

PILOT STUDY ON THE USE OF SARILUMAB IN PATIENTS WITH COVID-19 INFECTION

Protocol number: COVID-SARI-001
Version Date: April 15, 2020
Revision: 3.1

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<p>This study protocol has been designed and will be carried out in compliance with the principles of the Good Clinical Practice guidelines as far as they are applicable and in observance of the Helsinki declaration and the current guidelines in force for observational studies.</p>

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1 BACKGROUND

The zoonotic transmission of a novel coronavirus called COVID 19 caused an outbreak of viral pneumonia in late 2019 in Wuhan, China. The outbreak originated in a fish market in Wuhan, but it is evident that the virus is transmitted efficiently in an interhuman way by means of droplets from the respiratory tract. Currently an autochthonous epidemic is underway in Lombardy. Scientific knowledge about the virus and the course of the disease is still extremely limited. Patients with COVID 19 infection with a serious course develop a pneumonia that can quickly degenerate into respiratory failure. The elderly and comorbid subjects, especially with cardio-circulatory diseases, are at greater risk of complications which can lead to an ARDS. A recent study has shown that patients who need hospitalization in ICU show a perturbed cytokine profile with high levels of IL-6, IL-2, IL-7, IL-10, and TNF- α . These alterations correspond to the cytokine release syndrome (CRS) which is an acute systemic syndrome characterized by fever and multi-organ failure associated with CAR-T (chimeric antigen receptor (CAR) -T cell therapy) therapy¹⁻².

Although immuno-inflammatory therapy is not routinely recommended in COVID 19 pneumonia, the presence of such a CRS-like profile, and the pulmonary anatomopathological findings of edema and hyaline membrane formation, suggest that a temporally targeted therapeutic approach accompanied by adequate ventilatory support could be beneficial in patients with severe pneumonia who develop ARDS.

Given the clinical and cytokine picture in patients with severe COVID 19 pneumonia, the use of an anti-IL-6 receptor drug could be justified for blocking the SIRS caused by the virus, in patients with high levels of IL-6.

In a study conducted in China (Effective Treatment of Severe COVID-19 Patients with Tocilizumab), a single dose of 400 mg tocilizumab IV was used; a preliminary paper reports promising results on 21 treated patients, with significant reduction of IL-6, fever and improvement of lung function³. Always in China, a trial is underway in the Anhui Province Hospital for the use of tocilizumab in the PCN (ChiCTR 2000029765).

Sarilumab is an anti-interleukin-6 human monoclonal antibody, such as tocilizumab, which is administered subcutaneously every two weeks for the treatment of moderate to severe active rheumatoid arthritis in adult patients.

1.1 Study rationale

Despite the effectiveness reported for tocilizumab in the recently published experiences, the need to rapidly find alternative therapies to manage the complications of Covid-19 infection remains extremely high. The lack of clinical experience on the usage of sarilumab in such patients prevents the possibility of adopting early access programs for using commercially available sarilumab (prefilled syringe) packs in patients with severe Covid-19 pneumonia. The present study is aimed to generate a rapid, still robustly documented, evidence on the potential clinical efficacy and tolerability of a further IL-6R antagonist in Covid-19 pneumonia.

1.2 Rationale for dose selection

In February 2020 the emergence of the COVID-19 epidemic in Italy and, above all, in Lombardy, with a potential fatal outcome in a significant proportion of cases, determined the need for adopting new therapeutic approaches based on the few data available in literature. Among them, the use of tocilizumab in Covid-19 pneumonia as reported in the publication on the Chinese experience³ has rapidly grown.

