will be recorded and monitored in accordance with regulatory procedures. SARS-CoV-2019 in nasopharyngeal swab and a panel of cytokines (IL1- $\alpha$ , IL1- $\beta$ , IL6, IL8, IL10, IL12, IL18, IL38, INF $\gamma$ , TNF $\alpha$ , CCL2, CCL3, CCL4, MIF y PAI-1) will be determined before randomisation and on days 5, 10, 14, 21 and 28.

## **Randomisation and masking**

A total of 120 patients will be recruited (40 in each group). Patients who meet the selection criteria will be randomised to be included in the control group or the two experimental groups. Randomisation will be carried out by means of electronic case report forms (eCRFs). The ratio will be 1:1:1 for each group (balanced randomisation). The study design is open, but the investigator will not know the treatment assignment until the patient signs the informed consent form and randomisation is performed, thus minimising selection bias. Patients will be identified by a code that includes the centre code followed by the patient number (XX-YY).

## **Study medication**

The investigational medication (IM) is sarilumab (ATC code: L04AC14), a human monoclonal antibody (IgG1 subtype) that specifically binds to both soluble and membrane-bound IL-6 (IL-6Ra) receptors and inhibits the transmission of IL-6 mediated signals involving signal transducer glycoprotein 130 (gp130) and activator of transcription 3 (STAT-3).

The commercial subcutaneous medication available in Spain (SANOFI-AVENTIS) will be used. Administration of the IM will be carried out according to the technical sheet and the local practice of each centre.

The BAT will include any combination of drugs included in the current protocol of the Spanish Ministry of Health (<https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos.htm>) and complementary notes issued by the Spanish Agency of Medicines and Medical Products ([www.aemps.gob.es](http://www.aemps.gob.es))

## Study procedures

The duration of follow-up for each patient will be 28 days and will start from the moment the patient is randomised. A total of 6 visits will be scheduled during the trial: baseline, day 5, day 10, day 14, day 21 and day 28. The scheduled follow-up is shown in Table 1. The visit following the end of treatment will be considered as the end-of-treatment visit. Visit 5 (day 28 after randomisation) will be considered the final study visit. The final study visit can be moved forward to the day of hospital discharge. Additionally, data on clinical improvement (on a 7-point ordinal scale), axillary temperature, oxygen saturation (or PO<sub>2</sub>) and oxygen therapy will be collected daily.

Nasopharyngeal swabs will be performed on days 0, 5, 10, 14, 21 and 28. Plasma will also be obtained on days 0, 5, 10, 14, 21 and 28. The samples will be locally preserved (frozen at -80 °C) until dispatched to the Biobank of the Reina Sofía University Hospital of Córdoba, Spain.

The principal investigator will be responsible for the detection and documentation of adverse events (AE) throughout the study. All AEs must be notified during all phases of the study and followed up until resolution or until an adequate explanation is found, although the patient has completed study treatment. Periodic reports will also be submitted on AEs that occurred during the study, including causality assessment, severity and intensity.

## Statistical analysis

Since this is a phase II study, a sufficient number of patients are included to perform an initial analysis of efficacy and safety. We have calculated an overall sample size of 120 patients, 40 patients for each arm, to detect a 30% reduction in the primary outcome with an alpha error of 0.05, a beta risk of 0.2 and assuming that the modified intention-to-treat population will be 90% of the randomised patients.

Clinical data will be collected in an electronic case report form (eCRF). All analyses will be performed using PASW Statistics software V.15.0 (IBM Corporation) and R software (V.3.5.0). Frequencies will be calculated for the qualitative variables and compared using the X<sup>2</sup> test or Fisher's test. For quantitative variables, the mean and standard deviation will be calculated. Normality will be analysed using the Kolmogorov-Smirnov test and comparisons will be made using the Student's t-test or the Mann-Whitney test depending on whether or not they follow a normal distribution, respectively. For the comparison of three or more groups, the analysis of variance (ANOVA) or Kruskal-Wallis tests will be used. The analyses will be based on the intention-to treat population (randomised patients receiving treatment). The time until the primary outcome variable is reached will be plotted on a Kaplan-Meier curve and compared using a log-rank test. A Cox regression analysis will be performed for the primary efficacy variable and the results reported in terms of the hazard ratio (HR) with 95% confidence intervals.

## Patient and public involvement

No patient involved.

## ETHICAL ISSUES AND DISSEMINATION PLAN

This clinical trial will be conducted in accordance with the protocol and the ethics principles of the Declaration of Helsinki (Fortaleza, 2013) and in accordance with the applicable regulatory requirements, in particular the ICH Tripartite Guideline "Standards of Good Clinical Practice", Royal Decree 1090/2015 regulating clinical trials with medications in Spain and Regulation (EU) No. 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use. The protocol, the informed consent form, the patient information form and any documents applicable to the study have required approval by the appropriate regulatory agencies. The Committee for Biomedical Research Ethics of the Reina Sofia University Hospital approved the trial. Authorisation has also been obtained from the Spanish Agency of Medicines and Medical Products (AEMPS, 20-0262). The trial is registered in accessible public databases such as the Spanish Clinical Studies Registry (REec), EUDRACT (2020-001531-27) and ClinicalTrials.gov (NCT04357860).

## DISCUSSION

The number of people diagnosed with coronavirus disease 2019 (COVID-19) worldwide crossed the two million mark on April 25, 2020. The vast majority of patients with the COVID-19 have had a good prognosis, but there were critical individuals and deaths. ARDS is the leading cause of death in patients infected with SARS-CoV-2.<sup>[7]</sup> ARDS is a life-threatening lung condition that prevents enough oxygen from getting to the lungs and into circulation. Despite the efforts to characterise the clinical picture of COVID-19, very little is known about the pathologic manifestations, in particular lung inflammation. The first report of pathological findings from a severe COVID-19 patient showed pulmonary bilateral diffuse alveolar damage with cellular fibromyxoid exudates. Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were observed in both lungs. The authors suggested an over-activation of T cells manifested by an increase of Th17 and high cytotoxicity of CD8 T cells leading to severe immune injury and inflammation.<sup>[8]</sup> The clinical presentation of patients with severe forms of COVID-19 resembles cytokine release syndrome observed in some oncology patients treated with CAR-T cell therapies.

Cytokine dysregulation is of particular interest in patients with COVID-19, who have higher levels of inflammatory cytokines. Some cytokines seem to be up-regulated, especially in patients with more severe disease. The overwhelming release of proinflammatory cytokines and chemokines may be involved in the pulmonary injury characterised by diffuse alveolar damage with epithelial and endothelial apoptosis, dysregulated coagulation and pulmonary fibrinolysis. Among the cytokines produced by activated macrophages, IL-6 is one of the key cytokines. The role of IL-6 has been consistently reported in several studies of COVID-19.<sup>[9, 10, 11]</sup> A large retrospective cohort study found that IL-6 levels were correlated with mortality in 158 patients with COVID-19.<sup>[12]</sup> Interestingly, Chen et al. showed that levels of IL-6 are 10 times higher in critical patients compared with other patients. IL-6 levels were closely correlated with mortality.<sup>[13]</sup> Therefore, antiviral therapy alone may be inadequate for patients with uncontrolled inflammatory response. For this reason, numerous protocols have recommended tocilizumab, a humanised monoclonal antibody against the IL - 6 receptor, in critical patients with ARDS and elevated IL - 6.<sup>[14]</sup>

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2  
3 Another point of interest is the rapid increase in the number of cases of COVID-19 across  
4 the world, which has shown how quickly health systems can be challenged to provide adequate  
5 care. Mortality was 7-fold higher for patients in Hubei compared with other non-affected  
6 Chinese provinces, emphasising the importance of ICU capacity in the care of patients with  
7 COVID-19.<sup>[15]</sup> Access to ICU beds and ventilators can be rapidly saturated if the overwhelming  
8 inflammation is not stopped at early stages. Xie et al. highlighted the importance of the limited  
9 capacity of ICUs as only 25% of patients who died had received invasive mechanical  
10 ventilation.<sup>[16]</sup>

11  
12 Therefore, it seems plausible to speculate that the anti-IL6R plays a protective role if  
13 given at the time of overwhelming elevated immune response, preventing the cytokine storm.  
14 We propose that the early use of sarilumab, in addition to antiviral therapy, can attenuate the  
15 detrimental host immune response in patients with elevated markers of inflammation and  
16 reduce the development of severe respiratory failure and other organ damage. In conclusion,  
17 the SARICOR study aims to reduce the severity and mortality associated with COVID-19.

18  
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21  
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29  
30 **Contributors.** Each author has contributed significantly to, and is willing to take public  
31 responsibility for, one or more aspects of the study. All authors contributed to the  
32 implementation of the study protocol and will contribute to the data acquisition and analysis  
33 and interpretation of the study data. RL, AL and JT drafted the initial manuscript; all other  
34 authors provided critical revisions and approved the final revisions.

35  
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38  
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40  
41 **Ethics approval.** In accordance with Royal Decree 1090/2015 of 4 December concerning the  
42 regulation of clinical trials of medicinal products in Spain, multicentre clinical trials only require  
43 the approval of a single medicinal research ethics committee (reference MREC) and of the  
44 Spanish Agency of Medicines and Medical Products (AEMPS). This clinical trial has been  
45 approved by the reference MREC of the province of Córdoba and the AEMPS (Code: 20-0262;  
46 EudraCT Number: 020-001531-27).

47  
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**FIGURE LEGEND****Figure 1 – Flow diagram of the clinical trial****Table 1 - Chart of study procedures during the trial**

For peer review only

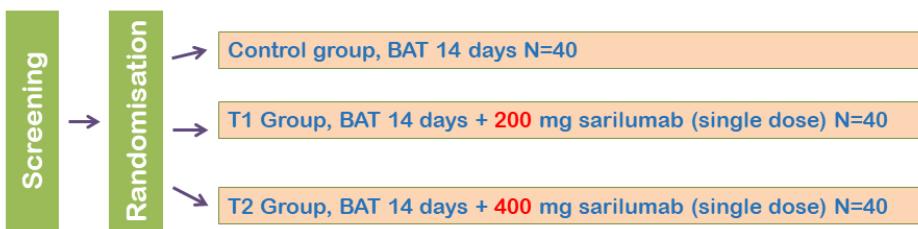
Table 1. Chart of study procedures	STUDY PERIOD											
	BASELINE		POST RANDOMISATION									
	Day 0	Day 1	Day 2 to 4	VISIT 1 Day 5	Day 6 to 9	VISIT 2 Day 10	Day 11 to 13	VISIT 3 Day 14	Day 15 to 20	VISIT 4 Day 21	Day 22 to 27	VISIT 5 Day 28
Recruitment												
Review of inclusion and exclusion criteria	X											
Informed consent	X											
Randomisation	X											
Baseline data, demographics and comorbidities*	X											
Clinical data												
Respiratory rate, saturation, applied oxygen [FiO <sub>2</sub> ] SpO <sub>2</sub> /FiO <sub>2</sub> ratio	X	X	X	X	X	X	X	X	X	X	X	X
Arterial pO <sub>2</sub> , pO <sub>2</sub> /FiO <sub>2</sub> ratio	X			X		X		X		X		X
SOFa score	X	X	X	X	X	X		X		X		X
7-point ordinal scale	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory data												
PCR COVID-19 (nasopharyngeal swab)	X				X		X		X		X	X
Analytical parameters†	X				X		X		X		X	X
Samples for cytokine determination	X				X		X		X		X	X
Pregnancy test	X											
Drugs												
IM administration	X											
Interaction assessment, AR, SAR, USAR, AA, AAG	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication record	X	X	X	X	X	X	X	X	X	X	X	X
Radiological tests												
Chest X-ray or CT scan	X											
Biological samples												
Samples for Biobank	X			X		X		X		X		X

\*Age, sex, weight, height, BMI, comorbidities, previous treatment (including therapeutic family; e.g. ACEI, ARA II, statins, etc.), current disease history, BP (mm Hg), HR, level of consciousness, temperature (°C), National Early Warning Score (NEWS).

† Haematimetry, glucose, creatinine, AST, ALT, C-reactive protein, albumin, LDH, ferritin, troponin I, protein kinase, procalcitonin, pregnancy test (at visit 0), lipid profile, interleukin-6, D-dimer, prothrombin time (PT%), INR.

### Scheme of assessments

254x190mm (96 x 96 DPI)



Groups of treatment and randomization

254x190mm (96 x 96 DPI)

# BMJ Open

**Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): protocol of a phase II, open-label, randomised, multicentre, controlled clinical trial.**

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<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Intensive care
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INFECTIOUS DISEASES, INTERNAL MEDICINE, VIROLOGY

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3     **Efficacy and safety of early treatment with sarilumab in**  
4     **hospitalised adults with COVID-19 presenting cytokine release**  
5     **syndrome (SARICOR STUDY): protocol of a phase II, open-label,**  
6     **randomised, multicentre, controlled clinical trial.**

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11 Rafael León-López<sup>1</sup>, Sheila Cárcel-Fernández<sup>1</sup>, Laura Limia-Pérez<sup>2</sup>, Alberto Romero-Palacios<sup>3</sup>,  
12 María Concepción Fernández Roldán<sup>4</sup>, Eduardo Aguilar-Alonso<sup>5</sup>, Inés Pérez-Camacho<sup>6</sup>, Jesús  
13 Rodríguez-Baño<sup>7,8</sup>, Nicolás Merchant<sup>9</sup>, Julián Olalla<sup>10</sup>, M. Ángeles Esteban-Moreno<sup>11</sup>, Marta  
14 Santos<sup>12</sup>, Antonio Luque-Pineda<sup>13</sup>, Julián Torre-Cisneros<sup>13,14,15</sup>  
15  
16

17     <sup>1</sup>Intensive Care Unit, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/  
18 Reina Sofía University Hospital/University of Córdoba, Córdoba, Spain.  
19

20     <sup>2</sup>Internal Medicine Unit, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/  
21 Reina Sofía University Hospital/University of Córdoba, Córdoba, Spain. CIBER Fisiopatología de  
22 la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain.  
23

24     <sup>3</sup>Infectious Diseases Unit, Puerto Real University Hospital, Puerto Real, Spain.  
25

26     <sup>4</sup>Infectious Diseases Unit, Virgen de las Nieves University Hospital, Granada, Spain.  
27

28     <sup>5</sup>Intensive Care Unit, Infanta Margarita Hospital, Cabra, Spain.  
29

30     <sup>6</sup>Infectious Diseases Unit, Málaga Regional University Hospital, Málaga, Spain.  
31

32     <sup>7</sup>Infectious Diseases Unit, Virgen Macarena University Hospital, Sevilla, Spain.  
33

34     <sup>8</sup>Spanish Network for Research in Infectious Diseases (REIPI, RD16/0016/0001), Instituto de  
35 Salud Carlos III, Madrid, Spain.  
36

37     <sup>9</sup>Infectious Diseases and Microbiology Unit, Virgen de Valme University Hospital, Sevilla, Spain.  
38

39     <sup>10</sup>Internal Medicine Service, Costa del Sol University Hospital, Marbella, Spain  
40

41     <sup>11</sup>Infectious Diseases Unit, Torrecárdenas University Hospital, Almería, Spain.  
42

43     <sup>12</sup>Infectious Diseases Unit, Jerez de la Frontera University Hospital, Jerez de la Frontera, Spain.  
44

45     <sup>13</sup>Clinical Trials Unit, Instituto Maimonides de Investigación Biomédica de Córdoba (IMIBIC)/  
46 Reina Sofia University Hospital/University of Córdoba (SCReN PT17/0017/0032), Córdoba, Spain.  
47

48     <sup>14</sup>Infectious Diseases Unit, Instituto Maimónides de Investigación Biomédica de Córdoba  
49 (IMIBIC)/Reina Sofía University Hospital/University of Córdoba, Córdoba, Spain  
50

51     <sup>15</sup>Spanish Network for Research in Infectious Diseases (REIPI, RD16/0016/0008), Instituto de  
52 Salud Carlos III, Madrid, Spain  
53

54     \*Author for correspondence: Antonio Luque-Pineda [antonio.luque@imibic.org](mailto:antonio.luque@imibic.org)

55     **WORD COUNT:**

56     Abstract: 342  
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58     Text: 3209  
59

60     **KEYWORDS:** COVID-19; IL-6; cytokines, SARS-CoV-2, sarilumab

## ABSTRACT

**Introduction** About 25% of patients with COVID-19 develop acute respiratory distress syndrome (ARDS) associated with a high release of pro-inflammatory cytokines such as interleukin-6 (IL-6). The aim of the SARICOR study is to demonstrate that early administration of sarilumab (an IL-6 receptor inhibitor) in hospitalised patients with COVID-19, pulmonary infiltrates and a high IL-6 or D-Dimer (DD) serum level could reduce the progression of ARDS requiring high-flow nasal oxygen or mechanical ventilation (non-invasive or invasive).

**Methods and analysis** Phase II, open-label, randomised, multicentre, controlled clinical trial to study the efficacy and safety of the administration of two doses of sarilumab (200 and 400 mg) plus best available therapy (BAT) in hospitalised adults with COVID-19 presenting cytokine release syndrome. This strategy will be compared with a BAT control group. The efficacy and safety will be monitored up to 28 days post-administration. A total of 120 patients will be recruited (40 patients in each arm).

**Ethics and public dissemination** The clinical trial has been approved by the Research Ethics Committee of the coordinating centre and authorised by the Spanish Agency of Medicines and Medical Products (AEMPS). If the hypothesis is verified, the dissemination of the results could change clinical practice by increasing early administration of sarilumab in adult patients with COVID-19 presenting cytokine release syndrome, thus reducing ICU admissions.

**Trial registration number** NCT04357860

### Strengths and limitations of this study

- Early use of sarilumab can reduce the progression of respiratory failure and prevent the saturation of ICUs.
- The trial will study two doses of the drug. One could be selected for phase III trials with a larger sample.
- Limitations include not being a blind trial and having a limited sample size.
- The stock of sarilumab is limited in Spain. The government distributes the drug to ensure treatment of patients with rheumatoid arthritis. Pharmacies must request authorisation for dispensation of the drug on a case-by-case basis.
- The incidence of new cases is decreasing in Spain.

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the newly discovered SARS-CoV-2 coronavirus. Data on the severity of confirmed cases have varied over time. Subjects with severe acute respiratory syndrome (SARS) and high levels of pro-inflammatory cytokines and chemokine are associated with T-cell depletion, pulmonary inflammation and extensive lung damage. The levels of these cytokines negatively correlate with absolute lymphocyte counts, thus inducing T-cell exhaustion and apoptosis and causing acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).<sup>[1]</sup>

A similar phenomenon is observed in the case of cytokine release syndrome (CRS) associated with chimeric antigen receptor T-cell (CAR-T) therapy. One of the key mediators of autoimmunity, inflammation, viral cytokine release syndromes and CRS-induced damage is interleukin-6 (IL-6). Patients with SARS-CoV-2 infection have high plasma IL-6 levels, especially those with a more severe presentation and high C-reactive protein (CRP) levels.<sup>[2]</sup>

1  
2  
3 It has been suggested that IL-6 blockade may constitute a novel therapeutic strategy for  
4 cytokine release syndrome and systemic inflammatory response syndrome in sepsis,  
5 macrophage activation syndrome and haemophagocytic lymphohistiocytosis.<sup>[3]</sup> Remarkable  
6 beneficial effects of IL-6 blockade therapy using an IL-6 receptor inhibitor have been described  
7 in patients with severe SARS-CoV-2 pneumonia in a retrospective case series from China.<sup>[4]</sup>  
8  
9

10 Sarilumab is a human monoclonal antibody against the IL-6 receptor that is currently  
11 licensed for rheumatoid arthritis. It is safe and well tolerated.<sup>[5]</sup> The most common side effects  
12 are upper respiratory tract infections, headache, hypertension and abnormal liver function tests.  
13 The most serious side effects are infections, such as diverticulitis, and hypersensitivity  
14 reactions.<sup>[6]</sup>  
15  
16

17 It is hypothesised that IL-6 might play a key role in the cytokine release syndrome in SARS-CoV-  
18 2 patients with pneumonia, and that blockade of IL-6 would be a suitable therapeutic target for  
19 these patients. The research question of this trial is: does early treatment with sarilumab reduce  
20 the evolution to respiratory distress syndrome that requires ventilatory support in hospitalized  
21 patients with COVID-19?  
22  
23

## 24 25 26 METHODS AND ANALYSIS 27 28

### 29 Design 30

31 This is a phase II, open-label, randomised, multicentre, controlled clinical trial. The  
32 patients will be assigned to three treatment groups (Figure 1):  
33

- 34 1. Control group: 40 patients will receive the best available therapy (BAT) for a maximum of 14  
35 days.
- 36 2. Treatment group 1 (T1): 40 patients will receive BAT for a maximum of 14 days + 200 mg of  
37 sarilumab subcutaneously (single dose).
- 38 3. Treatment group 2 (T2): 40 patients will receive BAT for a maximum of 14 days + 400 mg of  
39 sarilumab subcutaneously (single dose).

40 At the time the protocol has been written, and in the absence of scientific evidence, BAT  
41 is considered any combination of drugs authorized in Spain for this indication. This variable will  
42 be taken into account in the efficacy analysis.  
43

### 44 45 46 Study population and setting 47 48

49 Ten university hospitals located in Andalusia, Spain, will participate in the trial. The trial  
50 will include hospitalised patients with confirmed SARS-CoV-2 infection causing respiratory  
51 disease and presenting high serum levels of IL-6 or D-Dimer (DD). Patients who meet all the  
52 inclusion criteria and have no exclusion criteria will be prospectively included in the study.  
53 Following hospital admission, patients may be randomized as soon as they meet the inclusion  
54 criteria, even in the emergency department. The inclusion and exclusion criteria for the trial are  
55 described in Box 1.  
56  
57

**Box 1 Study selection criteria*****Inclusion criteria***

1. Age  $\geq 18$  years and  $<75$  years
2. Hospitalisation with COVID-19 (positive PCR in a respiratory tract sample) in absence of respiratory distress (defined as requiring high-flow nasal oxygen or mechanical ventilation).
3. Interstitial pneumonia confirmed by chest radiography or CT scan
4. IL-6 levels  $>40$  pg/ml. In the absence of IL-6, D-Dimer (DD)  $>1500$  or  $>1000$  if progressive increments between at least 2 determinations are documented after admission.
5. In women of childbearing age, a negative pregnancy test
6. Signed informed consent

***Exclusion criteria***

1. SOFA score  $>6$  points
2. Patient who, in the researcher's opinion, is not subsidiary of invasive mechanical ventilation.
3. Neutrophil count  $<2 \times 10^3/\mu\text{L}$
4. Platelet count  $<100 \times 10^3/\mu\text{L}$
5. ALT or AST levels  $>5$  times the upper limit of normal
6. Severe renal failure ( $\text{CrCl} <30 \text{ ml/min}$ )
7. Active bacterial infection
8. Active tuberculosis or history of not completing treatment against tuberculosis
9. Antecedents of diverticulitis
10. Hypersensitivity to sarilumab or its excipients
11. Treatment with TNF antagonists
12. Treatment with anti-IL6 in the previous 30 days
13. Chronic treatment ( $>1$  month<sup>a</sup>) with corticosteroids at doses  $>0.5 \text{ mg/kg/day}$  of prednisone or equivalent. Topical and inhaled corticosteroids are acceptable.
14. Concomitant treatment with immunomodulators, including vitamin D or statins. Macrolides such as azithromycin are acceptable.

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3     **15. Patients on immunosuppressive treatment for any cause**  
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5     **16. HIV-infected patients with CD4 <200/mm<sup>3</sup>**  
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7     **17. Past or current history of autoimmune disease**  
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9     **18. Patients receiving immunomodulatory antibody therapy, including immunoglobulins**  
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11     **19. Participation in any clinical trial that evaluated any investigational product in the last 3 months or less than 5 half-lives of the product under investigation**  
12  
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15     **20. Pregnancy**  
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18     **21. Any other condition that, in clinical judgement, prevents the patient's adherence to the protocol**

20  
21 Abbreviations: SOFA, sequential organ failure assessment. PCR, polymerase chain reaction. CT scan,  
22 computed tomography scan. ALT, alanine transaminase. AST, aspartate transaminase. CrCl, creatinine  
23 clearance. TNF, tumour necrosis factor. HIV, human immunodeficiency viruses.

- 24     <sup>a</sup> Based on:  
25       - National Institute for Health and Clinical Excellence (NICE) Clinical Knowledge Summaries:  
26       Corticosteroids - Oral. NICE; 2012.  
27       - Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the  
28       complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9(1):30.  
29       Published 2013 Aug 15. doi:10.1186/1710-1492-9-30

## 34     Withdrawal criteria

35  
36       Patients may withdraw from the study at any time, for any reason and without prejudice  
37       to future medical treatment. Patients who do not comply with the study procedure or have not  
38       been followed up will be considered a study "withdrawal". The reasons for withdrawal will be  
39       examined in full accordance with bioethical principles regarding the guarantee of patients'  
40       rights. The criteria for withdrawal from the study are described below.

- 41  
42     1. Patient request  
43     2. Violation or deviation from the protocol (e.g. breach of administration of treatment, need for  
44       prohibited treatment).  
45     3. Researchers decision, based on clinical reasons  
46     4. Administrative decision of the investigators, promoter or regulatory authorities  
47     5. Loss to follow-up  
48     6. Suspected unexpected serious adverse reaction (SUSAR)  
49     7. Serious adverse event (SAE) that at the discretion of the promoter or investigator is not  
50       acceptable.  
51     8. Any adverse event considered intolerable by either the patient or the investigator  
52     9. Pregnancy

53  
54       The inclusion and exclusion criteria can be modified in consecutive versions of the  
55       protocol, based on the scientific evidence that is published during the development of the trial,  
56       after justification and approval by the reference ethics committee.

## Study variables

### ***Outcome variables***

The primary outcome variable is the development of adult respiratory distress syndrome requiring high-flow nasal oxygenation (HFNO) or mechanical ventilation, both non-invasive and invasive.

The secondary outcome variables are: all-cause (crude) mortality at day 28, time (in days) to clinical improvement, time (in days) until oxygenation improvement for at least 48 hours, proportion of patients who require invasive mechanical ventilation, negativisation of PCR to SARS-CoV-2, cytokine kinetics and side effects.

Time to clinical improvement is defined as number of days until 2 points rise in the seven category ordinal scale.

Clinical improvement will be assessed on a seven-category ordinal scale consisting of the following categories: 1, not hospitalised with resumption of normal activities; 2, not hospitalised, but unable to resume normal activities; 3, hospitalised, not requiring supplemental oxygen; 4, hospitalised, requiring supplemental oxygen; 5, hospitalised, requiring high-flow oxygen therapy; 6, hospitalised requiring ECMO, invasive mechanical ventilation or both; and 7, death.

Time (in days) until improvement in oxygenation for at least 48 hours: (i) Time to verify an increase in the SpO<sub>2</sub> / FiO<sub>2</sub> ratio with respect to the worst SpO<sub>2</sub> / FiO<sub>2</sub> prior to treatment with Sarilumab and stratified according to levels of IL-6 or DD; (ii) Time until the absence of oxygen need to maintain a saturation in ambient air of ≥ 93%; (iii) Number of days in need of supplemental oxygen.

### ***Other variables***

The following demographics and clinical information will be collected from all patients: age, sex, weight, height, body mass index (BMI), comorbidities, previous treatment, history of the current disease, respiratory rate (bpm), basal oxygen saturation (%), arterial pO<sub>2</sub> (mm Hg), pO<sub>2</sub>/FiO<sub>2</sub> rate, oxygen saturation/FiO<sub>2</sub> rate, blood pressure (mmHg), heart rate (bpm), consciousness level, temperature (°C), clinical improvement, organ failure assessment score (SOFA), microbiological test, analytical parameters (haematimetry, glucose, creatinine, AST, ALT, C-reactive protein, albumin, LDH, ferritin, troponin I, protein kinase, procalcitonin, lipid profile, IL-6, D-dimer, prothrombin time, INR). All concomitant medication and adverse events will be recorded and monitored in accordance with regulatory procedures. SARS-CoV-2019 in nasopharyngeal swab and a panel of cytokines (IL1- $\alpha$ , IL1- $\beta$ , IL6, IL8, IL10, IL12, IL18, IL38, INF $\gamma$ , TNF $\alpha$ , CCL2, CCL3, CCL4, MIF  $\gamma$  PAI-1) RAGE, Ang-2 and Protein C will be determined before randomisation and on days 5, 10, 14, 21 and 28.

## Randomisation and masking

A total of 120 patients will be recruited (40 in each group). Patients who meet the selection criteria will be randomised to be included in the control group or the two experimental groups. Randomisation will be carried out by means of electronic case report forms (eCRFs). The ratio will be 1:1:1 for each group (balanced randomisation). The study design is open, but the

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3 investigator will not know the treatment assignment until the patient signs the informed consent  
4 form and randomisation is performed, thus minimising selection bias. Patients will be identified  
5 by a code that includes the centre code followed by the patient number (XX-YY).  
6  
7

## 8 Study medication

9 The investigational medication (IM) is sarilumab (ATC code: L04AC14), a human  
10 monoclonal antibody (IgG1 subtype) that specifically binds to both soluble and membrane-  
11 bound IL-6 (IL-6Ra) receptors and inhibits the transmission of IL-6 mediated signals involving  
12 signal transducer glycoprotein 130 (gp130) and activator of transcription 3 (STAT-3).  
13  
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15 The commercial subcutaneous medication available in Spain (SANOFI-AVENTIS) will be  
16 used. Administration of the IM will be carried out according to the technical sheet and the local  
17 practice of each centre.  
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19 The BAT will include any combination of drugs included in the current protocol of the  
20 Spanish Ministry of Health  
21 (<https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos.htm>) and complementary notes issued by the Spanish Agency of Medicines  
22 and Medical Products ([www.aemps.gob.es](http://www.aemps.gob.es))  
23  
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## 25 Study procedures

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## 27

28 The duration of follow-up for each patient will be 28 days and will start from the moment  
29 the patient is randomised. A total of 6 visits will be scheduled during the trial: baseline, day 5,  
30 day 10, day 14, day 21 and day 28. The scheduled follow-up is shown in Table 1. The visit  
31 following the end of treatment will be considered as the end-of-treatment visit. Visit 5 (day 28  
32 after randomisation) will be considered the final study visit. The final study visit can be moved  
33 forward to the day of hospital discharge. Additionally, data on clinical improvement (on a 7-  
34 point ordinal scale), axillary temperature, oxygen saturation (or PO<sub>2</sub>) and oxygen therapy will be  
35 collected daily.  
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38 Nasopharyngeal swabs will be performed on days 0, 5, 10, 14, 21 and 28. Plasma will  
39 also be obtained on days 0, 5, 10, 14, 21 and 28. The samples will be locally preserved (frozen at  
40 -80 °C) until dispatched to the Biobank of the Reina Sofía University Hospital of Córdoba, Spain.  
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43 The principal investigator will be responsible for the detection and documentation of  
44 adverse events (AE) throughout the study. All AEs must be notified during all phases of the study  
45 and followed up until resolution or until an adequate explanation is found, although the patient  
46 has completed study treatment. Periodic reports will also be submitted on AEs that occurred  
47 during the study, including causality assessment, severity and intensity.  
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Table 1. Chart of study procedures

	STUDY PERIOD											
	BASELINE		POST RANDOMISATION									
	Day 0	Day 1	Day 2 to 4	VISIT 1 Day 5	Day 6 to 9	VISIT 2 Day 10	Day 11 to 13	VISIT 3 Day 14	Day 15 to 20	VISIT 4 Day 21	Day 22 to 27	VISIT 5 Day 28
<b>Recruitment</b>												
Review of inclusion and exclusion criteria	X											
Informed consent	X											
Randomisation	X											
Baseline data, demographics data and comorbidities*	X											
<b>Clinical data</b>												
Respiratory rate, Saturation, Applied Oxygen ( $\text{FiO}_2$ ) $\text{SpO}_2$ / $\text{FiO}_2$ ratio	X	X	X	X	X	X	X	X	X	X	X	X
Arterial $\text{pO}_2$ , $\text{pO}_2$ / $\text{FiO}_2$ ratio	X			X		X		X		X		X
SOFA score	X	X	X	X	X	X		X		X		X
7-point ordinal scale	X	X	X	X	X	X	X	X	X	X	X	X
<b>Laboratory data</b>												
PCR COVID-19 (nasopharyngeal swab)	X			X		X		X		X		X
Analytical parameters**	X			X		X		X		X		X
Samples for cytokine determination	X			X		X		X		X		X
Pregnancy test	X											
<b>Drugs</b>												
IM Administration	X											
Interaction assessment, AR, SAR, SUSAR, AE, SAE	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication record	X	X	X	X	X	X	X	X	X	X	X	X
<b>Radiological tests</b>												
Chest X-ray or CT scan	X											
<b>Biological samples</b>												
Samples for Biobank	X			X		X		X		X		X

\*age, sex, weight, height, BMI, comorbidities, previous treatment (including therapeutic family; e.g. ACEI, ARA II, statins, etc.), current disease history, BP (mm Hg), HR, levels of consciousness, temperature (°C), National Early Warning Score (NEWS).

