Supplementary Materials

Sarilumab plus standard of care *versus* standard of care for the treatment of severe COVID-19: a phase 3, randomized, open-labeled, multi-center study (ESCAPE Study).

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Table S1. Probability of orotracheal intubation (IOT) or extracorporeal membrane oxygenation (ECMO) at 30 days.

	Arm A (treatment group)		**Arm B (SOC group)**			
	Number of events	Probability (95%CI)	Number of events	Probability (95%CI)	HR (95%CI)	Log-rank *p*-value
Day 30	9	7.5% (4.0-13.9)	5	7.3% (2.8-18.4)	0.81 (0.27-2.42)	0.703

Abbreviations: CI, confidence interval; HR, hazard ratio estimating the risk of the event in arm A vs arm B; SOC, standard of care.

Figure S1. Kaplan Meier survival curves estimating the cumulative proportion of patients experiencing orotracheal intubation (IOT) or extracorporeal membrane oxygenation (ECMO) at 30 days. ***Arm A:*** *sarilumab plus standard of care.* ***Arm B:*** *standard of care.*

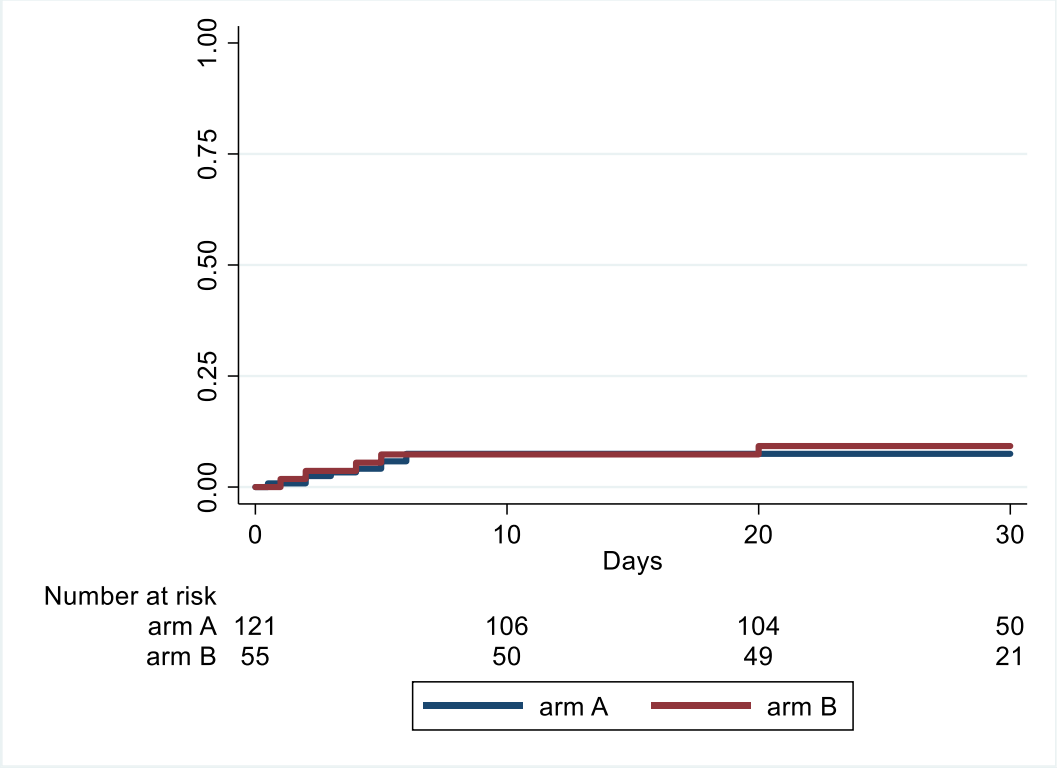

Table S2. Probability* of non-invasive ventilation (NIV) or orotracheal intubation (IOT) or extracorporeal membrane oxygenation (ECMO) at 30 days.

	Arm A (treatment group, *n=66)		**Arm B (SOC group, *n=31)**			
	Number of events	Probability (95%CI)	Number of events	Probability (95%CI)	HR* (95%CI)	Log-rank *p*-value
Day 30	16	24.2% (15.6-36.5)	9	29.0% (16.3-48.4)	0.79 (0.35-1.82)	0.567

*calculated only among participants requiring supplemental oxygen with venturi mask at baseline or not requiring supplemental oxygen at baseline.
Abbreviations: CI, confidence interval; HR, hazard ratio estimating the risk of the event in arm A vs arm B; SOC, standard of care.

Figure S2. Kaplan Meier survival curves estimating the cumulative proportion of patients experiencing non-invasive ventilation (NIV) or orotracheal intubation (IOT) or extracorporeal membrane oxygenation (ECMO) at 30 days (calculated among participants requiring supplemental oxygen with venturi mask at baseline or not requiring supplemental oxygen at baseline). ***Arm A:*** *sarilumab plus standard of care.* ***Arm B:*** *standard of care.*

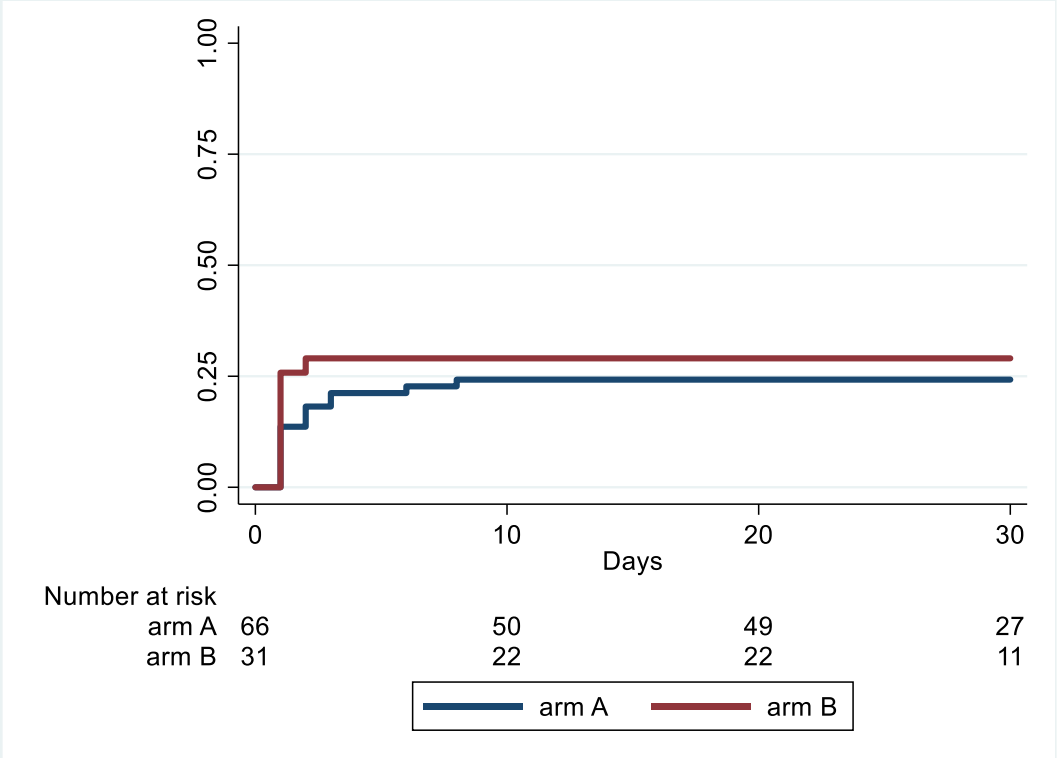

Table S3. Probability* of PaO_2/FiO_2 increasing of at least 50 mmHg for at least 48 hours, compared to the nadir PaO_2/FiO_2 at 10 days.

	Arm A (treatment group, *n=87)		Arm B (SOC group, *n=44)			
	Number of events	Probability (95%CI)	Number of events	Probability (95%CI)	HR (95%CI)	Log-rank *p*-value
Day 10	76	97.0% (90.8-99.4)	32	93.8% (76.9-99.5)	1.06 (0.69-1.62)	0.873

*calculated only among participants whose data were available.
Abbreviations: CI, confidence interval; HR, hazard ratio estimating the risk of the event in arm A vs arm B; SOC, standard of care.

Figure S3. Kaplan Meier survival curves estimating the cumulative proportion of patients experiencing PaO_2/FiO_2 increasing of at least 50 mmHg for at least 48 hours, compared to the nadir PaO_2/FiO_2, at 10 days (calculated among participants whose data were available: 87 in arm A and 44 in arm B). ***Arm A:*** *sarilumab plus standard of care.* ***Arm B:*** *standard of care.*

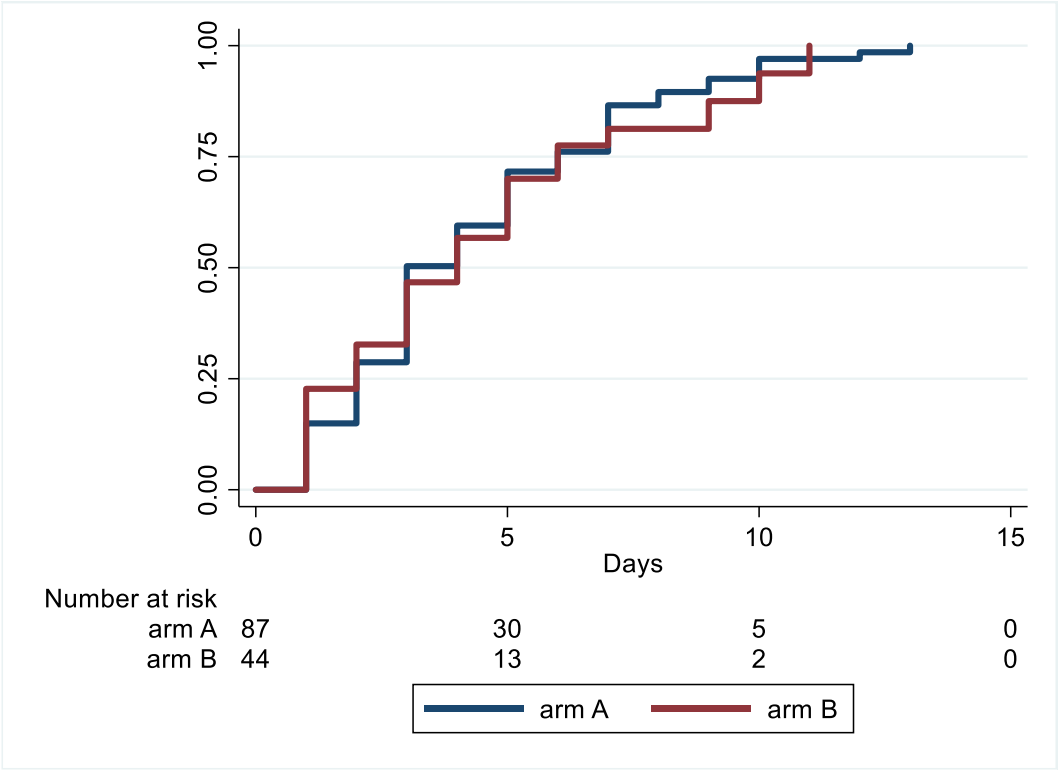

Table S4. Probability of oxygen weaning at 30 days.

	Arm A (treatment group)		**Arm B (SOC group)**			
	Number of events	Probability (95%CI)	Number of events	Probability (95%CI)	HR (95%CI)	Log-rank *p*-value
Day 30	98	86.4% (78.1-92.7)	46	81.5% (69.6-90.8)	1.06 (0.74-1.53)	0.377

Abbreviations: CI, confidence interval; HR, hazard ratio estimating the risk of the event in arm A vs arm B; SOC, standard of care.

