Cohort Multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients

CORIMUNO-19

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS CONCERNING MULTIPLE IMMUNE REGULATORY MEDICATIONS FOR HUMAN USE

Version N°6.0 of 04/05/2020

Project code number:APHP200375

The medication substance consists in multiple Immune regulatory product

Medication number1 : Anti IL-6 Receptor (Tocizilumab)

Medication number2 : Anti IL6 Receptor (Sarilumab)

The IMP or drug product consists in an antibody

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INTERVENTIONAL RESEARCH PROTOCOL
RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

PROTOCOL SIGNATURE PAGE

APHP200375

Title: Cohort multiple Randomized open-label control trial of Immunomodulatory drugs and other treatments in COVID-19 patients (CORIMUNO-19 trial)

Version N°6.0 of 04/05/2020

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

Principal Investigator

Pr. Olivier Hermine
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Date: ……/……/……..
Signature:

Sponsor

Assistance Publique – Hôpitaux de Paris
Département de la Recherche Clinique et du Développement
Hospital Saint Louis
1 avenue Claude Vellefaux - 75010 Paris

Date: ……/……/……..
Signature:

The study was approved by the Ethic committee (CPP) of ……. on …… and authorised by the ANSM on ……...

ABBREVIATIONS LIST

1. SUMMARY

AP-HP		STUDY CODE:
Trial Title	Cohort Multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients **CORIMUNO-19**	
Coordinating Investigator	COVID-19 group	
Trial site(s)	Hospitals involved in COVID care	
Clinical Phase	NA	
Objectives	The overall objective of the study is to determine which treatments (e.g. immune modulator drugs) have the most favourable benefit-risk in adult patients hospitalized with COVID-19. The specific aims of this Covid19 cohort are to collect observational data at regular intervals on an ongoing basis in order to embed a series of randomized controlled trials evaluating a various set of interventions.	

Methodology	The key features of the cohort multiple Randomized Controlled Trials (cmRCT) design are: (I) Recruitment of a large observational cohort of patients with the condition of interest (II) Regular measurement of outcomes for the whole cohort (III) Capacity for multiple randomised controlled trials over time Patients enrolled in the cohort agree to allow their longitudinal data to be used in the aggregate. They also allow their data to be used to identify them to be invited to participate in research interventions or for comparison purposes for intervention trials that may be conducted with other patients while they are participating in the cohort. In the cmRCT design, only eligible patients randomly selected to be offered an intervention, are contacted and offered treatment. Eligible patients not selected to be offered an intervention are not notified about this trial and will be in the control group. Consent for specific trials will be obtained from those eligible patients who are invited and accepted the offer to participate. In the cmRCT design, as described to patients when they consent to participate in the cohort, only eligible patients randomly selected to be offered an intervention, but not eligible non-selected patients, are contacted and offered treatment. Eligible patients not selected are not notified about the trial. Consent for specific trials will be obtained from those eligible patients who are invited and accept the offer to participate. Post-intervention outcomes among eligible patients who accept the offer to receive the intervention will be compared with outcomes among patients from the cohort who were identified as eligible for the intervention, but were not randomly selected to be offered the intervention and not contacted about the intervention. In the context of the COVID crisis, the advantage of the cmRCT design to conduct multiple trials that draw participants from the same patient cohort is important given the imperative that we have to answer multiple research questions (some identified and others not yet identified) in a very short time (a few weeks). The cmRCT design will enable the implementation of multiple trials over time with different inclusion and exclusion criteria (e.g. based on severity or comorbidities), testing different interventions that can be compared in the same overall population with similar trial methods, thus increasing the ability to compare and contrast different trial results. This design allows to perform a series of randomized, controlled adaptive trials, with frequent interim monitoring to facilitate the following: dropping of poorly performing arms, introduction of new candidate therapies and modification of current optimized standard-of-care (oSOC). In its simplest iteration, the study can be viewed as a series of 2-arm comparisons whereby the superior treatment, if identified, from each pairwise comparison becomes the basis of the new supportive care backbone (hence the term “optimized SOC”, or oSOC, to describe this potentially evolving backbone) common to each future arm of the study and against which additional investigational interventions may then be added to the protocol, tested and compared: Arm A: optimized SOC alone Arm B: Investigational treatment X + optimized SOC. If this pairwise comparison shows the superiority of Arm B over Arm A, then investigational treatment X featured in Arm B will be incorporated into the new oSOC common to each future arm of the study (assuming adequate drug supply exists to permit this). Conversely, if a given pairwise comparison of Arm A versus Arm B fails to yield a clear statistical winner in terms of the primary endpoint, then subsequent pairwise comparisons will not incorporate the “failed” intervention featured in current Arm B into the new oSOC backbone.

	The cmRCT design also offers advantages in that the patient consent process more closely replicates what occurs in actual healthcare settings compared with the consent procedures typically used in traditional RCT designs. In traditional RCTs, patients are usually told that they will be randomised to obtain the trial intervention or an alternative which is generally usual care. In the cmRCT design, patients are told about treatments that they will be able to access if they so choose. As part of the initial consent process, patients are made aware that a number of trials may occur via the cohort, and that they will not likely be offered to participate in all of them and may not be offered to participate in any. It is explained that patients will only be notified about trials for which they will be offered the intervention, but that their data may be used for comparison purposes in the context of some interventions not offered to them.