\*\*Haematometry, glucose, creatinine, AST, ALT, C-reactive protein, albumin, LDH, ferritin, troponin I, protein kinase, procalcitonin, pregnancy test (at visit 0), lipid profile, interlekin-6, D-dimer, prothrombin time (PT%), INR.

## Statistical analysis

Since this is a phase II study, a sufficient number of patients are included to perform an initial analysis of efficacy and safety. We have calculated an overall sample size of 120 patients, 40 patients for each arm, to detect a 30% reduction in the primary outcome with an alpha error of 0.05, a beta risk of 0.2 and assuming that the modified intention-to-treat population will be 90% of the randomised patients.

Clinical data will be collected in an electronic case report form (eCRF). All analyses will be performed using PASW Statistics software V.15.0 (IBM Corporation) and R software (V.3.5.0). Frequencies will be calculated for the qualitative variables and compared using the  $\chi^2$  test or Fisher's test. For quantitative variables, the mean and standard deviation will be calculated.

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2  
3 Normality will be analysed using the Kolmogorov-Smirnov test and comparisons will be made  
4 using the Student's t-test or the Mann-Whitney test depending on whether or not they follow a  
5 normal distribution, respectively. For the comparison of three or more groups, the analysis of  
6 variance (ANOVA) or Kruskal-Wallis tests will be used. The analyses will be based on the  
7 intention-to treat population (randomised patients receiving treatment). The time until the  
8 primary outcome variable is reached will be plotted on a Kaplan-Meier curve and compared  
9 using a log-rank test. A Cox regression analysis will be performed for the primary efficacy variable  
10 and the results reported in terms of the hazard ratio (HR) with 95% confidence intervals.  
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## Patient and public involvement

14 No patient involved.  
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## ETHICAL ISSUES AND DISSEMINATION PLAN

17  
18 This clinical trial will be conducted in accordance with the protocol and the ethics  
19 principles of the Declaration of Helsinki (Fortaleza, 2013) and in accordance with the applicable  
20 regulatory requirements, in particular the ICH Tripartite Guideline "Standards of Good Clinical  
21 Practice", Royal Decree 1090/2015 regulating clinical trials with medications in Spain and  
22 Regulation (EU) No. 536/2014 of 16 April 2014 on clinical trials on medicinal products for human  
23 use. The protocol, the informed consent form, the patient information form and any documents  
24 applicable to the study have required approval by the appropriate regulatory agencies. The  
25 Committee for Biomedical Research Ethics of the Reina Sofia University Hospital approved the  
26 trial. Authorisation has also been obtained from the Spanish Agency of Medicines and Medical  
27 Products (AEMPS, 20-0262). The trial is registered in accessible public databases such as the  
28 Spanish Clinical Studies Registry (REec), EUDRACT (2020-001531-27) and ClinicalTrials.gov  
29 (NCT04357860).  
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## DISCUSSION

35  
36 The number of people diagnosed with coronavirus disease 2019 (COVID-19) worldwide  
37 crossed the two million mark on April 25, 2020. The vast majority of patients with the COVID-19  
38 have had a good prognosis, but there were critical individuals and deaths. ARDS is the leading  
39 cause of death in patients infected with SARS-CoV-2.<sup>[7]</sup> ARDS is a life-threatening lung condition  
40 that prevents enough oxygen from getting to the lungs and into circulation. Despite the efforts  
41 to characterise the clinical picture of COVID-19, very little is known about the pathologic  
42 manifestations, in particular lung inflammation. The first report of pathological findings from a  
43 severe COVID-19 patient showed pulmonary bilateral diffuse alveolar damage with cellular  
44 fibromyxoid exudates. Interstitial mononuclear inflammatory infiltrates, dominated by  
45 lymphocytes, were observed in both lungs. The authors suggested an over-activation of T cells  
46 manifested by an increase of Th17 and high cytotoxicity of CD8 T cells leading to severe immune  
47 injury and inflammation.<sup>[8]</sup> The clinical presentation of patients with severe forms of COVID-19  
48 resembles cytokine release syndrome observed in some oncology patients treated with CAR-T  
49 cell therapies.  
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52 Cytokine dysregulation is of particular interest in patients with COVID-19, who have  
53 higher levels of inflammatory cytokines. Some cytokines seem to be up-regulated, especially in  
54 patients with more severe disease. The overwhelming release of proinflammatory cytokines and  
55 chemokines may be involved in the pulmonary injury characterised by diffuse alveolar damage  
56 with epithelial and endothelial apoptosis, dysregulated coagulation and pulmonary fibrinolysis.  
57 Among the cytokines produced by activated macrophages, IL-6 is one of the key cytokines. The  
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3 role of IL-6 has been consistently reported in several studies of COVID-19.<sup>[9, 10, 11]</sup> A large  
4 retrospective cohort study found that IL-6 levels were correlated with mortality in 158 patients  
5 with COVID-19.<sup>[12]</sup> Interestingly, Chen et al. showed that levels of IL-6 are 10 times higher in  
6 critical patients compared with other patients. IL-6 levels were closely correlated with  
7 mortality.<sup>[13]</sup> Therefore, antiviral therapy alone may be inadequate for patients with  
8 uncontrolled inflammatory response. For this reason, numerous protocols have recommended  
9 tocilizumab, a humanised monoclonal antibody against the IL - 6 receptor, in critical patients  
10 with ARDS and elevated IL - 6.<sup>[14]</sup>

11  
12 Another point of interest is the rapid increase in the number of cases of COVID-19 across  
13 the world, which has shown how quickly health systems can be challenged to provide adequate  
14 care. Mortality was 7-fold higher for patients in Hubei compared with other non-affected  
15 Chinese provinces, emphasising the importance of ICU capacity in the care of patients with  
16 COVID-19.<sup>[15]</sup> Access to ICU beds and ventilators can be rapidly saturated if the overwhelming  
17 inflammation is not stopped at early stages. Xie et al. highlighted the importance of the limited  
18 capacity of ICUs as only 25% of patients who died had received invasive mechanical  
19 ventilation.<sup>[16]</sup>

20  
21 Therefore, it seems plausible to speculate that the anti-IL6R plays a protective role if  
22 given at the time of overwhelming elevated immune response, preventing the cytokine release  
23 syndrome. We propose that the early use of sarilumab, in addition to antiviral therapy, can  
24 attenuate the detrimental host immune response in patients with elevated markers of  
25 inflammation and reduce the development of severe respiratory failure and other organ  
26 damage. In conclusion, the SARICOR study aims to reduce the severity and mortality associated  
27 with COVID-19.

28  
29  
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31 Garrido and Jesús Fernández from the Instituto Maimónides de Investigación Biomédica de  
32 Córdoba (IMIBIC)/Reina Sofía University Hospital/University of Córdoba. JRB and JTC have  
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34 RD16/0016). ALP is supported by SCReN (Spanish Clinical Research Network) funded by the  
35 ISCIII-Sub-Directorate General for Research Assessment and Promotion through project  
36 PT13/0002/0010-PT17/0017/0012 and PT17/0017/0032.

37  
38 **Contributors.** Dr. Julián Torre-Cisneros, Dr. Rafael León López and Antonio Miguel Luque Pineda  
39 collaborate in the design of the protocol and the informed consent form.

40  
41 The protocol was reviewed and agreed with Sheila Cárcel Fernández, Dr. Laura Limia Pérez, Dr.  
42 Alberto Romero Palacios, Dr. María Concepción Fernández-Roldán, Dr. Eduardo Aguilar Alonso,  
43 Dr. Inés Pérez Camacho, Dr. Jesús Rodríguez-Baño, Dr. Nicolás Merchante, Dr. Julián Olalla, Dr.  
44 M. Ángeles Esteban-Moreno and Dr. Marta Santos, who contributed in the definition of the  
45 eligibility criteria.

46  
47 Dr. Julián Torre-Cisneros contributed in the refinement, final review and approval of the protocol  
48 and the informed consent form.

49  
50 **Funding.** COVID-19 Research Programme. Ministry of Health and Families, Regional Government  
51 of Andalusia. Project code COVID-0013-2020.

52  
53 **Competing interests.** The authors declare no conflicts of interest.

54  
55 **Ethics approval.** In accordance with Royal Decree 1090/2015 of 4 December concerning the  
56 regulation of clinical trials of medicinal products in Spain, multicentre clinical trials only require

1  
2  
3 the approval of a single medicinal research ethics committee (reference MREC) and of the  
4 Spanish Agency of Medicines and Medical Products (AEMPS). This clinical trial has been  
5 approved by the reference MREC of the province of Córdoba and the AEMPS (Code: 20-0262;  
6 EudraCT Number: 020-001531-27).  
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9 **Open access.** This is an open access article distributed in accordance with the Creative Commons  
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12 terms, providing the original work is properly cited, appropriate credit is given, any changes  
13 made indicated and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.  
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15 **Figure legend**  
16 Figure 1. Flow diagram  
17 Table 1. Chart of study procedures  
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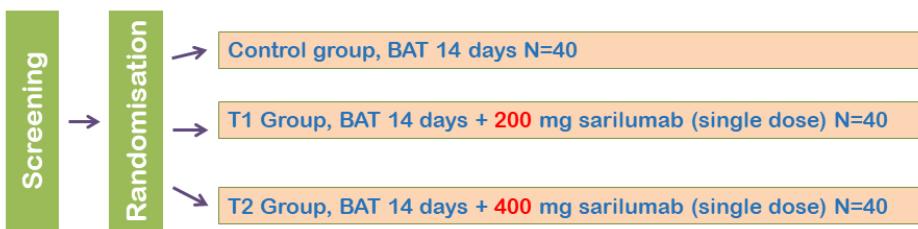


Figure 1 - Flow diagram

254x190mm (96 x 96 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description
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#### Administrative information

- Title 1 Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): protocol of a phase II, open-label, randomised, multicentre, controlled controlled clinical trial.
- Trial registration 2a Spanish Clinical Studies Registry (REec), EUDRACT (2020-001531-27) and ClinicalTrials.gov (NCT04357860).
- 2b

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04357860
Date of registration in primary registry	April, 2020
Secondary identifying numbers	EUDRACT (2020-001531-27)
Source(s) of monetary or material support	COVID-19 Research Programme. Ministry of Health and Families, Regional Government of Andalusia. Project code COVID-0013-2020. Non-financial support provided by IMIBIC Clinical Research Unit and SCReN (Spanish Clinical Research Network).
Primary sponsor	FIBICO (Fundación para la Investigación Biomédica de Córdoba)
Secondary sponsor(s)	Not applicable
Contact for public queries	IMIBIC Clinical Research Unit (uicec@imibic.org)

Contact for scientific queries	Dr. Julián de la Torre Cisneros (julian.torre.sspa@juntadeandalucia.es)
Public title	Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): protocol of a phase II, open-label, randomised, multicentre, controlled clinical trial.
Scientific title	Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): protocol of a phase II, open-label, randomised, multicentre, controlled clinical trial.
Countries of recruitment	Spain
Health condition(s) or problem(s) studied	SARS-CoV-2, COVID-19
Intervention(s)	Experimental arm #1: Subjects treated with the best available treatment up to 14 days plus Sarilumab 200 mg single dose.
	Experimental arm #2: Subjects treated with the best available treatment up to 14 days plus Sarilumab 400 mg single dose.
	Active comparator: Subjects treated with the best available treatment up to 14 days.
Key inclusion and exclusion criteria	Ages eligible for study: $\geq 18$ years and $<75$ years Sexes eligible for study: both Accepts healthy volunteers: no
	1. Age $\geq 18$ years and $<75$ years 2. Admission for confirmed respiratory symptoms to COVID-19 based on a positive PCR in a

	<p>sample of the respiratory tract in the local laboratory in the absence of respiratory distress syndrome requiring High flow nasal oxygenation or mechanical ventilation</p> <p>3. Interstitial pneumonia confirmed by chest radiography or CT</p> <p>4. IL-6 levels &gt; 40 pg / ml. In its absence, D-Dimer (DD) &gt; 1500 or &gt; 1000 may be included if progressive increases are documented</p> <p>5. Negative pregnancy test in women of childbearing age</p> <p>6. Signature of informed consent</p>
	<p>1. SOFA score &gt; 6 points</p> <p>2. Patient who, in the researcher's opinion, is not a subsidiary of invasive mechanical ventilation</p> <p>3. Neutrophil count &lt; 2 x 10<sup>3</sup> / μL</p> <p>4. Platelet count &lt; 100 x 10<sup>3</sup> / μL</p> <p>5. ALT or AST levels &gt; 5 times the upper limit of normal</p> <p>6. Severe renal failure (CrCr &lt; 30 ml / min)</p> <p>7. Treatment with TNF antagonists</p> <p>8. Previous treatment with anti-IL6 in the previous 30 days</p> <p>9. Chronic prior treatment with corticosteroids at doses greater than 0.5 mg / kg / day of prednisone or equivalent. Yes, inhaled and topical corticosteroids are acceptable</p> <p>10. Concomitant treatment with immunomodulators, among which are Vitamin D or statins. Macrolides such as azithromycin are acceptable</p> <p>11. Pregnancy</p>
Study type	Interventional

	Allocation: randomized Intervention model: Parallel groups Masking: open-label
	Primary purpose: curative
	Phase II
Date of first enrolment	Not recruiting
Target sample size	120
Recruitment status	Not recruiting
Primary outcome(s)	Proportion of patients requiring or time (in days) to that is required: -High flow nasal oxygenation. -BiPAP type non-invasive mechanical ventilation. -Non-invasive mechanical ventilation type CPAP. -Invasive mechanical ventilation.
Key secondary outcomes	<ul style="list-style-type: none"> <li>- All-cause (crude) mortality at day 28.</li> <li>- Time (in days) to clinical improvement, defined as mean change or time in days from randomization to any of the following criteria: (i) improvement of two points in the ordinal scale of 7 points of gravity or, (ii) discharge from the hospital alive. The criteria that is reached before.</li> <li>- Time (in days) until improvement in oxygenation for at least 48 hours.</li> <li>- Proportion of patients requiring invasive mechanical ventilation.</li> <li>- Proportion of patients who have negative COVID-19 PCR at each visit.</li> <li>- Mean of serum cytokine levels.</li> </ul>

			- Incidence of adverse events related to medication and its administration.
Protocol version	3	Version: 1.0, 24 March 2020	
Funding	4	COVID-19 Research Programme. Ministry of Health and Families, Regional Government of Andalusia. Project code COVID-0013-2020. Non-financial support provided by IMIBIC Clinical Research Unit and SCReN (Spanish Clinical Research Network).	
Roles and responsibilities	5a	Dr. Julián de la Torre Cisneros Unidad de Gestión Clínica de Enfermedades Infecciosas Hospital Universitario Reina Sofía Avenida Menéndez Pidal s/n – C.P. 14004 (Córdoba, SPAIN) Coordinating investigator  Dr. Rafael León López Unidad de Gestión Clínica de Medicina Intensiva Hospital Universitario Reina Sofía Avenida Menéndez Pidal s/n – C.P. 14004 (Córdoba, SPAIN) Principal investigator at Hospital Universitario Reina Sofía  Dr. Laura Limia Pérez Unidad de Gestión Clínica de Medicina Interna Hospital Universitario Reina Sofía Avenida Menéndez Pidal s/n – C.P. 14004 (Córdoba, SPAIN) Sub-investigator at Hospital Universitario Reina Sofía  Mr. Antonio Miguel Luque Pineda IMIBIC Clinical Research Unit Edificio IMIBIC Avenida Menéndez Pidal s/n – C.P. 14004 (Córdoba, SPAIN) Clinical Trial Manager	
		Dr. Julián de la Torre Cisneros conceived of the study. Dr. Rafael León López, Dr. Laura Limia Pérez and Antonio Miguel Luque Pineda collaborated in the protocol design. IMIBIC provided statistical expertise in clinical trial design and it will conduct the statistical analysis. Dr. Julián de la Torre Cisneros also contributed to refinement of the study protocol and approved the final manuscript.	

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5b FIBICO (Fundación para la Investigación Biomédica de Córdoba) Hospital  
6 Universitario Reina Sofía - Edificio IMIBIC  
7 Avenida Menéndez Pidal s/n – C.P. 14004 (Córdoba, SPAIN)  
8 Contact name: Mr. Antonio Miguel Luque Pineda  
9 Phone: +34 671 59 60 70  
10 E-mail: uicec@imibic.org  
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15 5c The funder Ministry of Health and Families, Regional Government of  
16 Andalusia had no role in the design of this study and will not have any role  
17 during its execution, analyses, interpretation of the data or decision to  
18 submit results.  
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5d     **Coordinating investigator (see section 5a)**

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- Design of the study protocol
  - Preparation and revision of new amendments to the protocol
  - Design of the CRF
  - Publication of study reports

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**Trial management and monitoring**

FIBICO (Fundación para la Investigación Biomédica de Córdoba) Clinical Research Unit  
Edificio IMIBIC  
Avenida Menéndez Pidal s/n – C.P. 14004 (Córdoba, SPAIN)  
Phone: +34 671 59 60 70 E-mail: [uicec@imibic.org](mailto:uicec@imibic.org)

- Study planning
- Provide annual report to AEMPS [Spanish Agency of Medicines and Medical Products] and Ethics Committee
- SAE & SUSAR reporting
- Responsible for trial master file
- Budget administration and contractual issues with sites
- Advice for principal investigators
- Assistance with international review, board/independent ethics committee applications
- Data verification and monitoring

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**Pharmacovigilance service (SCReN partner)**

Unidad de Investigación Clínica y Ensayos Clínicos UICEC-HUVR  
Dr. Clara M. Rosso Fernández, Dr. M Ángeles Lobo Acosta  
Hospital Universitario Virgen del Rocío  
Edificio de Documentación Clínica  
Avenida Manuel Siurot s/n - C.P. 41013 (Seville, SPAIN)  
Phone: 955 013 414 - 955 012 144 Fax: 954 232 992  
E-mail: [pv\\_saricor@scren.es](mailto:pv_saricor@scren.es)

- SAE & SUSAR review and reconciliation
- Safety reports design
- Advise to Data Safety Monitoring Committee

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**Data Safety Monitoring Committee**

Independent physicians will monitor the available data concerning safety and effectiveness of the treatment and they will meet on a regular basis to discuss about the risk/benefit balance and the conduction of the trial.

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

**Data manager (IMIBIC crew)**

- Maintenance of trial IT system

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6 • Data verification  
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9 **Principal investigators**  
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15 In each participating centre a principal investigator is identified, to be  
16 responsible for identification, recruitment, data collection and completion  
17 of CRFs, along with follow up of study patients and adherence to study  
18 protocol and SmPC.

19 **Introduction**  
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26 **Background and  
27 rationale**  
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35 6a It has been suggested that IL-6 blockade may constitute a novel  
36 therapeutic strategy for cytokine release syndrome and systemic  
37 inflammatory response syndrome in sepsis, macrophage activation  
38 syndrome and haemophagocytic lymphohistiocytosis.  
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45 Although currently approved for the treatment of rheumatoid arthritis,  
46 sarilumab, an interleukin-6 (IL-6) receptor antibody, is being investigated  
47 for its ability to reduce the overactive inflammatory immune response  
48 associated with COVID-19. This is based on evidence of markedly  
49 elevated levels of IL-6 in patients who develop severely acute respiratory  
50 distress syndrome.  
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53 The research question of this trial is: Does early treatment with sarilumab  
54 reduce the evolution to respiratory distress syndrome that requires  
55 ventilatory support in hospitalized patients with COVID-19?  
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58 6b At the time the protocol has been written, and in the absence of scientific  
59 evidence, best available therapy (BAT) is considered any combination of  
60 drugs authorized in Spain for this indication. This variable will be taken  
into account in the efficacy analysis.  
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63 The BAT will include any combination of drugs included in the current  
64 protocol of the Spanish Ministry of Health  
65 (<https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActuales/nCov-China/documentos.htm>) and complementary notes issued by the  
66 Spanish Agency of Medicines and Medical Products.  
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6 Objectives

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### Research hypothesis

It is hypothesised that IL-6 might play a key role in the cytokine release syndrome in SARS-CoV-2 patients with pneumonia, and that blockade of IL-6 would be a suitable therapeutic target for these patients.

#### Primary objective

Decrease cases of ARDS in adults requiring HFNO or either non-invasive or invasive mechanical ventilation.

#### Secondary objectives

- To reduce crude mortality at 28 days
- To reduce the time (in days) to clinical improvement
- To reduce the time (in days) until improvement in oxygenation for at least 48 hours
- To reduce the proportion of patients who require invasive mechanical ventilation
- To study the effect of the drug on the negativization of the PCR to COVID-19
- To study the effect of the drug on the profile of cytokines
- To study the safety of the experimental drug

32 Trial design

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Phase II, open-label, randomised, multicentre, controlled, three parallel groups clinical trial. The primary endpoint is crude mortality at 28 days. Randomization will be performed as block randomization with a 1:1:1 allocation.

## Methods: Participants, interventions, and outcomes

41 Study setting

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Ten university hospitals located in Andalusia (South of Spain) will participate in the trial, with sufficient incidence at the community level.

The site selected are sufficiently distant from each other so that almost all Andalusia Community population is covered (8.460.000 inhabitants).

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5 Eligibility criteria

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**Inclusion criteria**

- 7 1. Age  $\geq 18$  years and  $<75$  years
- 8 2. Hospitalisation with COVID-19 (positive PCR in a respiratory tract
- 9 simple) in absence of respiratory distress (defined as requiring high-flow
- 10 nasal oxygen or mechanical ventilation).
- 11 3. Interstitial pneumonia confirmed by chest radiography or CT scan
- 12 4. IL-6 levels  $>40$  pg/ml. In the absence of IL-6, D-Dimer (DD)  $>1500$  or
- 13  $>1000$  if progressive increments between at least 2 determinations after
- 14 admission are documented.
- 15 5. In women of childbearing age, a negative pregnancy test
- 16 6. Signed informed consent

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**Exclusion criteria**

1. SOFA score  $>6$  points
2. Patient who, in the researcher's opinion, is not subsidiary of invasive mechanical ventilation.
3. Neutrophil count  $<2 \times 10^3/\mu\text{L}$
4. Platelet count  $<100 \times 10^3/\mu\text{L}$
5. ALT or AST levels  $>5$  times the upper limit of normality
6. Severe renal failure ( $\text{CrCl} <30 \text{ ml/min}$ )
7. Active bacterial infection
8. Active tuberculosis or history of not completing treatment against tuberculosis
9. Antecedents of diverticulitis
10. Hypersensitivity to sarilumab or its excipients
11. Treatment with TNF antagonists
12. Treatment with anti-IL6 in the previous 30 days
13. Chronic treatment ( $>1$  month) with corticosteroids at doses  $>0.5 \text{ mg/kg/day}$  of prednisone or equivalent. Topical and inhaled corticosteroids are acceptable.
14. Concomitant treatment with immunomodulators, including vitamin D or statins. Macrolides such as azithromycin are acceptable.
15. Patients on immunosuppressive treatment for any cause
16. HIV-infected patients with  $\text{CD4} <200/\text{mm}^3$
17. Past or current history of autoimmune disease
18. Patients receiving immunomodulatory antibody therapy, including immunoglobulins
19. Participation in any clinical trial that evaluated any investigational product in the last 3 months or less than 5 half-lives of the product under investigation
20. Pregnancy
21. Any other condition that, in clinical judgement, prevents the patient's adherence to the protocol

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5 Interventions 11a Following hospital admission and before performing any study activity, the  
6 participating subjects must sign the informed consent form. To participate  
7 in the study, patients must meet all of the inclusion criteria and none of the  
8 exclusion criteria.  
9

10  
11 Once the selection criteria are confirmed the patient will be randomized  
12 and allocated to one of the following treatment groups:  
13

- 14  
15 1. Control group: 40 patients will receive the best available therapy (BAT)  
16 for a maximum of 14 days.  
17

18  
19 At the time the protocol has been written, and in the absence of scientific  
20 evidence, BAT is considered any combination of drugs authorized in  
21 Spain for this indication. This variable will be taken into account in the  
22 efficacy analysis.  
23

- 24  
25 2. Treatment group 1 (T1): 40 patients will receive BAT for a maximum of  
26 14 days + 200 mg of sarilumab subcutaneously (single dose).  
27

- 28  
29 3. Treatment group 2 (T2): 40 patients will receive BAT for a maximum of  
30 14 days + 400 mg of sarilumab subcutaneously (single dose).  
31

32  
33 The total expected duration of each patient in the study is up to 28 days  
34 (or until the last day they are hospitalized, if less than 28 days).  
35

36  
37 Every patient will be visited on days 5, 10, 14, 21 and 28 after  
38 randomization. These visits may be made at home if the patient has been  
39 discharged. An evaluation of the clinical improvement will be made daily  
40 according to the ordinal scale of 7 points of gravity, the measurement of  
41 axillary temperature, oxygen saturation (or blood gas with PpO<sub>2</sub>) and  
42 oxygen therapy or respiratory support. These values will be collected in  
43 the CRD on planned visits.  
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6 11b Patients may withdraw from the study at any time, for any reason and  
7 without prejudice to future medical treatment. Patients who do not comply  
8 with the study procedure or have not been followed up will be considered  
9 a study "withdrawal". The reasons for withdrawal will be examined in full  
10 accordance with bioethical principles regarding the guarantee of patients'  
11 rights. The criteria for withdrawal from the study are described below.  
12  
13

- 14  
15 1. Patient request  
16 2. Violation or deviation from the protocol (e.g. breach of administration of  
17 treatment, need for prohibited treatment).  
18 3. Researchers decision, based on clinical reasons  
19 4. Administrative decision of the investigators, promoter or regulatory  
20 authorities  
21 5. Loss to follow-up  
22 6. Suspected unexpected serious adverse reaction (SUSAR)  
23 7. Serious adverse event (SAE) that at the discretion of the promoter or  
24 investigator is not acceptable.  
25 8. Any adverse event considered intolerable by either the patient or the  
26 investigator  
27 9. Pregnancy  
28  
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31

32 The toxicity will come given by the adverse effects:  
33  
34

- 35 - Very common (may affect more than 1 in 10 people): low white blood  
36 cell count based on blood tests.  
37 - Frequent (may affect up to 1 in 10 people):  
38     • Sinus or throat infections, congestion, runny nose, and sore throat  
39         (upper respiratory tract infection).  
40     • Infection in the urinary tract.  
41     • Fevers (oral herpes).  
42     • Low platelet count based on blood tests.  
43     • High cholesterol, high triglycerides according to blood tests.  
44     • Abnormal liver function tests.  
45     • Injection site reactions (including redness and itching).  
46  
47

48  
49 11c The participating subjects will hospitalized and the site investigators will  
50 be responsible of the administration of the study treatment.  
51  
52

53  
54 11d During the study, concomitant treatments used in clinical practice are  
55 allowed, as well as BAT. The BAT will include any combination of drugs  
56 included in the current protocol of the Spanish Ministry of Health  
57 (<https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActuales/nCov-China/documentos.htm>).  
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5      Outcomes      12      **Primary outcome measure:** Proportion of patients requiring or time (in  
6                    days) to that is required:  
7                    - High flow nasal oxygenation.  
8                    - BiPAP type non-invasive mechanical ventilation.  
9                    - Non-invasive mechanical ventilation type CPAP.  
10                  - Invasive mechanical ventilation.  
11  
12  
13  
14  
15                  **Secondary outcomes measure:**  
16                  - All-cause (crude) mortality at day 28.  
17                  - Time (in days) to clinical improvement, defined as mean change or  
18                  time in days from randomization to any of the following criteria: (i)  
19                  improvement of two points in the ordinal scale of 7 points of gravity or,  
20                  (ii) discharge from the hospital alive. The criteria that is reached  
21                  before. The 7 point gravity scale includes the following categories:  
22                      1 - Not hospitalized with normal activity  
23                      2 - Not hospitalized but unable to have normal activity  
24                      3 - Hospitalized, without requiring oxygen supplementation  
25                      4 - Hospitalized, requiring oxygen supplementation  
26                      5 - Hospitalized, requiring high flow nasal oxygenation, non-  
27                      invasive mechanical ventilation or both  
28                      6 - Hospitalized requiring ECMO, invasive mechanical ventilation  
29                      or both  
30                      7 – Death  
31  
32  
33  
34  
35  
36                  - Time (in days) until improvement in oxygenation for at least 48 hours:  
37                      • Time to verify an increase in the SpO<sub>2</sub> / FiO<sub>2</sub> ratio with respect to  
38                      the worst SpO<sub>2</sub> / FiO<sub>2</sub> prior to treatment with Sarilumab and  
39                      stratified according to levels of IL-6 or DD.  
40                      • Time until the absence of oxygen need to maintain a saturation in  
41                      ambient air  $\geq 93\%$ .  
42                      • Number of days in need of supplemental oxygen.  
43                  - Proportion of patients requiring invasive mechanical ventilation.  
44                  - Proportion of patients who have negative COVID-19 PCR at each  
45                  visit.  
46                  - Mean of serum cytokine levels: the panel of cytokines to quantify; IL1-  
47                   $\alpha$ , IL1- $\beta$ , IL6, IL8, IL10, IL12, IL18, IL38, INF $\gamma$ , TNF $\alpha$ , CCL2, CCL3,  
48                  CCL4, MIF and PAI-1.  
49  
50  
51  
52  
53                  **Security outcomes measure**  
54                  - Incidence of adverse events related to medication and its  
55                  administration.  
56                  - Incidence in the appearance of serious bacterial, fungal or  
57                  opportunistic infections.  
58                  - Incidence of perforation of the gastrointestinal tract.  
59  
60

- Mean leukocyte and neutrophil count.
- Average haemoglobin levels.
- Average platelet count.
- Average levels of creatinemia.
- Average bilirubin levels.
- Average ALT and AST levels.

The following demographics and clinical information will be collected from all patients: age, sex, weight, height, body mass index (BMI), comorbidities, previous treatment, history of the current disease, respiratory rate (bpm), basal oxygen saturation (%), arterial pO<sub>2</sub> (mm Hg), pO<sub>2</sub>/FiO<sub>2</sub> rate, oxygen saturation/FiO<sub>2</sub> rate, blood pressure (mmHg), heart rate (bpm), consciousness level, temperature (°C), clinical improvement, organ failure assessment score (SOFA), microbiological test, analytical parameters (haematimetry, glucose, creatinine, AST, ALT, C-reactive protein, albumin, LDH, ferritin, troponin I, protein kinase, procalcitonin, lipid profile, IL-6, D-dimer, prothrombin time, INR).

