

LETTER

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# Subcutaneous Sarilumab in hospitalised patients with moderate-severe COVID-19 infection compared to the standard of care (SARCOVID): a structured summary of a study protocol for a randomised controlled trial

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## Abstract

**Objectives:** The main aim of the study is to evaluate the efficacy of a single dose of sarilumab, in subcutaneous administration, in hospitalised patients with moderate to early severe COVID-19 infection compared to the current standard of care, to prevent progression to systemic hyperinflammatory status. Our hypothesis is that use of subcutaneous sarilumab in early stages (window of opportunity) of COVID-19 moderate-severe pneumonia can prevent higher oxygenation requirements through non-invasive and invasive mechanical ventilation and decrease in-hospital stays, as well as death rate.

The secondary objectives of the study are to evaluate the safety of sarilumab through hospitalisation and up to day 14 after discharge, compared to the control arm as assessed by incidence of serious and non serious adverse events (SAEs).

In addition, as an exploratory objective, to compare the baseline clinical and biological parameters, including serum IL-6 levels, of the intervention population against controls of the same pandemic outbreak (using a propensity score) to search for markers that identify the best candidates for the treatment with subcutaneous IL-6R inhibitors and to attempt an approximation in the temporal frame of the “window of opportunity”

**Trial design:** SARCOVID is an investigator-initiated single center randomised proof of concept study.

**Participants:** Patients treated at the Hospital Universitario La Princesa, Madrid, Spain requiring hospitalisation will be consecutively recruited, meeting all inclusion criteria and none of the exclusion criteria

Inclusion criteria

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- a. Age >18, <80 years old
- b. COVID-19 infection documented by a positive RT-PCR test or, in absence of a RT-PCR positive test, case definition of COVID 19 infection/pneumonia as per local protocol and the presence of a positive serologic test (IgM/IgA by ELISA)
- c. Documented interstitial pneumonia requiring admission and at least two of the following parameters:
  - 1) Fever  $\geq 37.8^{\circ}\text{C}$  (tympenic)
  - 2) IL-6 in serum  $\geq 25$  pg/mL (in the absence of a previous dose of prednisone or equivalent  $> 1$  mg / kg) or PCR  $> 5$  mg/dL
  - 3) Lymphocytes  $< 600$  cells/mm<sup>3</sup>
  - 4) Ferritin  $> 300$   $\mu\text{g/L}$  that doubles in 24 hours
  - 5) Ferritin  $> 600$   $\mu\text{g/L}$  in the first determination and LDH  $> 250$  U/L
  - 6) D-dimer ( $> 1$  mg/L)
- d. Informed verbal consent or requested under urgent conditions, documented in the electronic medical record.

Exclusion criteria

- a. Patients who require mechanical ventilation at the time of inclusion.
- b. AST / ALT values  $> 5$  folds the ULN.
- c. Absolute neutrophil count below 500 cells/mm<sup>3</sup>
- d. Absolute platelet count below 50,000 cells/mm<sup>3</sup>
- e. Documented sepsis or high suspicion of superimposed infection by pathogens other than COVID-19.
- f. Presence of comorbidities that can likely lead to an unfavourable result according to clinical judgment.
- g. Complicated diverticulitis or intestinal perforation.
- h. Current skin infection (eg, uncontrolled dermatodermatitis).
- i. Immunosuppressive anti-rejection therapy.
- j. Pregnancy or lactation.
- k. Previous treatment with tocilizumab or sarilumab.
- l. Patients participating in another clinical trial for SARS-CoV-2 infection.
- m. Patients with known hypersensitivity or contraindication to sarilumab or excipients.

**Intervention and comparator:** The intervention group, sarilumab plus standard of care, will receive 400 mg single dose treatment with Sarilumab (Kevzara), 2 subcutaneous injections 200mg each in a pre-filled syringe. Treatment with drugs or procedures in routine clinical practice that the clinician responsible for the patient deems necessary is allowed.

The control group will receive drugs or procedures in routine clinical practice according to the best standard of care as per local protocol.

**Main outcomes:** Primary Outcome Measures

1. Mean change in clinical status assessment using the 7-point ordinal scale at day 7 after randomisation compared to baseline (Score ranges 1-7)
  1. Death;
  2. Hospitalised, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
  3. Hospitalised, requiring non-invasive ventilation or high flow oxygen devices;
  4. Hospitalised, requiring supplemental oxygen;
  5. Hospitalised, not requiring supplemental oxygen - but in need of ongoing medical care (COVID-19 related or otherwise)
  6. Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care (independent)
  7. Not hospitalised
2. Duration of hospitalisation: Days from the date of enrolment to the date of discharge
3. Number of deaths at the end of study

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**Randomisation:** Randomisation to treatment arms sarilumab plus standard of care or standard of care in a 2:1 ratio will be performed by the Clinical Research and Clinical Trials Unit (CRCTU) at the Hospital using a table of random numbers, an internet-based randomisation tool. After checking that all inclusion criteria are met and none of the exclusion criteria, CRCTU will communicate the recruiting investigator the assigned treatment.

**Blinding (masking):** This study is unblinded.

**Numbers to be randomised (sample size):** 30 patients treated by COVID-19 infection who require hospitalisation: 20 will receive sarilumab plus Standard of Care and 10 will receive Standard of Care.

**Trial Status:** The Protocol version number is 2, as of 6<sup>th</sup> April 2020, with amendment 1, as of 7<sup>th</sup> May 2020. The recruitment is ongoing. Recruitment started on April 13<sup>th</sup> 2020 and is anticipated to be completed by November 2020.

**Trial registration:** This trial was first registered in the European Union Clinical Trials Register on 4 April 2020, EudraCT Number [2020-001634-36](https://eudract.europa.eu/number/2020-001634-36). Then, posted on ClinicalTrials.gov on 22 April 2020, Identifier: [NCT04357808](https://clinicaltrials.gov/ct2/show/study/NCT04357808).

**Full protocol:** The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest in expediting dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol.

The study protocol has been reported in accordance with the International Council Harmonization guidelines: <https://www.ich.org/page/efficacy-guidelines>.

**Keywords:** COVID-19, Randomised controlled trial, Open label trial, protocol, SARS-CoV-2, Coronavirus infections, Sarilumab, IL-6 receptor inhibitors

## Supplementary information

**Supplementary information** accompanies this paper at <https://doi.org/10.1186/s13063-020-04588-5>.

**Additional file 1.** Full Study Protocol.

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## Authors' contributions

RGV: Principal investigator, Conceptualization, Methodology design, writing the study protocol and data collection sheet and writing this submission. Obtaining approval for ethics committee and regulatory competent authorities. Fund accounting. FAS: Writing the study protocol and data collection sheet. Obtaining approval for ethics committee and regulatory competent authorities. Editing and review of the English version of the protocol. IGA: Conceptualization, Methodology design. FRL: Translation into English of the Spanish version of the protocol. JSS: Clinical study coordinator and supervision of investigators. The authors read and approved the final protocol and this submission.

## Authors' information

RGV is the Head of the Rheumatology Unit at the Hospital Universitario la Princesa (HUP) and the actual coordinator of the Multidisciplinary Unit of Biologic and Directed Therapies at the Instituto de Investigación Sanitaria La Princesa (IIS-IP). She is assistant professor of Rheumatology at the Universidad Autónoma de Madrid (UAM). FAS is the Head of Clinical Pharmacology Department at HUP and Coordinator of the Clinical Research and clinical trial Unit (UICEC) of the HUP and IIS-IP. He also is member and promoter of the SCReN Platform (Spanish Clinical Research Network) and Professor in the Pharmacology Department, UAM. IGA is a Section chief in the Rheumatology Unit at HUP and the leader of its research group in the IIS-IP, as well as the coordinator of the investigational line "Advanced Therapies and personalized Medicine" at the IIS-IP which

bring together all activities focused in Biomarkers and personalized medicine.

FRL is Medical Advisor, Medical Affairs Department, Immunology Area at Sanofi Spain with more than 12 years of experience in basic research, before starting in the pharmaceutical industry.

JSS is the chief of the Infectious Diseases division at the Internal Medicine Department and the person in charge of the local protocol for the treatment of COVID-19 infection at HUP.

## Funding

Sanofi provides medication for the intervention arm sarilumab (Kevzara, 40 prefilled syringes). Funds for a data manager are subject to achievement of predefined milestones throughout the study. Sanofi has no role in the design of the study and data collection, analysis, and interpretation of data and in writing the manuscript.

## Availability of data and materials

RGV, FAS and IGA will have access to the final trial dataset. The data will be available from the author on reasonable request. Contact details: Rosario García de Vicuña. [mariadelrosario.garcia@salud.madrid.org](mailto:mariadelrosario.garcia@salud.madrid.org) Rheumatology Unit, Hospital Universitario de la Princesa, IIS-IP, Diego de León 62, 28006, Madrid

Until publication, only research staff have access to the scientific and personal data, in agreement with Regulation (EU) 2016/679, of the European Parliament and of the Council, of 27th April 2016.

## Ethics approval and consent to participate

The Ethics Committee for investigation with medicinal products (CEIm) of the Hospital Universitario La Princesa approved the study on March 9th, 2020. The Reference number of the ethical approval judgement is 4075. I certify that this trial has received ethical approval from the appropriate ethical committee as described above. Oral informed consent and request in urgent conditions according to the AEMPS (Spanish Agency for Drugs and Health Products) statement (<https://www.aemps.gob.es/informa-en/exceptional-measures-applicable-to-clinical-trials-to-manage-problems-arising-from-the-covid-19-emergency/?lang=en>) will be recorded for all participants before enrolling in the study and will be registered in the electronic medical records.

**Consent for publication**

Not applicable.

**Competing interests**

RGV declares no competing interests related to the present protocol; She reports she has received educational or research grants from Abbvie, BMS, Janssen Lilly, Novartis, MSD, Roche, and Sanofi; has received personal fees for advisory boards from Abbvie, Biogen, BMS, Celltrion, Mylan, Pfizer, Roche, Sandoz and Sanofi; has delivered presentations sponsored by BMS, Lilly, Pfizer, Sandoz and Sanofi; has received non-financial support for Abbvie, BMS, Lilly, MSD, Novartis, Pfizer and Sanofi, all outside the submitted work. FAS declares he has no competing interests.

FRL is Medical Advisor at Sanofi Spain. He declares no competing interests related to the present protocol.

IGA declares no competing interests related to the present protocol. He reports grants from ISCIII, grants from Fundación La Caixa; personal fees from Lilly, personal fees and non-financial support from BMS, personal fees from Sanofi, personal fees and non-financial support from Abbvie, grants, personal fees and non-financial support from Roche, non-financial support from MSD, non-financial support from Pfizer, non-financial support from Novartis, outside the submitted work;

JSS declares he has no competing interests.

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