Also at our Institution the treatment protocol reported there was initially adopted. The preliminary data obtained from 14 patients treated with tocilizumab 400 mg iv showed however a very modest

effect on respiratory function. According to the recommendation of the Società Italiana di Malattie Infettive e Tropicali (SIMIT) expert group, recently published online⁴, higher dose levels of tocilizumab seems to provide a more favorable efficacy, yet maintaining a convenient safety profile. Such an assumption has been confirmed by our direct experience, as higher doses (8-10 mg/Kg) of tocilizumab evidenced a more promising response in 12 further patients treated later, with 80% having a significant clinical improvement (i.e. significant reduction of ventilation support). Such dosage is currently the standard used in CRS at our Institution.

Although there are no clinical data available in COVID-19 patients concomitantly treated with Sarilumab subcutaneously (SC) nor intravenously (IV), there is scientific rationale that supports the exploration of sarilumab to treat pulmonary complications related to Covid-19⁵⁻⁶. By inhibiting IL-6 signaling, sarilumab may potentially interrupt cytokine-mediated pulmonary injury precipitated by infection with SARS-CoV-2 and thereby ameliorate severity and/or reduce mortality among patients presenting with Covid-19 pneumonia when administered in conjunction with antiviral therapy.

The PK, PD and safety of sarilumab and tocilizumab were compared in several Sarilumab randomized trials. In a single-dose, open-label randomized trial the PK and PD were assessed in patients with RA randomized 1:1:1:1 to either 150 mg or 200 mg (SC) of sarilumab, or 4 mg/kg or 8 mg/kg (IV) of tocilizumab. In a single dose PK/PD study, 150 mg of sarilumab (SC) was compared to 162 mg of tocilizumab (SC) in Japanese patients with RA randomized 1:1⁷. In these single dose studies, consistent with saturation of the target-mediated pathway for sarilumab and tocilizumab, all dose levels regardless of the route of administration demonstrated similar maximal effect in suppression in CRP and ANC lowering. Higher dose levels and the associated higher concentrations beyond that need to achieve saturation, resulted in a longer duration of the maximal PD response, but did not result in a deeper response. Subcutaneous single doses of sarilumab (150 mg) or tocilizumab (162 mg) resulted in similar concentration time profiles and yielded nearly identical PD response in CRP and ANC, as well as changes in sIL-6R and IL-6 over time⁸. Although PK/PD modeling suggested that the higher binding affinity to IL-6R α of sarilumab compared to tocilizumab translates to greater receptor occupancy⁹ there is currently no detailed information available on sIL-6R α concentrations in patients with COVID-19.

Therefore, given the apparent dose/dose PK/PD equivalence of 400 mg of tocilizumab to 400 mg of sarilumab, we propose a dose escalation protocol by which the first 5 included patients will be treated with a dosage of 200 mg of sarilumab IV as 1st dose, followed by clinical reassessment after 12 hours and in case of no major adverse events and lack of improvement in respiratory function and / or persistence of fever and persistently high inflammatory markers re-administration of 200 mg IV of sarilumab.

If no patients showed unfavorable safety signals, and no clear improvement is detected in >50% of the initially treated five patients after 96hrs since last administration, the dosage will be increase to sarilumab 400 mg IV as 1st and 2nd dose in the remaining patients.

2 OBJECTIVES

2.1 Primary objective

The primary objective of this study is to evaluate the safety and clinical efficacy of sarilumab in adult patients hospitalized due to severe Covid-19 pneumonia based on the proportion of patients who show an improvement of the respiratory function, described as $\geq 30\%$ decrease in oxygen requirement compared to baseline (as defined as the ratio of O₂ flow through the Venturi mask).

2.2 Secondary objective

Further investigate the potential effectiveness of sarilumab in Covid-19 pneumonia by means of:

- In patients with fever at baseline, evaluation of the time to resolution of fever, defined as body temperature $\leq 36.6^{\circ}\text{C}$ axilla, $\leq 37.8^{\circ}\text{C}$ rectal or tympanic for at least 48 hours without antipyretics;
- Evaluation of the viral load on blood and sputum for COVID-19 before administration of sarilumab, 48 hours and 96 hours after administration;
- Evaluation of the plasma concentration of IL-6, TNF- α , IL-10, and GM-CSF pre-treatment and 96 and 120 hours post-treatment;
- Evaluation of the rate of progression of WBC fraction of immature granulocytes - IG - (absolute and % counts) and the morphological-functional parameters defined by:
 - cytoplasmic complexity
 - fluorescence intensity
 - size
 - distribution magnitude of events on both axes of the WDF cytogram.