All concomitant medication and adverse events will be recorded and monitored in accordance with regulatory procedures.

SARS-CoV-2019 in nasopharyngeal swab and a panel of cytokines (IL1- $\alpha$ , IL1- $\beta$ , IL6, IL8, IL10, IL12, IL18, IL38, INF $\gamma$ , TNF $\alpha$ , CCL2, CCL3, CCL4, MIF y PAI-1) RAGE, Ang-2 and Protein C will be determined before randomisation and on days 5, 10, 14, 21 and 28.

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5 Participant timeline 13

The total expected duration of each patient in the study is up to 28 days (or until the last day they are hospitalized, if less than 28 days):

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7  
8  
9 Each patient will visit on days 5, 10, 14, 21 and 28 after randomization.  
10 These visits may be made at home if the patient has been discharged.

11  
12 An assessment of clinical improvement will be made daily according to the  
13 ordinal scale of 7 points of gravity, axillary temperature measurement,  
14 oxygen saturation (or blood gas with P<sub>p</sub>O<sub>2</sub>) and oxygen therapy or  
15 respiratory support. These values will be collected in the CRF on planned  
16 visits.

17  
18 See the table below.

19  
20  
21  
22  
23 Table 1. Chart of study procedures

	STUDY PERIOD											
	BASELINE		POST RANDOMISATION									
	Day 0	Day 1	Day 2 to 4	Visit 1 Day 5	Day 6 to 9	Visit 2 Day 10	Day 11 to 13	Visit 3 Day 14	Day 15 to 20	Visit 4 Day 21	Day 22 to 27	Visit 5 Day 28
<b>Recruitment</b>												
Review of inclusion and exclusion criteria	X											
Informed consent	X											
Randomisation	X											
<b>Baseline data, demographics and comorbidities*</b>	X											
<b>Clinical data</b>												
Respiratory rate, saturation, applied oxygen (FiO <sub>2</sub> ) SpO <sub>2</sub> /FiO <sub>2</sub> ratio	X	X	X	X	X	X	X	X	X	X	X	X
Arterial pO <sub>2</sub> , pO <sub>2</sub> /FiO <sub>2</sub> ratio	X			X		X		X		X		X
SOFA score	X	X	X	X	X	X		X		X		X
7-point ordinal scale	X	X	X	X	X	X	X	X	X	X	X	X
<b>Laboratory data</b>												
PCR COVID-19 (nasopharyngeal swab)	X			X		X		X		X		X
Analytical parameters†	X			X		X		X		X		X
Samples for cytokine determination	X			X		X		X		X		X
Pregnancy test	X											
<b>Drugs</b>												
IM administration	X											
Interaction assessment, AR, SAR, USAR, AA, AAG	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication record	X	X	X	X	X	X	X	X	X	X	X	X
<b>Radiological tests</b>												
Chest X-ray or CT scan	X											
<b>Biological samples</b>												
Samples for Biobank	X			X		X		X		X		X

\*Age, sex, weight, height, BMI, comorbidities, previous treatment (including therapeutic family; e.g. ACEI, ARA II, statins, etc.), current disease history, BP (mm Hg), HR, level of consciousness, temperature (°C), National Early Warning Score (NEWS).

† Haematemesis, glucose, creatinine, AST, ALT, C-reactive protein, albumin, LDH, ferritin, troponin I, protein kinase, procalcitonin, pregnancy test (at visit 0), lipid profile, interleukin-6, D-dimer, prothrombin time (PT%), INR.

## 51 Sample size 14

We have calculated an overall sample size of 120 patients, 40 patients for each arm, to detect a 30% reduction in the primary outcome with an alpha error of 0.05, a beta risk of 0.2 and assuming that the modified intention-to-treat population will be 90% of the randomised patients.

## 57 Recruitment 15

58 The enrolment will depend on the evolution of the pandemic in Spain.  
59 All COVID-19 teams in the participating sites are informed and involved.

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

Sequence generation 16a Patients will be randomly assigned to one of the three treatment groups in a 1: 1: 1 ratio, using a random allocation list generated by a specific computer system embedded in the eCRF.

For randomization, patients will be stratified using basal oxygen saturation by breathing room air or pO<sub>2</sub> on arterial blood gas.

- According to pulse oximetry in ambient air <90% or pO<sub>2</sub> <60 mmHg.
- In case of not having the previous data to ambient air, the relation pO<sub>2</sub> / FiO<sub>2</sub> <250 will be used.

Allocation concealment mechanism 16b The participating subjects will be randomized by a computerized system embedded in the electronic data capture and they will be allocated to one of the three treatment groups.

Participants will be randomised using REDCAP, which is an online eCRF which allows central randomisation.

Allocation concealment will be ensured, as the service will not release the randomisation code until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed.

Implementation 16c All patients who give consent for participation and who fulfil the inclusion criteria will be randomized. Randomisation will be performed by the principal investigator or delegated staff.

In return, the allocation will be shown in the eCRF. The investigator will provide the randomization information to the pharmacist.

Blinding (masking) 17a Not applicable, as the trial is open-label.

17b Not applicable, as the trial is open-label.

### **Methods: Data collection, management, and analysis**

Data collection methods 18a The main variable is a variable related to the efficacy of the study drug to avoid progression to SARD and avoid the need for ICU admission.

Secondary variables are designed to measure efficiency and safety objectives.

## **Training and certification plans**

All the participating sites will be trained centrally in the study methods and requirements. The data to be collected and the procedures to be conducted at each visit will be reviewed in detail. Each of the data collection forms and the nature of the required information will be discussed in detail on an item by item basis.

Study coordinators and investigators will learn how to enter the information in the eCRF and how to communicate any Adverse Event or Reaction. Entering data forms, responding to data discrepancy queries and general information about obtaining research quality data will also be covered during the training session.

## **Quality control of the collected data**

Data entered in the eCRF will be reviewed and monitored by Clinical Research Associates from the IMIBIC Clinical Research Unit and the corresponding queries will be raised in case inconsistencies are found.

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6 18b The subjects will be recruited once they are hospitalized and they will  
7 remain in the site until discharge.  
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9

10 The total expected duration of each patient in the study is up to 28 days  
11 (or until the last day they are hospitalized, if less than 28 days).  
12  
13

14 A subject will be considered to have completed the trial when they make  
15 the last scheduled visit.  
16  
17

18 Patients can withdraw at any time throughout the study, for whatever  
19 reason and without prejudice to future medical treatment.  
20  
21

22 The reasons for the withdrawal will be analysed with full compliance with  
23 the principles of Bioethics, in terms of guaranteeing the rights of patients  
24 and autonomous and informed decision.  
25  
26

27 Although patients can withdraw without having to explain why, as soon as  
28 a patient has decided to do so, the researchers will try to establish contact  
29 with the subjects and establish that the patient's decision is an informed  
30 choice, as well as to check to what extent the patient may be willing to  
31 continue participating in the study on a limited basis, eg if they would be  
32 willing to continue to contact or be seen in order to obtain follow-up  
33 information.  
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5 Data management 19

### Data collection

6  
7 The collected data will be electronically entered by the investigator at  
8 every participating site via the eCRF platform. Original study forms will be  
9 entered and kept on file at the participating site.  
10  
11

12 Participant files are to be stored in numerical order and stored in a secure  
13 and accessible place and manner. Participant files will be maintained in  
14 storage for a period of 25 years after completion of the study.  
15  
16

17 Data integrity will be enforced through a variety of mechanisms.  
18 Referential data rules, valid values, range checks, and consistency  
19 checks against data already stored in the database will be supported.  
20  
21

22 Modifications to data written to the database will be documented through  
23 either the data change system or an inquiry system.  
24  
25

26 Data entered into the database will be retrievable for viewing through the  
27 data entry applications. The type of activity that an individual user may  
28 undertake is regulated by the privileges associated with his/her user  
29 identification code and password.  
30  
31

32 Additional errors will be detected by programs designed to detect missing  
33 data or specific errors in the data. These errors will be summarized along  
34 with detailed descriptions for each specific problem in Data Query  
35 Reports, which will be sent to the sites.  
36  
37

38 The Study Coordinator who receives the queries will respond by checking  
39 the original forms for inconsistency, checking other sources to determine  
40 the correction, modifying the original (paper) form entering a response to  
41 the query.  
42  
43

44 The Coordinating Center (IMIBIC Clinical Research Unit) and participating  
45 site personnel will be responsible for making appropriate corrections to  
46 the original paper forms whenever any data item is changed. Written  
47 documentation of changes will be available via electronic logs and audit  
48 trails.  
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5 Statistical methods 20a

## Types of analysis

The analyses will be performed on the population by modified intention to treat. This includes all randomized patients to whom the drug or control is administered. Patients who die before administering the drug or those who are not administered for any other reason are excluded.

### Primary efficiency analysis

It will be performed based on the intention of treatment and will be measured by the proportion of patients requiring high-flow nasal oxygen / mechanical ventilation in the first 14 days. For this analysis, patients will be measured on day 14. The time in days until the end point is reached will be plotted on a Kaplan-Meier curve and compared using a Long Rank test. A univariate Cox regression analysis will be performed for the primary efficacy variable and

They will represent the results in terms of Hazard Ratio with 95% confidence intervals.

### Secondary efficiency analysis

CRUDE MORTALITY. Following the criteria of the primary efficacy analysis, mortality from any cause at 14 and 28 days will be analysed. For this 28-day analysis, the sample will be measured at 28 days, which will be the end point of the study.

CLINICAL IMPROVEMENT. Following the criteria of the primary analysis, an analysis of the time in days to clinical improvement or mean change according to the 7-point ordinal scale will be performed.

IMPROVEMENT OF OXYGENATION. Following the criteria of the primary analysis, an analysis of the time in days until oxygenation will be performed.

NEED FOR INVASIVE MECHANICAL VENTILATION. The proportion of patients requiring invasive mechanical ventilation in each arm will be compared.

NEGATIVIZATION OF THE PCR TO COVID-19. The proportion of patients who have negative PCR in each arm of the trial will be compared.

CYTOKIN LEVELS. The mean levels of each cytokine in each arm of the study will be compared.

SECURITY. A description of the adverse events will be made for each arm of the study and the proportion of the same in each arm of the trial will be compared.

54 20b Interim analysis

The sponsor will perform an Interim analysis of the data collected when it has been reached half the sample size (60 recruited subjects) in order to assess safety and efficacy of research treatment.

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6 20c **Security dataset**

7 The safety dataset covers all patients included in the study who have  
8 received at least one dose of any study medication.  
9

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11 **Modified intention-to-treat population**  
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17 The modified intention-to-treat population is defined as all randomized  
18 patients to whom the drug or control is administered. Patients who die  
19 before administering the drug or those who are not administered for any  
20 other reason are excluded.  
21

22 **Methods: Monitoring**  
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28

29 Data monitoring 21a A Data Safety Monitoring Committee has been established and it is  
30 independent of the sponsor. During the period of recruitment to the trial,  
31 monthly analyses will be provided to the Data Safety Monitoring  
32 Committee, together with any other analyses that the committee may  
33 request. The Data Safety Monitoring Committee will advise the sponsor  
34 about the study conduction, protocol modifications and/or trial halt if  
35 needed.  
36

37 21b Interim analysis  
38  
39

40 The sponsor will perform an Interim analysis of the data collected when it  
41 has been reached half the sample size (60 recruited subjects) in order to  
42 assess safety and efficacy of research treatment.  
43

44 The results of this analysis will be communicated to the participating  
45 researchers. In the event of detection of a significant lack of efficacy or an  
46 unacceptable risk-benefit balance, the sponsor will communicate this  
47 circumstance to the health authorities, Ethics Committee and local  
48 authorities and proceed to the premature termination of the study,  
49 according to what is indicated in the Royal Decree 1090/2015.  
50



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5      Harms

6      22      The principal investigator will be responsible for the detection and  
7      documentation, throughout the study, of adverse events.

8  
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10     It is the responsibility of the principal investigator to report all events in the  
11    eCRF, both observed by him/her and spontaneously reported by the  
12    participants, regardless of the relationship with the investigational  
13    medication.

14  
15     All the events should be reported during all phases of the study and  
16    followed up until resolution or until an adequate explanation is found, even  
17    if the patient has completed study treatment. In addition, reports will be  
18    made periodically on the events that occurred during the study, including  
19    evaluation of causality, severity and intensity.

20  
21  
22     Patients will be informed of possible adverse reactions of the  
23    investigational medication through the Patient Information Sheet, as well  
24    as their commitment to report any adverse event they experience. They  
25    will be given a way to contact the study researchers for this purpose. At all  
26    study visits, patients will be questioned about the presence of new events  
27    or about the evolution of pre-existing ones.

28  
29  
30     All events that are severe and manifest during the course of the study,  
31    regardless of the treatment group in which they occur, the sponsor must  
32    be notified in the course one working day (24 hours) from the time the  
33    investigator is aware of the event.

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36     The safety information will be recorded in the eCRF and it will be provided  
37    to the Data Safety Monitoring Committee for its analysis.



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Auditing

6 23 The clinical trial will be monitored by the IMIBIC Clinical Research Unit  
7 staff. According to the agreed Trial Monitoring Plan, the participating sites  
8 will be regularly monitored on-site and online by the CRA.  
9

10 The primary objectives of the CRA during the on-site visits are to educate,  
11 support and solve problems. The monitors will discuss the protocol in  
12 detail and identify and clarify any areas of weakness. At the initiation of  
13 the trial, the monitor will conduct a tutorial on the eCRF. The investigators  
14 will practice entering data so that the monitors can confirm that they are  
15 proficient in all aspects of data entry, query response, and communication  
16 with the CRA. They will audit the overall quality and completeness of the  
17 data, examine source documents, interview investigators and  
18 coordinators, and confirm that the clinical site has complied with the  
19 requirements of the protocol. The monitors will verify that all adverse  
20 events were documented in the correct format, and are consistent with  
21 protocol definition.  
22

23 The monitors will review the source documents as needed, to determine  
24 whether the data reported in the electronic data capture system are  
25 complete and accurate. Source documents are defined as medical charts,  
26 associated reports and records including initial hospital admission report.  
27

28 The monitors will confirm that the regulatory binder is complete and that  
29 all associated documents are up to date. The regulatory binder should  
30 include the protocol and informed consent (all revisions), Ethics  
31 Committee/Health Authorities approvals for all of the above documents,  
32 Ethics Committee/Health Authorities correspondence, case report form  
33 hardcopy templates, investigator's agreements, etc.  
34

35 Scheduling monitoring visits will be a function of patient enrolment, site  
36 status and other commitments. The CRA will notify the site in writing at  
37 least two weeks prior to a scheduled visit. The investigators must be  
38 available to meet with the monitors. Although notification of the visits will  
39 include the list of patients scheduled to be reviewed, the monitors reserve  
40 the right to review additional patients if possible.  
41

42 If a problem is identified during the visit, the monitor will assist the site in  
43 resolving the issues. Some issues may require input from the Data Safety  
44 Monitoring Committee, Sponsor or the coordinating investigator.  
45

46 The focus of the visit/electronic monitoring will be on source document  
47 review and confirmation of adverse events. The monitor will verify the  
48 following all the variables for all patients, eg. signed informed consent,  
49

eligibility criteria, date of randomization, treatment assignment, adverse events and endpoints.

## Ethics and dissemination

- Research ethics approval 24 The protocol and the informed consent form, as well as other required documents will be reviewed and approved by the sponsor and the applicable Ethics Committee/Health Authority with respect to scientific content and compliance with applicable research and human subjects regulations.
- The protocol, informed consent form, participant education and recruitment materials, and other requested documents—and any subsequent modifications — also will be reviewed and approved by the Ethics Committee/Health Authority.
- Subsequent to initial review and approval, the Ethics Committee/ Health Authority will review the protocol annually. The Investigator will make safety and progress reports to the Ethics Committee/ Health Authority at least annually and within twelve months of study termination or completion at his/her site. These reports will include the total number of participants enrolled y their status within the trial, as well as a review of safety and/or efficacy.
- Protocol amendments 25 Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol.
- Such amendment will be agreed upon by the sponsor and must be submitted for approval to the Ethics Committee/Health Authority prior to implementation in accordance with local regulations.
- Administrative changes of the protocol that are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed by the sponsor and will be documented in a memorandum. The Ethics Committee/Health Authority may be notified of administrative changes in the next protocol substantial amendment.

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5 Consent or assent 26a The site principal investigator or delegated subinvestigator will introduce  
6 the trial to patients. The site principal investigator or delegated  
7 subinvestigator will discuss the trial with patients in light of the information  
8 provided in the information sheets. Patients will then be able to have an  
9 informed discussion with the participating investigator. The site principal  
10 investigator or delegated subinvestigator will obtain written consent from  
11 patients willing to participate in the trial and file it in the site binder.  
12  
13  
14  
15 26b As biological samples would be collected, an additional informed consent  
16 form will be provided by the site principal investigator or delegated  
17 subinvestigator to the trial to patients. The consent procedure will be  
18 similar to the one explained in point 26a.

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5      Confidentiality      27      All study-related information will be stored securely at the study site. All  
6 participant information will be stored in locked file cabinets in areas with  
7 limited access. All laboratory specimens, reports, data collection, process,  
8 and administrative forms will be identified by a coded ID [XX-YY coding]  
9 number only to maintain participant confidentiality. All records that contain  
10 names or other personal identifiers, such as locator forms and informed  
11 consent forms, will be stored separately from study records identified by  
12 code number. All local databases will be secured with password-protected  
13 access systems. Forms, lists, logbooks, appointment books, and any  
14 other listings that link participant ID numbers to other identifying  
15 information will be stored in a separate, locked file in an area with limited  
16 access.  
17  
18      All test results will be kept strictly confidential, all counselling and blood  
19 draws will be conducted in private rooms, and study staff will be required  
20 to preserve the confidentiality of all participants.  
21  
22  
23  
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29  
30  
31  
32  
33      Participants' study information will not be released outside of the study  
34 without the written permission of the participant, except as necessary for  
35 monitoring, audit and or inspections by regulatory authorities or for safety  
36 reasons.  
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49      Declaration of      28      The sponsor guarantees that the data will be processed with security  
50 interests  
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measures established in compliance with REGULATION (EU) 2016/679  
OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of April 27,  
2016 regarding the protection of natural persons in what Regarding the  
processing of personal data and the free circulation of these data and by  
which Directive 95/46 / EC (General Data Protection Regulation) and the  
Organic Law are repealed 3/2018, of December 5, on Personal Data  
Protection and guarantee of rights digital. By signing the informed  
consent, the participant agrees with this use of the study data. Said  
authorization does not have an expiration date. The participant may  
withdraw it at any time, but must do so in writing.

- 1  
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5 Access to data 29 All Principal Investigators will be given access to the cleaned data sets.  
6 Project data sets will be housed on IMIBIC servers they will be accessible  
7 by password. Project Principal Investigators will have direct access to their  
8 own site's data sets, and will have access to other sites data by request.  
9 To ensure confidentiality, data dispersed to project team members will be  
10 blinded of any identifying participant information.  
11  
12  
13  
14 Once the trial has ended and the data has been collected, analysed and  
15 published, the anonymized database will be available to other researchers  
16 upon request.  
17  
18 Ancillary and post- 30 Patients that are enrolled into the study are covered by indemnity for non-  
20 trial care negligent harm through a specific insurance contracted by the sponsor.  
21  
22 Should this study provide evidence of the effectiveness of Sarilumab, it  
23 will be critical to provide access to the effective product(s) to study  
24 participants in a timely manner.  
25  
26  
27  
28 Dissemination 31a Once the study has been completed and the statistical report has been  
29 policy carried out, the investigating team shall prepare the final report of the  
30 study to be submitted to Ethics Committee/Health Authority. This final  
31 report will be the basis for the preparation of the manuscripts to be  
32 published in medical journals.  
33  
34  
35 31b The conditions of publication are in accordance with Royal Decree  
36 1090/2015 of 4 December concerning the regulation of clinical trials of  
37 medicinal products in Spain, multicentre clinical trials only require the  
38 approval of a single medicinal research ethics committee (reference  
39 MREC) and of the Spanish Agency of Medicines and Medical Products  
40 (AEMPS) and the Spanish Register of Clinical Studies in article 42.  
41  
42  
43  
44  
45 31c Once the trial has ended and the data has been collected, analysed and  
46 published, the anonymized database, the full protocol, statistical code and  
47 other materials will be available to other researchers upon request to  
48 IMIBIC Clinical Research Unit (uicec@imibic.org).  
49  
50  
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## Appendices

- 52 Informed consent 32 See attached forms (General informed consent and Biological Samples  
53 materials informed consent).  
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5     6 Biological specimens     33     The samples will be stored locally (frozen at -80oC) until they are sent to  
6     7 the Biobank of the Reina Sofía University Hospital in Córdoba.  
8

9  
10     The cytokines will be quantified centrally using the CUSTOM KITS  
11     MILIPLEX® MAP (Merk-Millipore) following the protocol provided by the  
12     manufacturer. Samples will be purchased on a Luminex LABScan 200  
13     platform, using xPONENT vs. 2.1 as acquisition and analysis software.  
14     The cytokine panel to be quantified will be the following: IL1-A, IL1-A, IL6,  
15     IL8, IL10, IL12, IL18, IL38, INF $\gamma$ , TNF, CCL2, CCL3, CCL4, MIF and PAI-  
16     1.  
17

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18     \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013  
19     Explanation & Elaboration for important clarification on the items. Amendments to the protocol  
20     should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the  
21     Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.  
22

**Appendix 1: Informed Consent Forms (General and Biological Samples)****HOJA DE INFORMACIÓN AL PARTICIPANTE**

A.

<b>Título del Estudio</b>	Ensayo clínico de Sarilumab en adultos hospitalizados con COVID-19 que presentan síndrome de liberación de citoquinas
<b>Código del estudio</b>	SARICOR
<b>Promotor</b>	Fundación para la Investigación Biomédica de Córdoba
<b>Investigador principal</b>	
<b>Centro</b>	

**Introducción**

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por un Comité de Ética de la Investigación con medicamentos y por la Agencia Española de Medicamentos y Productos Sanitarios, de acuerdo a la legislación vigente, el Real Decreto 1090/2015 de 4 de diciembre y el Reglamento Europeo 536/2014 de 16 de abril, por los que se regulan los ensayos clínicos con medicamentos.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda **decidir si acepta o no participar en este estudio**. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir. Además, puede consultar con las personas que considere oportuno.

**Participación voluntaria**

Le invitamos a participar en el estudio porque presenta un proceso infeccioso respiratorio por SARS-CoV-2 (COVID19). **Debe saber que su participación en este estudio es voluntaria y que puede decidir NO participar.** Si decide participar, puede cambiar su decisión y retirar el

1  
2  
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4  
5 consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se  
6 produzca perjuicio alguno en su atención sanitaria.  
7  
8

### 9 **Objetivo del estudio**

10 El objetivo principal del estudio es saber la eficacia y la seguridad de la  
11 administración precoz de Sarilumab en pacientes con infección respiratoria por SARS-CoV-  
12 2 (COVID19) para evitar el deterioro de la función pulmonar y la necesidad de requerir  
13 soporte respiratorio mediante diferentes métodos habitualmente utilizados en esta  
14 situación.  
15  
16

### 17 **Descripción del estudio**

18 Este estudio pretende incluir un total de 120 participantes con alto riesgo de que su  
19 función pulmonar se deteriore y precisen de dispositivos para ayudar a su respiración.  
20  
21

22 La literatura actual recoge un grupo de pacientes que por sus características clínicas  
23 y/o analíticas presentan mayor probabilidad de empeorar desde el punto de vista  
24 respiratorio y pueden necesitar mayor soporte respiratorio, incluso requerir ingreso en las  
25 Unidades de Cuidados Intensivos para ser intubados.  
26  
27

28 El SARS-CoV-2 (COVID19) es un coronavirus perteneciente a una extensa familia  
29 de virus que pueden causar enfermedades tanto en animales como en humanos. En los  
30 humanos, se sabe que varios coronavirus causan infecciones respiratorias que pueden ir  
31 desde el resfriado común hasta enfermedades más graves. El coronavirus que se ha  
32 descubierto más recientemente causa la enfermedad COVID-19.  
33  
34

35 Los síntomas más comunes de la COVID-19 son fiebre, cansancio y tos seca.  
36 Algunos pacientes pueden presentar dolores, congestión nasal, rinitis (emisión  
37 abundante de líquido por la nariz, generalmente debido a un aumento de la secreción de  
38 mucosidad nasal), dolor de garganta o diarrea. Estos síntomas suelen ser leves y aparecen  
39 de forma gradual. Algunas personas se infectan pero no desarrollan ningún síntoma y no  
40 se encuentran mal. La mayoría de las personas (alrededor del 80%) se recupera de la  
41 enfermedad sin necesidad de realizar ningún tratamiento especial. Alrededor de 1 de cada  
42 6 personas que contraen la COVID-19 desarrolla una enfermedad grave y tiene dificultad  
43 para respirar. Las personas mayores y las que padecen patologías subyacentes, como  
44

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5 hipertensión arterial, problemas cardiacos o diabetes, tienen más probabilidades de  
6 desarrollar una enfermedad grave. En torno al 2% de las personas que han contraído la  
7 enfermedad han muerto.  
8  
9

10  
11 El fármaco que se quiere estudiar se llama Sarilumab, el cual se administra mediante  
12 inyección subcutánea (por debajo de la piel). No se conoce si Sarilumab es útil en la  
13 situación que le describimos ni tampoco la dosis más apropiada, por eso queremos estudiar  
14 la eficacia y seguridad de dos dosis del fármaco (200 mg o 400 mg) conjuntamente con la  
15 mejor terapia disponible. Este estudio plantea comparar 3 posibilidades de tratamiento:  
16  
17

- 18 a) Cuarenta pacientes recibirán la mejor terapia disponible.  
19
  - 20 b) Cuarenta pacientes recibirán la mejor terapia disponible más Sarilumab a una  
21 dosis de 200 miligramos.  
22
  - 23 c) Cuarenta pacientes recibirán la mejor terapia disponible más Sarilumab a una  
24 dosis de 400 miligramos.  
25
- 26  
27  
28

29  
30 El procedimiento de asignación a uno de los tres grupos del estudio se realizará al  
31 azar. La probabilidad de que usted sea asignado a cualquiera de los tres grupos será de  
32 una entre tres o del 33%.  
33  
34

35  
36 En ningún caso usted dejará de estar tratado con los medicamentos habitualmente  
37 utilizados. Si usted decide no participar en este estudio es posible que usted reciba un  
38 fármaco similar pero más tarde, cuando el deterioro respiratorio ya ha sido establecido.  
39 Participando en este estudio usted tiene la posibilidad de recibirllo antes para estudiar si  
40 evita ese deterioro.  
41  
42

#### 43 **Actividad del estudio**

44  
45

46 Si decide participar en este estudio le haremos un seguimiento diario desde el día  
47 que firme el consentimiento informado hasta el día 28 de su inclusión en el estudio o hasta  
48 el último día que esté hospitalizado, lo que ocurra antes.  
49  
50

51 Evaluaremos diariamente su evolución clínica. En los días 0, 5, 10, 14, 21 y 28 (o  
52 hasta el último día que esté hospitalizado) le realizaremos un frotis nasofaríngeo para  
53  
54

estudiar si continúa teniendo el virus. Estas muestras se seguirán tomando aunque alguna de ellas fuera negativa.

También en los días 0, 5, 10, 14, 21 y 28 (o hasta el último día que esté hospitalizado) se le extraerá un tubo con 9 ml de sangre que será almacenada para posteriores estudios inmunológicos. Dependiendo de cómo monitorice la replicación de dicho virus su centro, es posible que se le precise extraer también un tubo con 6 ml de sangre más, para saber si el virus está replicando.

El calendario de las visitas, independientemente del grupo al que sea asignado, es el siguiente:

	Visita basal Día 0	Visita 1 (día 1) hasta visita 5 (día 28 o hasta último día hospitalizado)
Consentimiento Informado	X	
Tratamiento	X	
Historia clínica / Exploración física	X	X
Analítica	X	X <sup>1</sup>
Obtención de frotis nasofaríngeo y de muestra de sangre		X <sup>1</sup>

1 = en las visitas 5, 10, 14, 21 y 28 (o hasta el último día que esté hospitalizado)

#### Riesgos y molestias derivados de su participación en el estudio

Sarilumab es un medicamento ya aprobado y comercializado para el tratamiento de la artritis reumatoide avanzada.

Las reacciones adversas más frecuentemente notificadas con el tratamiento con Sarilumab son: disminución anormal de los neutrófilos y las plaquetas, aumento de las enzimas hepáticas, enrojecimiento en el lugar de la inyección, infecciones del tracto respiratorio superior e infecciones del tracto urinario.

1  
2  
3  
4  
5 Los riesgos de sufrir algún efecto no deseado con el uso de Sarilumab son: 1 de  
6 cada 10 pacientes sufren neutropenia (disminución de los neutrófilos en la sangre), 1 de  
7 cada 100 pacientes sufren trombocitopenia (disminución de las plaquetas en la sangre),  
8 infección del tracto respiratorio superior, infección del tracto urinario, nasofaringitis  
9 (resfriado), herpes oral, hipercolesterolemia (colesterol alto), hipertrigliceridemia  
10 (triglicéridos altos), enzimas hepáticas elevadas, enrojecimiento en el lugar de la inyección  
11 y picor en el lugar de la inyección.  
12  
13  
14  
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16

17  
18 Los resultados de los estudios disponibles no permiten establecer diferencias entre  
19 Sarilumab y otros fármacos biológicos, incluido Tocilizumab. Si usted no participa en el  
20 estudio usted podría recibir Tocilizumab por práctica clínica una vez que su función  
21 respiratoria se haya deteriorado.  
22  
23

24 Para conocer más sobre los posibles efectos no deseados de estos medicamentos,  
25 consulte al médico de este estudio.  
26  
27

28 Como riesgo derivado de la extracción de sangre puede producirse un pequeño  
29 hematoma, puede haber dolor local, hemorragia y muy excepcionalmente, puede  
30 producirse infección en el punto donde se extrae la sangre.  
31  
32

33 Como participante en el estudio tiene la responsabilidad de cumplir todas las visitas  
34 y actividades del estudio. También deberá notificar cualquier evento que le suceda o  
35 cambios en la medicación en caso de urgencia, ya que no podrá modificarla por su cuenta  
36 ni tomarla junto a "plantas medicinales" sin consultar antes con el médico del estudio.  
37  
38

#### 39 **Posibles beneficios**

40  
41

42 Si demostramos la hipótesis de este estudio, usted habrá contribuido a evitar el  
43 deterioro de la función pulmonar por COVID-19 en otros pacientes que, como usted,  
44 padecen una infección respiratoria con factores de riesgo para mala evolución y necesidad  
45 de oxigenación a alto flujo o ventilación mecánica tanto de forma invasiva como no invasiva.  
46 Esto evitirá medidas más agresivas de manejo de su función respiratoria, el ingreso en la  
47 Unidad de Cuidados Intensivos y la prolongación de la estancia hospitalaria.  
48  
49

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5 Es posible que usted no obtenga ningún beneficio adicional para su salud por  
6 participar en este estudio. Sin embargo, los datos obtenidos pueden resultar de utilidad para  
7 futuros pacientes que se encuentren en su misma situación.  
8  
9

10 **Advertencia relativa al embarazo**  
11

12 Las mujeres en edad fértil deben evitar un embarazo mediante el uso de métodos  
13 anticonceptivos eficaces durante y hasta tres meses después del tratamiento.  
14  
15  
16

17 No hay datos disponibles del efecto de Sarilumab sobre la fertilidad humana. Los  
18 estudios en animales mostraron que no se producía deterioro de la fertilidad ni en los  
19 machos ni en las hembras.  
20  
21

22 No hay datos o estos son limitados relativos al uso de Sarilumab en mujeres  
23 embarazadas. Los estudios en animales no sugieren efectos perjudiciales directos ni  
24 indirectos en términos de toxicidad para la reproducción.  
25  
26

27 Se desconoce si Sarilumab se excreta en la leche materna o si se absorbe de forma  
28 sistemática después de la ingestión. No se ha estudiado la excreción de Sarilumab en la  
29 leche en animales.  
30  
31

32 Dado que las inmunoglobulinas G1 se excretan en la leche humana, se debe decidir  
33 si es necesario interrumpir la lactancia o interrumpir el tratamiento con Sarilumab teniendo  
34 en cuenta el beneficio de la lactancia para el niño y el beneficio del tratamiento para la  
35 madre.  
36  
37

38 En caso de producirse un embarazo durante su participación en el estudio debe  
39 informar a su médico de inmediato para recibir la asistencia médica adecuada. En caso de  
40 producirse un embarazo, se solicitará mediante un consentimiento específico la recogida  
41 de datos del mismo y de datos de salud del bebé hasta 3 meses después del parto.  
42  
43

44 Los datos recopilados sobre usted y su bebé serán tratados por el promotor del  
45 estudio de acuerdo a la normativa de protección de datos personales vigente (consulte el  
46 apartado “Protección de datos personales” para más información).  
47  
48

## Tratamientos alternativos

En la actualidad, algunos de los tratamientos disponibles son moléculas de nuevo desarrollo y otras son usos nuevos de medicamentos ya autorizados en otras indicaciones.