Figure S4. Kaplan Meier survival curves estimating the cumulative proportion of patients weaned from oxygen at 30 days. ***Arm A:*** *sarilumab plus standard of care.* ***Arm B:*** *standard of care.*

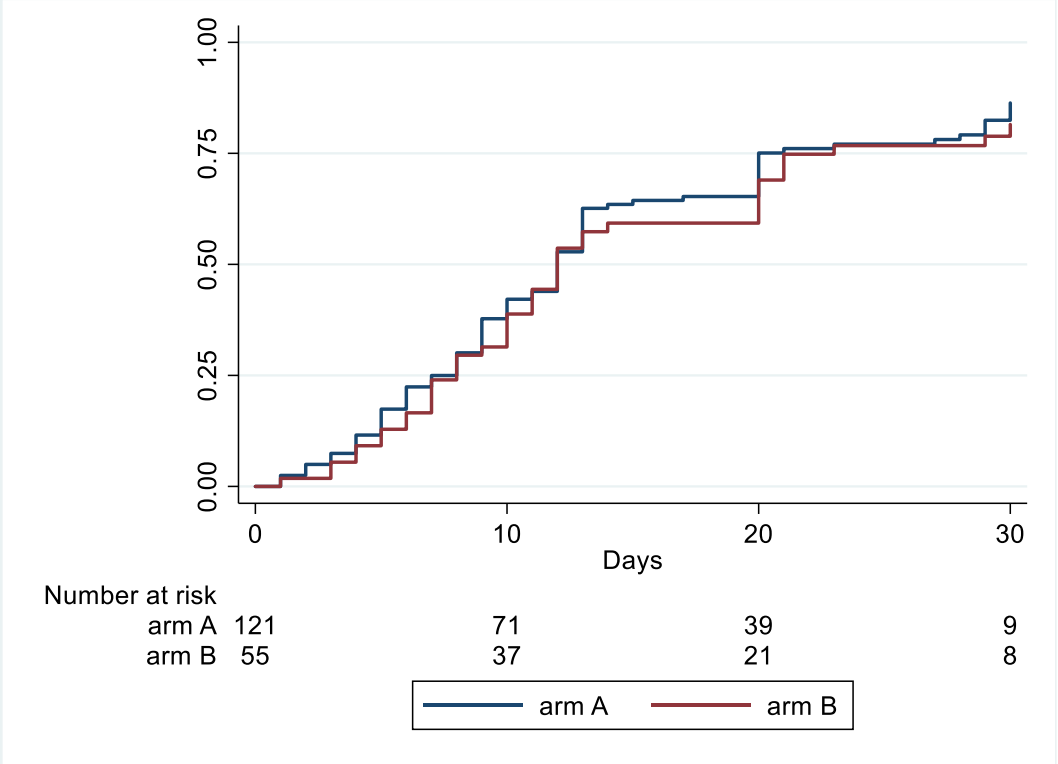

Table S5. Probability of hospital discharge at 30 days.

	Arm A (treatment group)		Arm B (SOC group)			
	Number of events	Probability (95%CI)	Number of events	Probability (95%CI)	HR (95%CI)	Log-rank *p*-value
Day 30	100	87.8% (80.0-93.6)	46	81.5% (69.6-90.8)	1.10 (0.77-1.58)	0.281

Abbreviations: CI, confidence interval; HR, hazard ratio estimating the risk of the event in arm A vs arm B; SOC, standard of care.

Figure S5. Kaplan Meier survival curves estimating the cumulative proportion of patients discharged at 30 days. ***Arm A:*** *sarilumab plus standard of care.* ***Arm B:*** *standard of care.*

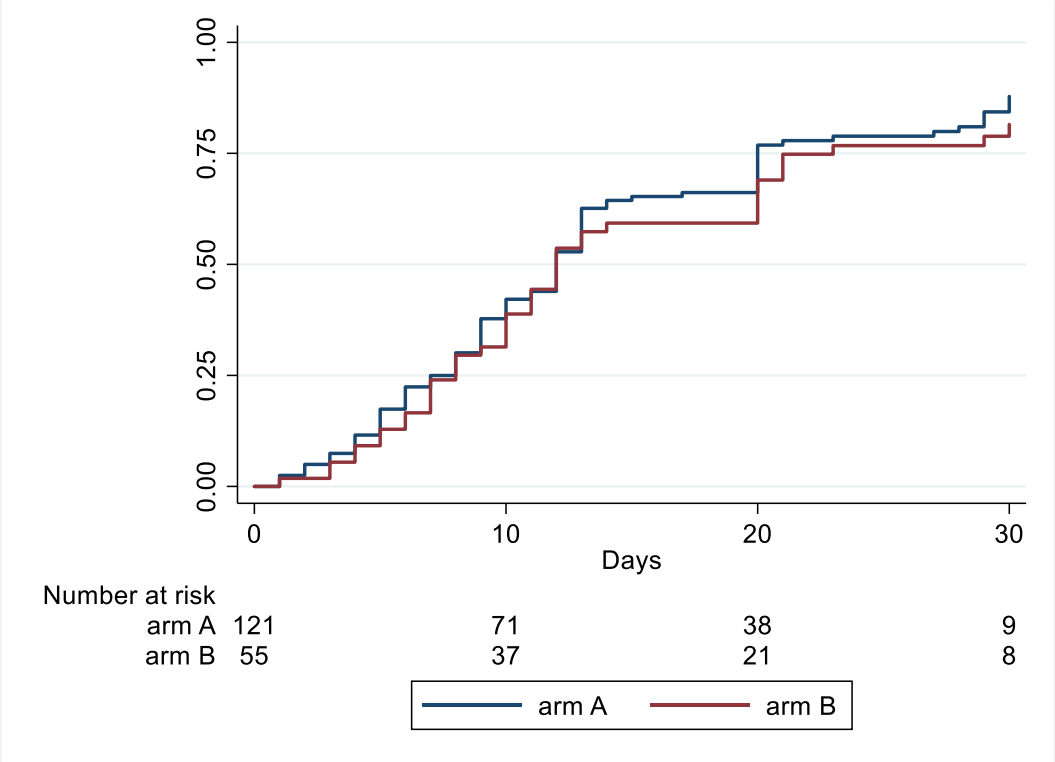

Table S6. Proportion* of patients achieving negative nasopharyngeal swabs at 30 days.

Arm A (treatment group, *n=79)	**Arm B (SOC group, *n=35)**	
Number of events	Number of events	*p*-value
62 (78.5%)	28 (80.0%)	0.854
*calculated only among participants whose data were available. **Abbreviations**: SOC, standard of care.		

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CLINICAL TRIAL PROTOCOL

Protocol Title: "*A phase 3, randomized, open-labeled, multi-center study comparing clinical efficacy and safety of intravenous sarilumab plus standard of care compared to standard of care, in the treatment of patients with severe COVID-19 pneumonia (ESCAPE Study)*"

Eudract Number: 2020-001390-76

Investigational compound: Sarilumab

Study promotor and legal registered address: National Institute for Infectious Diseases L. Spallanzani IRCCS, Via Portuense 292, Rome, Italy

Study phase: phase 3

Short title: ESCAPE study

Protocol version: 3.0 06 October 2020

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Co- principal Investigator: Nicola Petrosillo

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Clinical study writing and operative coordinating committee: Maria Maddalena Plazzi (Study Coordinator), Annalisa Mondi, Roberta Gagliardini, Patrizia Lorenzini, Federico De Zottis, Marta Camici, Sandrine Ottou.

Independent Data Monitoring Committee (IDMC): One expert in the clinical aspects of COVID-19 (Franco Maggiolo); One independent biostatisticians (Alessandro Cozzi-Lepri); One investigator with expertise in current COVID-19 clinical trials conduct and methodology (Antonio Di Biagio)

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SIGNATURE PAGE

The Principal Investigator:

- is agree with present study protocol;
- declare that study will be conducted according to study protocol.

Principal Investigator: Dr. Andrea Antinori

Date 6/10/2020

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APPENDIX F- Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

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PROTOCOL SYNOPSIS	
Study Title	***A phase 3, randomized, open-labeled, multi-center study comparing clinical efficacy and safety of intravenous sarilumab plus standard of care compared to standard of care, in the treatment of patients with severe COVID-19 pneumonia (ESCAPE Study)*** **Short title: Clinical *efficacy and safety of intravenous Sarilumab plus standard of care compared to standard of CAre, in the treatment of patients with severe COVID-19 Pneumonia* (ESCAPE Study)**
Rationale	On January 9 2020, the "World Health Organization" (WHO) declared the identification, by Chinese Health authorities, of a novel coronavirus, further classified as SARS-CoV-2[1]. This new virus, initially emerged in the Chinese city of Wuhan in December 2019, led to a sharply spreading outbreak of human respiratory disease (COVID-2019), both within People's Republic of China and in several other countries worldwide. On March 11 2020, WHO declared COVID-19 a pandemic [2]. The full spectrum of COVID-19 infection ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia with typical radiographic features on CT scan, which can worsen rapidly into acute respiratory distress and death [3,4]. Elderly patients with comorbidities and with a weaker immune function seem to be a higher risk of developing severe form of COVID-19 infection [5,6]. Thus far, the pathophysiology of COVID-19 has not been completely understood and, despite many attempts with antiviral and other therapeutic agents, no specific drug has been demonstrated to be efficacious for SARS-COV-2 infection. Several studies have suggested that in patients affected by severe forms of COVID-19 an aberrant host immune response with an increased production of proinflammatory cytokines, the so-called "cytokine storm", could be responsible for inflammation and long term and extensive lung damage. Indeed, in patients admitted in ICU with severe COVID-19 infection, higher plasma levels of cytokines including interleukin (IL)-6, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10), monocyte chemoattractant protein

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(MCP1), macrophage inflammatory protein 1 alpha (MIP1A), and TNF-α which correlate to the severity and prognosis of the disease were found [5,6]. Similar alterations have been described both in SARS- and in MERS-CoV infections [7,8].

Among inflammatory mediators, IL-6, a pleiotropic proinflammatory multifunctional cytokine produced by a variety of cell types, might play a key role in the cytokine storm. Thus, it has been speculated that interfering with IL-6 might have a therapeutic potential for patients with severe form of COVID-19. In the light of this hypothesis, a group of Chinese researchers recently treated 21 patients with severe or critical COVID-19 pneumonia with 400 mg intravenous of Tocilizumab, a recombinant humanized monoclonal antibody directed against IL-6, obtaining unexpectedly optimal results in terms of clinical and radiological improvement, normalization of laboratory parameters and duration of diseases [9].

While attending stronger evidences of tocilizumab efficacy from ongoing randomized clinical trial, early reports suggested that systemic inhibition of IL-6 signaling may have value as a supportive therapy. Thus, new therapeutic agents with similar mechanism of action have been proposed for COVID-19 treatment.

Sarilumab is a recombinant human IgG1 kappa monoclonal antibody directed against soluble and membrane-bound IL-6 receptor (IL-6Rα). It is formulated as a solution for subcutaneous injection at doses of 150 and 200 mg every 2 weeks. It is currently approved for the treatment of moderate to severe rheumatoid arthritis [10]. Sarilumab inhibition of IL-6 signaling leads to a decrease in concentration of free sIL-6Rα and normalization of levels of acute phase proteins and markers of inflammation, such as C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen [11]. Although there are not direct evidences of sarilumab efficacy on COVID-19 pneumonia, the inhibition of both soluble and membrane bound forms of IL-6Rα mediated by the drug with the consequent suppression of pro-inflammatory signaling by both pulmonary epithelial and immune cells, leads to the hypothesis that it could reduce the severity of pulmonary COVID-19 complications,

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	including respiratory failure.
Objectives	**Primary Objective:** To evaluate the efficacy of sarilumab, combined with standard of care, in patients affected by severe COVID-19 pneumonia. **Secondary Objectives:** To evaluate the effect of sarilumab on survival To evaluate the effect of sarilumab on clinical evolution To evaluate the effect of sarilumab on lung function To evaluate the effect of sarilumab on hyperinflammation parameters To evaluate the effect of sarilumab on immunological response To evaluate the effect of sarilumab on other relevant laboratory parameters To evaluate the effect of sarilumab on radiological response To evaluate the effect of sarilumab on virological response To evaluate the effect of sarilumab on duration of hospitalization To describe safety profile of sarilumab
Endpoints	**Primary Endpoint:** The primary end point will be the time to clinical improvement, defined as the time from receiving the first dose of drug to an improvement of two points (from the status at baseline) on a 7-point category ordinal scale. The 7-point category ordinal scale consisted of the following categories: 1. not hospitalized with resumption of normal activities; 2. not hospitalized, but unable to resume normal activities; 3. hospitalized, not requiring supplemental oxygen; 4. hospitalized, requiring supplemental oxygen; 5. hospitalized, requiring noninvasive mechanical ventilation (CPAP or NIV); 6. hospitalized, requiring ECMO, invasive mechanical ventilation, or both; 7. death.