3 STUDY DESIGN

This is an open-label, single arm, dose-escalation design, single center study.

3.1 Study Population

The study will enroll 40 patients in total, over a period of approximately 6 weeks (since the first patient enrolment), from adults hospitalized in the Interdepartemental Unit of Infectious Diseases of our Institution.

Patients eligibility will be assessed according to the Brescia-COVID respiratory severity scale (BCRSS) reported in Appendix 1, and only patients with documented (chest X-Ray or TC scan) Covid-19 (PCR+ swab test) interstitial pneumonia and BCRSS ≥ 3 and < 4 will be requested consent to the study.

3.2 Inclusion criteria

- Age ≥ 18 years and < 85 years.
- Documented (chest X-Ray or TC scan), severe (BCRSS ≥ 3 and < 4) interstitial pneumonia with respiratory failure (requiring supplemental oxygen) with positive Covid-19 swab testing.
- Worsening of respiratory exchanges such as to require ventilation with Venturi mask $> 31\%$ (6L/minute).
- Increased levels of D-dimer (> 1500 ng/mL) or D-dimer progressively increasing (over 3 consecutive measurements) and reaching ≥ 1000 ng/mL.
- Signed informed consent.

3.3 Exclusion criteria

- Age < 18 years or ≥ 85 years.
- AST / ALT $> 5 \times$ ULN.
- Neutrophil count lower than 500 cells / mL.
- PTL count lower than 50,000 cells / mL.
- Documented sepsis due to infections other than Covid-19.

- Presence of serious co-morbidities (such as COPD, diabetes, or cardiomyopathies) likely to cause, according to the clinical judgment, an unfavorable outcome.
- Complicated diverticulitis or intestinal perforation.
- Immunosuppressive therapy due to organ transplant.

4 PROCEDURES

Patients will be followed up for at least 6 weeks after enrollment. During hospitalization, vital sign, body temperature, and oxygen delivery will be measured twice daily, clinical status and blood samples daily, blood and sputum for Covid-19 viral load assessment before administration of sarilumab, 48 hours and 96 hours after administration, and blood to assess the plasma concentration of IL-6, TNF- α , IL-10, and GM-CSF pre-treatment and 96 and 120 hours post-treatment. Once patients are discharged subsequent visits may occur remotely via available options for telecommunication (eg., telephone, Internet).

4.1 Drug preparation and administration

The study has a dose-escalation design. As such, doses will be escalated according to the overall safety of the investigational drug, and the initial efficacy response shown by patients.

The first 5 (five) included patients will be in fact treated with a dosage of 200 mg of sarilumab IV as 1st dose, followed by clinical reassessment after 12 hours and, in case of no major adverse events and of lack of improvement in respiratory function and / or persistence of fever and persistently high inflammatory markers, re-administered with further 200 mg IV of sarilumab.

If no clear improvement (as defined in the Primary Objective) is detected in >50% of the initially treated five patients after 96hrs since last administration, the dosage will be increase to sarilumab 400 mg IV as 1st and 2nd dose in the remaining patients.

200 mg IV dose preparation: one single-dose pre-filled syringe containing 200 mg sarilumab in 1.14 ml solution (175 mg/ml) added to 100 mL 0.9% sodium chloride for a 1-hour intravenous infusion.

400 mg IV dose preparation: two single-dose pre-filled syringes, each containing 200 mg sarilumab in 1.14 ml solution (175 mg/ml) added to 100 mL 0.9% sodium chloride for a 1-hour intravenous infusion.