Aunque existen numerosos ensayos clínicos en marcha, no existe por el momento evidencia procedente de ensayos clínicos controlados que permitan recomendar un tratamiento específico para SARS-CoV-2. En estos momentos, se están poniendo en marcha diversos ensayos clínicos en España para el tratamiento de la infección respiratoria por SARS-CoV-2.

Se trata de un escenario que puede ir cambiando por la enorme cantidad de datos, comunicaciones y publicaciones que se están generando a nivel mundial. Hasta la fecha, solo hay datos parciales, preliminares, a veces únicamente *in vitro* o incluso contradictorios, sobre la eficacia de uno u otro producto por lo que, en la medida de lo posible, debe priorizarse la posibilidad de realizar estudios clínicos que, al tiempo que ofrecen una alternativa de tratamiento plausible, generen conocimiento útil.

La Agencia Española de Medicamentos y Productos Sanitarios está monitorizando de manera continua con los expertos de otras agencias sanitarias europeas, la Agencia Europea del Medicamento y otras agencias fuera de la Unión Europea todos los datos relativos al uso de medicamentos para el tratamiento o la profilaxis de la infección respiratoria por SARS-CoV-2.

El investigador principal del estudio le proporcionará toda la información que precise sobre los posibles tratamientos alternativos.

## Seguro

El Promotor del estudio dispone de una póliza de seguros que se ajusta a la legislación vigente (Real decreto 1090/2015) y que le proporcionará la compensación e indemnización en caso de menoscabo de su salud o de lesiones que pudieran producirse en relación con su participación en el estudio, siempre que no sean consecuencia de la

propia enfermedad que se estudia o de la evolución propia de su enfermedad como consecuencia de la ineeficacia del tratamiento. Si desea más información relativa a este apartado, consulte con el investigador principal del estudio en su centro.

Le recomendamos consultar las condiciones generales y particulares (cobertura) de sus pólizas de seguros privadas (vida, salud, accidente...) por si se ven afectadas por la participación en un ensayo clínico. El promotor no es responsable de estas potenciales modificaciones de cobertura debida a su participación y por tanto, le recomendamos que lo consulte con su aseguradora antes de dar su consentimiento.

## Protección de datos personales

En este estudio se cumplirá la normativa de protección de datos en vigor; la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales, así como con el Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD).

Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no se incluya información que pueda identificarle, y sólo su médico del estudio/colaboradores podrá relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran, o en casos de urgencia médica.

Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el Promotor, podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).

Los datos se recogerán en un fichero de investigación responsabilidad de la institución y se tratarán en el marco de su participación en este estudio. El promotor adoptará las medidas pertinentes para garantizar la protección de su privacidad y no permitirá que sus datos se crucen con otras bases de datos que pudieran permitir su identificación.

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3  
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6  
7 De acuerdo a lo que establece la legislación de protección de datos, usted puede  
8 ejercer los derechos de acceso, modificación, oposición y cancelación de datos. Además  
9 de los derechos que ya conoce, ahora también puede limitar el tratamiento de datos que  
10 sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos  
11 que usted ha facilitado para el estudio.  
12  
13  
14

15  
16  
17 Para ejercitar sus derechos, diríjase al investigador principal del estudio o al  
18 Delegado de Protección de Datos del promotor en [dpd@imibic.org](mailto:dpd@imibic.org). Le recordamos que los  
19 datos no se pueden eliminar aunque deje de participar en el ensayo para garantizar la  
20 validez de la investigación y cumplir con los deberes legales y los requisitos de autorización  
21 de medicamentos. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos  
22 si no queda satisfecho.  
23  
24

25 Si usted decide retirar el consentimiento para participar en este estudio, ningún dato  
26 nuevo será añadido a la base de datos, pero sí se utilizarán los que ya se hayan recogido.  
27  
28

29  
30  
31 El Investigador y el Promotor están obligados a conservar los datos recogidos para  
32 el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información  
33 personal sólo se conservará por el centro para el cuidado de su salud y por el promotor  
34 para otros fines de investigación científica si usted hubiera otorgado su consentimiento y si  
35 así lo permite la ley y requisitos éticos aplicables.  
36  
37

38 Si realizáramos transferencia de sus datos codificados fuera de la UE a las entidades  
39 de nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren  
40 con nosotros, los datos del participante quedarán protegidos con salvaguardas tales como  
41 contratos u otros mecanismos establecidos por las autoridades de protección de datos. Si  
42 el participante quiere saber más al respecto, puede contactar al Delegado de Protección de  
43 Datos del promotor en [dpd@imibic.org](mailto:dpd@imibic.org).  
44  
45

## 56 57 58 **Gastos y compensación económica** 59 60

1  
2  
3  
4  
5 Usted no tendrá que pagar por los medicamentos ni por pruebas específicas del  
6 estudio. Su participación en el estudio no le supondrá ningún gasto adicional a la práctica  
7 clínica habitual.  
8  
9

10  
11 **Otra información relevante**  
12

13 Una descripción de este ensayo clínico estará disponible en <https://reec.aemps.es>,  
14 según exige la legislación española, así como en <https://clinicaltrials.gov>.  
15  
16

17 Cualquier nueva información referente al fármaco utilizado en el estudio y que pueda  
18 afectar a su disposición para participar en el estudio, que se descubra durante su  
19 participación, le será comunicada por su médico lo antes posible.  
20  
21

22 Debe saber que puede ser excluido del estudio si el promotor o los investigadores  
23 del estudio lo consideran oportuno, ya sea por motivos de seguridad, por cualquier  
24 acontecimiento adverso que se produzca por la medicación en estudio o porque consideren  
25 que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos,  
26 usted recibirá una explicación adecuada del motivo que ha ocasionado su retirada del  
27 estudio.  
28  
29

30 Al firmar la hoja de consentimiento adjunta, se compromete a cumplir con los  
31 procedimientos del estudio que se le han expuesto. En aquellos casos en que un  
32 participante dejara de acudir a las visitas sin retirar el consentimiento, el promotor podrá  
33 realizar un seguimiento de dicho participante.  
34  
35

36 Debe usted saber que es posible que su médico de Atención Primaria tenga  
37 conocimiento de su participación en este estudio.  
38  
39

40 **¿Qué tratamiento recibiré cuando finalice el ensayo clínico?**  
41

42 Cuando acabe su participación recibirá el mejor tratamiento disponible y que su  
43 médico considere el más adecuado para su enfermedad.  
44

45 En caso de que el estudio se suspenda o finalice mientras usted está en tratamiento  
46 con la medicación en investigación, su enfermedad permanezca controlada, los datos del  
47 estudio indiquen que la medicación en investigación muestra un beneficio en el manejo de  
48 su enfermedad, y se disponga de existencias adecuadas del fármaco, el promotor le  
49  
50

asegurará el suministro adecuado y gratuito de dicha medicación, hasta que esté disponible, de manera que usted continuará su tratamiento mientras su enfermedad permanezca controlada.

## Contacto en caso de dudas

Si durante su participación tiene alguna duda o necesita obtener más información, póngase en contacto con Dr./Dra.:\_\_\_\_\_

Del servicio de \_\_\_\_\_ en el teléfono \_\_\_\_\_.

## Obtención y utilización de muestras biológicas

A cada participante se le extraerán en las visitas 0, 5, 10, 14, 21 y 28 (o hasta el último día que esté hospitalizado):

- Un frotis nasofaríngeo para la determinación del ARN del virus.
- Un tubo con 9 ml de sangre para el estudio de la inmunidad frente a este virus.

Dependiendo de cómo monitorice la replicación de dicho virus su centro, es posible que se le precise extraer también un tubo con 6 ml de sangre más, para saber si el virus está replicando.

En el caso de almacenamiento de estas muestras una vez terminado el ensayo, para su uso posterior en investigación se cumplirá con los requisitos éticos y legales dispuestos en el Real Decreto 1716/2011. Para ello, se le pedirá su consentimiento para que dichas muestras puedan ser almacenadas, una vez que acabe el ensayo clínico, en el Biobanco del Sistema Sanitario Público de Andalucía/Nodo de Córdoba.

Las muestras biológicas donadas, así como sus datos clínicos e información asociados se utilizarán de conformidad con lo establecido en la Ley 14/2007, de 3 de julio, de Investigación biomédica. La donación es voluntaria y altruista, por lo que usted no tendrá derecho alguno sobre los resultados que pudieran derivarse de las investigaciones que se lleven a cabo con dichas muestras biológicas y su información asociada, de conformidad con la normativa vigente.

## **CONSENTIMIENTO INFORMADO DEL PARTICIPANTE**

## **Ensayo clínico de Sarilumab en adultos hospitalizados con COVID-19 que presentan síndrome de liberación de citoquinas (ESTUDIO SARICOR)**

Yo (nombre y apellidos del participante): \_\_\_\_\_

He leído la hoja de información que se me ha entregado sobre el estudio.

He podido hacer preguntas sobre el estudio.

He recibido suficiente información sobre el estudio.

He hablado con (nombre del investigador): \_\_\_\_\_

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

- Cuando quiera.
  - Sin tener que dar explicaciones.
  - Sin que esto repercuta en mis cuidados médicos.

Deseo que me comuniquen la información derivada de la investigación que pueda ser relevante para mi salud:

□ sí

NO

Recibiré una copia firmada y fechada de este documento de consentimiento informado.

Presto libremente mi conformidad para participar en el estudio.

Nombre del participante:

Nombre del investigador:

Fecha:                  /                  /

Fecha:                  /                  /

Firma del participante:

Firma del investigador:

## CONSENTIMIENTO INFORMADO DEL REPRESENTANTE LEGAL DEL PARTICIPANTE

### Ensayo clínico de Sarilumab en adultos hospitalizados con COVID-19 que presentan síndrome de liberación de citoquinas (ESTUDIO SARICOR)

Nombre del representante: \_\_\_\_\_

Relación con el paciente: \_\_\_\_\_

Se me ha solicitado mi consentimiento en nombre de la siguiente persona, para que él/ella pueda participar en este estudio de investigación médica:

Nombre y apellidos del paciente: \_\_\_\_\_

He leído la hoja de información que se me ha entregado sobre el estudio.

He podido hacer preguntas sobre el estudio.

He recibido suficiente información sobre el estudio.

He hablado con (nombre del investigador): \_\_\_\_\_

Comprendo que la participación es voluntaria.

Comprendo que puedo retirarlo del estudio:

- Cuando quiera.
- Sin tener que dar explicaciones.
- Sin que esto repercuta en sus cuidados médicos.

Deseo que me comuniquen la información derivada de la investigación que pueda ser relevante para su salud:

SÍ

NO

Recibiré una copia firmada y fechada de este documento de consentimiento informado.

Presto libremente mi conformidad para que participe en el estudio.

Nombre del representante legal o familiar:

Nombre del investigador:

Fecha: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Fecha: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Firma del representante legal:

Firma del investigador:

## CONSENTIMIENTO INFORMADO DEL PARTICIPANTE ANTE TESTIGOS

### Ensayo clínico de Sarilumab en adultos hospitalizados con COVID-19 que presentan síndrome de liberación de citoquinas (ESTUDIO SARICOR)

Yo (nombre y apellidos del testigo): \_\_\_\_\_

como testigo, afirma que en mi presencia se ha informado a D/D<sup>a</sup> (nombre y apellidos del participante) \_\_\_\_\_ y se ha

leído o le han leído la hoja de información que se le ha entregado sobre el estudio, de modo que:

Ha podido hacer preguntas sobre el estudio.

Ha recibido suficiente información sobre el estudio.

Ha hablado con (nombre del investigador): \_\_\_\_\_

Comprende que su participación es voluntaria.

Comprende que puede retirarse del estudio:

- Cuando quiera.
- Sin tener que dar explicaciones.
- Sin que esto repercuta en sus cuidados médicos.

El participante desea que se le comunique la información derivada de la investigación que pueda ser relevante para su salud:

Sí

NO

Recibirá una copia firmada y fechada de este documento de consentimiento informado.

Presta libremente su conformidad para participar en el estudio.

Nombre del testigo:

Nombre del investigador:

Fecha: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

Fecha: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

Firma del testigo:

Firma del investigador:

*El participante del estudio ha indicado que no puede leer / escribir. Un miembro del personal del estudio le ha leído el documento de consentimiento, lo ha revisado y comentado con el participante y se le ha concedido la oportunidad de hacer preguntas o consultarlo con otras personas. El testigo es una persona imparcial, ajena al estudio.*

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7 **FORMULARIO DE RETIRADA DEL CONSENTIMIENTO CONCEDIDO CON**  
8 **ANTERIORIDAD**

9  
10  
11 **Ensayo clínico de Sarilumab en adultos hospitalizados con COVID-19 que presentan**  
12 **síndrome de liberación de citoquinas (ESTUDIO SARICOR)**

13  
14  
15  
16      Participación retirada por:

17       Paciente

18       Representante legal, nombre: \_\_\_\_\_

19  
20      Relación con el/la paciente: \_\_\_\_\_

21  
22      Por la presente comunico que retiro el consentimiento para la participación en la  
23      investigación.

24  
25  
26      Motivo de retirada (no obligatorio):  
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39      Nombre del/de la participante: \_\_\_\_\_

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41  
42  
43      Fecha de retirada: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

44  
45  
46  
47  
48      Firma del responsable de la retirada (paciente o representante legal, según proceda)

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5 **FORMULARIO DE INFORMACIÓN Y CONSENTIMIENTO INFORMADO ESCRITO Biobanco**  
6 **en Red del Sistema Sanitario Público de Andalucía**  
7  
8

9 **DOCUMENTO DE INFORMACIÓN PARA DONACIÓN DE MUESTRAS BIOLÓGICAS E**  
10 **INFORMACIÓN ASOCIADA AL BIOBANCO PARA INVESTIGACIÓN BIOMÉDICA**  
11  
12

13 Este documento sirve para que usted otorgue su consentimiento, o las del sujeto al que representa,  
14 para donar sus muestras biológicas, así como la información asociada ( datos clínicos,  
15 epidemiológicos, genéticos, imágenes, u otros - ESPECIFICAR-), o las del sujeto al que representa,  
16 al Biobanco indicado, establecimiento público, sin ánimo de lucro, dependiente de la Consejería de  
17 Salud/del Servicio Andaluz de Salud, que acoge colecciones de muestras biológicas e información  
18 asociada concebidas con fines diagnósticos, de investigación biomédica, o docencia o calidad, y  
19 organizadas como una unidad técnica con criterios de calidad, orden y destino, donde serán  
20 conservadas hasta que se agoten por su uso, salvo que usted solicitará su eliminación. Las muestras  
21 biológicas y su información asociada son un excelente elemento para la investigación de  
22 enfermedades. A través de dichas investigaciones se podrán obtener datos que permitirán mejorar el  
23 conocimiento sobre la aparición, desarrollo y tratamiento de multitud de enfermedades.  
24  
25

26 Esta hoja de información puede contener palabras que usted no entienda. Por favor, pídale al  
27 profesional sanitario que le explique la información que no comprenda. Tómese el tiempo necesario  
28 para decidir si quiere o no donar su muestra biológica y consulte a personas de su confianza si lo  
29 desea. Para consultas que desee plantear posteriormente, podrá dirigirse al Biobanco en Red del  
30 Sistema Sanitario Público de Andalucía. Dirección: Parque Tecnológico Ciencias de la Salud.  
31 Centro de Investigación Biomédica. Avda. del Conocimiento s/n · 18016 · Granada · España ·  
32 Teléfono: + 34 958 894 672. Correo electrónico: biobanco.sspa@juntadeandalucia.es.  
33  
34

35 Las muestras biológicas donadas y sus datos clínicos asociados e información asociada se utilizarán  
36 de conformidad con lo establecido en la Ley 14/2007, de 3 de julio, de Investigación biomédica (en  
37 adelante Ley de Investigación biomédica).  
38  
39

40 Es posible que la información obtenida de las investigaciones en las que se utilicen sus muestras  
41 biológicas e información asociada no le genere un beneficio directo, pero habrá contribuido al  
42 avance de la medicina y del conocimiento de diversas enfermedades, lo que supondrá, sin duda, un  
43 beneficio para la sociedad.  
44  
45

46 La donación es voluntaria y altruista, por lo que usted no tendrá derecho alguno sobre los resultados  
47 que pudieran derivarse de las investigaciones que se lleven a cabo con dichas muestras biológicas y  
48  
49

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5 su información asociada, de conformidad con la normativa vigente. Su decisión de donar o no, no  
6 afectará a su asistencia sanitaria.  
7

8 Existe un apartado en el consentimiento en el que podrá decidir si quiere que sus muestras  
9 biológicas e información asociada se conserven de forma codificada (en cuyo caso se identifican  
10 con un código que protege su identidad) o anonimizada (eliminándose de forma irreversible toda  
11 vinculación con su identidad).  
12  
13

14 Sus muestras y los datos asociados a las mismas sólo se cederán a terceros de manera anónima o  
15 disociada. Sus muestras biológicas e información asociada a las mismas sólo se podrán ceder a  
16 terceros como uso exclusivo para la investigación biomédica que ayuden a la obtención de nuevos  
17 conocimientos científicos, confirmación de hipótesis, adecuación tecnológica, controles de calidad,  
18 docencia, u otros usos de interés sanitario, pudiendo usted en cualquier momento establecer las  
19 restricciones de utilización que considere oportunas.  
20  
21

22 Si la naturaleza del proyecto en el que vaya a utilizarse la muestra biológica requiriese información  
23 asociada a la misma, y para la que fuese necesario la consulta de su historia clínica, el Biobanco  
24 establecerá un sistema de control y trazabilidad del acceso mediante una autorización previa y  
25 registros de acceso, que será responsabilidad del Director del nodo donde se lleve a cabo la  
26 consulta siempre que la muestra no hubiera sido anonimizada.  
27  
28

## 37 **1. Obtención de las muestras**

38 Las muestras serán obtenidas durante el procedimiento médico-quirúrgico al que va a someterse o  
39 se ha sometido durante su proceso asistencial, o a través de un procedimiento expreso para  
40 obtenerla, según lo indicado en el apartado del consentimiento referente a la obtención de muestras.  
41 Se podrán obtener diferentes tipos de muestras biológicas como sangre, tejidos, saliva, líquidos  
42 biológicos, uñas o pelo. En la hoja de consentimiento se indicarán los tipos de muestras a recoger de  
43 forma expresa en este acto de donación.  
44  
45

46 En el caso de que usted done las muestras obtenidas durante un procedimiento médico-quirúrgico  
47 asistencial, no existe ningún inconveniente adicional derivado de la donación de las mismas.  
48

49 Si, por el contrario, las muestras biológicas fueran extraídas expresamente para la donación al  
50 Biobanco, podrían existir inconvenientes vinculados con la obtención de las mismas, de las que será  
51 convenientemente informado en la hoja de información del procedimiento correspondiente.  
52  
53

## 2. Utilización de las muestras

Usted autoriza, con la firma del consentimiento informado, a que las muestras donadas puedan ser sean utilizadas en:

- *Investigación*: las muestras e información asociada podrán ser utilizados en cualquier investigación biomédica, en los términos que indica la ley. En el caso de que la obtención de la muestra se lleve a cabo a petición de un proyecto concreto, éste y su investigador principal quedarán reflejados en la hoja de consentimiento. El excedente de la muestra e información asociada, quedarán disponibles para su uso en otros proyectos de investigación biomédica si usted así lo indica. Sólo se cederán muestras a proyectos de investigación dentro de una misma línea y científicamente avalados, que cumplan las exigencias legales y los principios éticos que rigen la investigación en salud y que sean autorizados por los órganos competentes, de conformidad con lo establecido en la normativa vigente.
- *Docencia*: actividades de formación en el ámbito sanitario o biomédico.
- *Evaluación / Control de Calidad*: muchas de las actividades relacionadas con la investigación o el diagnóstico requieren la puesta a punto de equipos, validación de nuevas tecnologías y procedimientos, encaminados a mejorar el impacto en salud de la tecnología empleada. Para ello es necesario la utilización de muestras biológicas.

Para el caso de que las muestras se utilicen exclusivamente con fines docentes o de control de calidad, y no sea necesaria la información asociada, la conservación, cesión, y uso, se realizará siempre de forma anonimizada.

Las muestras sólo podrán ser utilizadas en proyectos de investigación científicamente avalados, que cumplan las exigencias legales y los principios éticos que rigen la investigación en salud y que sean autorizados por los órganos competentes, de conformidad con lo establecido en la normativa vigente.

Cuando, por razones de salud, usted o su familia lo necesiten, podrán hacer uso de las muestras, siempre que no se hayan agotado o eliminado y no se encuentren anonimizadas.

## 3. Información relacionada con las muestras

Si lo solicita, el Biobanco le facilitará la información sobre los proyectos de investigación en los que se utilicen las muestras donadas, si éstas no hubieran sido anonimizadas.

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5 Al donar sus muestras al Biobanco, en este momento puede no saberse el lugar de realización de los  
6 análisis. El Biobanco mantiene un registro detallado del lugar de realización de los análisis  
7 realizados.  
8  
9

10 La información que se obtenga puede tener implicaciones para sus familiares, por lo que debe  
11 transmitirles dicha información.  
12  
13

## 14 15 **4. Posibilidad de ponerse nuevamente en contacto**

16 Puede que sea necesario ponerse en contacto nuevamente con usted, con el fin de recabar datos o  
17 muestras adicionales, o proporcionarle la información relevante para su salud, salvo que haya  
18 solicitado que las muestras sean anonimizadas.  
19  
20

## 21 22 **5. Protección de datos y confidencialidad de la información**

23 La información proporcionada en este apartado será aplicable siempre que sus muestras no se  
24 encuentren anonimizadas.  
25  
26

27 Los datos personales recabados serán confidenciales y tratados de acuerdo con el Reglamento (UE)  
28 2016/679, General de Protección de Datos y la Ley 14/2007 de Investigación Biomédica.  
29  
30

31 En cumplimiento de lo dispuesto en los artículos 13 y 14 del Reglamento General de Protección de  
32 Datos, le informamos lo siguiente:  
33  
34

- 35 - El responsable de este tratamiento de sus datos personales es el Servicio Andaluz de Salud.  
36 Avda. de la Constitución, 18. 41071 Sevilla
- 37 - Podrá contactar con el Delegado de Protección de Datos en  
38 la dirección electrónica dpd.sspa@juntadeandalucia.es.
- 39 - Los datos personales que nos proporcione serán utilizados con la finalidad de poder gestionar  
40 las muestras biológicas, quedando almacenados durante el tiempo necesario para cumplir  
41 con las obligaciones legales estipuladas.
- 42 - La base jurídica de este tratamiento es el consentimiento que nos presta al cumplimentar y  
43 firmar el documento de consentimiento informado, sin el cual no podríamos cumplir con la  
44 finalidad descrita
- 45 - Sus datos no serán cedidos a terceros, salvo que se disponga en una obligación legal.
- 46 - Puede usted ejercer sus derechos de acceso, rectificación, supresión, portabilidad de sus  
47 datos, y la limitación u oposición a su tratamiento, solicitándolo por escrito, con copia del  
48

DNI, a la Dirección General de Asistencia Sanitaria del Servicio Andaluz de Salud, Avenida de la Constitución, núm. 18, de Sevilla.

## 6. Derecho de revocación del consentimiento

Salvo que sus muestras se encuentren anonimizadas, podrá revocar en cualquier momento, el consentimiento que ha firmado. Esta revocación podrá ser total o parcial. Si fuese parcial, podría especificar para los casos que quiere revocar su consentimiento que están identificados en el punto 2 de este documento. Además, usted puede solicitar la eliminación o la anonimización de dichas muestras biológicas. Para ello, deberá dirigirse al Biobanco en Red del Sistema Sanitario Público de Andalucía. Dirección: Parque Tecnológico Ciencias de la Salud. Centro de Investigación Biomédica. Avda. del Conocimiento s/n · 18100 Armilla · Granada · España · Teléfono: + 34 958 894 672. Correo electrónico: biobanco.sspa@juntadeandalucia.es

Los efectos de la revocación no se extenderán a los resultados de las investigaciones llevadas a cabo con anterioridad.

## 7. Información relativa a análisis genéticos

Salvo que usted manifieste lo contrario en el apartado dedicado al consentimiento, se podrán realizar análisis genéticos. Excepto si sus muestras son anonimizadas, tiene derecho a conocer los datos genéticos que se obtengan a partir del análisis de las muestras donadas, así como de la información relativa a su salud derivada de dichos análisis.

Si no desea recibir dicha información y ésta fuera necesaria para evitar un grave perjuicio para su salud o la de sus familiares biológicos, se informará a un familiar o a un representante. La comunicación se limitará exclusivamente a los datos necesarios para evitar tal perjuicio.

## 8. Otras consideraciones

Una vez informado/a de los aspectos relacionados anteriormente en este documento, si decide donar dichas muestras deberá firmar el consentimiento informado para la donación.

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5 **CONSENTIMIENTO INFORMADO PARA DONACIÓN DE MUESTRAS**  
6 **BIOLÓGICAS E INFORMACIÓN ASOCIADA AL BIOBANCO**

7  
8 **Biobanco en Red del Sistema Sanitario Público de Andalucía.**

9  
10 DATOS DEL/DE LA DONANTE Y DE SU REPRESENTANTE (éste último sólo en caso de  
11 incapacidad del/de la donante):  
12  
13

14 **Apellidos y nombre del/de la Donante:**

15 ..... **DNI / NIE:**

16 ..... **NUSHA:** .....

17 **Apellidos y nombre del/de la representante legal.**

18 .....  
19 .....  
20 .....  
21 .....  
22 .....  
23 **DNI / NIE:** .....

24 PROFESIONALES QUE INTERVIENEN EN EL PROCESO DE INFORMACIÓN Y/O  
25 CONSENTIMIENTO:  
26

27 Los siguientes profesionales declaran que se ha explicado la información relativa a la donación de  
28 muestras biológicas al Biobanco:  
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30

31 **B. Apellidos y nombre**

32 **Fecha**

33 **Firma**

34 CONSENTIMIENTO:  
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36  
37  
38

39 Yo, D./Dña. .... declaro bajo mi  
40 responsabilidad que **he leído y comprendido el Formulario de Información**, del que se me  
41 ha entregado un ejemplar.  
42  
43

44 He **recibido suficiente información** sobre la donación de muestras biológicas de (*detallar tipo*  
45 *de muestras a recoger*) ..... e  
46 información asociada, al Biobanco, y sobre la posible realización de análisis genéticos sobre las  
47 mismas. He podido hacer preguntas sobre la información recibida y hablar con el profesional  
48 indicado, quien me ha resuelto todas las dudas que le he planteado.  
49  
50

51 Dichas muestras son:  
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54  Excedentes del procedimiento médico-quirúrgico asistencia al que va a someterse o se ha  
55 sometido  
56 .....  
57 .....  
58 .....  
59 .....  
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9  Tomadas mediante el procedimiento expreso (*indicar procedimiento*):  
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17 Las muestras biológicas e información asociada serán recogidas para:  
18  
19 PROYECTO (actividades de investigación biomédica que ayuden a la obtención de nuevos  
20 conocimientos científicos):  
21  
22  
23 - Título: .....  
24 - Investigador Principal: .....  
25  
26 - Código de Biobanco: .....  
27  
28  
29

30 El excedente de las muestras biológicas e información asociada obtenidas en el proyecto original  
31 podrán utilizarse en otros proyectos relacionados con:  
32  
33

- 34  INVESTIGACION
- 35  EVALUACIÓN / CONTROL DE CALIDAD
- 36  DOCENCIA

37 Deseo que dichas muestras y los datos clínicos asociados sean tratados de forma:  
38  
39

40  **Codificada** (serán identificadas con un código que protege mi identidad, siendo posible volver a  
41 ligarlas conmigo) o  
42  
43  **Anonimizada** (no se podrán asociar las muestras conmigo, por haberse eliminado de forma  
44 irreversible la vinculación entre las mismas y mi identidad).  
45  
46

47 Deseo **establecer restricciones** respecto al uso de la muestra, para que no sea  
48 utilizada en  
49  
50

51 Autorizo que se pueda **contactar conmigo posteriormente**:  
52  
53  
54  
55  
56  
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58  
59  
60

SI  
 NO

En caso afirmativo, por favor, indique el medio de hacerlo:

- Teléfono: (*indicar número*).....

Correo electrónico: (*indicar dirección*).....

Otros:  
(identificar).....

Autorizo **recibir información** sobre datos genéticos y datos relevantes para mi salud (Si solicita que las muestras sean anonimizadas, no podrá recibir esta información)

Marque lo que proceda:

- SI  
 NO

Sé que puedo **revocar**, en cualquier momento, el consentimiento otorgado en este documento.