Randomisation	The study will include potentially all patients with COVID-19 infection and moderate or severe NCP. Among such large two groups of patients, subgroups of patients with specific characteristics will be randomized and proposed to receive treatments. The goal of the CORIMUNO-19 trial is to uncover large therapeutic effects. By default, the sample size will be 30 for the treated arms, but more than 30 subjects will be used as controls. Larger sample sizes can also be specified in trial protocols. For each trial, a random sample of eligible patients (e.g. n=30) will be selected. This number may be increased or decreased as a result of the efficacy and safety reviewed by the DSMB and sponsor by group of patients. Randomisation will be centralized and thus will be completely independent from patients and physicians participating in the study ensuring allocation concealment. Other trials may be conducted where patients are directly **randomised with a fixed allocation ratio to treatment or control**, with interim monitoring of the trial..
DSMB	A review of efficacy and safety data by DSMB will be performed every week. DSMB will review in priority: safety, hospitalization and discharge, organ functions, death, viral load, and decide whether any arm should be stopped prematurely or be the preferred arm to which other arm should be switched for any predefined group of patients (Age, comorbidities, severity assessed by clinical and biological parameters, antiviral therapy). The DSMB will submit its advice to the scientific and clinical committee. At the end of each trial, DSMB will recommend the treatment with the most favorable benefit-risk in the most appropriate endpoint for future studies.
Number of patients	We expect to recruit 1 000 patients in the cohort. The number of patients for each subtrial within the cohort is predefined for each trial and can be adjusted for each sub-trial following DMSB and scientific committee advices in real time analysis

Diagnosis and inclusion and Exclusion criteria for the cohort	**Inclusion Criteria for the cohort:** 1. Laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen and/or CT Scan prior to randomization (Following typical radiological findings (ground glass abnormalities, and absence of lymphadenopathy, pleural effusion, pulmonary nodules, lung cavitation) 2. Hospitalized patients 3. Illness of any duration and severity (mild, moderate, severe, critical, see annexe 1), with symptoms (fever, cough, respiratory difficulties, shortness of breath), and at least one of the following: a. Radiographic infiltrates by imaging (CT scan) b. Clinical assessment (evidence of rales/crackles on exam or respiratory rate >25/min) AND SpO2≤94% on room air c. SpO2≤97 % with O2 ≥ 5L/min or Respiratory rate>=30/min d. Requiring mechanical ventilation e. With any comorbidities (TBD such as acute kidney injury, cardiovascular condition, pulmonary disease, obesity, high blood pressure, diabetes, chronic kidney diseases, haematological diseases, sickle cell diseases, autoimmune and auto-inflammatory, pregnant women, HIV infected, etc) 4. Male or female adult ≥ 18 years of age at time of enrolment 5. Patients must be able and willing to comply with study visits and procedures. 6. Patient agrees to the collection of oropharyngeal and nasal swabs and venous blood per protocol 7. Written informed consent provided by the patient or alternatively by next-of-kin prior to any protocol-specific procedures. **Exclusion Criteria for the cohort:** Participation in another clinical trial is not an exclusion criterion depending on the medication. ***Patients included in the antiviral REACTING trial are not excluded as well as patients from COVIDICUS trial.*** Severe cardiovascular disease including acute myocardial infarction, unstable angina pectoris, coronary revascularization procedure, congestive heart failure of NYHA Class III or IV, stroke, including a transient ischemic attack, edema of cardiac origin and left ventricular ejection fraction ≤ 50% are not excluded and should be discussed in each therapeutic arm. ● Patients with any condition that the physician judges could be detrimental to the patient participating in this study; including any clinically important deviations from normal clinical laboratory values or concurrent medical conditions (active infection diseases such as severe bacterial infections, aspergillosis, tuberculosis, depending on the tested medication). ● Absence of Health Insurance ● Subject protected by law under guardianship or curatorship

Measures routinely collected during patient follow-up	A core set of clinical measures will be recorded daily the first 2 weeks and then every week. The core measures include measures of OMS progression scale, oxygenation, mechanical ventilation. These measures will allow us to classify the patients state according to the WHO Clinical Progression Scale. All-cause mortality at hospital discharge or 60 days and time to hospital discharge will be also recorded. In addition, biological measures routinely prescribed for care will be collected For patients who are eligible for an intervention trial (in both the intervention and control arms), this 3-days measurement may also include trial-specific measures related to the trial outcomes of interest taking into account the WHO core outcome set for clinical research.
	CORIMUNO-19 - TOCI
Rationale for using Tocilizumab in severe patients infected with COVID-19	**CORIMUNO-19 - TOCI** The SRAS-CoV-S protein induces direct up-regulation of IL-6, IL-1 and TNFα, some of the most potent pro-inflammatory cytokines Tocilizumab (TCZ) is an anti-human IL-6 receptor monoclonal antibody that inhibits signal transduction by binding sIL-6R and mIL-6R. The main approved indication is for rheumatoid arthritis, in association or not with methotrexate. The IV the approved dose in RA is 8 mg/kg every month. TCZ is also approved in the treatment of juvenile inflammatory arthritis and in the treatment of refractory giant cell arteritis. Interestingly, this later indication concerns aged patients and, in this population, the safety profile was the same as in younger patients. In 2017, the U.S. Food and Drug Administration approved TCZ for the treatment of cytokine release syndrome (CRS) consisting in a systemic inflammatory response caused by the massive release of pro-inflammatory cytokines in response to iatrogenic (e.g. CAR-t therapies) or infective stimuli. Despite the lack of clinical trials on TCZ efficacy and safety for COVID-19 treatment, in China TCZ was recently approved for patients affected by severe SARS-CoV-2 pulmonary complications by the National Health Commission of the People's Republic of China. Preliminary data from an observational study conducted in China on 21 severe cases receiving TCZ, showed an improvement of the clinical and radiological outcome.

Diagnosis and inclusion and Exclusion criteria for the Tocilizumab trial	**Inclusion Criteria for the Tocilizumab trial:** 1. Patients included in the CORIMUNO-19 cohort 2. Patients belonging to one of the 2 following groups: - *Group 1: patients **not requiring ICU** at admission with moderate and severe pneumopathy according to the WHO **Criteria of severity of COVID pneumopathy.*** ***Moderate cases*** Cases meeting all of the following criteria: ● Showing fever and respiratory symptoms with radiological findings of pneumonia. ● Requiring between 3L/min and 5L/min of oxygen to maintain SpO2 >97% ***Severe cases*** Cases meeting any of the following criteria: ● Respiratory distress (≧ 30 breaths/ min); ● Oxygen saturation ≤93% at rest in ambient air; or Oxygen saturation ≤97 % with O2 > 5L/min. ● PaO2/FiO2≦ 300mmHg - *Group 2: patients **requiring ICU** based on **Criteria of severity of COVID pneumopathy.*** ● Respiratory failure and requiring mechanical ventilation ● No do-not-resuscitate order (DNR order) **Exclusion Criteria for the Tocilizumab trial:** ● Patients with exclusion criteria to the CORIMUNO-19 cohort. ● Known hypersensitivity to Tocilizumab or to any of their excipients. ● Pregnancy ● Current documented bacterial infection ● Patient with any of following laboratory results out of the ranges detailed below at screening should be discussed depending of the medication: ○ Absolute neutrophil count (ANC) ≤ 1.0 x 10^9/L ○ Haemoglobin level: no limitation ○ Platelets (PLT) < 50 G /L ○ SGOT or SGPT > 5N