4.2 Study treatments

Sarilumab administration must be associated with an antiviral treatment as defined by the treatment protocol suggested by the SIMET Experts group⁴ and AIFA recommendations

- chloroquine 500 mg 1 tablet twice daily or
- hydroxychloroquine 400 mg 1 tablet twice daily in the first day and then 200 mg 1 tablet twice daily.

Patients with potential latent HBV infection (HBsAg positive, or HBcAb positive but HBsAb negative) can be treated also with lamivudine 100 mg 1 tablet daily as prophylaxis.

4.3 Study Visits

Adult patients selected on the basis of the inclusion/exclusion criteria will be asked to participate to the study and informed consent will be obtained.

The clinical history, laboratory and instrumental data of patients will be collected and recorded in the CRF according to the following scheme:

Study Procedure	Screening Visit ¹	Baseline Visit ¹	Daily Follow-up						Post-discharge
Day	-1 or 1	1	2	3	4	5	7	15 or discharge	45
Window (day)							±2	±3	±15
Screening/Baseline:									
Inclusion/Exclusion	X								
Informed Consent	X								
Demographics and Medical History	X								
Enrollment		X							
Treatment:									
Study Drug Administration		X							
Assessments:									
Body Temperature	X	Predose and 4 times a day Day 1-4; 2 times a day Day 5-Discharge						X	
Oxygen Delivery and Oxygenation	X	4 times a day (Day 1-4); Day 4-discharge record results as assessed						X	
Resting SpO ₂	X	4 times a day (Day 1-4); Day 4-discharge record results as assessed						X	
Clinical Daily Assessment	X	Daily until discharge						X	
Vital Status (and cause of death)		Daily until discharge						X	
Vital Signs (other than temperature and SpO ₂)	X	Daily until discharge						X	
Limited physical examination	X					X			
Record Targeted Medications		Daily until discharge						X	
Adverse Events	X	Daily until discharge						X	X
Laboratory Testing Standard-of-Care:									
Hematology Results	X	Daily (Day 1-4); Day 4-discharge record results as assessed						X	
Blood Chemistry Results	X	Daily (Day 1-4); Day 4-discharge record results as assessed						X	
C-Reactive Protein Results	X	Daily until discharge						X	
Biomarkers/Research:									
Serum cytokines including IL-6		X	X	X	X		X	X	X ⁴
Serum sIL-6R		X	X			X	X		
Blood/sputum for Covid-19 viral load assessment	X	Daily until discharge						X	X ⁴

4.4 Biological samples

Before each infusion and after 48, 96 and 148 hours from the last infusion, collect 1 plasma and 1 blood sample in EDTA to be stored at -20 °C (2-3 vials of 1 ml aliquots of plasma) or in liquid nitrogen (1 vial of cells after Ficoll centrifugation) for any post hoc analyses.

4.5 Safety variables

Safety variables include incidence of adverse events (AE), serious adverse events (SAE), and laboratory safety test results (white cell count including ANC, hemoglobin, platelets, creatinine, total bilirubin, ALT, AST).

4.6 Adverse events

Management

All events will be recorded in the CRF. All serious Adverse Events, either related or non-related, will be reported to Sanofi within 1 (one) working day.