En , a de de

## EL/LA DONANTE

## EL/LA REPRESENTANTE LEGAL

(sólo en caso de incapacidad del/de la donante)

Fdo.:

Fdo.:

# **CONSENTIMIENTO INFORMADO PARA DONACIÓN DE MUESTRAS BIOLÓGICAS E INFORMACIÓN ASOCIADA AL BIOBANCO**

## **Biobanco en Red del Sistema Sanitario Público de Andalucía.**

DATOS DEL/DE LA DONANTE Y DE SU REPRESENTANTE (éste último sólo en caso de incapacidad del/de la donante):

1

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5 **Apellidos y nombre del/de la Donante:**6 ..... **DNI / NIE:**7 ..... **NUSHA:** .....8 **Apellidos y nombre del/de la representante legal.**9 .....  
10 .....  
11 .....  
12 .....  
13 .....  
1415 **DNI / NIE:** .....16 **PROFESIONALES QUE INTERVIENEN EN EL PROCESO DE INFORMACIÓN Y/O  
17 CONSENTIMIENTO:**18 Los siguientes profesionales declaran que se ha explicado la información relativa a la donación de  
19 muestras biológicas al Biobanco:  
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2122 **C. Apellidos y nombre**23 **Fecha***Firma*24 **CONSENTIMIENTO:**25 Yo, D./Dña. .... declaro bajo mi  
26 responsabilidad que **he leído y comprendido el Formulario de Información**, del que se me  
27 ha entregado un ejemplar.  
2829 He **recibido suficiente información** sobre la donación de muestras biológicas de (*detallar tipo*  
30 *de muestras a recoger*) ..... e  
31 información asociada, al Biobanco, y sobre la posible realización de análisis genéticos sobre las  
32 mismas. He podido hacer preguntas sobre la información recibida y hablar con el profesional  
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3435 Dichas muestras son:  
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14 - Código de Biobanco:.....  
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22  INVESTIGACION  
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24  EVALUACIÓN / CONTROL DE CALIDAD  
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26  DOCENCIA  
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29 Deseo que dichas muestras y los datos clínicos asociados sean tratados de forma:  
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33  **Codificada** (serán identificadas con un código que protege mi identidad, siendo posible volver a  
34 ligarlas conmigo) o  
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36  **Anonimizada** (no se podrán asociar las muestras conmigo, por haberse eliminado de forma  
37 irreversible la vinculación entre las mismas y mi identidad).  
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41 Deseo **establecer restricciones** respecto al uso de la muestra, para que no sea  
42 utilizada en  
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47 Autorizo que se pueda **contactar conmigo posteriormente**:

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49  SI  
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53 En caso afirmativo, por favor, indique el medio de hacerlo:  
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- 55  Teléfono: (*indicar número*).....  
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57  Correo electrónico: (*indicar dirección*).....  
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Otros:  
(identificar).....

Autorizo **recibir información** sobre datos genéticos y datos relevantes para mi salud (Si solicita que las muestras sean anonimizadas, no podrá recibir esta información)

Marque lo que proceda:

□ SI

NO

Sé que puedo **revocar**, en cualquier momento, el consentimiento otorgado en este documento.

En  , a de de

## EL/LA DONANTE

**EL/LA REPRESENTANTE LEGAL**  
(sólo en caso de incapacidad del/de la donante)

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**CONSENTIMIENTO INFORMADO PARA DONACIÓN DE MUESTRAS BIOLÓGICAS E  
INFORMACIÓN ASOCIADA AL BIOBANCO**  
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11 **Biobanco en Red del Sistema Sanitario Público de Andalucía.**  
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14 DATOS DEL/DE LA DONANTE Y DE SU REPRESENTANTE (éste último sólo en caso de  
15 incapacidad del/de la donante):  
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17 **Apellidos y nombre del/de la Donante:**  
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22 **Apellidos y nombre del/de la representante legal.**  
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28 PROFESIONALES QUE INTERVIENEN EN EL PROCESO DE INFORMACIÓN Y/O  
29 CONSENTIMIENTO:  
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31 Los siguientes profesionales declaran que se ha explicado la información relativa a la donación de  
32 muestras biológicas al Biobanco:  
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42 CONSENTIMIENTO:  
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44 Yo, D./Dña. .... declaro bajo mi  
45 responsabilidad que **he leído y comprendido el Formulario de Información**, del que se me  
46 ha entregado un ejemplar.  
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48 He **recibido suficiente información** sobre la donación de muestras biológicas de (*detallar tipo*  
49 *de muestras a recoger*) ..... e  
50 información asociada, al Biobanco, y sobre la posible realización de análisis genéticos sobre las  
51 mismas. He podido hacer preguntas sobre la información recibida y hablar con el profesional  
52 indicado, quien me ha resuelto todas las dudas que le he planteado.  
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54 Dichas muestras son:  
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56  Excedentes del procedimiento médico-quirúrgico asistencia al que va a someterse o se ha  
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Ejemplar para Documentación Clínica



□ Tomadas mediante el procedimiento expreso (*indicar procedimiento*):

Las muestras biológicas e información asociada serán recogidas para:

PROYECTO (actividades de investigación biomédica que ayuden a la obtención de nuevos conocimientos científicos):

- Título: .....
  - Investigador Principal: .....
  - Código de Biobanco:.....

El excedente de las muestras biológicas e información asociada obtenidas en el proyecto original podrán utilizarse en otros proyectos relacionados con:

- INVESTIGACION
  - EVALUACIÓN / CONTROL DE CALIDAD
  - DOCENCIA

Deseo que dichas muestras y los datos clínicos asociados sean tratados de forma:

- Codificada** (serán identificadas con un código que protege mi identidad, siendo posible volver a ligarlas conmigo) o
  - Anonimizada** (no se podrán asociar las muestras conmigo, por haberse eliminado de forma irreversible la vinculación entre las mismas y mi identidad)

Deseo **establecer restricciones** respecto al uso de la muestra, para que no sea utilizada en

## Ejemplar para Documentación Clínica



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Autorizo que se pueda **contactar conmigo posteriormente**:

- SI
- NO

En caso afirmativo, por favor, indique el medio de hacerlo:

- Teléfono: (*indicar número*) .....
- Correo electrónico: (*indicar dirección*) .....
- Otros:  
(identificar) .....

Autorizo **recibir información** sobre datos genéticos y datos relevantes para mi salud (Si solicita que las muestras sean anonimizadas, no podrá recibir esta información)

Marque lo que proceda:

- SI
- NO

Sé que puedo **revocar**, en cualquier momento, el consentimiento otorgado en este documento.

En , a de de

EL/LA DONANTE

EL/LA REPRESENTANTE LEGAL

(sólo en caso de incapacidad del/de la donante)

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REVOCACIÓN / MODIFICACIÓN DEL CONSENTIMIENTO PARA USO DE  
MUESTRAS BIOLÓGICAS E INFORMACIÓN ASOCIADA DONADAS AL  
BIOBANCO DEL SISTEMA SANITARIO PÚBLICO DE ANDALUCÍA

Yo, D./Dña. \_\_\_\_\_ revoco el  
consentimiento informado otorgado en el documento  
\_\_\_\_\_ (especificar fecha aproximada y/o procedimiento).

Solicito:

- Revocación total:** las muestras biológicas e información asociada serán destruidas excepto aquellas que ya hayan sido utilizadas en proyectos.
- Revocación parcial:** solicito que mis muestras NO sean utilizadas para la/s siguiente/s finalidad/es:
- Investigación
  - Docencia
  - Control de Calidad

**Anonimización de las muestras biológicas e información asociada:** la anonimización no permitirá recibir ningún tipo de información relevante para la salud derivada de los proyectos en los que sea utilizada.

Otras consideraciones:  
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# BMJ Open

**Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): protocol of a phase II, open-label, randomised, multicentre, controlled clinical trial.**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039951.R2
Article Type:	Protocol
Date Submitted by the Author:	01-Aug-2020
Complete List of Authors:	León López, Rafael; Hospital Universitario Reina Sofia, Intensive Care Unit; IMIBIC Fernández, Sheila; IMIBIC; Hospital Universitario Reina Sofia, Intensive Care Unit Limia Pérez, Laura; Hospital Universitario Reina Sofia, Internal Medicine Unit; IMIBIC Romero Palacios, Alberto; Hospital Universitario de Puerto Real, Infectious Diseases Unit Fernández-Roldán, María Concepción; Hospital Universitario Virgen de las Nieves, Infectious Diseases Unit Aguilar Alonso, Eduardo; Hospital Infanta Margarita, Intensive Care Unit Pérez Camacho, Inés; Hospital Regional Universitario de Málaga, Infectious Diseases Unit Rodríguez-Baño, Jesús; Hospital Universitario Virgen Macarena, Infectious Diseases Unit; Carlos III Health Institute, Spanish Network for Research in Infectious Diseases Merchante, Nicolás; Hospital Universitario Virgen de Valme, Infectious Diseases and Microbiology Unit Olalla, Julián; Hospital Costa del Sol, Internal Medicine Service Esteban-Moreno, M. Ángeles; Complejo Hospitalario Torrecárdenas, Infectious Diseases Unit Santos, Marta; Hospital Universitario de Jerez de la Frontera, Infectious Diseases Unit Luque-Pineda, Antonio; IMIBIC, Clinical Trials Unit; Hospital Universitario Reina Sofia Torre-Cisneros, Julian; Hospital Universitario Reina Sofia, Infectious Diseases Unit; IMIBIC
<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Intensive care
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INFECTIOUS DISEASES, INTERNAL MEDICINE, VIROLOGY

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3 **Efficacy and safety of early treatment with sarilumab in**  
4 **hospitalised adults with COVID-19 presenting cytokine release**  
5 **syndrome (SARICOR STUDY): protocol of a phase II, open-label,**  
6 **randomised, multicentre, controlled clinical trial.**

7  
8  
9  
10 Rafael León-López<sup>1</sup>, Sheila Cárcel-Fernández<sup>1</sup>, Laura Limia-Pérez<sup>2</sup>, Alberto Romero-Palacios<sup>3</sup>,  
11 María Concepción Fernández Roldán<sup>4</sup>, Eduardo Aguilar-Alonso<sup>5</sup>, Inés Pérez-Camacho<sup>6</sup>, Jesús  
12 Rodríguez-Baño<sup>7,8</sup>, Nicolás Merchant<sup>9</sup>, Julián Olalla<sup>10</sup>, M. Ángeles Esteban-Moreno<sup>11</sup>, Marta  
13 Santos<sup>12</sup>, Antonio Luque-Pineda<sup>13</sup>, Julián Torre-Cisneros<sup>13,14,15</sup>

14  
15 <sup>1</sup>Intensive Care Unit, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/  
16 Reina Sofía University Hospital/University of Córdoba, Córdoba, Spain.

17 <sup>2</sup>Internal Medicine Unit, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/  
18 Reina Sofía University Hospital/University of Córdoba, Córdoba, Spain. CIBER Fisiopatología de  
19 la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain.

20 <sup>3</sup>Infectious Diseases Unit, Puerto Real University Hospital, Puerto Real, Spain.

21 <sup>4</sup>Infectious Diseases Unit, Virgen de las Nieves University Hospital, Granada, Spain.

22 <sup>5</sup>Intensive Care Unit, Infanta Margarita Hospital, Cabra, Spain.

23 <sup>6</sup>Infectious Diseases Unit, Málaga Regional University Hospital, Málaga, Spain.

24 <sup>7</sup>Infectious Diseases Unit, Virgen Macarena University Hospital, Sevilla, Spain.

25 <sup>8</sup>Spanish Network for Research in Infectious Diseases (REIPI, RD16/0016/0001), Instituto de  
26 Salud Carlos III, Madrid, Spain.

27 <sup>9</sup>Infectious Diseases and Microbiology Unit, Virgen de Valme University Hospital, Sevilla, Spain.

28 <sup>10</sup>Internal Medicine Service, Costa del Sol University Hospital, Marbella, Spain

29 <sup>11</sup>Infectious Diseases Unit, Torrecárdenas University Hospital, Almería, Spain.

30 <sup>12</sup>Infectious Diseases Unit, Jerez de la Frontera University Hospital, Jerez de la Frontera, Spain.

31 <sup>13</sup>Clinical Trials Unit, Instituto Maimonides de Investigación Biomédica de Córdoba (IMIBIC)/  
32 Reina Sofia University Hospital/University of Córdoba (SCReN PT17/0017/0032), Córdoba, Spain.

33 <sup>14</sup>Infectious Diseases Unit, Instituto Maimónides de Investigación Biomédica de Córdoba  
34 (IMIBIC)/Reina Sofía University Hospital/University of Córdoba, Córdoba, Spain

35 <sup>15</sup>Spanish Network for Research in Infectious Diseases (REIPI, RD16/0016/0008), Instituto de  
36 Salud Carlos III, Madrid, Spain

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38 \*Author for correspondence: Antonio Luque-Pineda [antonio.luque@imibic.org](mailto:antonio.luque@imibic.org)

39 WORD COUNT:

40 Abstract:

41 Text:

42 **KEYWORDS:** COVID-19; IL-6; cytokines, SARS-CoV-2, sarilumab

## ABSTRACT

**Introduction** About 25% of patients with COVID-19 develop acute respiratory distress syndrome (ARDS) associated with a high release of pro-inflammatory cytokines such as interleukin-6 (IL-6). The aim of the SARICOR study is to demonstrate that early administration of sarilumab (an IL-6 receptor inhibitor) in hospitalised patients with COVID-19, pulmonary infiltrates and a high IL-6 or D-Dimer (DD) serum level could reduce the progression of ARDS requiring high-flow nasal oxygen or mechanical ventilation (non-invasive or invasive).

**Methods and analysis** Phase II, open-label, randomised, multicentre, controlled clinical trial to study the efficacy and safety of the administration of two doses of sarilumab (200 and 400 mg) plus best available therapy (BAT) in hospitalised adults with COVID-19 presenting cytokine release syndrome. This strategy will be compared with a BAT control group. The efficacy and safety will be monitored up to 28 days post-administration. A total of 120 patients will be recruited (40 patients in each arm).

**Ethics and public dissemination** The clinical trial has been approved by the Research Ethics Committee of the coordinating centre and authorised by the Spanish Agency of Medicines and Medical Products (AEMPS). If the hypothesis is verified, the dissemination of the results could change clinical practice by increasing early administration of sarilumab in adult patients with COVID-19 presenting cytokine release syndrome, thus reducing ICU admissions.

**Trial registration number** NCT04357860

### Strengths and limitations of this study

- Early use of sarilumab can reduce the progression of respiratory failure and prevent the saturation of ICUs.
- The trial will study two doses of the drug. One could be selected for phase III trials with a larger sample.
- Limitations include not being a blind trial and having a limited sample size.
- The stock of sarilumab is limited in Spain. The government distributes the drug to ensure treatment of patients with rheumatoid arthritis. Pharmacies must request authorisation for dispensation of the drug on a case-by-case basis.
- The incidence of new cases is decreasing in Spain.

## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for coronavirus disease 2019 (COVID-19). Scientific evidence on the pathogenesis of severe COVID-19, which occurs with respiratory distress, indicates that there is a disordered inflammatory response, an imbalance in the renin–angiotensin system (RAS) and a characteristic coagulopathy [1,2,3]. Typically, patients present lymphopenia at the expense of CD4+ and CD8+ T cells. The deregulated and aberrant immune response affects innate immunity, T-cell activation and cytokine production [1,4]. The end point of this deregulation is diffuse alveolar damage (DAD) characterised by generalised inflammation of the lung with endothelial injury, thrombosis and angiogenesis [5].

At serum level, this deregulation translates into elevated levels of numerous cytokines and chemokines, such as interleukin-6 (IL-6), interleukin-8 (IL-8) and tumour necrosis factor alpha (TNF $\alpha$ ) [4]. A recent meta-analysis has shown a strong correlation between IL-6 levels and the most severe forms of the disease [6]. Furthermore, there is an inverse relationship between IL-6 levels and absolute lymphocyte counts related to DAD [7]. For this reason, IL-6 blockade is considered a therapeutic target to control cytokine release syndrome (CRS) related to COVID-19 [8].

Sarilumab is a human anti-IL-6 receptor monoclonal antibody licensed for the treatment of rheumatoid arthritis. It is a safe and well-tolerated drug [8]. The most common side effects are respiratory tract infections, neutropenia, hypercholesterolemia and mild hepatotoxicity. The most serious side effects are gastrointestinal infections and perforations [9].

This clinical trial tests the hypothesis that early blockade of IL-6 could halt the progression to severe respiratory failure in hospitalised patients infected with SARS-CoV-2. For this purpose, we investigated the efficacy and safety of early treatment with sarilumab added to standard treatment to prevent progression to severe pulmonary forms of COVID-19.

## METHODS AND ANALYSIS

### Design

This is a phase II, open-label, randomised, multicentre, controlled clinical trial. The patients will be assigned to three treatment groups (Figure 1):

1. Control group: 40 patients will receive the best available therapy (BAT) for a maximum of 14 days.
2. Treatment group 1 (T1): 40 patients will receive BAT for a maximum of 14 days + 200 mg of sarilumab subcutaneously (single dose).
3. Treatment group 2 (T2): 40 patients will receive BAT for a maximum of 14 days + 400 mg of sarilumab subcutaneously (single dose).

At the time the protocol has been written, and in the absence of scientific evidence, BAT is considered any combination of drugs authorized in Spain for this indication. This variable will be taken into account in the efficacy analysis.

### Study population and setting

Ten university hospitals located in Andalusia, Spain, will participate in the trial. The trial will include hospitalised patients with confirmed SARS-CoV-2 infection causing respiratory disease and presenting high serum levels of IL-6 or D-Dimer (DD). Patients who meet all the inclusion criteria and have no exclusion criteria will be prospectively included in the study. Following hospital admission, patients may be randomized as soon as they meet the inclusion criteria, even in the emergency department. The inclusion and exclusion criteria for the trial are described in Box 1.

**Box 1 Study selection criteria*****Inclusion criteria***

1. Age  $\geq 18$  years and  $<75$  years
2. Hospitalisation with COVID-19 (positive PCR in a respiratory tract sample) in absence of respiratory distress (defined as requiring high-flow nasal oxygen or mechanical ventilation).
3. Interstitial pneumonia confirmed by chest radiography or CT scan
4. IL-6 levels  $>40$  pg/ml. In the absence of IL-6, D-Dimer (DD)  $>1500$  or  $>1000$  if progressive increments between at least 2 determinations are documented after admission.
5. In women of childbearing age, a negative pregnancy test
6. Signed informed consent

***Exclusion criteria***

1. SOFA score  $>6$  points
2. Patient who, in the researcher's opinion, is not subsidiary of invasive mechanical ventilation.
3. Neutrophil count  $<2 \times 10^3/\mu\text{L}$
4. Platelet count  $<100 \times 10^3/\mu\text{L}$
5. ALT or AST levels  $>5$  times the upper limit of normal
6. Severe renal failure ( $\text{CrCl} <30 \text{ ml/min}$ )
7. Active bacterial infection
8. Active tuberculosis or history of not completing treatment against tuberculosis
9. Antecedents of diverticulitis
10. Hypersensitivity to sarilumab or its excipients
11. Treatment with TNF antagonists
12. Treatment with anti-IL6 in the previous 30 days
13. Chronic treatment ( $>1$  month<sup>a</sup>) with corticosteroids at doses  $>0.5 \text{ mg/kg/day}$  of prednisone or equivalent. Topical and inhaled corticosteroids are acceptable.
14. Concomitant treatment with immunomodulators, including dexamethasone, vitamin D or statins. Macrolides such as azithromycin are acceptable.

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3     **15. Patients on immunosuppressive treatment for any cause**  
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5     **16. HIV-infected patients with CD4 <200/mm<sup>3</sup>**  
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7     **17. Past or current history of autoimmune disease**  
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9     **18. Patients receiving immunomodulatory antibody therapy, including immunoglobulins**  
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11     **19. Participation in any clinical trial that evaluated any investigational product in the last 3 months or less than 5 half-lives of the product under investigation**  
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15     **20. Pregnancy**  
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18     **21. Any other condition that, in clinical judgement, prevents the patient's adherence to the protocol**

20  
21 Abbreviations: SOFA, sequential organ failure assessment. PCR, polymerase chain reaction. CT scan,  
22 computed tomography scan. ALT, alanine transaminase. AST, aspartate transaminase. CrCl, creatinine  
23 clearance. TNF, tumour necrosis factor. HIV, human immunodeficiency viruses.

- 24     <sup>a</sup> Based on:  
25       - National Institute for Health and Clinical Excellence (NICE) Clinical Knowledge Summaries:  
26       Corticosteroids - Oral. NICE; 2012.  
27       - Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the  
28       complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9(1):30.  
29       Published 2013 Aug 15. doi:10.1186/1710-1492-9-30

## 34     Withdrawal criteria

35  
36       Patients may withdraw from the study at any time, for any reason and without prejudice  
37       to future medical treatment. Patients who do not comply with the study procedure or have not  
38       been followed up will be considered a study "withdrawal". The reasons for withdrawal will be  
39       examined in full accordance with bioethical principles regarding the guarantee of patients'  
40       rights. The criteria for withdrawal from the study are described below.

- 41  
42     1. Patient request  
43     2. Violation or deviation from the protocol (e.g. breach of administration of treatment, need for  
44       prohibited treatment).  
45     3. Researchers decision, based on clinical reasons  
46     4. Administrative decision of the investigators, promoter or regulatory authorities  
47     5. Loss to follow-up  
48     6. Suspected unexpected serious adverse reaction (SUSAR)  
49     7. Serious adverse event (SAE) that at the discretion of the promoter or investigator is not  
50       acceptable.  
51     8. Any adverse event considered intolerable by either the patient or the investigator  
52     9. Pregnancy

53  
54       The inclusion and exclusion criteria can be modified in consecutive versions of the  
55       protocol, based on the scientific evidence that is published during the development of the trial,  
56       after justification and approval by the reference ethics committee.

## Study variables

### ***Outcome variables***

The primary outcome variable is the development of adult respiratory distress syndrome requiring high-flow nasal oxygenation (HFNO) or mechanical ventilation, both non-invasive and invasive.

The secondary outcome variables are: all-cause (crude) mortality at day 28, time (in days) to clinical improvement, time (in days) until oxygenation improvement for at least 48 hours, proportion of patients who require invasive mechanical ventilation, negativisation of PCR to SARS-CoV-2, cytokine kinetics and side effects.

Time to clinical improvement is defined as number of days until 2 points rise in the seven category ordinal scale.

Clinical improvement will be assessed on a seven-category ordinal scale consisting of the following categories: 1, not hospitalised with resumption of normal activities; 2, not hospitalised, but unable to resume normal activities; 3, hospitalised, not requiring supplemental oxygen; 4, hospitalised, requiring supplemental oxygen; 5, hospitalised, requiring high-flow oxygen therapy; 6, hospitalised requiring ECMO, invasive mechanical ventilation or both; and 7, death.

Time (in days) until improvement in oxygenation for at least 48 hours: (i) Time to verify an increase in the SpO<sub>2</sub> / FiO<sub>2</sub> ratio with respect to the worst SpO<sub>2</sub> / FiO<sub>2</sub> prior to treatment with Sarilumab and stratified according to levels of IL-6 or DD; (ii) Time until the absence of oxygen need to maintain a saturation in ambient air of ≥ 93%; (iii) Number of days in need of supplemental oxygen.

### ***Other variables***

The following demographics and clinical information will be collected from all patients: age, sex, weight, height, body mass index (BMI), comorbidities, previous treatment, history of the current disease, respiratory rate (bpm), basal oxygen saturation (%), arterial pO<sub>2</sub> (mm Hg), pO<sub>2</sub>/FiO<sub>2</sub> rate, oxygen saturation/FiO<sub>2</sub> rate, blood pressure (mmHg), heart rate (bpm), consciousness level, temperature (°C), clinical improvement, organ failure assessment score (SOFA), microbiological test, analytical parameters (haematimetry, glucose, creatinine, AST, ALT, C-reactive protein, albumin, LDH, ferritin, troponin I, protein kinase, procalcitonin, lipid profile, IL-6, D-dimer, prothrombin time, INR). All concomitant medication and adverse events will be recorded and monitored in accordance with regulatory procedures. SARS-CoV-2019 in nasopharyngeal swab and a panel of cytokines (IL1- $\alpha$ , IL1- $\beta$ , IL6, IL8, IL10, IL12, IL18, IL38, INF $\gamma$ , TNF $\alpha$ , CCL2, CCL3, CCL4, MIF  $\gamma$  PAI-1) RAGE, Ang-2 and Protein C will be determined before randomisation and on days 5, 10, 14, 21 and 28.

## Randomisation and masking

A total of 120 patients will be recruited (40 in each group). Patients who meet the selection criteria will be randomised to be included in the control group or the two experimental groups. Randomisation will be carried out by means of electronic case report forms (eCRFs). The ratio will be 1:1:1 for each group (balanced randomisation). The study design is open, but the

1  
2  
3 investigator will not know the treatment assignment until the patient signs the informed consent  
4 form and randomisation is performed, thus minimising selection bias. Patients will be identified  
5 by a code that includes the centre code followed by the patient number (XX-YY).  
6  
7

## 8 Study medication

9 The investigational medication (IM) is sarilumab (ATC code: L04AC14), a human  
10 monoclonal antibody (IgG1 subtype) that specifically binds to both soluble and membrane-  
11 bound IL-6 (IL-6Ra) receptors and inhibits the transmission of IL-6 mediated signals involving  
12 signal transducer glycoprotein 130 (gp130) and activator of transcription 3 (STAT-3).  
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15 The commercial subcutaneous medication available in Spain (SANOFI-AVENTIS) will be  
16 used. Administration of the IM will be carried out according to the technical sheet and the local  
17 practice of each centre.  
18

19 The BAT will include any combination of drugs included in the current protocol of the  
20 Spanish Ministry of Health  
21 (<https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos.htm>) and complementary notes issued by the Spanish Agency of Medicines  
22 and Medical Products ([www.aemps.gob.es](http://www.aemps.gob.es)). It includes Remdesivir.  
23  
24

## 25 Study procedures

26 The duration of follow-up for each patient will be 28 days and will start from the moment  
27 the patient is randomised. A total of 6 visits will be scheduled during the trial: baseline, day 5,  
28 day 10, day 14, day 21 and day 28. The scheduled follow-up is shown in Table 1. The visit  
29 following the end of treatment will be considered as the end-of-treatment visit. Visit 5 (day 28  
30 after randomisation) will be considered the final study visit. The final study visit can be moved  
31 forward to the day of hospital discharge. Additionally, data on clinical improvement (on a 7-  
32 point ordinal scale), axillary temperature, oxygen saturation (or PO<sub>2</sub>) and oxygen therapy will be  
33 collected daily.  
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36 Nasopharyngeal swabs will be performed on days 0, 5, 10, 14, 21 and 28. Plasma will  
37 also be obtained on days 0, 5, 10, 14, 21 and 28. The samples will be locally preserved (frozen at  
38 -80 °C) until dispatched to the Biobank of the Reina Sofía University Hospital of Córdoba, Spain.  
39  
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41 The principal investigator will be responsible for the detection and documentation of  
42 adverse events (AE) throughout the study. All AEs must be notified during all phases of the study  
43 and followed up until resolution or until an adequate explanation is found, although the patient  
44 has completed study treatment. Periodic reports will also be submitted on AEs that occurred  
45 during the study, including causality assessment, severity and intensity.  
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Table 1. Chart of study procedures

	STUDY PERIOD											
	BASELINE		POST RANDOMISATION									
	Day 0	Day 1	Day 2 to 4	VISIT 1 Day 5	Day 6 to 9	VISIT 2 Day 10	Day 11 to 13	VISIT 3 Day 14	Day 15 to 20	VISIT 4 Day 21	Day 22 to 27	VISIT 5 Day 28
<b>Recruitment</b>												
Review of inclusion and exclusion criteria	X											
Informed consent	X											
Randomisation	X											
Baseline data, demographics data and comorbidities*	X											
<b>Clinical data</b>												
Respiratory rate, Saturation, Applied Oxygen ( $\text{FiO}_2$ ) $\text{SpO}_2$ / $\text{FiO}_2$ ratio	X	X	X	X	X	X	X	X	X	X	X	X
Arterial $\text{pO}_2$ , $\text{pO}_2$ / $\text{FiO}_2$ ratio	X			X		X		X		X		X
SOFA score	X	X	X	X	X	X		X		X		X
7-point ordinal scale	X	X	X	X	X	X	X	X	X	X	X	X
<b>Laboratory data</b>												
PCR COVID-19 (nasopharyngeal swab)	X			X		X		X		X		X
Analytical parameters**	X			X		X		X		X		X
Samples for cytokine determination	X			X		X		X		X		X
Pregnancy test	X											
<b>Drugs</b>												
IM Administration	X											
Interaction assessment, AR, SAR, SUSAR, AE, SAE	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication record	X	X	X	X	X	X	X	X	X	X	X	X
<b>Radiological tests</b>												
Chest X-ray or CT scan	X											
<b>Biological samples</b>												
Samples for Biobank	X			X		X		X		X		X

\*age, sex, weight, height, BMI, comorbidities, previous treatment (including therapeutic family; e.g. ACEI, ARA II, statins, etc.), current disease history, BP (mm Hg), HR, levels of consciousness, temperature (°C), National Early Warning Score (NEWS).

\*\*Haematometry, glucose, creatinine, AST, ALT, C-reactive protein, albumin, LDH, ferritin, troponin I, protein kinase, procalcitonin, pregnancy test (at visit 0), lipid profile, interlekin-6, D-dimer, prothrombin time (PT%), INR.

## Statistical analysis

Since this is a phase II study, a sufficient number of patients are included to perform an initial analysis of efficacy and safety. We have calculated an overall sample size of 120 patients, 40 patients for each arm, to detect a 30% reduction in the primary outcome with an alpha error of 0.05, a beta risk of 0.2 and assuming that the modified intention-to-treat population will be 90% of the randomised patients.

Clinical data will be collected in an electronic case report form (eCRF). All analyses will be performed using PASW Statistics software V.15.0 (IBM Corporation) and R software (V.3.5.0). Frequencies will be calculated for the qualitative variables and compared using the  $\chi^2$  test or Fisher's test. For quantitative variables, the mean and standard deviation will be calculated.

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2  
3 Normality will be analysed using the Kolmogorov-Smirnov test and comparisons will be made  
4 using the Student's t-test or the Mann-Whitney test depending on whether or not they follow a  
5 normal distribution, respectively. For the comparison of three or more groups, the analysis of  
6 variance (ANOVA) or Kruskal-Wallis tests will be used. The analyses will be based on the  
7 intention-to treat population (randomised patients receiving treatment). The time until the  
8 primary outcome variable is reached will be plotted on a Kaplan-Meier curve and compared  
9 using a log-rank test. A Cox regression analysis will be performed for the primary efficacy variable  
10 and the results reported in terms of the hazard ratio (HR) with 95% confidence intervals.  
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12  
13

## Patient and public involvement

14 No patient involved.  
15  
16

## ETHICAL ISSUES AND DISSEMINATION PLAN

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18  
19 This clinical trial will be conducted in accordance with the protocol and the ethics  
20 principles of the Declaration of Helsinki (Fortaleza, 2013) and in accordance with the applicable  
21 regulatory requirements, in particular the ICH Tripartite Guideline "Standards of Good Clinical  
22 Practice", Royal Decree 1090/2015 regulating clinical trials with medications in Spain and  
23 Regulation (EU) No. 536/2014 of 16 April 2014 on clinical trials on medicinal products for human  
24 use. The protocol, the informed consent form, the patient information form and any documents  
25 applicable to the study have required approval by the appropriate regulatory agencies. The  
26 Committee for Biomedical Research Ethics of the Reina Sofia University Hospital approved the  
27 trial. Authorisation has also been obtained from the Spanish Agency of Medicines and Medical  
28 Products (AEMPS, 20-0262). The trial is registered in accessible public databases such as the  
29 Spanish Clinical Studies Registry (REec), EUDRACT (2020-001531-27) and ClinicalTrials.gov  
30 (NCT04357860).  
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## DISCUSSION

34  
35 Worldwide, the number of people infected with SARS-CoV-2 has continued to increase  
36 steadily to the millions. Although the vast majority of patients are asymptomatic or develop mild  
37 forms, a proportion develop severe forms of adult respiratory distress syndrome (ARDS) with high  
38 mortality [9]. The interaction between the virus and the immune system plays an essential role in  
39 the pathogenesis of this severe clinical presentation [10].