Randomisation and Treatment procedures	Group defined by **requiring** ICU vs. **not requiring** ICU. All consecutive patients meeting the inclusion criteria will be randomised 1:1 either in the Tocilizumab arm or control arm in a set of 120 patients in total (60 in each arm), **stratified on the group**. Trials within each groups are analyzed separately, but are conducted simultaneously (with stratification of the randomisation) for logistical reasons. If other subtrials are available, the inclusions will stop to allow inclusions in these other subtrials of the protocol and interim analysis. If the interim analysis indicates to continue the subtrial, a new set of 120 patients will be included on the same basis. If no other subtrial is available the inclusions will not be stopped in waiting for the interim analysis, given tocilizumab is already a drug with known safety. Inclusions of new sets will stop when statistical analyses conclude on futility or efficacy or by DSMB decision. ● Group 1: patients **not requiring ICU** ○ Patients will be randomized to be offered **Tocilizumab** 8mg/kg D1 and if no response (no decrease of oxygen requirement) a second injection with fixed dose of 400mg at D3. ○ Patients from the cohorts and with the same baseline characteristics will be used as controls (best standard of care) ● Group 2: patients **requiring ICU** ○ Patients will be randomized to receive **Tocilizumab** 8mg/kg at D1 and if no response a second injection with fixed dose of 400 mg at D3. These patients may receive or not steroids depending of the local procedures. ○ Patients from the cohorts with the same baseline characteristics will be used as controls
Duration of follow-up	90 days

Criteria for efficacy

Measures

A core set of clinical measures will be recorded daily the first 2 weeks and then every week. The core measures include measures of OMS progression scale, oxygenation, mechanical ventilation. For patients who are eligible for an intervention trial (in both the intervention and control arms), this days measurement will include trial-specific measures related to the trial outcomes of interest.

Primary and secondary endpoints:

The primary endpoint and secondary endpoints will depend on the group of patients and tested medication.

Groups will be redefined as follow :

- Group 1: Cases meeting all of the following criteria
  - Requiring more than 3L/min of oxygen
  - OMS/WHO progression scale = 5
  - No NIV or High flow

- Group 2: Cases meeting all of the following criteria

  - Respiratory failure AND (requiring mechanical ventilation OR NIV OR High flow)
  - WHO progression scale >=6
  - No do-not-resuscitate order (DNR order)

For the group 1 of patients *not requiring ICU*:

Co Primary Endpoints

1. Survival without needs of ventilator utilization (including non invasive ventilation and high flow) at day 14. Thus, events considered are needing ventilator utilization (including Non Invasive Ventilation, NIV or high flow), or death. New DNR order (if given after the inclusion of the patient) will be considered as an event at the date of the DNR.
2. Early endpoint : proportion of patients alive without non-invasive ventilation of high low at day 4 (WHO progression scale ≤ 5). A patient with new DNR order at day 4 will be considered as with a score > 5.

OMS Progression scale	Descriptor	Score
Uninfected	Uninfected; non viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
Ambulatory	Symptomatic; Independent	2
Ambulatory	Symptomatic; Assistance needed	3
Hospitalized : mild	Hospitalized; No oxygen therapy	4

disease		
Hospitalized : mild disease	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized : severe disease	Hospitalized; oxygen by NIV or High flow	6
Hospitalized : severe disease	Intubation and Mechanical ventilation, pO2/FIO2>=150 OR SpO2/FIO2>=200	7
Hospitalized : severe disease	Mechanical ventilation, (pO2/FIO2<150 OR SpO2/FIO2<200) OR vasopressors (norepinephrine >0.3 microg/kg/min)	8
Hospitalized : severe disease	Mechanical ventilation, pO2/FIO2<150 AND vasopressors (norepinephrine >0.3 microg/kg/min), OR Dialysis OR ECMO	9
Death	Dead	10

Secondary end-points will be OMS progression scale at 4, 7 and 14 days, overall survival at 14, 28 and 90 days, time to discharge, time to oxygen supply independency, time to negative viral excretion.
Biological parameters improvement:
Estimated GFR, CRP, myoglobin, CPK, cardiac troponin, ferritin, lactate, cell blood count, liver enzymes, LDH, D-Dimer, albumin, fibrinogen, triglycerides, coagulation tests, urine electrolyte, creatinuria, proteinuria, uricemia, IL6, procalcitonin, immunophenotype (Annexe 2), and exploratory tests (Annexe 3).

For the group 2 of patients *requiring ICU*:

Co Primary Endpoints

1. Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14 if patients have been intubated before day 14 ; or removal of NIV or high flow (for > 48h) if they were included under oxygen by NIV or High flow (score 6) and remained without intubation. Death or new DNR order (if given after the inclusion of the patient) will be considered as a competing event.
2. Early end point : proportion of patients with a decrease of WHO score of at least 1 point at day 4.

Secondary end points will be OMS progression scale at 4, 7 and 14 days, overall survival at 14, 28 and 90 days, the 28-day ventilator free-days, respiratory acidosis at day 4 (arterial blood pH of <7.25 with a partial pressure of arterial carbon dioxide [Paco2] of ≥60 mm Hg for >6 hours), the evolution of PaO2/FiO2 ratio, time to oxygen supply independency, duration of hospitalization, time to negative viral excretion, time to ICU and hospital discharge.