Definitions

- Adverse Event of Special Interest (AESI): An adverse event of special interest (AESI) is an adverse event (serious or non-serious) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AESIs may be added or removed during a study by protocol amendment.
- New safety finding : Any (other than reportable individual case safety report (ICSR)) safety issue that may require expedited reporting because providing information that may lead to a change in the known risk-benefit balance for the product and as mentioned, but not limited to, in the following regulatory texts: Europe: Good Pharmacovigilance Practices , modules VI and VII; and US: FDA: 21 CFR Parts 312 Investigational New Drug Application-Section 312.32, (c) (1) IND safety reports.
- Related Adverse Event, i.e. Adverse Drug Reaction (ADR): There is a reasonable possibility according to the Investigator that the product may have caused the event.
- Serious adverse event (SAE): any untoward medical occurrence that at any dose:
 - Results in death
 - Is life threatening, (Note: the term “life-threatening” refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)
 - Requires inpatient hospitalization or results in prolongation of existing hospitalization
 - Results in persistent or significant disability/incapacity
 - Is a congenital anomaly/birth defect, or
 - Is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.
- Unexpected related Adverse Event, i.e. Unexpected Adverse Drug Reaction (ADR): An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product or package insert/summary of product characteristics for an approved product). An expected ADR with a fatal outcome should be considered unexpected unless the

local/regional product labeling specifically states that the ADR might be associated with a fatal outcome.

5 DATA MANAGEMENT AND STATISTICAL ANALYSIS

5.1 Data Management

The Principal Investigator or the Co-investigator will perform all the assessments and collect all the measurements. This information will be recorded on an electronic database and statistically analyzed.

5.2 Sample size and statistical analysis

Considering that no data are available about the effectiveness of sarilumab in Covid-19 pneumonia, no formal sample size calculation has been performed. All collected Efficacy and Safety variables will be summarized by descriptive statistics, as total group observations or summarized by the type of concomitant antiviral treatment, and changes from baseline over time assessed with appropriate inferential statistical tests assuming an error alpha-level of 5%.

6 ADMINISTRATIVE PROCEDURES

6.1 Good Clinical Practice

This study will be conducted in accordance with the Good Clinical Practice [ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996 Directive 91/507/EEC; D.M. 15.7.1997], the Helsinki declaration and National regulations concerning observational studies. Signing the protocol, the investigator agrees to adhere to the listed procedures and the instructions and to conduct the study in accordance to GCP, the Helsinki declaration and National regulations concerning the conduction of observational studies.

6.2 Protocol Amendments

Any modification to the protocol will be made as an amendment. No modification to the protocol will be allowed during the study period.

6.3 Ethics Committee

The study protocol and relative documents will be submitted to the competent Ethics Committee for approval. The study will only begin after the necessary authorizations have been received, according to the internal procedures of the Institution.

Amendments related to safety measures can be applied without prior written authorization from the Ethics Committee, which has to be informed within 30 working days.

6.4 Study Insurance

Taking into consideration that not-for-profit nature of the study, study insurance is not foreseen as patients are already covered by the Institution insurance.

6.5 Informed consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

Each patient who meets the study's inclusion criteria will be asked to sign an informed consent for the participation into the study. Signing the consent will allow the blood samples collection for determining acid beta-glucosidase enzyme activity (screening and, if required, confirmatory test) and the access to personal and clinical data for the purpose of this study.

6.6 Document storage

Principal Investigator is responsible for storage of data and preservation of study documents, during and after the end of the study, in accordance with the regulations in force and the Good Clinical Practice.

6.7 Owner of scientific data

The study sponsor, Divisione Interdipartimentale di Malattie Infettive - ASST Fatebenefratelli Sacco, will be the owner of the collected data.

6.8 Privacy

Personal patient data will be collected on the Case Report Form (CRF) which contains only the patient's initials and a specific identification number, assigned to each participating center, followed by another progressive identification number for each patient, based on the recruitment order.

Study documents will be stored in a safe place to grant confidentiality and privacy. Data has not to be disclosed without written authorization by the Principal Investigator.

6.9 Result publication and communication policies

The Principal Investigator will undertake to draw up a final report and a scientific article, and to publish the results on completing the study in a peer-reviewed journal. In the final scientific article, the Principal Investigator will be listed as first author.

The patient's data will be made public in anonymous form and will be presented just as group data.

7 REFERENCES

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8 APPENDIXES

Appendix 1

Brescia-COVID respiratory severity scale (BCRSS)