40 To enter respiratory epithelial cells, SARS-CoV-2 spike protein (S-protein) binds to the  
41 cellular angiotensin-converting enzyme 2 (ACE2) for which the collaboration of transmembrane  
42 serine protease 2 (TMPRSS2) and cathepsin B/L are required. ACE2, a carboxypeptidase widely  
43 expressed in the respiratory tract, is the cornerstone of RAS and modulates the effect of  
44 angiotensin 2 on respiratory tissue. Excess angiotensin 2 is related to immune system activity and  
45 lung thrombogenesis [11,12,13]. The expression of ACE2 in the respiratory epithelium differs  
46 among patients depending on their genetic factors, sex, age and lifestyle. These variables may  
47 explain the variability of the clinical expression of COVID-19 [11,14].

48 However, prior to the evidence on the relationship between RAS and COVID-19, it had  
49 already been observed that ARDS produced by SARS-CoV-2 was clinically similar to the cytokine  
50 release syndrome (CRS) caused by chimeric antigen receptor (CAR) T-cell therapy [15]. The  
51 overproduction of pro-inflammatory cytokines, such as IL-6, IL-2, IL-17, TNF, IL-10, IFN- $\gamma$ -protein  
52 10 (IP-10) or macrophage inflammatory protein 1 (MCP-1), is a clinical marker of severity with  
53 intense pulmonary inflammation and thrombus formation [1]. IL-6 plays an essential role in this  
54 pathogenesis and has attracted therapeutic interest because it can be therapeutically blocked

[14,15, 16]. There is evidence that IL-6 levels are related to mortality [17,18]. It is logical to think that antiviral treatment is insufficient to control immune deregulation in severe cases. The use of humanised monoclonal antibody against the IL-6 receptor (IL-6R) has been proposed in patients with COVID-19 requiring invasive ventilation who present elevated levels of IL-6 [19]. As is usual in science, there is no lack of dissenting opinions regarding this hypothesis [20, 21,22].

At the healthcare level, improving the management of critical patients is not sufficient. It is necessary to detect patients at risk of progression to ARDS early on and to investigate therapeutic strategies that prevent the progression of the disease. This is the only way we will be able to reduce the need for mechanical ventilation, avoid collapsing intensive care units and reduce mortality [23,24].

Therefore, it seems rational to speculate that, if done early, blocking IL-6 could play a protective role in mitigating the elevated immune response to the virus and preventing the cytokine storm. We propose that the early use of sarilumab, in addition to standard therapy, can attenuate the detrimental host immune response in patients with elevated markers of inflammation by reducing the development of severe respiratory failure and other organ damage. In conclusion, the SARICOR study aims to reduce the severity and mortality associated with COVID-19.

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**Contributors.** Dr. Julian Torre-Cisneros, Dr. Rafael León López and Antonio Miguel Luque Pineda collaborate in the design of the protocol and the informed consent form.

The protocol was reviewed and agreed with Sheila Cárcel Fernández, Dr. Laura Limia Pérez, Dr. Alberto Romero Palacios, Dr. María Concepción Fernández-Roldán, Dr. Eduardo Aguilar Alonso, Dr. Inés Pérez Camacho, Dr. Jesús Rodríguez-Baño, Dr. Nicolás Merchante, Dr. Julián Olalla, Dr. M. Ángeles Esteban-Moreno and Dr. Marta Santos, who contributed in the definition of the eligibility criteria.

Dr. Julián Torre-Cisneros contributed in the refinement, final review and approval of the protocol and the informed consent form.

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**Competing interests.** The authors declare no conflicts of interest.

**Ethics approval.** In accordance with Royal Decree 1090/2015 of 4 December concerning the regulation of clinical trials of medicinal products in Spain, multicentre clinical trials only require the approval of a single medicinal research ethics committee (reference MREC) and of the Spanish Agency of Medicines and Medical Products (AEMPS). This clinical trial has been approved by the reference MREC of the province of Córdoba and the AEMPS (Code: 20-0262; EudraCT Number: 020-001531-27).

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13 **Figure legend:**  
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15 Figure 1. Flow diagram  
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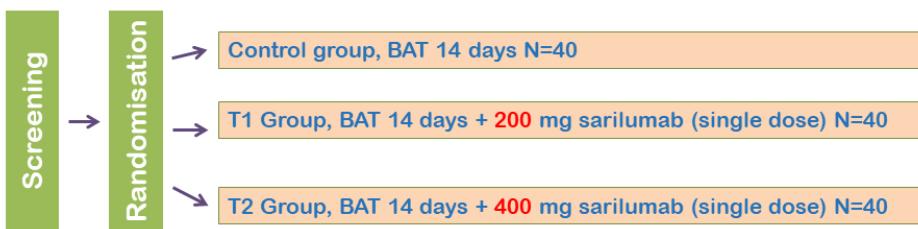


Figure 1 - Flow diagram

254x190mm (96 x 96 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item	Description	Addressed on page number
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**Administrative information**

Title	1	Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): protocol of a phase II, open-label, randomised, multicentre, controlled controlled clinical trial.	Page 1
Trial registration	2a	Spanish Clinical Studies Registry (REec), EUDRACT (2020-001531-27) and ClinicalTrials.gov (NCT04357860).	Pages 1 and 9

2b	Data category	Information	Throughout the document
	Primary registry and trial identifying number	ClinicalTrials.gov NCT04357860	
	Date of registration in primary registry	April, 2020	
	Secondary identifying numbers	EUDRACT (2020-001531-27)	
	Source(s) of monetary or material support	COVID-19 Research Programme. Ministry of Health and Families, Regional Government of Andalusia. Project code COVID-0013-2020. Non-financial support provided by IMIBIC Clinical Research Unit and SCReN (Spanish Clinical Research Network).	
	Primary sponsor	FIBICO (Fundación para la Investigación Biomédica de Córdoba)	
	Secondary sponsor(s)	Not applicable	
	Contact for public queries	IMIBIC Clinical Research Unit (uicec@imibic.org)	
	Contact for scientific queries	Dr. Julián de la Torre Cisneros (julian.torre.sspa@juntadeandalucia.es)	
	Public title	Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): protocol of a phase II, open-label, randomised, multicentre, controlled clinical trial.	
	Scientific title	Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): protocol of a phase II, open-label, randomised, multicentre, controlled clinical trial.	
	Countries of recruitment	Spain	
	Health condition(s) or problem(s) studied	SARS-CoV-2, COVID-19	

Intervention(s)	<p>Experimental arm #1: Subjects treated with the best available treatment up to 14 days plus Sarilumab 200 mg single dose.</p> <p>Experimental arm #2: Subjects treated with the best available treatment up to 14 days plus Sarilumab 400 mg single dose.</p> <p>Active comparator: Subjects treated with the best available treatment up to 14 days.</p>
Key inclusion and exclusion criteria	<p>Ages eligible for study: <math>\geq 18</math> years and <math>&lt;75</math> years</p> <p>Sexes eligible for study: both Accepts healthy volunteers: no</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"><li>1. Age <math>\geq 18</math> years and <math>&lt;75</math> years</li><li>2. Admission for confirmed respiratory symptoms to COVID-19 based on a positive PCR in a sample of the respiratory tract in the absence of respiratory distress syndrome requiring High flow nasal oxygenation or mechanical ventilation</li><li>3. Interstitial pneumonia confirmed by chest radiography or CT</li><li>4. IL-6 levels <math>&gt; 40</math> pg / ml. In its absence, D-Dimer (DD) <math>&gt; 1500</math> or <math>&gt; 1000</math> may be included if progressive increases are documented</li><li>5. Negative pregnancy test in women of childbearing age</li><li>6. Signature of informed consent</li></ol> <p>Exclusion criteria</p> <ol style="list-style-type: none"><li>1. SOFA score <math>&gt; 6</math> points</li><li>2. Patient who, in the researcher's opinion, is not a subsidiary of invasive mechanical ventilation</li><li>3. Neutrophil count <math>&lt; 2 \times 10^3</math> / <math>\mu\text{L}</math></li><li>4. Platelet count <math>&lt; 100 \times 10^3</math> / <math>\mu\text{L}</math></li></ol>

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	<p>5. ALT or AST levels &gt; 5 times the upper limit of normal</p> <p>6. Severe renal failure (<math>\text{CrCr} &lt; 30 \text{ ml / min}</math>)</p> <p>7. Treatment with TNF antagonists</p> <p>8. Previous treatment with anti-IL6 in the previous 30 days</p> <p>9. Chronic prior treatment with corticosteroids at doses greater than 0.5 mg / kg / day of prednisone or equivalent. Yes, inhaled and topical corticosteroids are acceptable</p> <p>10. Concomitant treatment with immunomodulators, among which are Vitamin D or statins. Macrolides such as azithromycin are acceptable</p> <p>11. Pregnancy</p>
Study type	<p>Interventional</p> <p>Allocation: randomized</p> <p>Intervention model. Parallel groups</p> <p>Masking: open-label</p> <p>Primary purpose: curative</p> <p>Phase II</p>
Date of first enrolment	Not recruiting
Target sample size	120
Recruitment status	Not recruiting
Primary outcome(s)	<p>Proportion of patients requiring or time (in days) to that is required:</p> <ul style="list-style-type: none"> <li>-High flow nasal oxygenation.</li> <li>-BiPAP type non-invasive mechanical ventilation.</li> <li>-Non-invasive mechanical ventilation type CPAP.</li> <li>-Invasive mechanical ventilation.</li> </ul>
Key secondary outcomes	<ul style="list-style-type: none"> <li>- All-cause (crude) mortality at day 28.</li> <li>- Time (in days) to clinical improvement, defined as mean change or time in days from randomization to any of the following criteria: (i)</li> </ul>

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5		improvement of two points in
6		the ordinal scale of 7 points of
7		gravity or, (ii) discharge from the
8		hospital alive. The criteria that is
9		reached before.
10		- Time (in days) until
11		improvement in oxygenation for
12		at least 48 hours.
13		- Proportion of patients requiring
14		invasive mechanical ventilation.
15		- Proportion of patients who have
16		negative COVID-19 PCR at each
17		visit.
18		- Mean of serum cytokine levels.
19		- Incidence of adverse events
20		related to medication and its
21		administration.
22		
23		

24 Protocol version 3 Version: 1.0, 24 March 2020 n/a  
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27 Funding 4 COVID-19 Research Programme. Ministry of Health and Families, Page 10  
28 Regional Government of Andalusia. Project code COVID-0013-2020.  
30 Non-financial support provided by IMIBIC Clinical Research Unit and  
31 SCReN (Spanish Clinical Research Network).  
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4 Roles and 5a Dr. Julián de la Torre Cisneros Pages 1  
5 responsibiliti Unidad de Gestión Clínica de Enfermedades Infecciosas Hospital and 10  
6 es Universitario Reina Sofía  
7 Avenida Menéndez Pidal s/n – C.P. 14004 (Córdoba, SPAIN)  
8 Coordinating investigator  
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10  
11 Dr. Rafael León López  
12 Unidad de Gestión Clínica de Medicina Intensiva Hospital Universitario  
13 Reina Sofía  
14 Avenida Menéndez Pidal s/n – C.P. 14004 (Córdoba, SPAIN) Principal  
15 investigator at Hospital Universitario Reina Sofía  
16  
17  
18 Dr. Laura Limia Pérez  
19 Unidad de Gestión Clínica de Medicina Interna Hospital Universitario  
20 Reina Sofía  
21 Avenida Menéndez Pidal s/n – C.P. 14004 (Córdoba, SPAIN) Sub-  
22 investigator at Hospital Universitario Reina Sofía  
23  
24 Mr. Antonio Miguel Luque Pineda IMIBIC Clinical Research Unit  
25 Edificio IMIBIC  
26 Avenida Menéndez Pidal s/n – C.P. 14004 (Córdoba, SPAIN) Clinical  
27 Trial Manager  
28  
29 Dr. Julián de la Torre Cisneros conceived of the study. Dr. Rafael León  
30 López, Dr. Laura Limia Pérez and Antonio Miguel Luque Pineda  
31 collaborated in the protocol design. IMIBIC provided statistical  
32 expertise in clinical trial design and it will conduct the statistical  
33 analysis. Dr. Julián de la Torre Cisneros also contributed to refinement  
34 of the study protocol and approved the final manuscript.  
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41 5b FIBICO (Fundación para la Investigación Biomédica de Córdoba) Pages 1  
42 Hospital Universitario Reina Sofía - Edificio IMIBIC and 10  
43 Avenida Menéndez Pidal s/n – C.P. 14004 (Córdoba, SPAIN)  
44 Contact name: Mr. Antonio Miguel Luque Pineda  
45 Phone: +34 671 59 60 70  
46 E-mail: uicec@imibic.org  
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50  
51 5c The funder Ministry of Health and Families, Regional Government of n/a  
52 Andalusia had no role in the design of this study and will not have any  
53 role during its execution, analyses, interpretation of the data or  
54 decision to submit results.  
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4 5d **Coordinating investigator (see section 5a)**

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- Design of the study protocol
- Preparation and revision of new amendments to the protocol
- Design of the CRF
- Publication of study reports

12 **Trial management and monitoring**

13 FIBICO (Fundación para la Investigación Biomédica de Córdoba)

14 Clinical Research Unit

15 Edificio IMIBIC

16 Avenida Menéndez Pidal s/n – C.P. 14004 (Córdoba, SPAIN)

17 Phone: +34 671 59 60 70

18 E-mail: uicec@imibic.org

- Study planning
- Provide annual report to AEMPS [Spanish Agency of Medicines and Medical Products] and Ethics Committee
- SAE & SUSAR reporting
- Responsible for trial master file
- Budget administration and contractual issues with sites
- Advice for principal investigators
- Assistance with international review, board/independent ethics committee applications
- Data verification and monitoring

35 **Pharmacovigilance service (SCReN partner)**

36 Unidad de Investigación Clínica y Ensayos Clínicos UICEC-HUVR Dr.

37 Clara M. Rosso Fernández, Dr. M Ángeles Lobo Acosta Hospital

38 Universitario Virgen del Rocío

39 Edificio de Documentación Clínica

40 Avenida Manuel Siurot s/n - C.P. 41013 (Seville, SPAIN)

41 Phone: 955 013 414 - 955 012 144 Fax: 954 232 992

42 E-mail: pv\_saricor@scren.es

- SAE & SUSAR review and reconciliation
- Safety reports design
- Advise to Data Safety Monitoring Committee

**Data Safety Monitoring Committee**

Independent physicians will monitor the available data concerning safety and effectiveness of the treatment and they will meet on a regular basis to discuss about the risk/benefit balance and the conduction of the trial.

**Data manager (IMIBIC crew)**

- Maintenance of trial IT system
- Data verification

**Principal investigators**

In each participating centre a principal investigator is identified, to be responsible for identification, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol and SmPC.

Background and rationale	6a	<p>It has been suggested that IL-6 blockade may constitute a novel therapeutic strategy for cytokine release syndrome and systemic inflammatory response syndrome in sepsis, macrophage activation syndrome and haemophagocytic lymphohistiocytosis.</p> <p>Although currently approved for the treatment of rheumatoid arthritis, sarilumab, an interleukin-6 (IL-6) receptor antibody, is being investigated for its ability to reduce the overactive inflammatory immune response associated with COVID-19. This is based on evidence of markedly elevated levels of IL-6 in patients who develop severely acute respiratory distress syndrome.</p> <p>The research question of this trial is: Does early treatment with sarilumab reduce the evolution to respiratory distress syndrome that requires ventilatory support in hospitalized patients with COVID-19?</p>	Pages 2 and 3
	6b	<p>At the time the protocol has been written, and in the absence of scientific evidence, best available therapy (BAT) is considered any combination of drugs authorized in Spain for this indication. This variable will be taken into account in the efficacy analysis.</p> <p>The BAT will include any combination of drugs included in the current protocol of the Spanish Ministry of Health (<a href="https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasA ctu al/nCov-China/documentos.htm">https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasA ctu al/nCov-China/documentos.htm</a>) and complementary notes issued by the Spanish Agency of Medicines and Medical Products.</p>	Page 3

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4 Objectives 7 **Research hypothesis** Page 3  
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7 It is hypothesised that IL-6 might play a key role in the cytokine release  
8 syndrome in SARS-CoV-2 patients with pneumonia, and that blockade  
9 of IL-6 would be a suitable therapeutic target for these patients.  
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12 **Primary objective**  
13 Decrease cases of ARDS in adults requiring HFNO or either non-  
14 invasive or invasive mechanical ventilation.  
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16

17 **Secondary objectives**  
18

- 19 • To reduce crude mortality at 28 days  
20 • To reduce the time (in days) to clinical improvement  
21 • To reduce the time (in days) until improvement in oxygenation for at  
22 least 48 hours  
23 • To reduce the proportion of patients who require invasive mechanical  
24 ventilation  
25 • To study the effect of the drug on the negativization of the PCR to  
26 COVID-19  
27 • To study the effect of the drug on the profile of cytokines  
28 • To study the safety of the experimental drug  
29

30 Trial design 8 Phase II, open-label, randomised, multicentre, controlled, three parallel Page 3  
31 groups clinical trial. The primary endpoint is crude mortality at 28 days.  
32 Randomization will be performed as block randomization with a 1:1:1  
33 allocation.  
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36 **Methods: Participants, interventions, and outcomes**  
37

38 Study setting 9 Ten university hospitals located in Andalusia (South of Spain) will Page 3  
39 participate in the trial, with sufficient incidence at the community level.  
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42 The site selected are sufficiently distant from each other so that almost  
43 all Andalusia Community population is covered (8.460.000 inhabitants).  
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Pages 4  
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Eligibility  
criteria

10 **Inclusion criteria**

1. Age  $\geq 18$  years and  $<75$  years
2. Hospitalisation with COVID-19 (positive PCR in a respiratory tract sample) in absence of respiratory distress (defined as requiring high-flow nasal oxygen or mechanical ventilation).
3. Interstitial pneumonia confirmed by chest radiography or CT scan
4. IL-6 levels  $>40$  pg/ml. In the absence of IL-6, D-Dimer (DD)  $>1500$  or  $>1000$  if progressive increments between at least 2 determinations after admission are documented.
5. In women of childbearing age, a negative pregnancy test
6. Signed informed consent

Exclusion criteria

1. SOFA score  $>6$  points
2. Patient who, in the researcher's opinion, is not subsidiary of invasive mechanical ventilation.
3. Neutrophil count  $<2 \times 10^3/\mu\text{L}$
4. Platelet count  $<100 \times 10^3/\mu\text{L}$
5. ALT or AST levels  $>5$  times the upper limit of normality
6. Severe renal failure ( $\text{CrCl} <30 \text{ ml/min}$ )
7. Active bacterial infection
8. Active tuberculosis or history of not completing treatment against tuberculosis
9. Antecedents of diverticulitis
10. Hypersensitivity to sarilumab or its excipients
11. Treatment with TNF antagonists
12. Treatment with anti-IL6 in the previous 30 days
13. Chronic treatment ( $>1$  month) with corticosteroids at doses  $>0.5 \text{ mg/kg/day}$  of prednisone or equivalent. Topical and inhaled corticosteroids are acceptable.
14. Concomitant treatment with immunomodulators, including vitamin D or statins. Macrolides such as azithromycin are acceptable.
15. Patients on immunosuppressive treatment for any cause
16. HIV-infected patients with  $\text{CD4} <200/\text{mm}^3$
17. Past or current history of autoimmune disease
18. Patients receiving immunomodulatory antibody therapy, including immunoglobulins
19. Participation in any clinical trial that evaluated any investigational product in the last 3 months or less than 5 half-lives of the product under investigation
20. Pregnancy
21. Any other condition that, in clinical judgement, prevents the patient's adherence to the protocol

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4 Interventions 11a Following hospital admission and before performing any study activity, Pages 7  
5 the participating subjects must sign the informed consent form. To and 8  
6 participate in the study, patients must meet all of the inclusion criteria  
7 and none of the exclusion criteria.  
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10 Once the selection criteria are confirmed the patient will be randomized  
11 and allocated to one of the following treatment groups:  
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- 14 1. Control group: 40 patients will receive the best available  
15 therapy (BAT) for a maximum of 14 days.  
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18 At the time the protocol has been written, and in the absence of  
19 scientific evidence, BAT is considered any combination of drugs  
20 authorized in Spain for this indication. This variable will be taken into  
21 account in the efficacy analysis.  
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- 24 2. Treatment group 1 (T1): 40 patients will receive BAT for a  
25 maximum of 14 days + 200 mg of sarilumab subcutaneously  
26 (single dose).  
27  
28 3. Treatment group 2 (T2): 40 patients will receive BAT for a  
29 maximum of 14 days + 400 mg of sarilumab subcutaneously  
30 (single dose).  
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33 The total expected duration of each patient in the study is up to 28  
34 days (or until the last day they are hospitalized, if less than 28 days).  
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37 Every patient will be visited on days 5, 10, 14, 21 and 28 after  
38 randomization. These visits may be made at home if the patient has  
39 been discharged. An evaluation of the clinical improvement will be  
40 made daily according to the ordinal scale of 7 points of gravity, the  
41 measurement of axillary temperature, oxygen saturation (or blood gas  
42 with PpO<sub>2</sub>) and oxygen therapy or respiratory support. These values  
43 will be collected in the CRD on planned visits.  
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4 11b Patients may withdraw from the study at any time, for any reason and Page 5  
5 without prejudice to future medical treatment. Patients who do not  
6 comply with the study procedure or have not been followed up will be  
7 considered a study "withdrawal". The reasons for withdrawal will be  
8 examined in full accordance with bioethical principles regarding the  
9 guarantee of patients' rights. The criteria for withdrawal from the study  
10 are described below.  
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14 1. Patient request  
15 2. Violation or deviation from the protocol (e.g. breach of administration  
16 of treatment, need for prohibited treatment).  
17 3. Researchers decision, based on clinical reasons  
18 4. Administrative decision of the investigators, promoter or regulatory  
19 authorities  
20 5. Loss to follow-up  
21 6. Suspected unexpected serious adverse reaction (SUSAR)  
22 7. Serious adverse event (SAE) that at the discretion of the promoter or  
23 investigator is not acceptable.  
24 8. Any adverse event considered intolerable by either the patient or the  
25 investigator  
26 9. Pregnancy  
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32 The toxicity will come given by the adverse effects:  
33 - Very common (may affect more than 1 in 10 people): low white blood  
34 cell count based on blood tests.  
35 - Frequent (may affect up to 1 in 10 people):  
36     • Sinus or throat infections, congestion, runny nose, and sore throat  
37 (upper respiratory tract infection).  
38     • Infection in the urinary tract.  
39     • Fevers (oral herpes).  
40     • Low platelet count based on blood tests.  
41     • High cholesterol, high triglycerides according to blood tests.  
42     • Abnormal liver function tests.  
43     • Injection site reactions (including redness and itching).  
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47 11c The participating subjects will be hospitalized and the site investigators n/a  
48 will be responsible of the administration of the study treatment.  
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51 11d During the study, concomitant treatments used in clinical practice are Page 7  
52 allowed, as well as BAT. The BAT will include any combination of  
53 drugs included in the current protocol of the Spanish Ministry of Health  
54 (<https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasA>  
55 ctu al/nCov-China/documentos.htm).  
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4 Outcomes 12 **Primary outcome measure:** Proportion of patients requiring or time Page 6  
5 (in days) to that is required:

- 6 - High flow nasal oxygenation.  
7 - BiPAP type non-invasive mechanical ventilation.  
8 - Non-invasive mechanical ventilation type CPAP.  
9 - Invasive mechanical ventilation.

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13 **Secondary outcomes measure:**

- 14 - All-cause (crude) mortality at day 28.  
15 - Time (in days) to clinical improvement, defined as mean change or  
16 time in days from randomization to any of the following criteria: (i)  
17 improvement of two points in the ordinal scale of 7 points of gravity or,  
18 (ii) discharge from the hospital alive. The criteria that is reached before.  
19 The 7 point gravity scale includes the following categories:

- 20  
21 1 - Not hospitalized with normal activity  
22 2 - Not hospitalized but unable to have normal activity  
23 3 - Hospitalized, without requiring oxygen supplementation 4 -  
24 Hospitalized, requiring oxygen supplementation  
25 5 - Hospitalized, requiring high flow nasal oxygenation, non-  
26 invasive mechanical ventilation or both  
27 6 - Hospitalized requiring ECMO, invasive mechanical ventilation  
28 or both  
29 7 – Death

- 30  
31 - Time (in days) until improvement in oxygenation for at least 48 hours:  
32 • Time to verify an increase in the SpO<sub>2</sub> / FiO<sub>2</sub> ratio with respect  
33 to the worst SpO<sub>2</sub> / FiO<sub>2</sub> prior to treatment with Sarilumab and  
34 stratified according to levels of IL-6 or DD.  
35 • Time until the absence of oxygen need to maintain a saturation  
36 in ambient air  $\geq$  93%.  
37 • Number of days in need of supplemental oxygen.  
38 - Proportion of patients requiring invasive mechanical ventilation.  
39 - Proportion of patients who have negative COVID-19 PCR at each  
40 visit.  
41 - Mean of serum cytokine levels: the panel of cytokines to quantify; IL1-  
42  $\alpha$ , IL1- $\beta$ , IL6, IL8, IL10, IL12, IL18, IL38, INF $\gamma$ , TNF $\alpha$ , CCL2, CCL3,  
43 CCL4, MIF and PAI-1.

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52 **Security outcomes measure**

- 53 - Incidence of adverse events related to medication and its  
54 administration.  
55 - Incidence in the appearance of serious bacterial, fungal or  
56 opportunistic infections.  
57 - Incidence of perforation of the gastrointestinal tract.

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4     - Mean leukocyte and neutrophil count.  
5     - Average haemoglobin levels.  
6     - Average platelet count.  
7     - Average levels of creatinemia.  
8     - Average bilirubin levels.  
9     - Average ALT and AST levels.  
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13     The following demographics and clinical information will be collected  
14     from all patients: age, sex, weight, height, body mass index (BMI),  
15     comorbidities, previous treatment, history of the current disease,  
16     respiratory rate (bpm), basal oxygen saturation (%), arterial pO<sub>2</sub> (mm  
17     Hg), pO<sub>2</sub>/FiO<sub>2</sub> rate, oxygen saturation/FiO<sub>2</sub> rate, blood pressure  
18     (mmHg), heart rate (bpm), consciousness level, temperature (°C),  
19     clinical improvement, organ failure assessment score (SOFA),  
20     microbiological test, analytical parameters (haematimetry, glucose,  
21     creatinine, AST, ALT, C-reactive protein, albumin, LDH, ferritin,  
22     troponin I, protein kinase, procalcitonin, lipid profile, IL-6, D-dimer,  
23     prothrombin time, INR).  
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31     All concomitant medication and adverse events will be recorded and  
32     monitored in accordance with regulatory procedures.  
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Participant timeline	13	SARS-CoV-2019 in nasopharyngeal swab and a panel of cytokines (IL1- $\alpha$ , IL1- $\beta$ , IL6, IL8, IL10, IL12, IL18, IL38, INF $\gamma$ , TNF $\alpha$ , CCL2, CCL3, CCL4, MIF y PAI-1) RAGE, Ang-2 and Protein C will be determined before randomisation and on days 5, 10, 14, 21 and 28.	Page 7 and 8
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38     The total expected duration of each patient in the study is up to 28  
39     days (or until the last day they are hospitalized, if less than 28 days):  
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45     Each patient will visit on days 5, 10, 14, 21 and 28 after randomization.  
46     These visits may be made at home if the patient has been discharged.  
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52     An assessment of clinical improvement will be made daily according to  
53     the ordinal scale of 7 points of gravity, axillary temperature  
54     measurement, oxygen saturation (or blood gas with PpO<sub>2</sub>) and oxygen  
55     therapy or respiratory support. These values will be collected in the  
56     CRF on planned visits.  
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See the table below.

Table 1. Chart of study procedures	STUDY PERIOD							
	BASELINE	Day 0	Day 1	Day 2 to 6	VISIT 1 Day 5	Day 6 to 9	VISIT 2 Day 10	Day 11 to 13
Recruitment								
Review of inclusion and exclusion criteria	X							
Informed consent	X							
Randomisation	X							
Baseline data, demographics and comorbidities*	X							
Clinical data								
Respiratory rate, saturation, applied oxygen (FiO <sub>2</sub> ) SpO <sub>2</sub> /FiO <sub>2</sub> ratio	X	X	X	X	X	X	X	X
Arterial pO <sub>2</sub> , pO <sub>2</sub> /FiO <sub>2</sub> ratio	X				X		X	X
SOFA score	X	X	X	X	X	X	X	X
7-point ordinal scale	X	X	X	X	X	X	X	X
Laboratory data								
PCR COVID-19 (nasopharyngeal swab)	X				X		X	X
Analytical parameters†	X				X		X	X
Samples for cytokine determination	X				X		X	X
Pregnancy test	X							
Drugs								
IM administration	X							
Interaction assessment, AB, SAB, USAB, AA, AAG	X	X	X	X	X	X	X	X
Concomitant medication record	X	X	X	X	X	X	X	X
Radiological tests								
Chest X-ray or CT scan	X							
Biological samples								
Samples for Biobank	X				X		X	X

\*Age, sex, weight, height, BMI, comorbidities, previous treatment (including therapeutic family; e.g. ACEI, ARB, history, BP (mm Hg), HR, level of consciousness, temperature (°C), National Early Warning Score (NEWS).

† Haematometry, glucose, creatinine, AST, ALT, C-reactive protein, albumin, LDH, ferritin, troponin I, protein test (at visit 0), lipid profile, interleukin-6, D-dimer, prothrombin time (PT%), INR.

Sample size 14 We have calculated an overall sample size of 120 patients, 40 patients for each arm, to detect a 30% reduction in the primary outcome with an alpha error of 0.05, a beta risk of 0.2 and assuming that the modified intention- to-treat population will be 90% of the randomised patients. Page 8

Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment 15 The enrolment will depend on the evolution of the pandemic in Spain. All COVID-19 teams in the participating sites are informed and involved. n/a

## Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence 16a Patients will be randomly assigned to one of the three treatment groups in a 1: 1: 1 ratio, using a random allocation list generated by a specific computer system embedded in the eCRF. Page 6 and 7

For randomization, patients will be stratified using basal oxygen saturation by breathing room air or pO<sub>2</sub> on arterial blood gas.

- According to pulse oximetry in ambient air <90% or pO<sub>2</sub> <60 mmHg.
- In case of not having the previous data to ambient air, the relation pO<sub>2</sub> / FiO<sub>2</sub> <250 will be used.

Allocation concealment mechanism	16b	The participating subjects will be randomized by a computerized system embedded in the electronic data capture and they will be allocated to one of the three treatment groups.	Page 6 and 7
	16c	Participants will be randomised using REDCAP, which is an online eCRF which allows central randomisation.	
		Allocation concealment will be ensured, as the service will not release the randomisation code until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed.	
Implementation	16c	All patients who give consent for participation and who fulfil the inclusion criteria will be randomized. Randomisation will be performed by the principal investigator or delegated staff.	Page 6 and 7
		In return, the allocation will be shown in the eCRF. The investigator will provide the randomization information to the pharmacist.	
Blinding (masking)	17a	Not applicable, as the trial is open-label.	n/a
	17b	Not applicable, as the trial is open-label.	n/a

### Methods: Data collection, management, and analysis

Data collection methods

18a The main variable is a variable related to the efficacy of the study drug to avoid progression to SARD and avoid the need for ICU admission.

Secondary variables are designed to measure efficiency and safety objectives.

### Training and certification plans

All the participating sites will be trained centrally in the study methods and requirements. The data to be collected and the procedures to be conducted at each visit will be reviewed in detail. Each of the data collection forms and the nature of the required information will be discussed in detail on an item by item basis.

Study coordinators and investigators will learn how to enter the information in the eCRF and how to communicate any Adverse Event or Reaction. Entering data forms, responding to data discrepancy queries and general information about obtaining research quality data will also be covered during the training session.