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	Secondary Endpoints: The secondary endpoints of the study are: • Mortality rate within 30 days from baseline; • Time from treatment initiation to death • Time to mechanical ventilation or extracorporeal membrane oxygenation (ECMO) • Time to non-invasive ventilation (in patients requiring only supplemental oxygen with venturi mask or not requiring oxygen at baseline) • Time to increase in PaO2/FiO2 of 50 or greater compared to the nadir PaO2/FiO2 for at least 48 hours; • Days of hypoxemia (SpO2 <93% on room air, or requiring supplemental oxygen, or non-invasive ventilation support) • Change from baseline in PaO2/FiO2 • Time to change in MEWS from baseline • Time to resolution of fever (≤36.6°C [axilla], or ≤37.2 °C [oral], or ≤37.8°C [rectal or tympanic]) • Days with fever (>36.6°C [axilla], or >37.2 °C [oral], or >37.8°C [rectal or tympanic]) • Change from baseline in lymphocyte count, ferritin, D-dimer, LDH, C-reactive protein • Change from baseline in inflammatory cytokines (IL1b, IL-6, IL-8, TNF-a) levels quantified by automated ELISA assay. • Change from baseline in differentiation and activation profile of CD4 and CD8 T cells analysed by flow cytometry. • Evolution from baseline of TLR expression and cytokines production by lymphocytes and monocytes tested by flow cytometry • Change from baseline in platelet count, fibrinogen creatinine • Improvement of CT scan findings repeated within 15 days from baseline • Proportion of patients achieving confirmed negative nasopharyngeal swabs (2 negative swabs within 24 hours)

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	• Evolution of SARS-CoV2 serology • Days of hospitalization among survivors • Proportion of patients discharged hospital • Time to hospital discharge • Serious adverse events (including severe bacterial or fungal infections) • Treatment-emergent laboratory abnormalities
Study Design	Open-label, randomized study assessing clinical efficacy and safety of intravenous Sarilumab plus standard of care, compared to standard of care, in the treatment of patients with severe COVID-19 pneumonia
Number of Subjects	Fixing a power of 80% and a two-sided significance level of 5%, assuming that the median time to clinical improvement of participants in the standard-of-care (SOC) group was estimated as 16 days [14], to observe a reduction in the experimental arm of the endpoint to 10 days (reduction of 37%), 171 patients are needed. Patients will be randomized, according to a design 2:1, to experimental arm (n=114) and to control group (n=57). The randomization will be stratified byrespiratory function: a) PaO2/FiO2 >=200 mmHg or b) PaO2/FiO2 <200 mmHg or the presence of non-invasive ventilation (NIV or CPAP) and
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Duration of Recruitment	12 months
Duration of Treatment	Experimental treatment will consist of a single dose, repeatable after 12 hours in patients without or with not complete improvement.
Anticipated Start Date / Anticipated End Date	1st May 2020. The end of study is defined as the date the last patient completes the last study assessment (in the hospital or via a follow-up phone call if the patient was discharged from the hospital before day 30), withdraws from the study or is lost to follow-up.
Target Population / Demographics	Hospitalized patients with documented SARS-CoV-2 infection and radiological evidence of pneumonia in severe or critical clinical condition. Eligible patients can have the following situations: have planned to assume, are assuming or have recently assumed antiviral therapy as standard of care, or are not assuming any antivirals
Eligibility Criteria	**Inclusion criteria:** 1. Age ≥ 18 years 2. Signed informed consent provided by the patient, or by the patient's legally authorized representative(s), as applicable. Orally provisions could be considered in emergency conditions if deemed necessary by the investigator (signature of the informed consent will occur if and as soon as clinical conditions improve). 3. Virological diagnosis of SARS-CoV-2 infection (SARS-CoV-2 infection confirmed by PCR test or positive serology) 4. Evidence of pulmonary infiltrates at CT scan or Chest XRay 5. Oxygen saturation (SpO2) at rest without oxygen supplementation < 93% or PaO2/FiO2 < 300 at rest in patients requiring oxygen supplementation (either Venturi mask or cPAP or NIV). 6. Evidence of hyperinflammation defined as at least two of the following: i. Blood lymphocytes <1000/mm^3

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	ii. Ferritin > 500ng/mL; iii. LDH > 300 U/L; iv. D-Dimers > 1000 ng/mL v. C-reactive protein > 3 mg/dL 7. Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix F.
	Exclusion criteria: 1. Known hypersensitivity to sarilumab or its excipients 2. Known active infections or other clinical condition that contraindicate sarilumab and cannot be treated or solved according to the judgement of the clinician 3. Patient being treated with immunomodulators or anti-rejection drugs 4. Pregnancy/lactation 5. Neutrophils count < 500 cell/mm3 6. Platelets count < 50.000/mm3 7. ALT / AST> 5 times the upper limit of the normality 8. Bowel diverticulitis or perforation 9. Existence of any life-threatening co-morbidity or any other medical condition which, in the opinion of the investigator, makes the patient unsuitable for inclusion. 10. Severe hepatic dysfunction 11. Creatinine clearance < 30 ml/min/1.73 m2 12. Mechanical ventilation or ECMO 13. Enrolment in another concurrent clinical interventional study 14. Intake of an investigational drug within 3 months
Experimental Therapy	Participants who satisfy the inclusion and exclusion criteria will be randomized (2:1) to receive: • **Treatment Group A (experimental arm):** <u>continued standard of care (SOC)</u> as below

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	reported + <u>one single infusion of sarilumab 400 mg IV</u> (two sarilumab 200 mg, single dose prefilled syringes (PFS) mixed in 100 ml 0.9% sodium chloride solution for intravenous use). A second dose could be administered at the discretion of the investigator after 12 hours from the first dose. • **Treatment group B (control arm):** <u>continued SOC</u> as below reported.
Standard of care (SOC) Therapy	All patients enrolled will receive standard of care (SOC). SOC can include corticosteroids and/or antivirals, according to decision of clinical investigator and current guidelines.
Rescue therapy	For patients enrolled in the control arm who withdraw from the study for safety reasons, according to clinical judgment, a rescue therapy with intravenous sarilumab is expected.
Study Procedures / Frequency	**SCREENING (day -1/day 1)** At screening the investigators have to check the eligibility of patient for the study and obtain informed consent. The following procedures will be performed: • Demographic characteristics • Focused medical history and current medication • Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature) • Respiratory status (PaO2/FiO2, SpO2 at rest when applicable) • Oxygen supplementation (room air, nasal canula, Venturi mask, noninvasive ventilation or high flow oxygen devices) • Serum pregnancy test at screening (for women of childbearing potential) • Electrocardiogram (ECG) • Routine blood tests (blood count, creatinine, BUN, sodium, potassium, ALT, AST, LDH, fibrinogen, D-dimers, ferritin, PCR) • Immunologic parameters: IL-6, IL-1b, IL-8, TNFα, quantitative and qualitative analysis of CD4 and CD8 T cells, TLR expression and cytokines production by lymphocytes and

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	monocytes • SARS-CoV2 serology • PCR SARS-Cov2 on nasopharyngeal swab (if recent SARS-CoV-2 PCR on other respiratory specimen is not available) According to patient's clinical status and investigator judgment, following tests may be performed at screening to exclude active or latent infections: • Procalcitonin (PCT) • Hepatitis B markers (HBsAg, HbsAb, HBcAb) • IGRA - Quantiferon test • Urinary Antigen for Legionella pneumoniae and Streptococcus pneumoniae • Multiplex FilmArray for respiratory pathogens **BASELINE (day 1)** Screening, randomization and baseline visit may be performed on the same day and no other procedures need to be repeated. On baseline visit, eligible participants will be randomized in a 2:1 ratio to receive: • **Treatment Group A (experimental arm):** continued standard of care therapy together with the first dose of sarilumab ev. A second dose could be administered at the discretion of the investigator after 12 hours, in case of no clinical response or poor clinical response. • **Treatment Group B (control arm):** continued standard of care therapy After randomization will be completed the following evaluations will be performed on baseline: • Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature) • Respiratory status (pO2/FiO2 and SpO2 at rest if applicable) • Oxygen supplementation (room air, nasal canula, Venturi mask, noninvasive ventilation

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	or high flow oxygen devices) • Concomitant medications • Review of adverse events **DAILY STUDY ASSESSMENT (day 2- day 14)** The following evaluations are to be completed from days 2 – 14 or until discharge (if the patient will be discharged before day 14): • Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature) • Respiratory status (pO2/FiO2 and SpO2 at rest if applicable) • Oxygen supplementation (room air, nasal canula, Venturi mask, noninvasive ventilation or high flow oxygen devices) • Routine blood tests (blood count, creatinine, BUN, sodium, potassium, ALT, AST, LDH, fibrinogen, D-dimers, ferritin, PCR) at day 3, day 5, day 7, day 9 • Immunologic parameters: IL-6, IL-1b, IL-8, TNFα, quantitative and qualitative analysis of CD4 and CD8 T cells, TLR expression and cytokines production by lymphocytes and monocytes at day 9 • SARS-CoV2 serology at day 9 • PCR SARS-Cov2 on nasopharyngeal swab at day 9 (repeat within 24 hours if negative and if there is not previous evidence of two consecutive [within 24 hours] negative PCR on nasopharyngeal swabs) • Concomitant medications • Review of adverse events The frequency of the evaluations will be daily If not otherwise specified **DAY 15 VISIT** The following procedures will be performed at day 15 of study or at patient discharge if it will occur before day 14: • CT scan (if a CT scan is performed as per clinical practice between days 7-14 of study, it will not be performed on day 15)

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	• Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature) • Respiratory status (pO2/FiO2 and SpO2 at rest if applicable) • Oxygen supplementation (room air, nasal canula, Venturi mask, noninvasive ventilation or high flow oxygen devices) • Routine blood tests (blood count, creatinine, BUN, sodium, potassium, ALT, AST, LDH, fibrinogen, D-dimers, ferritin, PCR) • PCR SARS-Cov2 on nasopharyngeal swab (repeat within 24 hours if negative). • Concomitant medications • Review of adverse events **FOLLOW-UP VISITS 1 and 2 (day 21,30)** For hospitalized patient, physical examination, vital signs, concomitant medications and adverse events will be assessed and data on respiratory status and oxygen supplementation will be collected. Routine blood test will be repeated on follow-up visits (if recent [within 1 week] routine blood test performed for clinical practice are available there is no need to repeat them). SARS-CoV2 serology will be repeated at day 30. PCR for SARS-CoV2 on nasopharyngeal swab will be performed every 7 days until 2 consecutive negative results within 24 hours. For discharged patient, a phone call assessment will be performed. It will include reported body temperature and respiratory symptoms. **WITHDRAWN VISIT** If the subject withdrawn from the study drug occurs before the follow-up visit 2, the subject will undergo to a unscheduled withdrawn visit in which physical examination, vital signs concomitant medications and adverse events will be assessed and data on respiratory status and oxygen supplementation will be collected (for discharged patient, a phone call assessment will be performed). Unless the reason is the withdrawal of informed consent, the subject will be asked to continue study assessments until the end of the study.

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Statistical Methods	For the statistical analysis, the median time to clinical improvement will be estimated by Kaplan Meier method and it will be compared by stratified log-rank test. Hazard ratios and 95% CI will be estimated using the Cox proportional-hazards model. The primary efficacy analysis will be performed on the Intention-To-Treat population. Similarly, secondary endpoints based on "time to event" analysis will be estimated by Kaplan Meier method and compared by stratified log-rank test. Student t-test or Wilcoxon rank-sum test will be used for inter-group comparison of continuous variables according to data distribution. The difference in proportion will be used for inter-group comparison of categorical variables. Secondary efficacy rate and proportions endpoints will be described and compared using the Cochran-Mantel-Haenszel test adjusted by the stratification variable at baseline. P<0.05 (two-sided) would indicate a statistically significant difference in the variable tested. Statistical analyses will be performed using STATA 15.1 software.
Regulations and ethical aspects	The clinical study will be performed under the regulations of the National Agency for Drug Development (AIFA) and of the Italian Ministry of Health. An Independent Data Monitoring Committee (IDMC) will advise the coordinating group of the study to provide oversight and monitoring of the conduct of clinical trials, to protect ethical interests and to ensure the safety of participants and the validity and integrity of study data. The IDMC will be made of 2 to 5 members, selected among trialists experts in Infectious disease, statisticians, hospital pharmacist and expert in Resuscitation. No member of the IDMC have direct involvement in the design or conducting of the study.