	Biological parameters improvement (estimated GFR, CRP, cardiac troponin, urine electrolyte and creatinine, proteinuria, uricemia, IL6, myoglobin, KIM-1, NGAL, CPK, ferritin, lactate, cell blood count, liver enzymes, LDH, D-Dimer, albumin, fibrinogen, triglycerides, coagulation tests (including activated partial thromboplastin time), procalcitonin, immunophenotype (Annexe 2), and exploratory tests (Frozen samples Annexe 3). Rate of renal replacement therapy, ventilation parameters. **For each comorbidities group secondary criteria will be specifically addressed:** For each tested medication, specific markers of efficacy and safety may be used and will be defined.
Criteria of safety	● Number of serious adverse events ● Cumulative incidence of serious adverse events (SAEs) ● Cumulative incidence of Grade 3 and 4 AEs. ● Investigational medication discontinuation (for any reason)

Statistical Method	To maximize information from limited data generated, while allowing rapid decision, a Bayesian monitoring of the trial based on tco-primary outcomes will be used. The overall strategy has been determined so as to control for a frequentist one sided 5% type I error rate. The following methods pertain to the conduct and analysis of the subtrial in a given group of patients (group I or group II), that are analyzed separately with different primary outcomes, but conducted simultaneously (with stratified randomization) for logistical reasons. **The total sample size will be 120 (60 in each arm) at the interim analysis, and 240 (120 per arm) at the second analysis.** Since it is not possible to determine in advance how many patients will be recruited in each stratum, the sample sizes used for the following calculations are indicative, considering equally sized strata (groups). At the interim analysis, two posterior probabilities will be calculated: 1) the posterior probability of a lower event rate in the experimental than in the control arm (posterior probability of efficacy) and 2) the posterior probability of achieving at least a predefined effect corresponding to a hazard ratio of 0.85 (for time-to-event primary outcomes) or a risk difference of 5.5% (for binary co-primary outcomes) (posterior probability of sufficient efficacy). If the posterior probability of sufficient efficacy is less than 0.20, the trial can be stopped for futility. If the posterior probability of efficacy is higher than 0.99, the trial can be stopped for efficacy. Otherwise, the trial will continue with inclusion of additional patients, as predefined, and a final analysis is conducted with decision boundary at a posterior probability of efficacy > 0.95. Decision boundaries are non-binding, and the DSMB can recommend continuing recruitment, in the whole population or a subgroup. Final decision boundaries are then readapted to control for a one-sided type I error rate close to 5%. If the strata (groups I or II) are equally sized, the interim analysis should occur after 60 patients, and the second one with 120. This design (with only two stages) has then type I error rate 0.047 if event rates are 50% in each arm, and power 0.972 to detect a decrease from 0.50 to 0.20 and 0.739 to detect a decrease from 0.50 to 0.30. In the cmRCT design, randomisation occurs prior to offering the intervention, and some number of eligible patients who are randomly selected to be offered an intervention will not accept the offer. An intention to treat analysis could therefore dilute any treatment effects. Relton et al. suggested to use a complier average causal effect (CACE) analysis which provides unbiased estimates of the treatment effect for patients who comply with the protocol. Thus, all final primary analyses will be performed in both Intention To Treat (ITT) and CACE basis. For this purpose, it will be assumed that a patient's decision not to accept the intervention will not affect the outcome. For the ITT analysis, patients will be analysed according to the treatment arm they were randomized to (i.e. offer or no offer group), even if the participant did not accept the intervention.
	CORIMUNO-19 - SARI

Rationale for using Sarilumab in severe patients infected with COVID-19	CORIMUNO-19 **- SARI** The SRAS-CoV-S protein induces direct up-regulation of IL-6, IL-1 and TNFα, some of the most potent pro-inflammatory cytokines Sarilumab is a human IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6Rs (sIL-6Rα and mIL-6Rα) and has been shown to inhibit IL-6-mediated signalling through these receptors. Sarilumab is formulated for subcutaneous (SC) injection and was approved for the treatment of rheumatoid arthritis in the US, EU and Japan in 2017 at a dose of 200 mg Q2W. In this protocol involving critically ill patients, it is preferable to use an IV injection. While there is limited experience in the use of sarilumab by IV infusion, the choice of the dose the use of sarilumab to be given by the IV route in this setting is supported by the high degree of bio-similarity of sarilumab to tocilizumab including a number of similarities in clinically observed pharmacokinetics, pharmacodynamics (to include safety, and PD endpoints). Based on available data, on a per mg basis, tocilizumab and sarilumab behave comparably in vivo with respect to potency, PK, PD, efficacy, and safety. Thus, the safety of sarilumab at doses as high as 400 mg IV can be extrapolated from the experience with similar and even higher doses of tocilizumab. Thus, it will be an IV dose of 400 mg of sarilumab in a 1 hour-infusion that will be given in this study
Diagnosis and inclusion and Exclusion criteria for the Sarilumab trial	**Inclusion Criteria for the Sarilumab trial:** 1. Patients included in the CORIMUNO-19 cohort 2. Patients belonging to one of the 2 following groups: - *Group 1: patients **not requiring ICU** at admission with moderate and severe pneumopathy according to the OMS **Criteria of severity of COVID pneumopathy.*** ***Moderate cases*** Cases meeting all of the following criteria: ● Showing fever and respiratory symptoms with radiological findings of pneumonia. ● Requiring between 3L/min and 5L/min of oxygen to maintain SpO2 >97% ***Severe cases*** Cases meeting any of the following criteria: ● Respiratory distress (≧ 30 breaths/ min); ● Oxygen saturation≤93% at rest in ambient air; or Oxygen saturation ≤97 % with O2 > 5L/min. ● PaO2/FiO2≦ 300mmHg - *Group 2: patients **requiring ICU** based on **Criteria of severity of COVID pneumopathy.*** ● Respiratory failure and requiring mechanical ventilation ● No do-not-resuscitate order (DNR order) **Exclusion Criteria for the Sarilumab trial:**