### Quality control of the collected data

Data entered in the eCRF will be reviewed and monitored by Clinical Research Associates from the IMIBIC Clinical Research Unit and the corresponding queries will be raised in case inconsistencies are found.

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4 18b The subjects will be recruited once they are hospitalized and they will n/a  
5 remain in the site until discharge.  
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8 The total expected duration of each patient in the study is up to 28  
9 days (or until the last day they are hospitalized, if less than 28 days).  
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11  
12 A subject will be considered to have completed the trial when they  
13 make the last scheduled visit.  
14  
15  
16 Patients can withdraw at any time throughout the study, for whatever  
17 reason and without prejudice to future medical treatment.  
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19  
20 The reasons for the withdrawal will be analysed with full compliance  
21 with the principles of Bioethics, in terms of guaranteeing the rights of  
22 patients and autonomous and informed decision.  
23  
24  
25 Although patients can withdraw without having to explain why, as soon  
26 as a patient has decided to do so, the researchers will try to establish  
27 contact with the subjects and establish that the patient's decision is an  
28 informed choice, as well as to check to what extent the patient may be  
29 willing to continue participating in the study on a limited basis, eg if  
30 they would be willing to continue to contact or be seen in order to  
31 obtain follow-up information.  
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4	Data management	19 Data collection	n/a
5		The collected data will be electronically entered by the investigator at	
6		every participating site via the eCRF platform. Original study forms will	
7		be entered and kept on file at the participating site.	
8			
9		Participant files are to be stored in numerical order and stored in a	
10		secure and accessible place and manner. Participant files will be	
11		maintained in storage for a period of 25 years after completion of the	
12		study.	
13			
14		Data integrity will be enforced through a variety of mechanisms.	
15		Referential data rules, valid values, range checks, and consistency	
16		checks against data already stored in the database will be supported.	
17			
18		Modifications to data written to the database will be documented	
19		through either the data change system or an inquiry system.	
20			
21		Data entered into the database will be retrievable for viewing through	
22		the data entry applications. The type of activity that an individual user	
23		may undertake is regulated by the privileges associated with his/her	
24		user identification code and password.	
25			
26		Additional errors will be detected by programs designed to detect	
27		missing data or specific errors in the data. These errors will be	
28		summarized along with detailed descriptions for each specific problem	
29		in Data Query Reports, which will be sent to the sites.	
30			
31			
32		The Study Coordinator who receives the queries will respond by	
33		checking the original forms for inconsistency, checking other sources	
34		to determine the correction, modifying the original (paper) form	
35		entering a response to the query.	
36			
37			
38		The Coordinating Center (IMIBIC Clinical Research Unit) and	
39		participating site personnel will be responsible for making appropriate	
40		corrections to the original paper forms whenever any data item is	
41		changed. Written documentation of changes will be available via	
42		electronic logs and audit trails.	
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4	Statistical	20a <b>Types of analysis</b>	Page 8 and
5	methods	The analyses will be performed on the population by modified intention	9
6		to treat. This includes all randomized patients to whom the drug or	
7		control is administered. Patients who die before administering the drug	
8		or those who are not administered for any other reason are excluded.	
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12		<b>Primary efficiency analysis</b>	
13		It will be performed based on the intention of treatment and will be	
14		measured by the proportion of patients requiring high-flow nasal	
15		oxygen / mechanical ventilation in the first 14 days. For this analysis,	
16		patients will be measured on day 14. The time in days until the end	
17		point is reached will be plotted on a Kaplan-Meier curve and compared	
18		using a Long Rank test. A univariate Cox regression analysis will be	
19		performed for the primary efficacy variable and	
20		They will represent the results in terms of Hazard Ratio with 95%	
21		confidence intervals.	
22			
23			
24		<b>Secondary efficiency analysis</b>	
25		CRUDE MORTALITY. Following the criteria of the primary efficacy	
26		analysis, mortality from any cause at 14 and 28 days will be analysed.	
27		For this 28-day analysis, the sample will be measured at 28 days,	
28		which will be the end point of the study.	
29		CLINICAL IMPROVEMENT. Following the criteria of the primary	
30		analysis, an analysis of the time in days to clinical improvement or	
31		mean change according to the 7-point ordinal scale will be performed.	
32		IMPROVEMENT OF OXYGENATION. Following the criteria of the	
33		primary analysis, an analysis of the time in days until oxygenation will	
34		be performed.	
35		NEED FOR INVASIVE MECHANICAL VENTILATION. The proportion	
36		of	
37		patients requiring invasive mechanical ventilation in each arm will be	
38		compared.	
39		NEGATIVIZATION OF THE PCR TO COVID-19. The proportion of	
40		patients who have negative PCR in each arm of the trial will be	
41		compared. CYTOKIN LEVELS. The mean levels of each cytokine in	
42		each arm of the study will be compared.	
43		SECURITY. A description of the adverse events will be made for each	
44		arm of the study and the proportion of the same in each arm of the trial	
45		will be compared.	
46		20b The sponsor will perform an Interim analysis of the data collected when	n/a
47		it has been reached half the sample size (60 recruited subjects) in	
48		order to assess safety and efficacy of research treatment.	
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4 20c **Security dataset**

5 The safety dataset covers all patients included in the study who have n/a  
6 received at least one dose of any study medication.  
7  
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9 **Modified intention-to-treat population**

10 The modified intention-to-treat population is defined as all randomized  
11 patients to whom the drug or control is administered. Patients who die  
12 before administering the drug or those who are not administered for  
13 any other reason are excluded.  
14  
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16 **Methods: Monitoring**

17 Data monitoring 21a A Data Safety Monitoring Committee has been established and it is n/a  
18 independent of the sponsor. During the period of recruitment to the  
19 trial, monthly analyses will be provided to the Data Safety Monitoring  
20 Committee, together with any other analyses that the committee may  
21 request. The Data Safety Monitoring Committee will advise the sponsor  
22 about the study conduction, protocol modifications and/or trial halt if  
23 needed.  
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26 21b Interim analysis n/a  
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29 The sponsor will perform an Interim analysis of the data collected when  
30 it has been reached half the sample size (60 recruited subjects) in  
31 order to assess safety and efficacy of research treatment.  
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34 The results of this analysis will be communicated to the participating  
35 researchers. In the event of detection of a significant lack of efficacy or  
36 an unacceptable risk-benefit balance, the sponsor will communicate  
37 this circumstance to the health authorities, Ethics Committee and local  
38 authorities and proceed to the premature termination of the study,  
39 according to what is indicated in the Royal Decree 1090/2015.  
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4 Harms 22 The principal investigator will be responsible for the detection and Page 7  
5 documentation, throughout the study, of adverse events.  
6  
7  
8 It is the responsibility of the principal investigator to report all events in  
9 the eCRF, both observed by him/her and spontaneously reported by  
10 the participants, regardless of the relationship with the investigational  
11 medication.  
12  
13  
14 All the events should be reported during all phases of the study and  
15 followed up until resolution or until an adequate explanation is found,  
16 even if the patient has completed study treatment. In addition, reports  
17 will be made periodically on the events that occurred during the study,  
18 including evaluation of causality, severity and intensity.  
19  
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21  
22 Patients will be informed of possible adverse reactions of the  
23 investigational medication through the Patient Information Sheet, as  
24 well as their commitment to report any adverse event they experience.  
25 They will be given a way to contact the study researchers for this  
26 purpose. At all study visits, patients will be questioned about the  
27 presence of new events or about the evolution of pre-existing ones.  
28  
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31 All events that are severe and manifest during the course of the study,  
32 regardless of the treatment group in which they occur, the sponsor  
33 must be notified in the course one working day (24 hours) from the  
34 time the investigator is aware of the event.  
35  
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37 The safety information will be recorded in the eCRF and it will be  
38 provided to the Data Safety Monitoring Committee for its analysis.  
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## Auditing

- 23 The clinical trial will be monitored by the IMIBIC Clinical Research Unit Page 6 staff. According to the agreed Trial Monitoring Plan, the participating sites will be regularly monitored on-site and online by the CRA.

The primary objectives of the CRA during the on-site visits are to educate, support and solve problems. The monitors will discuss the protocol in detail and identify and clarify any areas of weakness. At the initiation of the trial, the monitor will conduct a tutorial on the eCRF. The investigators will practice entering data so that the monitors can confirm that they are proficient in all aspects of data entry, query response, and communication with the CRA. They will audit the overall quality and completeness of the data, examine source documents, interview investigators and coordinators, and confirm that the clinical site has complied with the requirements of the protocol. The monitors will verify that all adverse events were documented in the correct format, and are consistent with protocol definition.

The monitors will review the source documents as needed, to determine whether the data reported in the electronic data capture system are complete and accurate. Source documents are defined as medical charts, associated reports and records including initial hospital admission report.

The monitors will confirm that the regulatory binder is complete and that all associated documents are up to date. The regulatory binder should include the protocol and informed consent (all revisions), Ethics Committee/Health Authorities approvals for all of the above documents, Ethics Committee/Health Authorities correspondence, case report form hardcopy templates, investigator's agreements, etc.

Scheduling monitoring visits will be a function of patient enrolment, site status and other commitments. The CRA will notify the site in writing at least two weeks prior to a scheduled visit. The investigators must be available to meet with the monitors. Although notification of the visits will include the list of patients scheduled to be reviewed, the monitors reserve the right to review additional patients if possible.

If a problem is identified during the visit, the monitor will assist the site in resolving the issues. Some issues may require input from the Data Safety Monitoring Committee, Sponsor or the coordinating investigator.

The focus of the visit/electronic monitoring will be on source document review and confirmation of adverse events. The monitor will verify the following all the variables for all patients, eg. signed informed consent, eligibility criteria, date of randomization, treatment assignment, adverse events and endpoints.

**Ethics and dissemination**

- Research ethics approval 24 The protocol and the informed consent form, as well as other required documents will be reviewed and approved by the sponsor and the applicable Ethics Committee/Health Authority with respect to scientific content and compliance with applicable research and human subjects regulations.
- The protocol, informed consent form, participant education and recruitment materials, and other requested documents—and any subsequent modifications — also will be reviewed and approved by the Ethics Committee/Health Authority.
- Subsequent to initial review and approval, the Ethics Committee/ Health Authority will review the protocol annually. The Investigator will make safety and progress reports to the Ethics Committee/ Health Authority at least annually and within twelve months of study termination or completion at his/her site. These reports will include the total number of participants enrolled y their status within the trial, as well as a review of safety and/or efficacy.
- Protocol amendments 25 Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol.
- Such amendment will be agreed upon by the sponsor and must be submitted for approval to the Ethics Committee/Health Authority prior to implementation in accordance with local regulations.
- Administrative changes of the protocol that are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed by the sponsor and will be documented in a memorandum. The Ethics Committee/Health Authority may be notified of administrative changes in the next protocol substantial amendment.
- Consent or assent 26a The site principal investigator or delegated subinvestigator will introduce the trial to patients. The site principal investigator or delegated subinvestigator will discuss the trial with patients in light of the information provided in the information sheets. Patients will then be able to have an informed discussion with the participating investigator. The site principal investigator or delegated subinvestigator will obtain written consent from patients willing to participate in the trial and file it in the site binder.

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5	26b	As biological samples would be collected, an additional informed	Pages 7
6		consent form will be provided by the site principal investigator or	and 9
7		delegated subinvestigator to the trial to patients. The consent	
8		procedure will be similar to the one explained in point 26a.	
9			
10	Confidentialit	27 All study-related information will be stored securely at the study site. All	Page 6 and
11	y	participant information will be stored in locked file cabinets in areas	7
12		with limited access. All laboratory specimens, reports, data collection,	
13		process, and administrative forms will be identified by a coded ID [XX-	
14		YY coding] number only to maintain participant confidentiality. All	
15		records that contain names or other personal identifiers, such as	
16		locator forms and informed consent forms, will be stored separately	
17		from study records identified by code number. All local databases will	
18		be secured with password-protected access systems. Forms, lists,	
19		logbooks, appointment books, and any other listings that link	
20		participant ID numbers to other identifying information will be stored in	
21		a separate, locked file in an area with limited access.	
22			
23		All test results will be kept strictly confidential, all counselling and blood	
24		draws will be conducted in private rooms, and study staff will be	
25		required to preserve the confidentiality of all participants.	
26			
27		Participants' study information will not be released outside of the study	
28		without the written permission of the participant, except as necessary	
29		for monitoring, audit and or inspections by regulatory authorities or for	
30		safety reasons.	
31			
32		The sponsor guarantees that the data will be processed with security	
33		measures established in compliance with REGULATION (EU)	
34		2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE	
35		COUNCIL of April 27,	
36		2016 regarding the protection of natural persons in what Regarding the	
37		processing of personal data and the free circulation of these data and	
38		by which Directive 95/46 / EC (General Data Protection Regulation)	
39		and the Organic Law are repealed 3/2018, of December 5, on Personal	
40		Data Protection and guarantee of rights digital. By signing the informed	
41		consent, the participant agrees with this use of the study data. Said	
42		authorization does not have an expiration date. The participant may	
43		withdraw it at any time, but must do so in writing.	
44			
45	Declaration	28 The authors declare no conflicts of interest.	Page 10
46	of interests		
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1	Access to data	29	All Principal Investigators will be given access to the cleaned data sets. Project data sets will be housed on IMIBIC servers they will be accessible by password. Project Principal Investigators will have direct access to their own site's data sets, and will have access to other sites data by request.	Pages 1 and 9
2			To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.	
3			Once the trial has ended and the data has been collected, analysed and published, the anonymized database will be available to other researchers upon request.	
4	Ancillary and post-trial care	30	Patients that are enrolled into the study are covered by indemnity for non-negligent harm through a specific insurance contracted by the sponsor.	n/a
5			Should this study provide evidence of the effectiveness of Sarilumab, it will be critical to provide access to the effective product(s) to study participants in a timely manner.	
6	Dissemination policy	31a	Once the study has been completed and the statistical report has been carried out, the investigating team shall prepare the final report of the study to be submitted to Ethics Committee/Health Authority. This final report will be the basis for the preparation of the manuscripts to be published in medical journals.	Pages 1 and 9
7		31b	The conditions of publication are in accordance with Royal Decree 1090/2015 of 4 December concerning the regulation of clinical trials of medicinal products in Spain, multicentre clinical trials only require the approval of a single medicinal research ethics committee (reference MREC) and of the Spanish Agency of Medicines and Medical Products (AEMPS) and the Spanish Register of Clinical Studies in article 42.	Pages 1 and 9
8		31c	Once the trial has ended and the data has been collected, analysed and published, the anonymized database, the full protocol, statistical code and other materials will be available to other researchers upon request to IMIBIC Clinical Research Unit (uicec@imibic.org).	n/a

## Appendices

Informed consent materials	32	See attached forms (General informed consent and Biological Samples informed consent).	n/a
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4 Biological specimens 33 The samples will be stored locally (frozen at -80oC) until they are sent Pages 7  
5 to the Biobank of the Reina Sofía University Hospital in Córdoba. and 8  
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The cytokines will be quantified centrally using the CUSTOM KITS MILIPLEX® MAP (Merk-Millipore) following the protocol provided by the manufacturer. Samples will be purchased on a Luminex LABScan 200 platform, using xPONENT vs. 2.1 as acquisition and analysis software. The cytokine panel to be quantified will be the following: IL1-A, IL1-A, IL6, IL8, IL10, IL12, IL18, IL38, INF $\gamma$ , TNF, CCL2, CCL3, CCL4, MIF and PAI- 1.

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons [“Attribution-NonCommercial-NoDerivs 3.0 Unported” license](#).

**Appendix 1: Informed Consent Forms (General and Biological Samples)****HOJA DE INFORMACIÓN AL PARTICIPANTE**

<b>Título del Estudio</b>	Ensayo clínico de Sarilumab en adultos hospitalizados con COVID-19 que presentan síndrome de liberación de citoquinas
<b>Código del estudio</b>	SARICOR
<b>Promotor</b>	Fundación para la Investigación Biomédica de Córdoba
<b>Investigador principal</b>	
<b>Centro</b>	

**Introducción**

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por un Comité de Ética de la Investigación con medicamentos y por la Agencia Española de Medicamentos y Productos Sanitarios, de acuerdo a la legislación vigente, el Real Decreto 1090/2015 de 4 de diciembre y el Reglamento Europeo 536/2014 de 16 de abril, por los que se regulan los ensayos clínicos con medicamentos.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda **decidir si acepta o no participar en este estudio**. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir. Además, puede consultar con las personas que considere oportuno.

**Participación voluntaria**

Le invitamos a participar en el estudio porque presenta un proceso infeccioso respiratorio por SARS-CoV-2 (COVID19). **Debe saber que su participación en este estudio es voluntaria y que puede decidir NO participar**. Si decide participar, puede cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su atención sanitaria.

**Objetivo del estudio**

El objetivo principal del estudio es saber la eficacia y la seguridad de la administración precoz de Sarilumab en pacientes con infección respiratoria por SARS-CoV- 2 (COVID19) para evitar el

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deterioro de la función pulmonar y la necesidad de requerir soporte respiratorio mediante diferentes métodos habitualmente utilizados en esta situación.

## Descripción del estudio

Este estudio pretende incluir un total de 120 participantes con alto riesgo de que su función pulmonar se deteriore y precisen de dispositivos para ayudar a su respiración.

La literatura actual recoge un grupo de pacientes que por sus características clínicas y/o analíticas presentan mayor probabilidad de empeorar desde el punto de vista respiratorio y pueden necesitar mayor soporte respiratorio, incluso requerir ingreso en las Unidades de Cuidados Intensivos para ser intubados.

El SARS-CoV-2 (COVID19) es un coronavirus perteneciente a una extensa familia de virus que pueden causar enfermedades tanto en animales como en humanos. En los humanos, se sabe que varios coronavirus causan infecciones respiratorias que pueden ir desde el resfriado común hasta enfermedades más graves. El coronavirus que se ha descubierto más recientemente causa la enfermedad COVID-19.

Los síntomas más comunes de la COVID-19 son fiebre, cansancio y tos seca. Algunos pacientes pueden presentar dolores, congestión nasal, rinorrea (emisión abundante de líquido por la nariz, generalmente debido a un aumento de la secreción de mucosidad nasal), dolor de garganta o diarrea. Estos síntomas suelen ser leves y aparecen de forma gradual. Algunas personas se infectan pero no desarrollan ningún síntoma y no se encuentran mal. La mayoría de las personas (alrededor del 80%) se recupera de la enfermedad sin necesidad de realizar ningún tratamiento especial. Alrededor de 1 de cada 6 personas que contraen la COVID-19 desarrolla una enfermedad grave y tiene dificultad para respirar. Las personas mayores y las que padecen patologías subyacentes, como hipertensión arterial, problemas cardiacos o diabetes, tienen más probabilidades de desarrollar una enfermedad grave. En torno al 2% de las personas que han contraído la enfermedad han muerto.

El fármaco que se quiere estudiar se llama Sarilumab, el cual se administra mediante inyección subcutánea (por debajo de la piel). No se conoce si Sarilumab es útil en la situación que le describimos ni tampoco la dosis más apropiada, por eso queremos estudiar la eficacia y seguridad de dos dosis del fármaco (200 mg o 400 mg) conjuntamente con la mejor terapia disponible. Este estudio plantea comparar 3 posibilidades de tratamiento:

- a) Cuarenta pacientes recibirán la mejor terapia disponible.
- b) Cuarenta pacientes recibirán la mejor terapia disponible más Sarilumab a una dosis de 200 miligramos.
- c) Cuarenta pacientes recibirán la mejor terapia disponible más Sarilumab a una dosis de 400 miligramos.

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5 El procedimiento de asignación a uno de los tres grupos del estudio se realizará al azar. La  
6 probabilidad de que usted sea asignado a cualquiera de los tres grupos será de una entre tres o del  
7 33%.

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9  
10 En ningún caso usted dejará de estar tratado con los medicamentos habitualmente utilizados.  
11 Si usted decide no participar en este estudio es posible que usted reciba un fármaco similar pero  
12 más tarde, cuando el deterioro respiratorio ya ha sido establecido. Participando en este estudio  
13 usted tiene la posibilidad de recibirla antes para estudiar si evita ese deterioro.

## 17 18 Actividad del estudio

19  
20 Si decide participar en este estudio le haremos un seguimiento diario desde el día que firme  
21 el consentimiento informado hasta el día 28 de su inclusión en el estudio o hasta el último día que  
22 esté hospitalizado, lo que ocurra antes.

23  
24  
25 Evaluaremos diariamente su evolución clínica. En los días 0, 5, 10, 14, 21 y 28 (o hasta el  
26 último día que esté hospitalizado) le realizaremos un frotis nasofaríngeo para estudiar si continúa  
27 teniendo el virus. Estas muestras se seguirán tomando aunque alguna de ellas fuera negativa.

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29  
30 También en los días 0, 5, 10, 14, 21 y 28 (o hasta el último día que esté hospitalizado) se le  
31 extraerá un tubo con 9 ml de sangre que será almacenada para posteriores estudios inmunológicos.  
32 Dependiendo de cómo monitorice la replicación de dicho virus su centro, es posible que se le precise  
33 extraer también un tubo con 6 ml de sangre más, para saber si el virus está replicando.

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35  
36 El calendario de las visitas, independientemente del grupo al que sea asignado, es el  
37 siguiente:

	Visita basal Día 0	Visita 1 (día 1) hasta visita 5 (día 28 o hasta último día hospitalizado)
Consentimiento Informado	X	
Tratamiento	X	
Historia clínica / Exploración física	X	X
Analítica	X	X <sup>1</sup>
Obtención de frotis nasofaríngeo y de muestra de sangre		X <sup>1</sup>

57  
58 1 = en las visitas 5, 10, 14, 21 y 28 (o hasta el último día que esté hospitalizado)

#### Riesgos y molestias derivados de su participación en el estudio

Sarilumab es un medicamento ya aprobado y comercializado para el tratamiento de la artritis reumatoide avanzada.

Las reacciones adversas más frecuentemente notificadas con el tratamiento con Sarilumab son: disminución anormal de los neutrófilos y las plaquetas, aumento de las enzimas hepáticas, enrojecimiento en el lugar de la inyección, infecciones del tracto respiratorio superior e infecciones del tracto urinario.

Los riesgos de sufrir algún efecto no deseado con el uso de Sarilumab son: 1 de cada 10 pacientes sufren neutropenia (disminución de los neutrófilos en la sangre), 1 de cada 100 pacientes sufren trombocitopenia (disminución de las plaquetas en la sangre), infección del tracto respiratorio superior, infección del tracto urinario, nasofaringitis (resfriado), herpes oral, hipercolesterolemia (colesterol alto), hipertrigliceridemia (triglicéridos altos), enzimas hepáticas elevadas, enrojecimiento en el lugar de la inyección y picor en el lugar de la inyección.

Los resultados de los estudios disponibles no permiten establecer diferencias entre Sarilumab y otros fármacos biológicos, incluido Tocilizumab. Si usted no participa en el estudio usted podría recibir Tocilizumab por práctica clínica una vez que su función respiratoria se haya deteriorado.

Para conocer más sobre los posibles efectos no deseados de estos medicamentos, consulte al médico de este estudio.

Como riesgo derivado de la extracción de sangre puede producirse un pequeño hematoma, puede haber dolor local, hemorragia y muy excepcionalmente, puede producirse infección en el punto donde se extrae la sangre.

Como participante en el estudio tiene la responsabilidad de cumplir todas las visitas y actividades del estudio. También deberá notificar cualquier evento que le suceda o cambios en la medicación en caso de urgencia, ya que no podrá modificarla por su cuenta ni tomarla junto a "plantas medicinales" sin consultar antes con el médico del estudio.

#### Potenciales beneficios

Si demostramos la hipótesis de este estudio, usted habrá contribuido a evitar el deterioro de la función pulmonar por COVID-19 en otros pacientes que, como usted, padecen una infección respiratoria con factores de riesgo para mala evolución y necesidad de oxigenación a alto flujo o ventilación mecánica tanto de forma invasiva como no invasiva. Esto evitará medidas más agresivas de manejo de su función respiratoria, el ingreso en la Unidad de Cuidados Intensivos y la prolongación de la estancia hospitalaria.

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3 Es posible que usted no obtenga ningún beneficio adicional para su salud por participar en  
4 este estudio. Sin embargo, los datos obtenidos pueden resultar de utilidad para futuros pacientes que  
5 se encuentren en su misma situación.  
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10 **Advertencia relativa al embarazo**  
11

12 Las mujeres en edad fértil deben evitar un embarazo mediante el uso de métodos  
13 anticonceptivos eficaces durante y hasta tres meses después del tratamiento.  
14  
15

16 No hay datos disponibles del efecto de Sarilumab sobre la fertilidad humana. Los estudios  
17 en animales mostraron que no se producía deterioro de la fertilidad ni en los machos ni en las  
18 hembras.  
19  
20

21 No hay datos o estos son limitados relativos al uso de Sarilumab en mujeres embarazadas.  
22 Los estudios en animales no sugieren efectos perjudiciales directos ni indirectos en términos de  
23 toxicidad para la reproducción.  
24  
25

26 Se desconoce si Sarilumab se excreta en la leche materna o si se absorbe de forma  
27 sistemática después de la ingestión. No se ha estudiado la excreción de Sarilumab en la leche en  
28 animales.  
29  
30

31 Dado que las inmunoglobulinas G1 se excretan en la leche humana, se debe decidir si es  
32 necesario interrumpir la lactancia o interrumpir el tratamiento con Sarilumab teniendo en cuenta el  
33 beneficio de la lactancia para el niño y el beneficio del tratamiento para la madre.  
34  
35

36 En caso de producirse un embarazo durante su participación en el estudio debe informar a  
37 su médico de inmediato para recibir la asistencia médica adecuada. En caso de producirse un  
38 embarazo, se solicitará mediante un consentimiento específico la recogida de datos del mismo y de  
39 datos de salud del bebé hasta 3 meses después del parto.  
40  
41

42 Los datos recopilados sobre usted y su bebé serán tratados por el promotor del estudio de  
43 acuerdo a la normativa de protección de datos personales vigente (consulte el apartado “Protección  
44 de datos personales” para más información).  
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## Tratamientos alternativos

En la actualidad, algunos de los tratamientos disponibles son moléculas de nuevo desarrollo y otras son usos nuevos de medicamentos ya autorizados en otras indicaciones.

Aunque existen numerosos ensayos clínicos en marcha, no existe por el momento evidencia procedente de ensayos clínicos controlados que permitan recomendar un tratamiento específico para SARS-CoV-2. En estos momentos, se están poniendo en marcha diversos ensayos clínicos en España para el tratamiento de la infección respiratoria por SARS-CoV-2.

Se trata de un escenario que puede ir cambiando por la enorme cantidad de datos, comunicaciones y publicaciones que se están generando a nivel mundial. Hasta la fecha, solo hay datos parciales, preliminares, a veces únicamente *in vitro* o incluso contradictorios, sobre la eficacia de uno u otro producto por lo que, en la medida de lo posible, debe priorizarse la posibilidad de realizar estudios clínicos que, al tiempo que ofrecen una alternativa de tratamiento plausible, generen conocimiento útil.

La Agencia Española de Medicamentos y Productos Sanitarios está monitorizando de manera continua con los expertos de otras agencias sanitarias europeas, la Agencia Europea del Medicamento y otras agencias fuera de la Unión Europea todos los datos relativos al uso de medicamentos para el tratamiento o la profilaxis de la infección respiratoria por SARS-CoV-2.

El investigador principal del estudio le proporcionará toda la información que precise sobre los posibles tratamientos alternativos.

## Seguro

El Promotor del estudio dispone de una póliza de seguros que se ajusta a la legislación vigente (Real decreto 1090/2015) y que le proporcionará la compensación e indemnización en caso de menoscabo de su salud o de lesiones que pudieran producirse en relación con su participación en el estudio, siempre que no sean consecuencia de la propia enfermedad que se estudia o de la evolución propia de su enfermedad como consecuencia de la ineficacia del tratamiento. Si desea más información relativa a este apartado, consulte con el investigador principal del estudio en su centro.

Le recomendamos consultar las condiciones generales y particulares (cobertura) de sus pólizas de seguros privadas (vida, salud, accidente...) por si se ven afectadas por la participación en un ensayo clínico. El promotor no es responsable de estas potenciales modificaciones de cobertura debida a su participación y por tanto, le recomendamos que lo consulte con su aseguradora antes de dar su consentimiento.

#### 1 2 3 4 **Protección de datos personales**

5 En este estudio se cumplirá la normativa de protección de datos en vigor; la Ley Orgánica  
6 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales,  
7 así como con el Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril  
8 de 2016 de Protección de Datos (RGPD).

9  
10 Los datos recogidos para el estudio estarán identificados mediante un código, de manera  
11 que no se incluya información que pueda identificarle, y sólo su médico del estudio/colaboradores  
12 podrá relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será  
13 revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran, o en  
14 casos de urgencia médica.

15  
16 Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en  
17 materia de inspección y el personal autorizado por el Promotor, podrán acceder para comprobar los  
18 datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena  
19 práctica clínica (siempre manteniendo la confidencialidad de la información).

20  
21 Los datos se recogerán en un fichero de investigación responsabilidad de la institución y se  
22 tratarán en el marco de su participación en este estudio. El promotor adoptará las medidas  
23 pertinentes para garantizar la protección de su privacidad y no permitirá que sus datos se crucen  
24 con otras bases de datos que pudieran permitir su identificación.

25  
26 De acuerdo a lo que establece la legislación de protección de datos, usted puede ejercer los  
27 derechos de acceso, modificación, oposición y cancelación de datos. Además de los derechos que  
28 ya conoce, ahora también puede limitar el tratamiento de datos que sean incorrectos, solicitar una  
29 copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio.

30  
31 Para ejercitar sus derechos, diríjase al investigador principal del estudio o al Delegado de  
32 Protección de Datos del promotor en [dpd@imibic.org](mailto:dpd@imibic.org). Le recordamos que los datos no se pueden  
33 eliminar aunque deje de participar en el ensayo para garantizar la validez de la investigación y  
34 cumplir con los deberes legales y los requisitos de autorización de medicamentos. Así mismo tiene  
35 derecho a dirigirse a la Agencia de Protección de Datos si no queda satisfecho.

36  
37 Si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo  
38 será añadido a la base de datos, pero sí se utilizarán los que ya se hayan recogido.