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1. INTRODUCTION

1.1. Background

On January 9 2020, the "World Health Organization" (WHO) declared the identification, by Chinese Health authorities, of a novel coronavirus, further classified as SARS-CoV-2[1]. This new virus, initially emerged in the Chinese city of Wuhan in December 2019, led to a sharply spreading outbreak of human respiratory disease (COVID-2019), both within People's Republic of China and in several other countries worldwide. On March 11 2020, WHO declared COVID-19 a pandemic [2]. The full spectrum of COVID-19 infection ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia with typical radiographic features on CT scan, which can worsen rapidly into acute respiratory distress and death [3,4]. Although the pathophysiology of COVID-19 has not been completely understood yet, several reports have suggested a role of an aberrant response of host immunity in the severe form of COVID-19 infections. Thus far, despite many attempts with antiviral and other therapeutic agents, no specific drug has been demonstrated to be efficacious for SARS-COV-2 infection.

1.2 Rationale of the study

The full spectrum of COVID-19 infection ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia with typical radiographic features on CT scan, which can worsen rapidly into acute respiratory distress and death [3,4]. Elderly patients with comorbidities and with a weaker immune function seem to be a higher risk of developing severe form of COVID-19 infection [5,6]. Thus far, the pathophysiology of COVID-19 has not been completely understood. However, several studies have suggested that in patients affected by severe forms of COVID-19 an aberrant host immune response with an increased production of proinflammatory cytokines, the so-called "cytokine storm", could be responsible for inflammation and long term and extensive lung damage.

Indeed, in patients admitted in ICU with severe COVID-19 infection, higher plasma levels of cytokines including interleukin (IL)-6, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), and TNF-α which correlate to the severity and prognosis of the disease were found [5,6]. Similar alterations have been described both in SARS- and in MERS-CoV infections [7,8]

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Among inflammatory mediators, IL-6, a pleiotropic proinflammatory multifunctional cytokine produced by a variety of cell types, might play a key role in the cytokine storm. Thus, it has been speculated that interfering with IL-6 might have a therapeutic potential for patients with severe form of COVID-19. In the light of this hypothesis, a group of Chinese researchers recently treated 21 patients with severe or critical COVID-19 pneumonia with 400 mg intravenous of Tocilizumab, a recombinant humanized monoclonal antibody, obtaining unexpectedly optimal results in terms of clinical and radiological improvement, normalization of laboratory parameters and duration of diseases [9].

While attending stronger evidences of tocilizumab efficacy from ongoing randomized clinical trial, early reports suggested that systemic inhibition of IL6 signaling may have value as a supportive therapy. Thus, new therapeutic agents with similar mechanism of action have been proposed for COVID-19 treatment.

Sarilumab is a recombinant human IgG1 kappa monoclonal antibody directed against soluble and membrane-bound IL-6 receptor (IL-6Rα). It is formulated as a solution for subcutaneous injection at doses of 150 and 200 mg every 2 weeks. Currently it is approved for the treatment of moderate to severe rheumatoid arthritis [10]. Sarilumab inhibition of IL-6 signaling leads to a decrease in concentration of free sIL-6Rα and normalization of levels of acute phase proteins and markers of inflammation, such as C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen [11]. Although there are not direct evidences of sarilumab efficacy on COVID-19 pneumonia, the inhibition of both soluble and membrane bound forms of IL-6Rα mediated by the drug with the consequent suppression of pro-inflammatory signaling by both pulmonary epithelial and immune cells, leads to the hypothesis that it could reduce the severity of pulmonary COVID-19 complications, including respiratory failure. According to a recent Sanofi press release, the phase 3 trial investigating intravenously administered Sarilumab in severe or critically ill patients in hospitalized patients (NCT04315298) with COVID-19 did not meet its primary endpoint [12], but quantitative results are not available and other trial results with sarilumab are pending. However, the other IL6 antagonist (Tocilizumab), recently demonstrated encouraging results. The phase III EMPACTA study met its primary endpoint, showing that patients with COVID-19 associated pneumonia who received tocilizumab plus standard of care were 44% less likely to progress to mechanical ventilation or death compared to patients who received placebo plus standard of care (log-rank p-value = 0.0348; HR [95% CI] = 0.56 [0.32, 0.97]) [13].

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1.3 Benefit/risk assessment

For patients with RA, sarilumab 150 mg and 200 mg every 2 weeks by subcutaneous injection has demonstrated clinically meaningful reductions of inflammatory joint swelling and tenderness of RA, improvements in physical function, and reduced progression of joint damage as measured by radiography.

However, in clinical trials of patients with RA sarilumab was associated with an increased risk of infections, including serious infections. As with other immunomodulatory therapies for RA, serious and sometimes fatal infections have been reported on sarilumab.

For this study it is proposed to administer sarilumab IV to patients with a confirmed viral pneumonia for which no antiviral therapy has demonstrated effectiveness. However, the potential benefit of sarilumab for patients with COVID-19 is suppression of the cytokine storm which may be a more important and long-lasting contributor to lung damage than the viral infection itself.

One of the features of COVID-19 pneumonia is a local and systemic increase in activated neutrophils which function to eliminate the viral infection but also inflict collateral damage to the pulmonary epithelium [15]. In this context the dose-related reduction of absolute neutrophil count associated with IL-6rα inhibition may help to mitigate the coronavirus-induced neutrophilia.

Uncertainties associated with this study include the route of administration, IV, and the sarilumab 400 mg dose; both intended to increase Cmax and decrease tmax compared to SC route. Given that changes in absolute neutrophil count (ANC) of antibody-mediated sIL-6Rα are dose-dependent, irrespective of route of administration, it is anticipated that sarilumab delivered IV will rapidly suppress ANC. Based on analyses of 7985.5 patient-years of sarilumab exposure collected over 7.3 years from 3358 clinical trial patients with RA, the incidence of infection and serious infection did not increase with increasing severity of ANC. ANC values on sarilumab were normal for the majority of infections occurring within 12 weeks after sample collection (3452/3943 [88%] and 370/434 [85%] of patients reporting infections from patients treated with sarilumab plus conventional anti-rheumatic disease-modifying drug and sarilumab monotherapy, respectively.

Both observations support the consistent finding that low ANC is not associated with an increased rate of infection for patients treated with sarilumab. In this study, to mitigate the established risk of additional

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serious infection, patients with suspected or confirmed bacterial infection must be treated with appropriate antibiotic therapy. To mitigate the uncertainty around safety and tolerability of sarilumab IV, review of safety data by an independent data monitoring committee (IDMC) after the dosing of the first 12 patients will be required prior to enrolling additional patients and through the duration of the study.

Although risks of treatment with sarilumab are established and benefits for patients with COVID- 19 are potential, the absence of effective treatments of COVID-19 complications associated with excessive cytokine release during this ongoing pandemic, investigations such as this study are warranted.

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2. OBJECTIVES AND ENDPOINTS

PRIMARY OBJECTIVE:	**PRIMARY ENDPOINT:**
To evaluate the efficacy of sarilumab, combined with standard of care, in patients affected by severe COVID-19 pneumonia.	Time to clinical improvement, defined as the time from receiving the first dose of drug to an improvement of two points (from the status at baseline) on a 7-point category ordinal scale.
SECONDARY OBJECTIVES:	**PRIMARY ENDPOINTS:**
To evaluate the effect of sarilumab on survival	Mortality rate within 30 days from baseline Time from treatment initiation to death
To evaluate the effect of sarilumab on clinical evolution	Time to resolution of fever (≤36.6°C [axilla], or ≤37.2 °C [oral], or ≤37.8°C [rectal or tympanic]) Time to change in MEWS from baseline Days with fever (>36.6°C [axilla], or >37.2 °C [oral], or >37.8°C [rectal or tympanic])
To evaluate the effect of sarilumab on lung function	Time to mechanical ventilation or extracorporeal membrane oxygenation (ECMO) Time to non-invasive ventilation (in patients requiring only supplemental oxygen at baseline) Time to increase in PaO2/FiO2 of 50 or greater compared to the nadir PaO2/FiO2 for at least 48 hours; Days of hypoxemia (SpO2 <93% on room air, or requiring supplemental oxygen, or non-invasive ventilation support) Change from baseline in PaO2/FiO2

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To evaluate the effect of sarilumab on hyperinflammation parameters	Change from baseline in lymphocyte count, ferritin, D-dimer, LDH, PCR.
To evaluate the effect of sarilumab on immunological response by: - Defining the effect of treatment on inflammatory cytokine profile - Defining the effect of treatment on differentiation and function of innate and adaptive T cells	Change from baseline in inflammatory cytokines (IL1b, IL-6, IL-8, TNF-a) levels quantified by automated ELISA assay Change from baseline in differentiation and activation profile of CD4 and CD8 T cells analysed by flow cytometry Evolution from baseline of TLR expression and cytokines production by lymphocytes and monocytes tested by flow cytometry
To evaluate the effect of sarilumab on other relevant laboratory parameters	Change from baseline in IL-6 levels, platelet count, fibrinogen, creatinine
To evaluate the effect of sarilumab on radiological response	Improvement of CT scan findings repeated within 15 days from baseline
To evaluate the effect of sarilumab on virological response	Proportion of patients achieving confirmed negative nasopharingeal swabs (2 negative swabs within 24 hours) Evolution of SARS-CoV2 serology
To evaluate the effect of sarilumab on duration of hospitalization	Days of hospitalization among survivors Proportion of patients discharged hospital Time to hospital discharge
To describe safety profile of sarilumab	Serious adverse events (including severe bacterial or fungal infections) Treatment-emergent laboratory abnormalities

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3. STUDY DESIGN

3.1 Overall design

This is an open-label, phase 3, randomized clinical trial, which aims to explore the clinical efficacy and safety of intravenous sarilumab, added to standard of care, in the treatment of hospitalized patients with severe COVID-19 pneumonia.

Seven clinical centers will be included in this multicenter study:

- Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani IRCCS, COVID Hospital 1, Roma (Promoter and coordinator center)
- Fondazione Policlinico Gemelli, Università Cattolica S. Cuore, COVID Hospital 2, Roma (partecipating center)
- Policlinico Tor Vergata, Università Tor Vergata, COVID Hospital 4, Roma (partecipating center)
- Policlinico Umberto I, Università Sapienza, Roma (partecipating center)
- ASST Santi Paolo e Carlo, Università di Milano (partecipating center)
- Ospedale Amedeo di Savoia, Università di Torino (partecipating center)
- Ospedale Santa Maria Goretti, Latina (partecipating center)

The study will include:

- Screening phase: day -1 or day 1
- Baseline visit and Randomization: day 1
- Daily follow-up until day 30: daily clinical evaluation and regular blood test assessment during hospitalization time followed by weekly clinical assessment performed by phone call after patient discharge, until day 30.

3.2 End of study definition

The end of study will be the date in which the last patient completes the last study assessment (in hospital or via a follow-up phone call if the patient will be discharged from the hospital before day 30). Patients could be withdrawn from the study for safety reasons, according to the physician' clinical judgment. Patients must be withdrawn from the study if the subject withdraws the inform consent. The date and the reason for

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discontinuation must be noted and reported. Unless the subject withdraws consent, each subject prematurely discontinuing the trial must be seen for a final examination (withdrawal visit). All subjects who are prematurely withdrawn from the trial will be followed for survival until the last follow-up visit of the last subject in this trial, unless they withdraw their consent.

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4. STUDY POPULATION

Target population includes hospitalized patients with documented SARS-Cov2 infection and radiological evidence of pneumonia in severe or critical clinical condition. Eligible patients will be assuming antiviral therapy as standard of care.

4.1 Inclusion criteria

Participants are eligible to be included in the study if the following criteria apply:

1. Age ≥ 18 years
2. Signed informed consent provided by the patient, or by the patient's legally authorized representative(s), as applicable. Orally provisions could be considered in emergency conditions if deemed necessary by investigator (signature of the informed consent will occur if and as soon as clinical conditions improve)
3. Virological diagnosis of SARS-CoV-2 infection (SARS-CoV-2 infection confirmed by PCR test or positive serology)
4. Evidence of pulmonary infiltrates at CT scan or Chest Xray
5. Oxygen saturation (SpO2) at rest without oxygen supplementation < 93% or PO2/FiO2 < 300 at rest in patients requiring oxygen supplementation (either Venturi mask or CPAP or NIV).
6. Evidence of hyperinflammation defined as at least two of the following:
   i. Blood lymphocytes <1000/mm^3
   ii. Ferritin > 500ng/mL;
   iii. LDH > 300 U/L;
   iv. D-Dimers > 1000 ng/mL
   v. C-reactive protein > 3 mg/dL
7. Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix F.