	1. Patients with exclusion criteria to the CORIMUNO-19 cohort. 2. Known hypersensitivity to Sarilumab or to any of their excipients. 3. Pregnancy 4. Current documented bacterial infection 5. Patient with any of following laboratory results out of the ranges detailed below at screening should be discussed depending of the medication: a. Absolute neutrophil count (ANC) ≤ 1.0 x 10^9/L b. Haemoglobin level: no limitation c. Platelets (PLT) < 50 G /L d. SGOT or SGPT > 5N
Randomisation and Treatment procedures	Group defined by **requiring** ICU vs. **not requiring** ICU. All consecutive patients meeting the inclusion criteria will be randomised 1:1 either in the Sarilumab arm or control arm in a set of 120 patients in total (60 in the each arm), **stratified on the group**. Trials within each groups are analyzed separately, but are conducted simultaneously (with stratification of the randomisation) for logistical reasons. If other subtrials are available, the inclusions will stop to allow inclusions in these other subtrials of the protocol and interim analysis. If the interim analysis indicates to continue the subtrial, a new set of 120 patients will be included on the same basis. If no other subtrial is available the inclusions will not be stopped in waiting for the interim analysis, given tocilizumab is already a drug with known safety. Inclusions of new sets will stop when statistical analyses conclude on futility or efficacy or by DSMB decision. ● Group 1: patients **not requiring ICU** ○ Patients will be randomized to be offered **Sarilumab (**an IV dose of 400 mg of sarilumab in a 1 hour-infusion at D1). In the absence of a clinical response, a second dose of **Sarilumab** will be administered on day 3 (D3). ○ Patients from the cohorts and with the same baseline characteristics will be used as controls (best standard of care)

	● Group 2: patients **requiring ICU** ○ Patients will be randomized to receive **Sarilumab (**an IV dose of 400 mg of sarilumab in a 1 hour-infusion at D1). In the absence of a clinical response, a second dose of **Sarilumab** will be administered on day 3 (D3). These patients may receive or not steroids depending on the local procedures. ○ Patients from the cohorts with the same baseline characteristics will be used as controls
Duration of follow-up	90 days

Criteria for efficacy

Measures

A core set of clinical measures will be recorded daily the first 2 weeks and then every week. The core measures include measures of OMS progression scale, oxygenation, mechanical ventilation. For patients who are eligible for an intervention trial (in both the intervention and control arms), this days measurement will include trial-specific measures related to the trial outcomes of interest.

Primary and secondary endpoints:

The primary endpoint and secondary endpoints will depend on the group of patients and tested medication.

Groups will be redefined as follow :

- Group 1: Cases meeting all of the following criteria
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- Group 2: Cases meeting all of the following criteria

  - Respiratory failure AND (requiring mechanical ventilation OR NIV OR High flow)
  - WHO progression scale >=6
  - No do-not-resuscitate order (DNR order)

For the group 1 of patients *not requiring ICU*:

Co Primary Endpoints

1. Survival without needs of ventilator utilization (including non invasive ventilation and high flow) at day 14. Thus, events considered are needing ventilator utilization (including Non Invasive Ventilation, NIV or high flow), or death. New DNR order (if given after the inclusion of the patient) will be considered as an event at the date of the DNR.
2. Early endpoint : proportion of patients alive without non-invasive ventilation of high low at day 4 (WHO progression scale ≤ 5). A patient with new DNR order at day 4 will be considered as with a score > 5.
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OMS Progression scale	Descriptor	Score
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For the group 2 of patients *requiring ICU*:

Co Primary Endpoints

1. Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14 if patients have been intubated before day 14 ; or removal of NIV or high flow (for > 48h) if they were included under oxygen by NIV or High flow (score 6) and remained without intubation. Death or new DNR order (if given after the inclusion of the patient) will be considered as a competing event.
2. Early end point : proportion of patients with a decrease of WHO score of at least 1 point at day 4.

Secondary end points will be OMS progression scale at 4, 7 and 14 days, overall survival at 14, 28 and 90 days, the 28-day ventilator free-days, respiratory acidosis at day 4 (arterial blood pH of <7.25 with a partial pressure of arterial carbon dioxide [Paco2] of ≥60 mm Hg for >6 hours), the evolution of PaO2/FiO2 ratio, time to oxygen supply independency, duration of hospitalization, time to negative viral excretion, time to ICU and hospital discharge.

	Biological parameters improvement (estimated GFR, CRP, cardiac troponin, urine electrolyte and creatinine, proteinuria, uricemia, IL6, myoglobin, KIM-1, NGAL, CPK, ferritin, lactate, cell blood count, liver enzymes, LDH, D-Dimer, albumin, fibrinogen, triglycerides, coagulation tests (including activated partial thromboplastin time), procalcitonin, immunophenotype (Annexe 2), and exploratory tests (Frozen samples Annexe 3). Rate of renal replacement therapy, ventilation parameters. **For each comorbidities group secondary criteria will be specifically addressed:** For each tested medication, specific markers of efficacy and safety may be used and will be defined.
Criteria of safety	● Number of serious adverse events ● Cumulative incidence of serious adverse events (SAEs) ● Cumulative incidence of Grade 3 and 4 AEs. ● Investigational medication discontinuation (for any reason)