39  
40 El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio  
41 al menos hasta 25 años tras su finalización. Posteriormente, su información personal sólo se  
42 conservará por el centro para el cuidado de su salud y por el promotor para otros fines de  
43 investigación científica si usted hubiera otorgado su consentimiento y si así lo permite la ley y  
44 requisitos éticos aplicables.  
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3 Si realizáramos transferencia de sus datos codificados fuera de la UE a las entidades de  
4 nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren con nosotros,  
5 los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros  
6 mecanismos establecidos por las autoridades de protección de datos. Si el participante quiere saber  
7 más al respecto, puede contactar al Delegado de Protección de Datos del promotor en  
8 [dpd@imibic.org](mailto:dpd@imibic.org).  
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## 13 **Gastos y compensación económica**

14 Usted no tendrá que pagar por los medicamentos ni por pruebas específicas del estudio. Su  
15 participación en el estudio no le supondrá ningún gasto adicional a la práctica clínica habitual.  
16  
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## 19 **Otra información relevante**

20 Una descripción de este ensayo clínico estará disponible en <https://reec.aemps.es>, según  
21 exige la legislación española, así como en <https://clinicaltrials.gov>.  
22  
23

24 Cualquier nueva información referente al fármaco utilizado en el estudio y que pueda afectar  
25 a su disposición para participar en el estudio, que se descubra durante su participación, le será  
26 comunicada por su médico lo antes posible.  
27  
28

29 Debe saber que puede ser excluido del estudio si el promotor o los investigadores del estudio  
30 lo consideran oportuno, ya sea por motivos de seguridad, por cualquier acontecimiento adverso que  
31 se produzca por la medicación en estudio o porque consideren que no está cumpliendo con los  
32 procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada  
33 del motivo que ha ocasionado su retirada del estudio.  
34  
35

36 Al firmar la hoja de consentimiento adjunta, se compromete a cumplir con los procedimientos  
37 del estudio que se le han expuesto. En aquellos casos en que un participante dejara de acudir a las  
38 visitas sin retirar el consentimiento, el promotor podrá realizar un seguimiento de dicho participante.  
39  
40

41 Debe usted saber que es posible que su médico de Atención Primaria tenga conocimiento  
42 de su participación en este estudio.  
43  
44

## 45 **¿Qué tratamiento recibiré cuando finalice el ensayo clínico?**

46 Cuando acabe su participación recibirá el mejor tratamiento disponible y que su médico  
47 considere el más adecuado para su enfermedad.  
48  
49

50 En caso de que el estudio se suspenda o finalice mientras usted está en tratamiento con la  
51 medicación en investigación, su enfermedad permanezca controlada, los datos del estudio indiquen  
52 que la medicación en investigación muestra un beneficio en el manejo de su enfermedad, y se  
53 disponga de existencias adecuadas del fármaco, el promotor le asegurará el suministro adecuado  
54 y gratuito de dicha medicación, hasta que esté disponible, de manera que usted continuará su  
55 tratamiento mientras su enfermedad permanezca controlada.  
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#### Contacto en caso de dudas

Si durante su participación tiene alguna duda o necesita obtener más información, póngase en contacto con Dr./Dra.: \_\_\_\_\_ del servicio de \_\_\_\_\_ en el teléfono \_\_\_\_\_.

#### Obtención y utilización de muestras biológicas

A cada participante se le extraerán en las visitas 0, 5, 10, 14, 21 y 28 (o hasta el último día que esté hospitalizado):

- Un frotis nasofaríngeo para la determinación del ARN del virus.
- Un tubo con 9 ml de sangre para el estudio de la inmunidad frente a este virus. Dependiendo de cómo monitorice la replicación de dicho virus su centro, es posible que se le precise extraer también un tubo con 6 ml de sangre más, para saber si el virus está replicando.

En el caso de almacenamiento de estas muestras una vez terminado el ensayo, para su uso posterior en investigación se cumplirá con los requisitos éticos y legales dispuestos en el Real Decreto 1716/2011. Para ello, se le pedirá su consentimiento para que dichas muestras puedan ser almacenadas, una vez que acabe el ensayo clínico, en el Biobanco del Sistema Sanitario Público de Andalucía/Nodo de Córdoba.

Las muestras biológicas donadas, así como sus datos clínicos e información asociados se utilizarán de conformidad con lo establecido en la Ley 14/2007, de 3 de julio, de Investigación biomédica. La donación es voluntaria y altruista, por lo que usted no tendrá derecho alguno sobre los resultados que pudieran derivarse de las investigaciones que se lleven a cabo con dichas muestras biológicas y su información asociada, de conformidad con la normativa vigente.

**CONSENTIMIENTO INFORMADO DEL PARTICIPANTE****Ensayo clínico de Sarilumab en adultos hospitalizados con COVID-19 que presentan síndrome de liberación de citoquinas (ESTUDIO SARICOR)**

Yo (nombre y apellidos del participante): \_\_\_\_\_

He leído la hoja de información que se me ha entregado sobre el estudio.

He podido hacer preguntas sobre el estudio.

He recibido suficiente información sobre el estudio.

He hablado con (nombre del investigador): \_\_\_\_\_

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

- Cuando quiera.
- Sin tener que dar explicaciones.
- Sin que esto repercuta en mis cuidados médicos.

Deseo que me comuniquen la información derivada de la investigación que pueda ser relevante para mi salud:

SÍ

NO

Recibiré una copia firmada y fechada de este documento de consentimiento informado.

Presto libremente mi conformidad para participar en el estudio.

Nombre del participante:

Nombre del investigador:

Fecha: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

Fecha: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

Firma del participante:

Firma del investigador:

**CONSENTIMIENTO INFORMADO DEL REPRESENTANTE LEGAL DEL PARTICIPANTE****Ensayo clínico de Sarilumab en adultos hospitalizados con COVID-19 que presentan síndrome de liberación de citoquinas (ESTUDIO SARICOR)**

Nombre del representante: \_\_\_\_\_

Relación con el paciente: \_\_\_\_\_

Se me ha solicitado mi consentimiento en nombre de la siguiente persona, para que él/ella pueda participar en este estudio de investigación médica:

Nombre y apellidos del paciente: \_\_\_\_\_

He leído la hoja de información que se me ha entregado sobre el estudio.

He podido hacer preguntas sobre el estudio.

He recibido suficiente información sobre el estudio.

He hablado con (nombre del investigador): \_\_\_\_\_

Comprendo que la participación es voluntaria.

Comprendo que puedo retirarlo del estudio:

- Cuando quiera.
- Sin tener que dar explicaciones.
- Sin que esto repercuta en sus cuidados médicos.

Deseo que me comuniquen la información derivada de la investigación que pueda ser relevante para su salud:

 SÍ NO

Recibiré una copia firmada y fechada de este documento de consentimiento informado.

Presto libremente mi conformidad para que participe en el estudio.

Nombre del representante legal o familiar:

Nombre del investigador:

Fecha: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

Fecha: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

Firma del representante legal:

Firma del investigador:

**CONSENTIMIENTO INFORMADO DEL PARTICIPANTE ANTE TESTIGOS****Ensayo clínico de Sarilumab en adultos hospitalizados con COVID-19 que presentan síndrome de liberación de citoquinas (ESTUDIO SARICOR)**

Yo (nombre y apellidos del testigo):\_\_\_\_\_

como testigo, afirmo que en mi presencia se ha informado a D/D<sup>a</sup> (nombre y apellidos del participante)\_\_\_\_\_y se ha

leído o le han leído la hoja de información que se le ha entregado sobre el estudio, de modo que:

Ha podido hacer preguntas sobre el estudio.

Ha recibido suficiente información sobre el estudio.

Ha hablado con (nombre del investigador):\_\_\_\_\_

Comprende que su participación es voluntaria.

Comprende que puede retirarse del estudio:

- Cuando quiera.
- Sin tener que dar explicaciones.
- Sin que esto repercuta en sus cuidados médicos.

El participante desea que se le comunique la información derivada de la investigación que pueda ser relevante para su salud:

SÍ

NO

Recibirá una copia firmada y fechada de este documento de consentimiento informado.

Presta libremente su conformidad para participar en el estudio.

Nombre del testigo:

Nombre del investigador:

Fecha: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

Fecha: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

Firma del testigo:

Firma del investigador:

*El participante del estudio ha indicado que no puede leer / escribir. Un miembro del personal del estudio le ha leído el documento de consentimiento, lo ha revisado y comentado con el participante y se le ha concedido la oportunidad de hacer preguntas o consultarla con otras personas. El testigo es una persona imparcial, ajena al estudio.*

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8 FORMULARIO DE RETIRADA DEL CONSENTIMIENTO CONCEDIDO CON  
9 ANTERIORIDAD

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11 **Ensayo clínico de Sarilumab en adultos hospitalizados con COVID-19 que presentan síndrome**  
12 **de liberación de citoquinas (ESTUDIO SARICOR)**

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15 Participación retirada por:

16  Paciente

17  Representante legal, nombre: \_\_\_\_\_

18 Relación con el/la paciente: \_\_\_\_\_

19 Por la presente comunico que retiro el consentimiento para la participación en la investigación.

20 Motivo de retirada (no obligatorio):  
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37 Nombre del/de la participante: \_\_\_\_\_  
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42 Fecha de retirada: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_  
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47 Firma del responsable de la retirada (paciente o representante legal, según proceda)  
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5 **FORMULARIO DE INFORMACIÓN Y CONSENTIMIENTO INFORMADO ESCRITO Biobanco**  
6 **en Red del Sistema Sanitario Público de Andalucía**  
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10 **DOCUMENTO DE INFORMACIÓN PARA DONACIÓN DE MUESTRAS BIOLÓGICAS E**  
11 **INFORMACIÓN ASOCIADA AL BIOBANCO PARA INVESTIGACIÓN BIOMÉDICA**  
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14 Este documento sirve para que usted otorgue su consentimiento, o las del sujeto al que representa, para donar  
15 sus muestras biológicas, así como la información asociada ( datos clínicos, epidemiológicos, genéticos,  
16 imágenes, u otros - ESPECIFICAR-), o las del sujeto al que representa, al Biobanco indicado, establecimiento  
17 público, sin ánimo de lucro, dependiente de la Consejería de Salud/del Servicio Andaluz de Salud, que acoge  
18 colecciones de muestras biológicas e información asociada concebidas con fines diagnósticos, de  
19 investigación biomédica, o docencia o calidad, y organizadas como una unidad técnica con criterios de  
20 calidad, orden y destino, donde serán conservadas hasta que se agoten por su uso, salvo que usted solicitará su  
21 eliminación. Las muestras biológicas y su información asociada son un excelente elemento para la  
22 investigación de enfermedades. A través de dichas investigaciones se podrán obtener datos que permitirán  
23 mejorar el conocimiento sobre la aparición, desarrollo y tratamiento de multitud de enfermedades.  
24  
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26 Esta hoja de información puede contener palabras que usted no entienda. Por favor, pídale al profesional  
27 sanitario que le explique la información que no comprenda. Tómese el tiempo necesario para decidir si  
28 quiere o no donar su muestra biológica y consulte a personas de su confianza si lo desea. Para consultas que  
29 desee plantear posteriormente, podrá dirigirse al Biobanco en Red del Sistema Sanitario Público de  
30 Andalucía. Dirección: Parque Tecnológico Ciencias de la Salud.  
31  
32

33 Centro de Investigación Biomédica. Avda. del Conocimiento s/n · 18016 · Granada · España ·  
34 Teléfono: + 34 958 894 672. Correo electrónico: biobanco.sspa@juntadeandalucia.es.  
35  
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37 Las muestras biológicas donadas y sus datos clínicos asociados e información asociada se utilizarán de  
38 conformidad con lo establecido en la Ley 14/2007, de 3 de julio, de Investigación biomédica (en adelante Ley  
39 de Investigación biomédica).  
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42 Es posible que la información obtenida de las investigaciones en las que se utilicen sus muestras biológicas  
43 e información asociada no le genere un beneficio directo, pero habrá contribuido al avance de la medicina y  
44 del conocimiento de diversas enfermedades, lo que supondrá, sin duda, un beneficio para la sociedad.  
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47 La donación es voluntaria y altruista, por lo que usted no tendrá derecho alguno sobre los resultados que  
48 pudieran derivarse de las investigaciones que se lleven a cabo con dichas muestras biológicas y  
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5 su información asociada, de conformidad con la normativa vigente. Su decisión de donar o no, no afectará  
6 a su asistencia sanitaria.  
7  
8 Existe un apartado en el consentimiento en el que podrá decidir si quiere que sus muestras biológicas e  
9 información asociada se conserven de forma codificada (en cuyo caso se identifican con un código que  
10 protege su identidad) o anonimizada (eliminándose de forma irreversible toda vinculación con su  
11 identidad).  
12  
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14 Sus muestras y los datos asociados a las mismas sólo se cederán a terceros de manera anónima o disociada.  
15 Sus muestras biológicas e información asociada a las mismas sólo se podrán ceder a terceros como uso  
16 exclusivo para la investigación biomédica que ayuden a la obtención de nuevos conocimientos científicos,  
17 confirmación de hipótesis, adecuación tecnológica, controles de calidad, docencia, u otros usos de interés  
18 sanitario, pudiendo usted en cualquier momento establecer las restricciones de utilización que considere  
19 oportunas.  
20  
21 Si la naturaleza del proyecto en el que vaya a utilizarse la muestra biológica requiriése información asociada  
22 a la misma, y para la que fuese necesario la consulta de su historia clínica, el Biobanco establecerá un  
23 sistema de control y trazabilidad del acceso mediante una autorización previa y registros de acceso, que será  
24 responsabilidad del Director del nodo donde se lleve a cabo la consulta siempre que la muestra no hubiera  
25 sido anonimizada.  
26  
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### 34 1. Obtención de las muestras

35 Las muestras serán obtenidas durante el procedimiento médico-quirúrgico al que va a someterse o se ha  
36 sometido durante su proceso asistencial, o a través de un procedimiento expreso para obtenerla, según lo  
37 indicado en el apartado del consentimiento referente a la obtención de muestras. Se podrán obtener diferentes  
38 tipos de muestras biológicas como sangre, tejidos, saliva, líquidos biológicos, uñas o pelo. En la hoja de  
39 consentimiento se indicarán los tipos de muestras a recoger de forma expresa en este acto de donación.  
40  
41 En el caso de que usted done las muestras obtenidas durante un procedimiento médico-quirúrgico  
42 asistencial, no existe ningún inconveniente adicional derivado de la donación de las mismas.  
43  
44 Si, por el contrario, las muestras biológicas fueran extraídas expresamente para la donación al Biobanco,  
45 podrían existir inconvenientes vinculados con la obtención de las mismas, de las que será convenientemente  
46 informado en la hoja de información del procedimiento correspondiente.  
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## 2    5 **2. Utilización de las muestras**

6    Usted autoriza, con la firma del consentimiento informado, a que las muestras donadas puedan ser sean  
7    utilizadas en:

8                    10 *- Investigación:* las muestras e información asociada podrán ser utilizados en cualquier investigación  
9                    12 biomédica, en los términos que indica la ley. En el caso de que la obtención de la muestra se lleve a  
10                  14 cabo a petición de un proyecto concreto, éste y su investigador principal quedarán reflejados en la  
11                  16 hoja de consentimiento. El excedente de la muestra e información asociada, quedarán disponibles  
12                  18 para su uso en otros proyectos de investigación biomédica si usted así lo indica. Sólo se cederán  
13                  20 muestras a proyectos de investigación dentro de una misma línea y científicamente avalados, que  
14                  22 cumplan las exigencias legales y los principios éticos que rigen la investigación en salud y que sean  
15                  24 autorizados por los órganos competentes, de conformidad con lo establecido en la normativa  
16                  26 vigente.

17                  28 *- Docencia:* actividades de formación en el ámbito sanitario o biomédico.

18                  30 *- Evaluación / Control de Calidad:* muchas de las actividades relacionadas con la investigación o el  
19                  32 diagnóstico requieren la puesta a punto de equipos, validación de nuevas tecnologías y  
20                  34 procedimientos, encaminados a mejorar el impacto en salud de la tecnología empleada. Para ello es  
21                  36 necesario la utilización de muestras biológicas.

22                  38 Para el caso de que las muestras se utilicen exclusivamente con fines docentes o de control de calidad, y  
23                  40 no sea necesaria la información asociada, la conservación, cesión, y uso, se realizará siempre de forma  
24                  42 anonimizada.

25                  44 Las muestras sólo podrán ser utilizadas en proyectos de investigación científicamente avalados, que cumplan  
26                  46 las exigencias legales y los principios éticos que rigen la investigación en salud y que sean autorizados por  
27                  48 los órganos competentes, de conformidad con lo establecido en la normativa vigente.

28                  50 Cuando, por razones de salud, usted o su familia lo necesiten, podrán hacer uso de las muestras, siempre  
29                  52 que no se hayan agotado o eliminado y no se encuentren anonimizadas.

## 3    49 **3. Información relacionada con las muestras**

50                  51 Si lo solicita, el Biobanco le facilitará la información sobre los proyectos de investigación en los que se  
52                  53 utilicen las muestras donadas, si éstas no hubieran sido anonimizadas.

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5 Al donar sus muestras al Biobanco, en este momento puede no saberse el lugar de realización de los análisis.

6 El Biobanco mantiene un registro detallado del lugar de realización de los análisis realizados.

7  
8 La información que se obtenga puede tener implicaciones para sus familiares, por lo que debe  
9 transmitirles dicha información.  
10  
11

#### 12 **4. Posibilidad de ponerse nuevamente en contacto**

13 Puede que sea necesario ponerse en contacto nuevamente con usted, con el fin de recabar datos o  
14 muestras adicionales, o proporcionarle la información relevante para su salud, salvo que haya solicitado  
15 que las muestras sean anonimizadas.  
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#### 18 **5. Protección de datos y confidencialidad de la información**

19 La información proporcionada en este apartado será aplicable siempre que sus muestras no se  
20 encuentren anonimizadas.  
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22

23 Los datos personales recabados serán confidenciales y tratados de acuerdo con el Reglamento (UE)  
24 2016/679, General de Protección de Datos y la Ley 14/2007 de Investigación Biomédica.  
25  
26

27 En cumplimiento de lo dispuesto en los artículos 13 y 14 del Reglamento General de Protección de Datos,  
28 le informamos lo siguiente:  
29  
30

- 31 - El responsable de este tratamiento de sus datos personales es el Servicio Andaluz de Salud. Avda.  
32 de la Constitución, 18. 41071 Sevilla  
33  
34 - Podrá contactar con el Delegado de Protección de Datos en  
35 la dirección electrónica dpd.sspa@juntadeandalucia.es.  
36  
37 - Los datos personales que nos proporcione serán utilizados con la finalidad de poder gestionar las  
38 muestras biológicas, quedando almacenados durante el tiempo necesario para cumplir con las  
39 obligaciones legales estipuladas.  
40  
41 - La base jurídica de este tratamiento es el consentimiento que nos presta al cumplimentar y firmar el  
42 documento de consentimiento informado, sin el cual no podríamos cumplir con la finalidad descrita.  
43  
44 - Sus datos no serán cedidos a terceros, salvo que se disponga en una obligación legal.  
45  
46 - Puede usted ejercer sus derechos de acceso, rectificación, supresión, portabilidad de sus datos, y la  
47 limitación u oposición a su tratamiento, solicitándolo por escrito, con copia del  
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DNI, a la Dirección General de Asistencia Sanitaria del Servicio Andaluz de Salud, Avenida de la Constitución, núm. 18, de Sevilla.

## 6. Derecho de revocación del consentimiento

Salvo que sus muestras se encuentren anonimizadas, podrá revocar en cualquier momento, el consentimiento que ha firmado. Esta revocación podrá ser total o parcial. Si fuese parcial, podría especificar para los casos que quiere revocar su consentimiento que están identificados en el punto 2 de este documento. Además, usted puede solicitar la eliminación o la anonimización de dichas muestras biológicas. Para ello, deberá dirigirse al Biobanco en Red del

Sistema Sanitario Público de Andalucía. Dirección: Parque Tecnológico Ciencias de la Salud. Centro de Investigación Biomédica. Avda. del Conocimiento s/n · 18100 Armilla · Granada · España · Teléfono: + 34 958 894 672. Correo electrónico: biobanco.sspa@juntadeandalucia.es

Los efectos de la revocación no se extenderán a los resultados de las investigaciones llevadas a cabo con anterioridad.

## 7. Información relativa a análisis genéticos

Salvo que usted manifieste lo contrario en el apartado dedicado al consentimiento, se podrán realizar análisis genéticos. Excepto si sus muestras son anonimizadas, tiene derecho a conocer los datos genéticos que se obtengan a partir del análisis de las muestras donadas, así como de la información relativa a su salud derivada de dichos análisis.

Si no desea recibir dicha información y ésta fuera necesaria para evitar un grave perjuicio para su salud o la de sus familiares biológicos, se informará a un familiar o a un representante. La comunicación se limitará exclusivamente a los datos necesarios para evitar tal perjuicio.

## 8. Otras consideraciones

Una vez informado/a de los aspectos relacionados anteriormente en este documento, si decide donar dichas muestras deberá firmar el consentimiento informado para la donación.

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5       **CONSENTIMIENTO INFORMADO PARA DONACIÓN DE MUESTRAS**  
6       **Biológicas e Información Asociada al Biobanco**

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8       **Biobanco en Red del Sistema Sanitario Público de Andalucía.**  
9

10 DATOS DEL/DE LA DONANTE Y DE SU REPRESENTANTE (éste último sólo en caso de  
11 incapacidad del/de la donante):  
12

13       **Apellidos y nombre del/de la Donante:**  
14

15 ..... **DNI / NIE:**  
16

17 ..... **NUSHA:** .....

18       **Apellidos      y      nombre      del/de      la      representante      legal.**  
19 .....  
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21       **DNI / NIE:** .....

22 PROFESIONALES QUE INTERVIENEN EN EL PROCESO DE INFORMACIÓN Y/O  
23 CONSENTIMIENTO:  
24

25 Los siguientes profesionales declaran que se ha explicado la información relativa a la donación de  
26 muestras biológicas al Biobanco:  
27

28       **Apellidos y nombre**  
29

30       **Fecha** ..... **Firma**  
31

32       **CONSENTIMIENTO:**  
33

34 Yo, D./Dña..... declaro bajo mi  
35 responsabilidad que **he leído y comprendido el Formulario de Información**, del que se me ha entregado  
36 un ejemplar.  
37

38 He **recibido suficiente información** sobre la donación de muestras biológicas de (*detallar tipo de muestras*  
39 *a recoger*) ..... e  
40 información asociada, al Biobanco, y sobre la posible realización de análisis genéticos sobre las mismas.  
41 He podido hacer preguntas sobre la información recibida y hablar con el profesional indicado, quien me  
42 ha resuelto todas las dudas que le he planteado.  
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44 Dichas muestras son:  
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46  Excedentes del procedimiento médico-quirúrgico asistencia al que va a someterse o se ha  
47 sometido  
48 .....  
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Tomadas mediante el procedimiento expreso (*indicar procedimiento*):

Las muestras biológicas e información asociada serán recogidas para:

PROYECTO (actividades de investigación biomédica que ayuden a la obtención de nuevos conocimientos científicos):

- Título: .....
  - Investigador Principal: .....
  - Código de Biobanco:.....

El excedente de las muestras biológicas e información asociada obtenidas en el proyecto original podrán utilizarse en otros proyectos relacionados con:

## INVESTIGACION

## **EVALUACIÓN / CONTROL DE CALIDAD**

□ DOCENCIA

Deseo que dichas muestras y los datos clínicos asociados sean tratados de forma:

**Codificada** (serán identificadas con un código que protege mi identidad, siendo posible volver a ligarlas conmigo) o

**Anonimizada** (no se podrán asociar las muestras conmigo, por haberse eliminado de forma irreversible la vinculación entre las mismas y mi identidad).

Deseo establecer restricciones respecto al uso de la muestra, para que no sea utilizada en

Autorizo que se pueda **contactar conmigo** posteriormente:

- SI
- NO

En caso afirmativo, por favor, indique el medio de hacerlo:

Teléfono: (*indicar número*) .....

Correo electrónico: (*indicar dirección*).....

Otros:  
(identificar).....

Autorizo **recibir información** sobre datos genéticos y datos relevantes para mi salud (Si solicita que las muestras sean anonimizadas, no podrá recibir esta información)

Marque lo que proceda:

SI

NO

Sé que puedo **revocar**, en cualquier momento, el consentimiento otorgado en este documento.

En , a de de

EL/LA DONANTE

EL/LA REPRESENTANTE LEGAL

(sólo en caso de incapacidad del/de la donante)

Fdo.:

Fdo.:

# **CONSENTIMIENTO INFORMADO PARA DONACIÓN DE MUESTRAS BIOLÓGICAS E INFORMACIÓN ASOCIADA AL BIOBANCO**

## **Biobanco en Red del Sistema Sanitario Público de Andalucía.**

**DATOS DEL/DE LA DONANTE Y DE SU REPRESENTANTE** (éste último sólo en caso de incapacidad del/de la donante):

Apellidos y nombre del/de la Donante:

..... DNI / NIE: **NUSHAN**

Apellidos y nombre del/de la representante legal.

DNI / NIE: .....

**PROFESIONALES QUE INTERVIENEN EN EL PROCESO DE INFORMACIÓN Y/O CONSENTIMIENTO:**

Los siguientes profesionales declaran que se ha explicado la información relativa a la donación de muestras biológicas al Biobanco:

### Apellidos y nombre

Fecha \_\_\_\_\_ Firma \_\_\_\_\_

## CONSENTIMIENTO:

Yo, D./Dña..... declaro bajo mi responsabilidad que **he leído y comprendido el Formulario de Información**, del que se me ha entregado un ejemplar.

He **recibido suficiente información** sobre la donación de muestras biológicas de (*detallar tipo de muestras a recoger*) ..... e información asociada, al Biobanco, y sobre la posible realización de análisis genéticos sobre las mismas. He podido hacer preguntas sobre la información recibida y hablar con el profesional indicado, quien me ha resuelto todas las dudas que le he planteado.

Dichas muestras son:

Excedentes del procedimiento médico-quirúrgico asistencia al que va a someterse o se ha sometido

□ Tomadas mediante el procedimiento expreso (*indicar procedimiento*):

Las muestras biológicas e información asociada serán recogidas para:

PROYECTO (actividades de investigación biomédica que ayuden a la obtención de nuevos conocimientos científicos):

- Título: .....
  - Investigador Principal: <http://bmjopen.bmjjournals.org/site/about/guidelines>

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3 - Código de Biobanco:.....  
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7 El excedente de las muestras biológicas e información asociada obtenidas en el proyecto original podrán  
8 utilizarse en otros proyectos relacionados con:  
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- 11  INVESTIGACION  
12  EVALUACIÓN / CONTROL DE CALIDAD  
13  DOCENCIA  
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16 Deseo que dichas muestras y los datos clínicos asociados sean tratados de forma:  
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- 19  **Codificada** (serán identificadas con un código que protege mi identidad, siendo posible volver a ligarlas  
20 conmigo) o  
21  **Anonimizada** (no se podrán asociar las muestras conmigo, por haberse eliminado de forma irreversible la  
22 vinculación entre las mismas y mi identidad).  
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26 Deseo **establecer restricciones** respecto al uso de la muestra, para que no sea  
27 utilizada en.....  
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30 Autorizo que se pueda **contactar conmigo posteriormente**:

- 31  SI  
32  NO  
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35 En caso afirmativo, por favor, indique el medio de hacerlo:

- 36  Teléfono: (*indicar número*).....  
37  
38  Correo electrónico: (*indicar dirección*).....  
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40  Otros:  
41 (*identificar*).....  
42  
43

44 Autorizo **recibir información** sobre datos genéticos y datos relevantes para mi salud (Si solicita que las  
45 muestras sean anonimizadas, no podrá recibir esta información)  
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48 Marque lo que proceda:

- 49  SI  
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51  NO  
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54 Sé que puedo **revocar**, en cualquier momento, el consentimiento otorgado en este documento.  
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57 En , a de de  
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60 EL/LA DONANTE

EL/LA REPRESENTANTE LEGAL

(sólo en caso de incapacidad del/de la donante)



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**CONSENTIMIENTO INFORMADO PARA DONACIÓN DE MUESTRAS BIOLÓGICAS E  
INFORMACIÓN ASOCIADA AL BIOBANCO**

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**Biobanco en Red del Sistema Sanitario Público de Andalucía.**

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16 DATOS DEL/DE LA DONANTE Y DE SU REPRESENTANTE (éste último sólo en caso de  
17 incapacidad del/de la donante):  
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**Apellidos y nombre del/de la Donante:**

..... DNI / NIE:

..... NUSHA: .....

**Apellidos y nombre del/de la representante legal.**

**DNI / NIE:** .....

PROFESIONALES QUE INTERVIENEN EN EL PROCESO DE INFORMACIÓN Y/O  
CONSENTIMIENTO:

Los siguientes profesionales declaran que se ha explicado la información relativa a la donación de  
muestras biológicas al Biobanco:

Apellidos y nombre

*Fecha*

*Firma*

CONSENTIMIENTO:

Yo, D./Dña..... declaro bajo mi  
responsabilidad que **he leído y comprendido el Formulario de Información**, del que se me ha entregado  
un ejemplar.

He **recibido suficiente información** sobre la donación de muestras biológicas de (*detallar tipo de muestras a recoger*) ..... e  
información asociada, al Biobanco, y sobre la posible realización de análisis genéticos sobre las mismas.  
He podido hacer preguntas sobre la información recibida y hablar con el profesional indicado, quien me  
ha resuelto todas las dudas que le he planteado.

Dichas muestras son:

Excedentes del procedimiento médico-quirúrgico asistencia al que va a someterse o se ha  
sometido

Ejemplar para Documentación Clínica



1            Tomadas mediante el procedimiento expreso (*indicar procedimiento*):  
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6           Las muestras biológicas e información asociada serán recogidas para:  
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10           PROYECTO (actividades de investigación biomédica que ayuden a la obtención de nuevos  
11           conocimientos científicos):  
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- 15           - Título: .....  
16           - Investigador Principal: .....  
17           - Código de Biobanco: .....

18           El excedente de las muestras biológicas e información asociada obtenidas en el proyecto original podrán  
19           utilizarse en otros proyectos relacionados con:  
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- 23            INVESTIGACION  
24            EVALUACIÓN / CONTROL DE CALIDAD  
25            DOCENCIA  
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30           Deseo que dichas muestras y los datos clínicos asociados sean tratados de forma:  
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- 33            **Codificada** (serán identificadas con un código que protege mi identidad, siendo posible volver a ligarlas  
34           conmigo) o  
35            **Anonimizada** (no se podrán asociar las muestras conmigo, por haberse eliminado de forma irreversible la  
36           vinculación entre las mismas y mi identidad).  
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40           Deseo establecer restricciones respecto               al uso de           la muestra, para que no           sea  
41           utilizada               en  
42           .....  
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44

45           Autorizo que se pueda contactar conmigo posteriormente:

- 46            SI  
47            NO  
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50           En caso afirmativo, por favor, indique el medio de hacerlo:  
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- 53            Teléfono: (*indicar número*) .....  
54            Correo electrónico: (*indicar dirección*) .....  
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56            Otros:  
57            (identificar) .....

58  
59           Autorizo recibir información sobre datos genéticos y datos relevantes para mi salud (Si solicita que las  
60           muestras sean anonimizadas, no podrá recibir esta información)

1 Marque lo que proceda:  
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- 7  SI  
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9  NO

10 Sé que puedo **revocar**, en cualquier momento, el consentimiento otorgado en este documento.  
11  
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13 EL/LA DONANTE

14 EL/LA REPRESENTANTE LEGAL

15 (sólo en caso de incapacidad del/de la donante)

16 Fdo.:  
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Ejemplar para Documentación Clínica



## REVOCACIÓN / MODIFICACIÓN DEL CONSENTIMIENTO PARA USO DE MUESTRAS BIOLÓGICAS E INFORMACIÓN ASOCIADA DONADAS AL BIOBANCO DEL SISTEMA SANITARIO PÚBLICO DE ANDALUCÍA

Yo, D./Dña. \_\_\_\_\_ revoco el consentimiento informado otorgado en el documento \_\_\_\_\_ (especificar fecha aproximada y/o procedimiento). Solicito:

**Revocación total:** las muestras biológicas e información asociada serán destruidas excepto aquellas que ya hayan sido utilizadas en proyectos.

**Revocación parcial:** solicito que mis muestras NO sean utilizadas para la/s siguiente/s finalidad/es:

Investigación Docencia

Control de Calidad

**Anonimización de las muestras biológicas e información asociada:** la anonimización no permitirá recibir ningún tipo de información relevante para la salud derivada de los proyectos en los que sea utilizada.

Otras consideraciones:  
.....

En \_\_\_\_\_, a \_\_\_\_\_ de \_\_\_\_\_ de \_\_\_\_\_

EL/LA DONANTE	EL/LA REPRESENTANTE LEGAL (sóly en caso de incapacidad del/de la donante)
Fdo.:	Fdo.: