PROTOCOL: SARCOVID
EUDRA CT number: 2020-001634-36

Randomized open pilot study to evaluate the efficacy of subcutaneous sarilumab in patients with moderate-severe COVID-19 infection.
(Estudio piloto abierto aleatorizado para evaluar la eficacia de Sarilumab subcutáneo en pacientes con infección por COVID-19 moderada-grave.)

FINAL REPORT

VERSION 1

Madrid, 10thMarch 2022

1. TITLE PAGE

STUDY TITLE: Randomized open pilot study to evaluate the efficacy of subcutaneous sarilumab in patients with moderate-severe COVID-19 infection.

INVESTIGATIONAL PRODUCT: Kevzara® 200 mg solution for injection pre-filled syringes. Marketing Authorization Holder: Sanofi-Aventis Group

INDICATION STUDIED: COVID-19 infection requiring hospitalization.

STUDY DESIGN: Open label phase II, low-level intervention trial, controlled with active drug in paralleled groups, randomized, that will develop in one centre in Spain.

NAME OF THE SPONSOR: Rosario García de Vicuña, Rheumatology Service of Hospital Universitario de la Princesa.

PROTOCOL IDENTIFICATION CODE: SARCOVID, Version 2, 6th April 2020

EUDRA-CT: 2020-001634-36

DEVELOPMENT PHASE OF STUDY: Phase II

DATE OF APPROVAL BY THE INDEPENDENT ETHICS COMMITTEE (IEC) OF THE HOSPITAL "LA PRINCESA": 09th April 2020, 13th May 2020 (Relevant modification).

DATE OF APPROVAL BY THE SPANISH AGENCY OF MEDICINES AND HEALTHCARE PRODUCTS (AEMPS): 09th April 2020 (first version protocol), 08th June 2020 (Relevant modification).

STUDY INITIATION DATE (first subject included): 13th April 2020

STUDY COMPLETION DATE (last subject completed follow up): 04th December 2020

PRINCIPAL INVESTIGATOR: Dra. Rosario García de Vicuña[1], Rheumatology Service,

COORDINATING INVESTIGATOR: Dr. Jesús Sanz Sanz[2], Internal Medicine Service,
SUB-INVESTIGATORS: Ángela Gutiérrez2, José Curbelo2, Miguel Martínez Marín2, Azucena Bautista Hernández2, Natalia Villalba3, Andrés von Wernitz[3], Tamara Alonso Pérez[4], Pedro Landete[4], Irene Llorente Cubas[1], Eva Tomero Muriel[1], Sebastián Rodriguez García[1], Esther Ramírez Herráiz[5], Laura Cardeñoso Domingo[6], Aránzazu Alfranca[7], Isidoro González Álvaro[1], María Ángeles Sanz de Benito[8], Francisco Abad Santos[9], Gina Mejia Abril[9].
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NAME OF COMPANY / SPONSOR SIGNATORY:
Dra. Rosario García de Vicuña (non comercial sponsor).
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Both the development of the study as archiving the documents have been made in accordance with the guide of good clinical practice.

MONITOR: Elena SantosMolina, Clinical Pharmacology Service, Hospital Universitario de la Princesa.

REPORT AUTHORS: Rosario García de Vicuña, Jesús Sanz Sanz, Isidoro González, Francisco Abad and Jesús Novalbos

DATE OF FINAL REPORT: 19th August 2021

2. SYNOPSIS

Name of the Sponsor: Dra. Rosario García de Vicuña.	Individual Study Table referring to Part of the Dossier Module 5. Section 5.3.1.2.	(For National Authority Use only)
Name of Active Ingredient: **Kevzara® 200 mg solution for injection pre-filled syringes.**		

Title of study: Randomized open pilot study to evaluate the efficacy of subcutaneous sarilumab in patients with moderate-severe COVID-19 infection.

Investigators:
Principal Investigator: Dra. Rosario García de Vicuña, .**Coordinating investigator**: Dr. Jesús Sanz Sanz,
Sub-Investigators: Ángela Gutiérrez, José Curbelo, Miguel Martínez Marín, Azucena Bautista Hernández, Natalia Villalba, Andrés von Wernitz, Tamara Alonso Pérez, Pedro Landete, Irene Llorente Cubas, Eva Tomero Muriel, Sebastián Rodriguez García, Esther Ramírez Herráiz, Laura Cardeñoso Domingo, Aránzazu Alfranca, Isidoro González Álvaro, María Ángeles Sanz de Benito, Francisco Abad Santos, Gina Mejia Abril.

Study Centres:
Rheumatology, Internal Medicine, Emergency, Pneumology, Hospital Pharmacy, Microbiology, Inmunology, Clinical Analysis, and Clinical Pharmacology Services of Hospital Universitario de la Princesa. Madrid. Spain
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Publication (references): WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Shankar-Hari M, et al. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. JAMA. 2021 Jul 6:e2111330. doi: 10.1001/jama.2021.11330. Epub ahead of print. PMID: 34228774; PMCID: PMC8261689.

Study Period: Start of the study: 13th April 2020 End of the study: 4th December 2020	**Study development phase:** Phase II.

Objectives:
Main objective: To evaluate the efficacy of the early administration of sarilumab subcutaneously in patients with moderate-severe COVID-19 infection in early stages compared to the current treatment standard..
Secondary objective: To compare the baseline clinical and biological parameters, including serum IL-6, of the intervention population against historical controls, to search for possible markers that identify candidates for treatment with subcutaneous IL-6 inhibitors and attempt an approximation to the time frame of "window of opportunity".

Methodology: Phase II exploratory clinical trial (pilot study), controlled with parallel design, low-level intervention trial,sigle dose of 200 mg sarilumab +SC versus SC, randomised, open label**.**

Number of subjects: 30 patients adult patients admitted with microbiology documented COVID-19 infection, imaging confirmed pneumonia, fever and/or laboratory evidence of inflammatory phenotype and no need for invasive ventilation.

Diagnosis and main criteria for inclusion:
Adult patients who for recruitment, at least 2 of the following additional criteria needed to be fulfilled: Fever $\geq$ 37.8° C; IL-6 in serum $\geq$ 25 pg/mL or PCR> 5mg / dL; Lymphocytes <600/mm3; Ferritin > 300 μ g /L doubling in 24 hours; Ferritin > 600 μ g /L in the first determination and LDH > 250, or D-dimer > 1 mg / L. Exclusion criteria included: requirements of IMV at inclusion; AST / ALT values > 5 folds the upper normal limit; absolute neutrophil count <500/ mm3; absolute platelet count <50,000/ mm3; superimposed infection by pathogens other than COVID-19; complicated diverticulitis or intestinal perforation; immunosuppressive anti-rejection therapy; pregnancy or lactation; previous treatment with TCZ or SAR; contraindication to SAR or excipients and comorbidities that can likely lead to an unfavorable result.

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Participants were randomly assigned to receive sarilumab, a single 400 mg dose in two 200 mg subcutaneous injections, added to standard care or standard care in a 2:1 proportion.

Criteria for evaluation:
The primary end points were mortality by 30 days, mean change in functional status at day 7 on a 7-cathegory ordinal scale as recommended by the WHO R&D Blueprint Group(16) (1. death; 2. hospitalized, requiring ECMO, IMV, or both; 3. hospitalized, requiring high-flow oxygen therapy, NIMV, or both; 4. hospitalized, requiring supplemental oxygen; 5. hospitalized, not requiring supplemental oxygen but in need of ongoing medical care; 6. hospitalized, not requiring ongoing medical care; and 7. not hospitalized), and time to discharge from randomization. Secondary outcomes included time to become afebrile during 48 hours without antipyretics, mean change in 7-cathegory ordinal scale at day 14, time to NIMV and IMV, time to oxygen supply independence, and adverse events (AE). As no events occurred in SC, the outcomes time to NIMV and IMV were changed to progression to NIMV and IMV. More details are shown in the section 8 of this report. Safety also was analyzed

Results:
Thirty patients underwent randomization: 20 to sarilumab and 10 to standard care. Most patients were male (20/30, 67%) with a median (interquartile range) age of 61.5 years (56-72). At day 30, 2/20 (10%) patients died in the sarilumab arm vs none (0/10) in standard care (Log HR 15.11, SE 22.64; p 0.54). At day 7, no significant differences were observed in the median change in clinical status (2 [0-3]) vs 3 [0-3], p 0.32). Median time to discharge (days) were similar (7 [6-11] vs 6 [4-12]; HR 0.65, SE 0.26; p 0.27). No significant differences were detected in the rate of progression to invasive and noninvasive mechanical ventilation

Conclusions:
This pragmatic pilot study has failed to demonstrate a benefit of adding subcutaneous sarilumab to standard care for mortality by 30 days, functional status at day 7, or hospital stay. Findings herein do not exclude a potential effect of sarilumab in severe COVID-19 but adequately powered blinded randomized phase 3 trials are warranted to assess the impact of the subcutaneous route and a more selected target population.

Date of final report: March 10th, 2022