Statistical Method	To maximize information from limited data generated, while allowing rapid decision, a Bayesian monitoring of the trial based on tco-primary outcomes will be used. The overall strategy has been determined so as to control for a frequentist one sided 5% type I error rate. The following methods pertain to the conduct and analysis of the subtrial in a given group of patients (group I or group II), that are analyzed separately with different primary outcomes, but conducted simultaneously (with stratified randomization) for logistical reasons. **The total sample size will be 120 (60 in each arm) at the interim analysis, and 240 (120 per arm) at the second analysis.** Since it is not possible to determine in advance how many patients will be recruited in each stratum, the sample sizes used for the following calculations are indicative, considering equally sized strata (groups). At the interim analysis, two posterior probabilities will be calculated: 1) the posterior probability of a lower event rate in the experimental than in the control arm (posterior probability of efficacy) and 2) the posterior probability of achieving at least a predefined effect corresponding to a hazard ratio of 0.85 (for time-to-event primary outcomes) or a risk difference of 5.5% (for binary co-primary outcomes) (posterior probability of sufficient efficacy). If the posterior probability of sufficient efficacy is less than 0.20, the trial can be stopped for futility. If the posterior probability of efficacy is higher than 0.99, the trial can be stopped for efficacy. Otherwise, the trial will continue with inclusion of additional patients, as predefined, and a final analysis is conducted with decision boundary at a posterior probability of efficacy > 0.95. Decision boundaries are non-binding, and the DSMB can recommend continuing recruitment, in the whole population or a subgroup. Final decision boundaries are then readapted to control for a one-sided type I error rate close to 5%. If the strata (groups I or II) are equally sized, the interim analysis should occur after 60 patients, and the second one with 120. This design (with only two stages) has then type I error rate 0.047 if event rates are 50% in each arm, and power 0.972 to detect a decrease from 0.50 to 0.20 and 0.739 to detect a decrease from 0.50 to 0.30. In the cmRCT design, randomisation occurs prior to offering the intervention, and some number of eligible patients who are randomly selected to be offered an intervention will not accept the offer. An intention to treat analysis could therefore dilute any treatment effects. Relton et al. suggested to use a complier average causal effect (CACE) analysis which provides unbiased estimates of the treatment effect for patients who comply with the protocol. Thus, all final primary analyses will be performed in both Intention To Treat (ITT) and CACE basis. For this purpose, it will be assumed that a patient's decision not to accept the intervention will not affect the outcome. For the ITT analysis, patients will be analysed according to the treatment arm they were randomized to (i.e. offer or no offer group), even if the participant did not accept the intervention.

2. SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1. Overview of COVID-19

COVID-19 is a respiratory disease caused by a novel coronavirus (SARS-CoV-2) and causes substantial morbidity and mortality (1-4). There is currently no vaccine to prevent Covid-19 or infection with SARS-CoV-2 or therapeutic agent to treat COVID-19. This clinical trial is designed to evaluate the efficacy and tolerance of various immune modulators of adult patients hospitalized with COVID-19.

Coronavirus (CoVs) are positive-sense single stranded enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past two decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle Eastern respiratory syndrome coronavirus (MERS- CoV) (5).

In December 2019, the Wuhan Municipal Health Committee (Wuhan, China) identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been abbreviated as SARS- COV-2 and has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV (6). Most of the infections outside China have been travel- associated cases in those who had recently visited Wuhan City and are thought to have acquired the virus through contact with infected animals or contact with infected people. This novel coronavirus has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19. Outbreak forecasting and mathematical modelling suggest that these numbers will continue to rise (7, 8). Global efforts to evaluate novel antivirals and therapeutic strategies to treat COVID-19 have intensified. Due to the recent increase in the number of overflow patients in ICU and dying adult patients, previously healthy or with comorbidities at all ages, there is an urgent public health need for rapid development of novel interventions.

There is currently no treatment approved in the treatment of patients with COVID-19. Remdesivir, which failed against Ebola Virus, is being tested in China as an emergency countermeasure. Other antiviral agents including hydroxychloroquine and azithromycine, protease inhibtors (lopinavir/ritonavir) alone or in combination, interferon are currently tested. However, the severe and critically ill patients display high inflammatory state. While most people with COVID-19 develop only mild or uncomplicated illness, approximately 14%

develop severe disease that requires hospitalization and oxygen support, and 5% require admission to an intensive care unit. In severe cases, COVID-19 can be complicated by the acute respiratory distress syndrome (ARDS), sepsis and septic shock, multiorgan failure, including acute kidney injury and cardiac injury (9, 10). Older age and co-morbid disease have been reported as risk factors for death, and recent multivariable analysis confirmed older age, higher Sequential Organ Failure Assessment (SOFA) score (11) and d-dimer > 1 µg/L on admission were associated with higher mortality.

COVID-19 infection causes clusters of severe respiratory illness similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and MERS-CoV and is associated with intensive care unit admission and high mortality (1). COVID-19 pneumonia manifests with chest computed Tomography (CT) imaging abnormalities, even in asymptomatic patients (12-15). On hospital admission, abnormalities in chest CT images were detected among all patients. Complications included acute respiratory distress syndrome (29% cases), RNAaemia (15%), acute cardiac injury (12%) and secondary infection (10%).

2.2. Rationale for using immune regulatory drug

2.2.1. Immune pathology of COVID infection

Histopathological observations and imaging features of pulmonary lesions in COVID-19 patients overlap with those of SARS-CoV and MERS-CoV. COVID-2019 patients present non-specific inflammatory responses, including edema and inflammatory cell infiltration, and exhibit severe exfoliation of alveolar epithelial cells, alveolar septal widening, damage to alveolar septa, and alveolar space infiltration in a distinctly organized manner. This pathological inflammation includes tissue necrosis, infiltration, and hyperplasia. Thus, damage to the pulmonary interstitial arteriolar walls indicates that inflammatory response plays an important role throughout the course of disease in spite of the pathogenic effect of CoVs . These deleterious excessive and aberrant non-effective host immune responses are related to a “cytokine storm” reported in most Cov-infected patients (COVID-19, SARS-CoV and MERS-CoV). They present a hypercytokenia displaying an increased plasma concentration of a number of pro-inflammatory cytokines and chemokines such as IL-1β, IL-1α, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-37, IL-17, bFGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα, or VEGF, Endothelin-1, Complement C5a…and this list is far to be exhaustive (16-31).

Host-directed therapy could constitute a strategy of choice to efficiently treat COVID-19 patients by controlling inflammation in order to promote tolerance to disease (31, 32). Existing safe therapies could potentially be repurposed to treat COVID-19 infection, including metformin, glitazones, fibrates, sartans, and atorvastatin as well as nutrients (Zinc and others metal formulation) or biologics such as Anakinra an IL-1 trap, Canakinumab an antibody targeting IL-1beta, antikinases compounds such as Abl or JAK inhibitors, or Tocilizumab and Sarilumab, two monoclonal antibodies targeting IL6R. All these compounds could be used in adjunct therapy or in combination with antiviral therapies including Remdesivir, Lopinavir–Ritonavir, interferon beta-1β, or ribavirin (33)(doi: 10.1038/d41587-020-00003-1).