4.2 Exclusion criteria

1. Known hypersensitivity to sarilumab or its excipients
2. Known active infections or other clinical condition that contraindicate sarilumab and cannot be treated or solved according to the judgement of the clinician
3. Patient being treated with immunomodulators or anti-rejection drugs

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4. Pregnancy/lactation
5. Neutrophils count < 500 cell/mm3
6. Platelets count < 50.000/mm3
7. ALT / AST> 5 times the upper limit of the normality
8. Bowel diverticulitis or perforation
9. Existence of any life-threatening co-morbidity or any other medical condition which, in the opinion of the investigator, makes the patient unsuitable for inclusion.
10. Severe hepatic dysfunction
11. Creatinine clearance < 30 ml/min/1.73 m2
12. Mechanical ventilation or ECMO
13. Enrolment in another concurrent clinical interventional study
14. Intake of an investigational drug within 3 months

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5. TREATMENT

5.1 Study intervention

5.1.1 Study groups:

Participants who satisfy the inclusion and exclusion criteria will be randomized (2:1) to receive:

- **Treatment Group A (experimental arm):** continued standard of care (SOC) as below reported + one single infusion of sarilumab 400 mg IV (two sarilumab 200 mg, single dose prefilled syringes (PFS) mixed in 100 ml 0.9% sodium chloride solution for intravenous use). A second dose could be administered at the discretion of the investigator after 12 hours from the first dose.
- **Treatment group B (control arm):** continued SOC as below reported

5.1.2 Experimental Treatment:

Participants in the experimental arm will receive one single infusion of sarilumab 400 mg IV (two sarilumab 200 mg, single dose prefilled syringes (PFS) mixed in 100 ml 0.9% sodium chloride solution for intravenous use) added to standard of care. A second dose could be administered at the discretion of the investigator.

5.1.3 Standard of Care Therapy

All patients enrolled will receive standard of care (SOC). SOC can include corticosteroids and/or antivirals, according to decision of clinical investigator and current guidelines.. Eligible patients can have the following situations: have planned to assume, are assuming or have recently assumed antiviral therapy as standard of care, or are not assuming any antivirals At the time of this amendment, the antiviral therapy consists of remdesivir 200 mg iv (loading dose) followed by remdesivir 100 mg iv every 24 hours for 5 to 10 days, prescribed according EMA authorization and according to decision of clinical investigator. Further antiviral therapies that will become available could be used.

Investigator can decide to change or prematurely stop the SOC therapy for safety reasons without the subject being withdrawn from the study.

There are no contraindication to the use of corticosteroids, that will be use according to clinical practice and current guidelines.

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5.2 Investigational medicinal product

5.2.1. Drug characteristics

Sarilumab (KEVZARA) is a recombinant human IgG kappa monoclonal antibody (mAb) direct against soluble and membrane-bound IL-6 receptor (IL-6Ra). Sarilumab, formulated as a solution for subcutaneous injection at dose of 150 mg and 200 mg every 2 weeks was first approved for the treatment of adult patients with rheumatoid arthritis in Canada on 12 January 2017, United States o 22 May 2017, European Union, Norway, Iceland, and Liechtenstein on 23 June 2017, and Japan on 27 September 2017. Sarilumab is currently approved for the treatment of moderate to severe rheumatoid arthritis in multiple countries across the world. Sarilumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6- mediate signaling through these receptors. IL-6 is pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes, and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. Sarilumab inhibition of IL-6 signaling leads to a decrease in concentration of free sIL-6Ra and normalization of levels of acute phase proteins and markers of inflammation, such as C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen. The potential benefit of sarilumab for patients with COVID-19 is to reduce the severity of pulmonary COVID-19 complications including respiratory failure by suppression of the cytokine storm which may be a more important and long-lasting contributor to lung damage and pro-inflammatory signaling by both pulmonary epithelial and immune cells.

5.2.2. Formulation

Sarilumab solution for injection is formulated as a colorless to pale yellow, sterile solution with ph 6.0. it is supplied in two single-use pharmaceutical forms, pre-filleds syringes and pre-filled pens, containing 150 mg or 200 mg sarilumab in 1.14 ml solution (in two dosage strengths 131.6 and 175 mg /ml respectively). Composition and concentration of the excipients are identical for the two strengths: arginine (8.94 mg), histidine (3.71 mg), polysorbate 20 (2.28 mg), sucrose (57 mg) and water for injection.

5.2.3. Route of administration

Intravenous (IV)

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5.2.4. Dose regimen

One infusion of sarilumab 400 mg IV, (two sarilumab 200 mg, single dose prefilled syringes (PFS), mixed in 100 mL 0.9% sodium chloride solution for intravenous use**)**

5.2.5. Storage and Handling

Refrigerate at 2°C to 8 °C in original carton to protect from light. Do not freeze. Do not shake. After removal from the refrigerator, use the drug within 14 days or discard

5.2.6 Drug supply

Sarilumab will be provided by National Health System and bought by Hospital Pharmacies of each participant sites as in routine clinical practice. More detailed information see the summary of product characteristic (Appendix B)

5.3 Standard of care therapy

5.3.1. Drug characteristics

For drug characteristics of antivirals and or corticosteroids, refer to specific product sheets and indications.5.3.2 Formulation and Route of Administration

For formulation and route of administration of antivirals and or corticosteroids, refer to specific product sheet and indications.

5.3.3 Drug supply

Remdesivir nor other antivirals nor corticosteroids will not be provided by this study. Remdesivir will be supplied according the current procedures through Emergency Support Instrument (ESI) by requesting it to AIFA, until it will not be available by standard procedures.

5.4 Rescue therapy

For patients enrolled in the control arm who withdraw from the study for safety reasons, according to clinical judgment, a rescue therapy with intravenous sarilumab could be administrated. In patients who are withdrawn from the study and undergo to the rescue therapy, clinical and laboratoristic data will be collected until the end of the study.

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6. STUDY ASSESSMENT AND PROCEDURES

Flow Chart procedure is shown in Appendix A

Diagnostic tests performed at the time of hospital admission and within screening visit, may be used to assess eligibility. However, written informed consent must be obtained prior to any study specific procedures.

All the additional tests/procedures required in accordance with local practice should be performed to patients, in order to guaranty best standard of care.

6.1. Screening (day -1/day 1)

At screening the investigators have to check the eligibility of patient for the study and obtain informed consent.

The following procedures will be performed:

- Demographic characteristics
- Focused medical history and current medication
- Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature)
- Respiratory status (PaO2/FiO2, SpO2 at rest when applicable)
- Oxygen supplementation (room air, nasal canula, Venturi mask, noninvasive ventilation or high flow oxygen devices)
- Serum pregnancy test at screening (for women of childbearing potential)
- Electrocardiogram (ECG)
- Routine blood tests (blood count, creatinine, BUN, sodium, potassium, ALT, AST, LDH, fibrinogen, D-dimers, ferritin, PCR)
- Immunologic parameters: IL-6, IL-1b, IL-8, TNFα, quantitative and qualitative analysis of CD4 and CD8 T cells, TLR expression and cytokines production by lymphocytes and monocytes
- SARS-CoV2 serology
- PCR SARS-Cov2 on nasopharyngeal swab (if recent SARS-CoV-2 PCR on other respiratory specimens is not available)

According to patient's clinical status and investigator judgment, following tests may be performed at screening to exclude active or latent infections:

- Procalcitonin (PCT)

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- Hepatitis B markers (HBsAg, HbsAb, HBcAb)
- IGRA - Quantiferon test
- Urinary Antigen for Legionella pneumoniae and Streptococcus pneumoniae
- Multiplex FilmArray for respiratory pathogens

6.2. Baseline and Randomization (day 1)

Screening, randomization and baseline visit may be performed on the same day and no other procedures need to be repeated.

On baseline visit, eligible participants will be randomized in a 2:1 ratio to receive:

- **Treatment Group A (experimental arm):** continued standard of care therapy together with the first dose of sarilumab ev. A second dose could be administered at the discretion of the investigator after 12 hours, in case of no clinical response or poor clinical response.
- **Treatment Group B (control arm):** continued standard of care therapy

Randomization will be web-based through the use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. The randomization will consider two strata: 1) PaO2/FiO2 >=200 mmHg and 2) PaO2/FiO2 <200 mmHg or the presence of non-invasive ventilation (NIV or CPAP).

After randomization procedure will be completed the following evaluations will be performed on baseline:

- Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature)
- Respiratory status (pO2/FiO2 and SpO2 at rest if applicable)
- Oxygen supplementation (room air, nasal canula, Venturi mask, noninvasive ventilation or high flow oxygen devices)
- Concomitant medications
- Review of adverse events

6.3. Daily study assessment (day 2- day 14)

The following evaluations are to be completed from days 2 – 14 or until discharge (if the patient will be discharged before day 14):

- Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature)

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- Respiratory status (pO2/FiO2 and SpO2 at rest if applicable)
- Oxygen supplementation (room air, nasal canula, Venturi mask, noninvasive ventilation or high flow oxygen devices)
- Routine blood tests (blood count, creatinine, BUN, sodium, potassium, ALT, AST, LDH, fibrinogen, D-dimers, ferritin, PCR) at day 3, day 5, day 7, day 9
- Immunologic parameters: IL-6, IL-1b, IL-8, TNFα, quantitative and qualitative analysis of CD4 and CD8 T cells, TLR expression and cytokines production by lymphocytes and monocytes at day 9
- PCR SARS-Cov2 on nasopharyngeal swab at day 9 (repeat within 24 hours if negative and if there is not previous evidence of two consecutive [within 24 hours] negative PCR on nasopharyngeal swabs)
- Concomitant medications
- Review of adverse events

The frequency of the evaluations will be daily If not otherwise specified

6.4. Day 15 visit

The following procedures will be performed at day 15 of study or at patient discharge if it will occur before day 14:

- CT scan (if a CT scan is performed as per clinical practice between days 7-14 of study, it will not be performed on day 15)
- Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature)
- Respiratory status (pO2/FiO2 and SpO2 at rest if applicable)
- Oxygen supplementation (room air, nasal canula, Venturi mask, noninvasive ventilation or high flow oxygen devices)
- Routine blood tests (blood count, creatinine, BUN, sodium, potassium, ALT, AST, LDH, fibrinogen, D-dimers, ferritin, PCR)
- SARS-CoV2 serology
- PCR SARS-Cov2 on nasopharyngeal swab (repeat within 24 hours if negative).
- Concomitant medications
- Review of adverse events

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6.5. Follow-up visits 1 and 2 (day 21,30)

For hospitalized patient, physical examination, vital signs concomitant medications and adverse events will be assessed and data on respiratory status and oxygen supplementation will be collected. Routine blood test will be repeated on follow-up visits (if recent [within 1 week] routine blood test performed for clinical practice are available there is no need to repeat them). SARS-CoV2 serology will be repeated at day 30. PCR for SARS-CoV2 on nasopharyngeal swab will be performed every 7 days until 2 consecutive negative results within 24 hours.

For discharged patient, a phone call assessment will be performed. It will include reported body temperature and respiratory symptoms.

6.6 Withdrawn visit

If the subject withdrawn from the study drug occurs before the follow-up visit 2, the subject will undergo to a unscheduled withdrawn visit in which physical examination, vital signs concomitant medications and adverse events will be assessed and data on respiratory status and oxygen supplementation will be collected (for discharged patient, a phone call assessment will be performed). Unless the reason is the withdrawal of informed consent, the subject will be asked to continue study assessment until the end of the study.

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7. STATISTICAL CONSIDERATION

7.1. Sample size calculation

The primary endpoint will be the time to clinical improvement, defined as the time from receiving the first dose of drug to an improvement of two points (from the status at baseline) on a 7-point category ordinal scale.

Fixing a power of 80% and a two-sided significance level of 5%, assuming that the median time to clinical improvement of participants in the standard-of-care group was estimated as 16 days (Cao B et al, N Engl J Med. 2020 Mar 18), to observe a reduction in the experimental arm of the endpoint to 10 days (reduction of 37%), 171 patients are needed. Patients were randomized, according to a design 2:1, to experimental arm 114 and to control group 57. Sample size calculation have been performed using PASS, Version 12.

Randomization will be based on 1) respiratory function: a) PaO2/FiO2 >=200 mmHg or b) PaO2/FiO2 <200 mmHg or the presence of non-invasive ventilation (NIV or CPAP) and 2) SOC therapy: a) lopinavir/ritonavir (400/100 mg BID orally for 14 days) or b) hydroxychloroquine (loading dose of 400 mg BID on day 1, followed by 200 mg BID for a total of 10 days).

7.2. Statistical analysis

The efficacy analysis will be performed on the Intention-To-Treat (ITT) population. The ITT population is defined as all patients randomized in the study that received any amount of study medication. Participants will be assessed according to the group to which they are randomly assigned, regardless of the treatment they receive.

Safety analyses will be performed on the safety evaluable population, which consists of all patients who receive any amount of study medication. In all safety analyses, patients will be grouped according to the treatment that the patients actually received rather than the treatment assigned at randomization.

Descriptive results will be presented as means $\pm$ standard deviation (SD), medians with interquartile range (IQR), and percentages with 95% confidence intervals (CI). Summaries will be presented by treatment group and will be presented for the ITT and for the safety population.

Student t-test or Wilcoxon rank-sum test will be used for inter-group comparison of continuous variables as appropriate according to data distribution. Chi-square or Fisher's exact test will be used for inter-group comparison of categorical variables.

$P<0.05$ (two-sided) would indicate a statistically significant difference in the variable tested. Statistical

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analyses will be performed using STATA 15.1 software.

7.3 Efficacy and safety analysis

For the primary efficacy analysis, the median time to clinical improvement will be estimated by Kaplan Meier method and stratified log-rank test will be used for inter-group comparison. Hazard ratios (HR) and 95% CI will be estimated using the Cox proportional-hazards regression. The Kaplan-Meier plot will be presented. Similarly, secondary efficacy endpoints based on "time to event" analysis (listed behind) will be estimated by Kaplan Meier method and compared by stratified log-rank test. The baseline of the following "time to" analysis will be treatment initiation:

- Time to death,
- Time to mechanical ventilation or extracorporeal membrane oxygenation (ECMO),
- Time to non-invasive ventilation (in patients requiring only supplemental oxygen with venturi mask or not requiring oxygen at baseline)
- Time to definitive extubation (if previously intubated)
- Time to increase in PaO2/FiO2 of 50 or greater compared to the nadir PaO2/FiO2 for at least 48 hours;
- Time to change in MEWS from baseline
- Time to resolution of fever ($\leq$36.6°C [axilla], or $\leq$37.2 °C [oral], or $\leq$37.8°C [rectal or tympanic])
- Time to hospital discharge

Secondary efficacy rate and proportions endpoints (listed behind) will be described and compared using the Cochran-Mantel-Haenszel test adjusted by the stratification variable at baseline. The weighted difference in proportions for two arms comparison will be presented, together with a 95% CI, using the extended Mantel-Haenszel method.

- Mortality rate within 30 days from baseline,
- Days of hypoxemia (SpO2 <93% on room air, or requiring supplemental oxygen, or non-invasive or mechanical ventilation support),
- Days with fever (>36.6°C [axilla], or >37.2 °C [oral], or >37.8°C [rectal or tympanic]),
- Proportion of patients achieving confirmed negative nasopharyngeal swabs (2 negative swabs within 24 hours) at day 28 and 56,
- Evolution of SARS-CoV2 serology defined as appearance of both IgA, IgM and IgG in patients with negative serology at baseline or appearance of IgG in patients with only IgM (with or without IgA) at

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baseline or disappearance of IgM in patients with positivity of both IgG and IgM at baseline.

- Days of hospitalization among survivors,

- Proportion of patients discharged hospital at day 30.

Changes intra group of immunological parameters from baseline to various time-point were compared using paired Wilcoxon test.

As regarding safety analysis, the number of subjects experiencing AEs and SAEs and the number of AEs an SAEs occurrences during the treatment period will be summarized by treatment arm. The overall incidence and incidences by treatment group will be summarized both for AEs and SAEs.

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8. ETHICS/PROTECTION OF HUMAN SUBJECTS, QUALITY ASSURANCE AND MONITORING

8.1 ICH guidance E6: Good Clinical Practice: consolidated guideline/Declaration of Helsinki

The study will be conducted with the approval of the Ethics Committee, after verification of compliance with the European Union Clinical Practice Standards and in accordance with ICH Good Clinical Practice (GCP) and the ethical principles expressed in Declaration of Helsinki. The clinical study will be performed under the regulations of the National Agency for Drug Development (AIFA) and of the Italian Ministry of Health.

The study will be carried out adhering to local legal requirements and the applicable national law, whichever represents the greater protection for the individual. Study protocol, patient information and informed consent will be submitted to the appropriate Ethical Committee for approval. Will inform the Ethical Committee about any changes in the study protocol which could interfere with the patient's safety.

8.2 Study conduct and monitoring

The management of the study was committed to CRO Clinical Research Technology.

Before study initiation, at a site initiation visit, designated CRO will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrolment, and to ensure that study treatment is being stored, dispensed, and accounted according to specifications. Key study personnel must be available to assist the field monitor during these visits. The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient). The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. The Sponsor monitoring standards require full verification for the presence of informed consent and adherence to the inclusion/exclusion criteria

8.3 Data Collection

This study will use an Electronic Data Capture (EDC) system. The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). Investigator site staff will not be

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given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs allow modification or verification of the entered data by the investigator staff. The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

8.4 Database management and quality control

Personnel designated CRO will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system or via email. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data. Concomitant treatments entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology. The occurrence of any protocol violations will be determined. After the data has been verified to be complete and accurate, the database will be declared locked. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Biostatistics and Data Management.

8.5 Acquisition of informed consent

The participant, adequately informed in clear, simple and understandable words of the technical terms used, will be invited to provide written informed consent. The participant will be provided with a description of the general aims of the research, the methodology and procedures used, the indication of any benefits or possible risks and adverse effects. The physicians treating the hospitalized patient are responsible for information of the patient and obtaining of the Informed Consent. The consent can be oral if a written consent cannot be expressed. If the subject is incapable of giving an informed consent and an authorized representative is not available without a delay that would, in the opinion of the Investigator, compromise the potential life-saving effect of the treatment this can be administered without consent.

In the event that the interested party revokes consent to the processing of data for research purposes, the biological sample taken for such purposes would also be destroyed. Blood samples will be collected during routinely performed samples during the investigations necessary for the pathology in progress. Participation in the research will not entail any additional costs for the participant. Should a medical problem arise due to

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the study, the participant will be provided with the most appropriate treatment. In accordance with the law on the protection of personal data (Legislative Decree 30/6/2003 No. 196, Guidelines for the processing of personal data in the context of clinical trials of medicinal products - 24 July 2008 - OJ No. 190 of August 14, 2008; 2016/679 European Regulation, as well as the Deliberation of the Guarantor (Del.52 of 24/7/08) will be specified that the Center of experimentation in accordance with the responsibilities established by the rules of good clinical practice (legislative decree 211/2003), will process personal data, especially those on health and, only to the extent that they are indispensable in relation to the objective of the study, other data related to the demographic characteristics, exclusively according to the realization of the study.

8.6 Participant confidentiality

All subject related information including Case Report Forms, laboratory specimens, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Subjects will be identified only by means of a coded number specific to each subject. All computerized databases will identify subjects by numeric codes only, and will be password protected.

Upon request, subject records will be made available to the study audit, monitoring groups representative of the study promoter, representatives of regulatory agencies (AIFA).

8.7 Source documents and access to source data/documents

Each participating site must maintain appropriate medical and research records for this trial and regulatory/institutional requirements for the protection of confidentiality of study subjects. The Principal Investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

Study data will be collected on study specific case report forms (CRF's). Source documentation should support the data collected on the CRF's. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical trial.

8.8 Data monitoring committee (IDMC)

An external Data Monitoring Committee (IDMC) includes independent experts that do not have direct involvement in the conduct of the study. The IDMC will review the progress of the study and perform

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interim reviews of efficacy and safety data and protect ethical interests and to ensure the safety of participants and the validity and integrity of study data.

The IDMC will be made of 2 to 4 members, selected among trialists experts in Infectious disease, statisticians, hospital pharmacist and expert in Resuscitation. No member of the IDMC have direct involvement in the design or conducting of the study.

The IDMC should conclude each review with their recommendations as to whether the study should continue without change, be modified, or be terminated.

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9. ASSESSMENT OF SAFETY AND PHARMACOVIGILANCE

9.1 Safety monitoring

Article 16 of Directive 2001/20/EC reads as follows: The investigator shall report all serious adverse events immediately to the promoter except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter. The purpose of this obligation is to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial, in accordance with Article 3(a) of Directive 2001/20/EC.

The investigator is responsible for reporting and documenting events falling within the protocol definitions of AEs or SAEs. During the treatment period (when safety must be evaluated), the investigator or designated sub-investigator shall be responsible for reporting AEs and SAEs as described in this section of the protocol. In order to satisfy international safety requirements, the investigator must include in his/her evaluation every SAE caused by participation in the study (e.g. any complications arising from blood sampling).

9.2 Definition of adverse events *(AE's) and* serious adverse events *(SAE's*)

9.2.1 Adverse Events

An 'adverse event' is defined in Article 2 (m) of Directive 2001/20/EC as follows: 'Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment'. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

An "adverse event" is any worsening in the general condition of a subject, or a subject participating in a clinical experiment to whom a pharmaceutical product is administered, regardless of its relationship with the given treatment. An AE may also be any unexpected adverse sign (which can include an abnormal laboratory result of clinical significance), and each symptom or pathology temporarily associated with the use of a pharmaceutical product, regardless of its relationship with the same product. AEs may be **expected** (consistent with the information leaflet provided with the product) or **unexpected** (inconsistent with the information available).

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Adverse events include:

- The exacerbation of a pre-existing pathology;
- An increase in the frequency or intensity of an episodic event or pre-existing condition;
- A condition occurring or diagnosed after the administration of the study drug, even if current before the start of the study;
- Persistent diseases/symptoms at the baseline visit that worsen after the start of the study.

Adverse events do NOT include:

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusions), but the condition requiring the procedure is an adverse event
- Diseases or conditions present at the beginning of the study that have not worsened but remained stable during the course of the study.
- Situations in which no unexpected adverse event has occurred (e.g. hospital admission for elective cosmetic surgery/social problems).
- An overdose of antiviral agents or concomitant drugs without onset of symptoms or associated signs.
- Laboratory abnormalities deemed by the investigator to be of no clinical significance.

Grade 1 and Grade 2 events are not considered adverse events, but details of these events must be documented in detail in the subject's study files.

Stable chronic conditions which are present prior to clinical trial entry and do not worsen are not considered adverse events and will be accounted for in the subject's medical history.

9.2.2 Serious Adverse Events *(SAE's)*

A 'serious adverse event' is defined in Article 2(o) of Directive 2001/20/EC as follows: 'Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalizations, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect'. These characteristics/consequences have to be considered at the time of the event. For example, regarding a life- threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. Some medical events may jeopardize the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events (hereinafter referred to

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as 'important medical events') should also be considered as 'serious' in accordance with the definition. Medical and scientific judgement should be exercised in deciding whether an event is 'serious' in accordance with these criteria

A Serious Adverse Event is defined as an SAE meeting one of the following:

- Death during the period of protocol-defined surveillance
- Life Threatening Event (defined as a participant at immediate risk of death at the time of the event)
- In-patient hospitalization or prolongation of existing hospitalization during the period of protocol-defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity

Any other important medical event that may not result in one of the above outcomes, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

9.3 AE/SAE relationship assignment

For all collected AE's/SAE's, the clinician who examines and evaluates the subject will determine the adverse event's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

- Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

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- Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- Not related: The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

9.4 SAE reporting procedures

The information to be reported for each SAE is: the date of event occurrence, the date of event resolution, a brief description of the event, concomitant therapy, lab test reports, maximum intensity of the event or correlation with the agent. If there is any change in the information over time, an updated SAE report must be sent. All adverse reactions simultaneously defined as serious and unexpected must be reported by the investigator to the study sponsor as soon as possible.

The investigator will report all SAE to Eudravigilance through the specific form, to Ethical Committees, and to the manufacturer, within the timelines of the article 17 of the European Directive 2001/20/EC. The investigator will provide an annual Development Safety Update Report, including all Serious Adverse Events occurring in the Study, to the Regulatory Agency, and to the Ethical Committee as per local requirements.

Notification deadlines:

- if, in addition to being serious and unexpected, a SAE is also fatal or life-threatening, a preliminary SAE report must be completed as soon as possible and, in any case, within 24 hours after being informed about the event.

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- For all other serious and unexpected adverse events, the investigator must complete a SAE report as soon as possible after the manifestation of the event and, in any case, no later than 15 days after becoming aware of the event.

9.5 Monitoring of AE'S/SAE'S

Any AE/SAE that occurs between the times a study participant signs the informed consent form and the time s/he departs the study at the end of the final follow-up visit (or at the time of early discontinuation of the subject from the study for any reason) will be captured and recorded. At each contact with the subject, the investigator (or designate) must seek information on adverse events by specific questioning and, as appropriate, by examination.

All AEs and SAEs must be followed up:

- until their complete resolution
- until their stabilization
- until the event can be attributed a new etiology
- until the patient ceases to be in the care of the Centre

The investigator must ensure that the follow-up reports include all supplementary information allowing a complete evaluation of the nature and/or the cause-effect relationship of the AE or SAE, including further laboratory and other tests, pathology reports, and any specialist examinations.

9.6 Suspected unexpected serious adverse reactions (SUSARS)

The investigator shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Database Eudravigilance, and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected serious unexpected adverse reactions shall be reported to the database Eudravigilance concerned and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the coordinator center. The coordinator center should also inform all investigators.

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Adverse reaction — causality An adverse reaction' is defined in Article 2(n) of Directive 2001/20/EC as follows: 'all untoward and unintended responses to an investigational medicinal product related to any dose administered'. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Unexpected' adverse reaction - Definition: Article 2(p) of Directive 2001/20/EC defines 'unexpected adverse reaction' as follows: 'an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)'.

The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'. Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events

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APPENDIX A – Study procedures flow chart

	Screening (day -1/day 1)	Baseline (day 1)	Daily visits (day 2 - 14)*	Day 15 visit or hospital discharge	Follow-up visits** (day 21-30)
Informed Consent	x				
Randomization		X			
Demographic Characteristics	x				
Medical History	x				
Physical Examination	x	x	x	x	x
Vital Signs[a]	x	x	x	x	x
Study Laboratory Testing[b]	x		x (day 3-5-7-9)	x	x
ECG	x				
Immunological Tests[c]	x		x (day 9)		
SARS-CoV2 serology[d]	x			x	x (only day 30)
PCR SARS-Cov2 Swab[e]	x		x (day 9)	x	x (every 7 days until 2 negative)
CT Scan[f]				x	
Infection Screening[g]	x				
Serum Pregnancy Test[h]	x				
Respiratory Status[i]	x	x	x	x	x
Oxygen Supplementation[j]	x	x	x	x	x
Sarilumab dose (group 1) [k]		x			
Adverse Events[l]	x	x	x	x	x
Concomitant Medications[m]	x	x	x	x	x

* Procedures from day 2 to day 14 will be daily if not otherwise specified; ** **for discharged patient a phone call assessment will be performed**.

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a) blood pressure, heart rate, respiratory rate, temperature.
b) blood count, creatinine, BUN, sodium, potassium, ALT, AST, LDH, fibrinogen, D-dimers, ferritin, PCR will be collected at screening, days 3,5,7,9,15 and after 15 days according to clinical practice (at least once a week)
c) IL-6, IL-1b, IL-8, TNFα, quantitative and qualitative analysis of CD4 and CD8 T cells, TLR expression and cytokines production by lymphocytes and monocytes collected at day 0 and day 9
d) collected at day15 and 30,
e) performed at screening and at day 9, 15 and then every 7 days until two consecutive negative swabs.
f) Pre-treatment CT scan is acceptable also if done extra hospital. Control CT scan should not be repeated at day 15 if done between 2 and 14 days according to clinical necessities.
g) performed according to patient's clinical status and investigator judgment, it includes PCT, hepatitis B markers, Quantiferon test, urinary Ag for L. pneumoniae and S. pneumoniae, film array for respiratory pathogens.
h) for woman of childbearing potential.
i) PaO2/FiO2, SpO2 at rest when applicable.
j) room air, nasal canula, Venturi mask, noninvasive ventilation or high flow oxygen devices.
k) A second dose of Sarilumab ev could be administrated at the discretion of the investigator after 12 hours from the first dose if poor or incomplete clinical response.
l) Any AE/SAE that occurs between the times a study participant signs the informed consent form and the time s/he departs the study at the end of the final follow-up visit (or at the time of early discontinuation of the subject from the study for any reason) will be captured and recorded
m) Concomitant medications will be captured and recorded from screening to the final follow-up visit (or at the time of early discontinuation of the subject from the study for any reason)

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Studio ESCAPE

Studio clinico di fase 3, randomizzato, in aperto, multicentrico volto a confrontare l'efficacia clinica e la sicurezza di Sarilumb per via endovenosa in aggiunta allo standard of care rispetto allo standard of care, nel trattamento di pazienti con polmonite severa da COVID-19.

Foglio informativo per il/la paziente

Egregio/a Signore/a,

Le è stato proposto di partecipare a questo studio. Prima di dare il suo consenso, è importante che lei sia consapevole dei motivi per i quali lo studio verrà svolto e ciò che comporterà. La preghiamo di dedicare qualche minuto del suo tempo alla lettura di queste informazioni per poi porre eventuali domande.

Lei è stato ricoverato presso questo istituto perché affetto da infezione da nuovo Coronavirus (SARS-COV-2). Attualmente non esiste un farmaco con approvazione specifica per il trattamento di questa patologia. Oltre ai Farmaci di supporto, come ad esempio gli antipiretici e la reidratazione e a quelli che si usano per allievare i sintomi, non esistono terapie specifiche per questo virus di cui siano state dimostrate la sicurezza e l'efficacia. Solo il remdesivir ad oggi è autorizzato in Europa per il trattamento dei pazienti COVID-19, dai 12 anni in su, con polmonite che richiede ossigenoterapia supplementare. Se acconsente di partecipare, Lei sarà uno/a dei 171 pazienti che aderiranno a questo studio, che si svolgerà presso circa 8 centri in Italia.

Lo scopo principale dello studio è di valutare l'efficacia del sarilumab, combinato con altra terapia standard, in pazienti con polmonite severa conseguente ad infezione da COVID-19.

Cosa è COVID-19

COVID-19 è una malattia causata dal virus SARS-CoV-2, che può mettere a rischio la vita di chi la contrae. Il motivo è che in casi severi di COVID-19, si può sviluppare una polmonite virale che conduce a problemi respiratori acuti.

Cosa è il Sarilumab

Il Farmaco sperimentale che le viene proposto è il Sarilumab, un anticorpo monoclonale umano diretto contro il recettore dell'interleuchina 6 (IL-6) solubile e legato alla membrana che, a causa della sua malattia, è presente eccessivamente nel suo corpo. Attualmente in Italia è approvato per il trattamento dell'artrite reumatoide attiva da moderata a severa alla dose di 200 mg ogni 2 settimane mediante iniezione sottocutanea.

L'IL-6, una citochina (proteina di piccole dimensioni che controlla lo stato infiammatorio) multifunzionale proinfiammatoria prodotta da una varietà di tipi di cellule, potrebbe svolgere un ruolo chiave. Pertanto, è stato ipotizzato che l'interferenza con IL-6 potrebbe avere un potenziale terapeutico per i pazienti con forma grave di COVID-19. Alla luce da questa ipotesi, un gruppo di ricercatori cinesi ha recentemente

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trattato 21 pazienti con polmonite COVID-19 grave o critica con 400 mg endovenosa di Tocilizumab, un anticorpo monoclonale umanizzato ricombinante diretto contro l'IL-6, ottenendo risultati inaspettatamente ottimali in termini di miglioramento clinico e radiologico, normalizzazione dei parametri di laboratorio e durata della malattia. Mentre attendiamo nuove evidenze sull'efficacia di tocilizumab dallo studio clinico randomizzato in corso, i primi dati hanno suggerito che l'inibizione sistemica della segnalazione di IL-6 può avere una certa validità come terapia di supporto nelle forme gravi da COVID-19. Pertanto, sono stati proposti nuovi agenti terapeutici con un meccanismo d'azione simile per il trattamento COVID-19, come il Sarilumab. Sebbene non vi siano evidenze dirette dell'efficacia di Sarilumab sulla polmonite COVID-19, ipotizziamo che potrebbe ridurre la gravità delle complicanze polmonari della COVID-19, inclusa l'insufficienza respiratoria. In base ad una recente dichiarazione dell'azienda Sanofi, un trial di fase 3 che indaga l'uso di sarilumab in pazienti ospedalizzati critici o severi con Covid-19 non ha raggiunto l'endpoint primario di efficacia, ma i rislutati estesi di tale studio e degli altri trial in corso sono ancora mancanti. Inoltre, l'altro antagonista di IL6 ha dimostrato risultato incoraggianti.

Il meccanismo d'azione paragonabile al Tocilizumab e il profilo di sicurezza dimostrato durante l'uso in ambito reumatologico, ci danno le basi per proporle l'utilizzo di sarilumab al dosaggio di 400 mg per via endovenosa, eventualmente ripetibili.

Chi può partecipare allo studio?

Pazienti ospedalizzati con infezione SARS-CoV-2 documentata e evidenza radiologica di polmonite in condizioni cliniche gravi o critiche. I pazienti eleggibili assumeranno la terapia antivirale come standard di cura.

Trattamento farmacologico previsto

Il medico dello studio le chiederà di sottoporsi ad una visita di screening per verificare che lei soddisfi tutti i requisiti per la partecipazione. Successivamente verrà fatta un'assegnazione casuale o al braccio sperimentale (Gruppo di trattamento A) più lo *standard of care* (SOC), ossia un normale standard di cura, oppure al braccio di controllo (Gruppo di trattamento B) che assume solo lo *standard of care*, secondo il seguente schema:

- Gruppo di trattamento A (Braccio sperimentale): *standard of care* (abbreviato come "SOC") + una singola infusione di sarilumab 400 mg per via endovenosa. Una seconda dose può essere somministrata, a discrezione dello sperimentatore, dopo 12 ore dalla prima dose.

- Gruppo di trattamento B (braccio di controllo): **proseguimento** dello SOC come di seguito riportato:

Lo standard of care (SOC) verrà deciso dal medico sperimentatore e potrà includere corticosteroidi e/o antivirali, secondo pratica clinica e linee guida correnti,

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L'assegnazione casuale avverrà tramite un processo di randomizzazione in aperto. "Randomizzazione" significa che il trattamento dello studio assunto sarà scelto in maniera casuale, come il lancio di una moneta. "In aperto" significa che sia Lei sia il medico dello studio conoscerete quale trattamento riceverà e la sua durata.

Le stiamo quindi proponendo di assumere, in associazione alla terapia standard prevista dalla pratica medica, un farmaco potenzialmente attivo nei confronti della polmonite causata dal nuovo coronavirus SARS-COV2; tale Farmaco è già in utilizzo per indicazioni terapeutiche diverse e non è stato ancora studiato per il trattamento specifico della patologia causata da SARS-COV-2 e, pertanto, ad oggi non è prevista la sua regolare immissione sul mercato per il trattamento dell'infezione COVID-19.

Qualunque sia l'assegnazione casuale al trattamento, lei assumerà come terapia Standard a discrezione del suo medico.

Procedure dello studio

Lo studio si svolgerà in 3 fasi. La sua partecipazione potrà riguardare una o più fasi, a seconda dei suoi requisiti

- Fase di screening (valutazione della presenza dei requisiti per la partecipazione allo studio): entro le prime 24 ore dal suo ricovero, si valuterà il suo stato di salute e l'esito del tampone effettuato per valutare l'infezione da COVID-19.

  Se risulterà eleggibile passerà alla fase successiva.

- Fase di trattamento e controllo del suo stato di salute, della durata di massimo 15 giorni.

In questa fase le verrà somministrato il farmaco previsto dall'assegnazione casuale, verranno eseguiti degli esami per valutare le sue condizioni di salute durante il trattamento. Dovrà sottoporsi a prelievi di sangue, controllo dei parametri vitali (misurazione della temperatura, pressione sanguigna e battiti cardiaci) ed eventuali esami radiologi. Si tratta comunque di procedure di routine per il suo stato di salute. Sarà inoltre ripetuto il tampone per COVID-19 per verificare l'andamento dell'infezione.

- Fase di follow-up (successiva al trattamento): nei giorni **21, 28, 42 e 56** (che si contano a partire dal giorno 1, in cui ha iniziato il trattamento) sarà visitato per verificare il suo stato di salute in seguito alla Terapia e Dovrà sottoporsi a prelievi di sangue, controllo dei parametri vitali (misurazione della temperatura, pressione sanguigna e battiti cardiaci),

Che cosa è richiesto al paziente

Se decide di partecipare a questo studio, le verrà chiesto di:

- Fornire informazioni accurate e complete sulla sua anamnesi medica e sulla sua condizione attuale.
- Attenersi alle procedure dello studio.

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- Informare il medico dello studio/il personale medico su eventuali farmaci assunti prima e durante lo studio, anche se si tratta di farmaci da banco o di rimedi erboristici.

- Comunicare al medico dello studio eventuali nuovi effetti collaterali, nuovi sintomi o cambiamenti dei sintomi esistenti, disturbi quali ad esempio diarrea, orticaria, febbre, affaticamento e dolore. Tali eventi vanno riferiti al medico dello studio anche al termine del trattamento, può utilizzare i recapiti riportati nel frontespizio del presente documento.

Se decide di partecipare a questo studio, inoltre, non dovrà avviare una gravidanza o procreare.

Rischi e benefici dell'uso del sarilumab e della partecipazione allo studio

Esistono dei rischi e disagi che possono essere associati a questo studio, alcuni di questi sono noti altri possono invece essere imprevisti. Tenga comunque presente che, qualora dovesse presentarsi un qualsiasi disagio o effetto collaterale, Lei sarà assistita nel modo più adeguato.

Se ulteriori informazioni dovessero rendersi disponibili nel corso dello studio, e se queste informazioni saranno rilevanti, Lei ne sarà tempestivamente tenuta aggiornato.

Durante la Sua partecipazione allo studio, nel caso in cui effettui il trattamento con Sarilumab, Lei potrà manifestare effetti collaterali, ma sarà tenuto attentamente sotto controllo dal medico dello studio per qualsiasi eventuale problema. Il Prodotto sperimentale potrebbe essere associato a rischi o effetti collaterali al momento sconosciuti. Lei dovrà informare il medico o il personale dello studio nel caso in cui dovesse insorgere qualsiasi problema o effetto collaterale, anche qualora non lo ritenesse correlato al Prodotto sperimentale.

Segue un elenco degli effetti collaterali più significativi dal punto di vista clinico o più frequenti considerati correlati al prodotto. L'elenco non è esaustivo e qualora avesse altre domande da porre in merito ai rischi o agli effetti collaterali, La preghiamo di rivolgersi al medico dello studio.

Nei pazienti trattati con sarilumab sono stati osservati:

Effetti collaterali gravi: Infezioni attive

Informi immediatamente il medico se ritiene di avere un'infezione attiva in corso (che può colpire fino a 1 persona su 10). I sintomi possono includere febbre, sudorazione o brividi.

Altri effetti indesiderati

- Molto comuni (possono colpire più di 1 persona su 10):
  - Bassa conta dei globuli bianchi, rilevata dagli esami del sangue
- Comuni (possono colpire fino a 1 persona su 10):
  - infezioni dei seni paranasali o della gola, naso bloccato o che cola e dolore alla gola ("infezioni delle vie respiratorie superiori")

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- infezione delle vie urinarie
- vescicole ("herpes orale")
- bassa conta delle piastrine, rilevata dagli esami del sangue
- colesterolo alto, trigliceridi alti, rilevati dagli esami del sangue
- prove di funzionalità epatica anormali
- reazioni in sede di iniezione (compresi arrossamento e sensazione di prurito)

FERTILITA, GRAVIDANZA E ALLATTAMENTO

Donne in età fertile

Le donne in età fertile devono usare misure contraccettive efficaci durante e fino a 3 mesi dopo il trattamento.

I dati relativi all'uso di sarilumab in donne in gravidanza non esistono o sono in numero limitato. Gli studi sugli animali non indicano effetti dannosi diretti o indiretti di tossicità riproduttiva.

Kevzara (nome con cui il farmaco è commercializzato) non deve essere usato durante la gravidanza, salvo nel caso in cui le condizioni cliniche della donna richiedano trattamento con sarilumab.

Non è noto se sarilumab sia escreto nel latte materno o sia assorbito per via sistemica dopo l'ingestione. L'escrezione di sarilumab nel latte non è stata studiata sugli animali.

Poichè le IgG1 (molecole che agiscono da anticorpi) vengono secrete nel latte umano, deve essere presa la decisione se interrompere l'allattamento con latte materno o interrompere la terapia con sarilumab, tenendo in considerazione sia il beneficio dell'allattamento con latte materno per il bambino sia il beneficio della terapia per la donna.

ALTRI MEDICINALI E SARILUMAB

Informi il medico dello studio se sta usando, ha recentemente usato o potrebbe usare qualsiasi altro medicinale, in particolare:

- un gruppo di medicinali denominati "inibitori delle janus chinasi (JAK)" (utilizzati per malattie come l'artrite reumatoide e per il cancro)
- altri medicinali biologici utilizzati per il trattamento dell'artrite reumatoide
- statine, utilizzate per ridurre il livello di colesterolo
- contraccettivi orali
- teofillina, utilizzata per curare l'asma

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- warfarina, utilizzata per prevenire i coaguli di sangue

AVVERTENZE E PRECAUZIONI

Si rivolga al medico dello studio se:

- Soffre di una qualsiasi infezione o se ha molte infezioni. Sarilumab può ridurre la capacità dell'organismo di combattere le infezioni: ciò significa che La renderà più suscettibile alle infezioni o farà peggiorare eventuali infezioni di cui Lei soffre.
- Ha la tubercolosi (TB), sintomi di TB (tosse persistente, perdita di peso, svogliatezza, febbre lieve) o è stato a stretto contatto con una persona affetta da TB. Prima che Le venga somministrato sarilumab, il Suo medico controllerà se ha la TB.
- Ha avuto l'epatite virale o un'altra malattia del fegato. Prima che Lei usi sarilumab, il Suo medico effettuerà un esame del sangue per controllare il funzionamento del Suo fegato.
- Ha l'infezione da HIV.
- Ha avuto la diverticolite (una condizione dell'intestino inferiore) o un'ulcera dello stomaco o dell'intestino, oppure sviluppa sintomi quali febbre e dolore nella regione dello stomaco (addominale) che non passano.
- Ha avuto qualsiasi tipo di cancro.
- È stato sottoposto recentemente a vaccinazione o ha in programma di esservi sottoposto

I rischi associati alla terapia standard non rappresentano rischi aggiuntivi perché si tratta di terapie considerate standard secondo la pratica clinica per la sua patologia

Cosa succede se decide di non fornire il suo consenso o di ritirarlo

Lei può rifiutarsi di iniziare o proseguire il trattamento e potrà ritirare il Suo consenso in qualsiasi momento, senza che ciò comprometta in alcun modo l'assistenza di cui necessita e che continuerà ad esserle fornita. Tutti i suoi dati personali e sanitari rimarranno riservati.

Se invece decide di assumere il trattamento proposto, firmando il consenso informato Lei autorizza gli operatori sanitari al monitoraggio delle Sue condizioni e alla verifica dell'efficacia e sicurezza del trattamento, e autorizza il Comitato Etico e le autorità regolatorie ad accedere direttamente alla documentazione medica originale per una verifica delle procedure della somministrazione del farmaco e/o di ulteriori dati, anche di efficacia, senza violare la riservatezza dei Suoi dati in applicazione delle normative e regolamentazioni vigenti.

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Modulo di consenso del paziente

Nome del paziente_____

Io sottoscritto _____ (nome in stampatello) dichiaro di avere letto e compreso l'allegato Foglio informativo e acconsento a partecipare a questo studio clinico.
Ho avuto la possibilità di rivolgere al medico curante tutte le domande e richieste di chiarimento in merito alla mia malattia, al trattamento proposto ed alle alternative disponibili. Confermo che mi sono stati spiegati i rischi e i benefici possibili di questa sperimentazione e delle terapie alternative disponibili per la mia malattia.

Confermo di aver ben compreso che i farmaci che mi saranno somministrati non sono stati ancora autorizzati all'immissione in commercio per il trattamento della mia malattia e che non sono ancora disponibili dati sull'efficacia e la sicurezza del loro impiego nel trattamento della stessa. Sono pertanto consapevole delle incertezze relative ai possibili effetti benefici e ai rischi connessi al trattamento proposto.
Confermo di avere avuto il tempo necessario e l'opportunità di porre domande sulla sperimentazione e di avere ricevuto risposte soddisfacenti a tutte le mie domande.

Sono consapevole che la presente sperimentazione clinica è stata esaminata e approvata da un Comitato Etico Indipendente (CEI).
Sono libero di ritirarmi dalla sperimentazione in qualsiasi momento senza dovere giustificare la mia decisione e senza che ciò comporti degli svantaggi per la terapia medica che potrà essermi prescritta.
Sono consapevole che lo sperimentatore potrà chiedermi di firmare un nuovo consenso qualora debba sottopormi ad analisi aggiuntive e che io potrò rifiutarmi di conferirlo.
Dichiaro di aver ricevuto informazioni esaurienti riguardo al trattamento dei miei dati personali compresi quelli sensibili che avverrà conformemente al REGOLAMENTO (UE) 2016/679 DEL PARLAMENTO EUROPEO E DEL CONSIGLIO del 27 aprile 2016 relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati. Abroga la direttiva 95/46/CE (regolamento generale sulla protezione dei dati).

SISTEMA SANITARIO REGIONALE
IRCCS
LAZZARO SPALLANZANI

SALUTE LAZIO
SISTEMA SANITARIO REGIONALE

ISTITUTO NAZIONALE PER LE MALATTIE INFETTIVE
"Lazzaro Spallanzani"
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UOC Immunodeficienze Virali
Direttore: Dott. Andrea Antinori

Sono consapevole che la mia partecipazione allo Studio è volontaria.
Sono stato informato/a del mio diritto di avere accesso a tutta la documentazione che mi riguarda relativa allo Studio e della possibilità, nel caso in cui lo richieda, di conoscere tramite il responsabile della Ricerca (lo Sperimentatore principale) eventuali scoperte inattese che emergano a mio carico nel corso dello Studio.
Accetto che le mie informazioni personali possano essere utilizzate ai fini dello studio, come spiegato in questo modulo. Acconsento volontariamente a partecipare a questa sperimentazione.

Nome del paziente (in stampatello)

_____

Firma del paziente

_____

Data della firma del paziente (GG/MMM/AAAA)

_____

Confermo di avere spiegato la natura, la finalità e gli effetti prevedibili della sperimentazione al soggetto il cui nome è riportato qui sopra in stampatello. Il paziente ha confermato tale consenso apponendo personalmente data e firma sul presente modulo.

Nome del Medico che ottiene il Consenso informato (in stampatello)

_____

Firma del Medico che ottiene il Consenso informato

_____

Data della firma del Medico che ottiene il Consenso informato (GG/MMM/AAAA)

_____

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Rappresentante legale (se applicabile)

Nome del rappresentante legale (in stampatello)

_____

Firma del rappresentante legale

_____

Data della firma del rappresentante legale (GG/MMM/AAAA)

_____

Tutti i firmatari devono firmare e datare il modulo personalmente. *In conformità al Decreto Ministeriale del 15 luglio 1997 "Recepimento delle linee guida dell'Unione Europea di buona pratica clinica per l'esecuzione delle sperimentazioni cliniche dei medicinali".

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Revoca del MODULO DI CONSENSO

Io sottoscritto/a _____dichiaro di voler revocare volontariamente il mio consenso alla partecipazione allo studio.
Dichiaro, inoltre, di essere consapevole che la revoca del consenso non pregiudicherà in alcun modo le cure mediche a cui ho diritto e che le informazioni già ottenute fino al momento del mio ritiro saranno utilizzate per assicurare la corretta valutazione dei risultati dello studio, in conformità alle disposizioni di legge.

Desidero

❒ ritirarmi solo dal trattamento sperimentale, acconsento ad essere contatto per ulteriori informazioni sul mio futuro stato di salute

❒ ritirarmi dal trattamento sperimentale e non essere contattato per ulteriori informazioni sul mio stato di salute

❒ Altro, specificare _____

_____ Data: _____/_____/_____

Firma del paziente

_____

Nome in stampatello del paziente

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PER IL MEDICO CHE HA REGISTRATO LA REVOCA

Io sottoscritto/a _____dichiaro che alla paziente è stato correttamente spiegato il significato del presente modulo di revoca e che la paziente ha dichiarato di voler liberamente e volontariamente revocare il consenso alla partecipazione allo Studio.

È stata fornita al paziente copia del presente modulo di revoca sono consapevole che è mia responsabilità informare lo Sponsor di tale revoca.

_____ _____

Data Firma del medico che ha registrato la revoca

_____

Data della firma del Medico che ottiene il Consenso informato (GG/MMM/AAAA)

_____