Some others class of drugs, presenting potent anti-inflammatory or antiviral properties, such as the tyrosine kinase inhibitors which target the JAK/STAT pathway (Ruxolitinib, Tofacitinib, Bafecitinib)(34), or these that block the SARS-CoV/MERS-CoV early entry and/or post entry events (Imatinib (35)) have been proposed to be of interest for the treatment of severe cases of COVID-19, when the host inflammatory response becomes a major cause of lung damage and subsequent mortality (36, 37).

Recently, Kritas et al., have proposed to use anti-inflammatory cytokines belonging to the IL-1 family members, such as IL-37, to treat coronavirus pathogenic inflammation based on the fact that Coronavirus infection activate the early release of inflammatory compounds (IL-6, TNFα) by mast cells (MCs), while late MCs activation provokes the generation of pro-inflammatory IL-1 family members including IL-1 and IL-33 (38).

IL-6 is a pleotropic cytokine promptly and transiently produced by multiple cell types including fibroblasts, keratinocytes, mesangial cells, vascular endothelial cells, mast cells, macrophages, dendritic cells, and T and B cells in response to tissue damage and infections. IL-6 stimulates diverse cellular responses such as proliferation, differentiation, survival, and apoptosis and can activate hepatocytes to release acute-phase proteins, including C-reactive protein (CRP) and serum amyloid A. IL-6 is also involved in diverse physiological processes such as migration and activation of T-cells, B-cells, monocytes, macrophages and osteoclasts leading to systemic and local inflammation. IL-6 facilitates the transition from the innate to adaptive immune response by driving down neutrophil activity while concurrently promoting the recruitment, differentiation, and activity of monocytes and T cells (19).

It is well recognized that dysregulated continual synthesis of IL-6 plays a pathological effect on chronic inflammation and autoimmunity (39-41). IL-6 contributes to many of the key symptoms of cytokine release syndromes (CRS). Via trans-signaling IL-6 leads to characteristic symptoms of severe (CRS), i.e. vascular leakage, and activation of the complement and coagulation cascade inducing disseminated intravascular coagulation (DIC)(42). In addition, IL-6 likely contributes to cardiomyopathy that is often observed in patients with CRS, and COVID-19 (41, 42), promoting myocardial dysfunction (43).

The SRAS-CoV-S protein induces direct up-regulation of IL-6 and TNFα, SARS-CoV infection also induces up-regulation of TLR4 and TLR9 which correlate with the induction of inflammatory response. Elevated levels of IL-6 are found in the plasma of patients with COVID-19 pneumonia (doi.org/10.1101/2020.02.25.20025643, doi.org/10.1101/2020.02.16.20023903)(44-46). These data suggest that high levels of IL-6 play a key role in the coronavirus-induced pathogenic inflammation.

2.2.2. Tocilizumab : Rationale for the use and mechanism of action

Tocilizumab (TCZ)(Actemra) is an anti-human IL-6 receptor monoclonal antibody that inhibits signal transduction by binding sIL-6R and mIL-6R (47). The main approved indication is for rheumatoid arthritis, in association or not with methotrexate (48). Tocilizumab has been approved for the treatment of rheumatoid arthritis, idiopathic multicentric Castleman's disease (iMCD) and in 2017, the U.S. Food and Drug Administration approved TCZ for the treatment of cytokine release syndrome (CRS) consisting in a systemic inflammatory response caused by the massive release of pro-inflammatory cytokines in response to iatrogenic (e.g. CAR-t therapies) or infective stimuli (49-54), including with high production in the lungs (55).

2.2.3. Sarilumab: Rationale for the use and mechanism of action

Sarilumab (Kevzara) is a human monoclonal antibody (IgG1 subtype) that specifically binds to both soluble and membrane-bound IL-6 receptors (IL-6Ra), and inhibits IL-6-mediated signalling which involves ubiquitous signal-transducing glycoprotein 130 (gp130) and the Signal Transducer and Activator of Transcription-3 (STAT-3). Sarilumab is FDA- and EMA-approved for rheumatoid arthritis and is being investigated in clinical trials in other rheumatologic conditions (56-58).

Based on available data, on a per mg basis, tocilizumab and sarilumab behave comparably *in vivo* with respect to potency, PK, PD, efficacy, and safety.

2.3. Summary of relevant pre-clinical and clinical trials on IL-6R Inhibition

Although the lack of data on SARS-CoV-2 pathogenesis, studies in China showed a possible correlation of massive inflammation and severe lung damage on the rapid evolution of fatal pneumonia. Indeed, in COVID-19 patients, significant differences in IL-6 plasmatic levels were observed at different stages of disease with a higher expression in severe cases than mild ones. Moreover, in the biopsy samples at autopsy from a severe COVID-19 patient, histological examination showed diffuse alveolar damage with cellular fibromyxoid exudates and interstitial mononuclear inflammatory infiltrates suggesting severe immune injury (59).
Despite the lack of clinical trials on TCZ efficacy and safety for COVID-19 treatment, in China TCZ was recently approved for patients affected by severe SARS-CoV-2 pulmonary complications by the National Health Commission of the People's Republic of China. Preliminary data from an observational study conducted in China on 21 severe cases receiving TCZ, showed an improvement of the clinical and radiological outcome (www.chinaxiv.org/user/download.htm?id=30387&filetype=pdf).

2.4. Description of the population of the cohort and justification for the choice of subjects

The novel coronavirus pneumonia (NCP) is a fast-emerging disease with a severe health and economic burden. The kinetics of the epidemics provokes an overflow of patients to hospitals and critically, to Intensive Care units because a number of patients experience acute respiratory distress syndrome (ARDS) with poor prognosis. For instance, a recent study of 99 patients with 2019-nCoV pneumonia reported that 17% patients developed acute respiratory distress syndrome and, among them, 11% patients worsened in a short period of time and died of multiple organ failure (3). In another single-center case series of 138 hospitalized patients with confirmed NCIP in Wuhan, China, 26% of patients received ICU care, and mortality was 4.3% (10). A large range of age is affected. The case studies of Li et al., encapsulates the first 425 cases recorded in Wuhan indicate that the patients' median age was 59 years, with a range of

15 to 89 years (60) with no significant gender differences. They reported no clinical cases in children below 15 years of age.

3. OBJECTIVES

The overall objective of the study is to determine which treatments (e.g. immune modulator drugs) have the most favourable benefit-risk in adult patients hospitalized with COVID-19.
The specific aims of this Covid-19 cohort are to collect observational data at regular intervals on an ongoing basis in order to embed a series of randomized controlled trials evaluating a various set of interventions.

3.1. Primary objective

The primary objectives of this study are to decrease the rate of transfer to ICU and mechanical ventilation for the group of no ICU patients and to decrease the time of mechanical ventilation for the ICU group

3.2. Secondary objectives

Secondary objectives are improvement of clinical and biological parameters and overall survival at 90 days

4. DESCRIPTION OF THE COHORT STUDY

This study is a prospective cohort of patients with confirmed Covid (infection by SARS-CoV-2). The cohort will be split in different groups, 1) patients requiring or not ICU, and 2) groups based on comorbidities and tested medications.

This cohort is specifically designed to nest trials using a cohort multiple Randomized Controlled Trials (cmRCT) design.

4.1. Cohort multiple Randomized Controlled Trials (cmRCT) design

The key features of the cohort multiple Randomized Controlled Trials (cmRCT) design (61-63) are:

(I) Recruitment of a large observational cohort of patients with the condition of interest

(II) Regular measurement of outcomes for the whole cohort

(III) Capacity for multiple randomised controlled trials over time

Patients enrolled in the cohort agree to allow their longitudinal data to be used in the aggregate. They also allow their data to be used to identify them to be invited to participate in research interventions or for comparison purposes for intervention trials that may be conducted with other patients while they are participating in the cohort.

In the cmRCT design, only eligible patients randomly selected to be offered an intervention, are contacted and offered treatment. Eligible patients not selected to be offered an intervention are not notified about this trial and will be in the control group. Consent for specific trials will be obtained from those eligible patients who are invited and accepted the offer to participate.

In the cmRCT design, as described to patients when they consent to participate in the cohort, only eligible patients randomly selected to be offered an intervention, but not eligible non-selected patients, are contacted and offered treatment. Eligible patients not selected are not notified about the trial. Consent for specific trials will be obtained from those eligible patients who are invited and accept the offer to participate. Post-intervention outcomes among eligible patients who accept the offer to receive the intervention will be compared with outcomes among patients from the cohort who were identified as eligible for the intervention, but were not randomly selected to be offered the intervention and not contacted about the intervention.

In the context of the COVID crisis, the advantage of the cmRCT design to conduct multiple trials that draw participants from the same patient cohort is important given the imperative that we have to answer multiple research questions (some identified and others not yet identified) in a very short time (a few weeks).

The cmRCT design will enable the implementation of multiple trials over time with different inclusion and exclusion criteria (e.g based on severity or comorbidities), testing different interventions that can be compared in the same overall population with similar trial methods, thus increasing the ability to compare and contrast different trial results.

The cmRCT design also offers advantages in that the patient consent process more closely replicates what occurs in actual healthcare settings compared with the consent procedures typically used in traditional RCT designs. In traditional RCTs, patients are usually told that they will be randomised to obtain the trial intervention or an alternative, which is generally usual care. In the cmRCT design, patients are told about treatments that they will be able to access if they so choose. As part of the initial consent process, patients are made aware that a number of trials may occur via the cohort, and that they will not likely be offered to participate in all of them and may not be offered to participate in any. It is explained that patients will only

be notified about trials for which they will be offered the intervention, but that their data may be used for comparison purposes in the context of some interventions not offered to them.

4.2. Settings

Ten Hospitals have already accepted to participate (Bichat, Saint Louis-Lariboisière, HEGP, Cochin-Hotel Dieu, Necker, Pitié, Bicêtre, CHU Strasbourg, CHU Lille, Institut Gustave Roussy (IGR)

4.3. Study population

The study will include potentially all patients with confirmed COVID-19 infection and moderate or severe NCP.

- Illness of any duration and severity, with symptoms (fever, cough, respiratory difficulties, shortness of breath), and at least one of the following:
    - Radiographic infiltrates by imaging (CT scan), and
    - Clinical assessment (evidence of rales/crackles on exam) OR SpO2 ≤ 94% on room air, or oxygen saturation ≤97 % with O2 ≥ 5L/min.
    - Requiring mechanical ventilation and/or supplemental oxygen
    - With any comorbidities (TBD such as acute kidney injury, cardiovascular condition, pulmonary disease, obesity, high blood pressure, diabetes, chronic kidney diseases, haematological diseases, Solid cancer, sickle cell diseases, autoimmune and auto-inflammatory, pregnant women, HIV infected).
- Male or female adult ≥ 18 years of age at time of enrolment
- Any Weight
- Written informed consent provided by the patient or alternatively by next-of-kin prior to any protocol-specific procedures.

Three populations will be identified at baseline.

Moderate cases according the CDC classification:

- Showing fever and respiratory symptoms with radiological findings of pneumonia.
- Requiring between 3L/min>Oxygen <5L/min

Severe cases, meeting any of the following criteria:

- Respiratory distress (≧30 breaths/ min);
- Oxygen saturation≤93% at rest in ambient air; or Oxygen saturation ≤97 % with O2 ≥ 5L/min.
- PaO2/FiO2≦300mmHg (l mmHg=0.133kPa).
- PaO2/ FiO2 in high-altitude areas (at an altitude of over 1,000 meters above the sea level) shall be corrected by the following formula: PaO2/ FiO2 x[Atmospheric pressure (mmHg)/760]
- Cases with chest imaging that showed obvious lesion progression within 24-48 hours >50% shall be managed as severe cases.

Critical cases, meeting any of the following criteria:

- Respiratory failure and requiring mechanical ventilation;
- Shock;
- With other organ failure that requires ICU care

After inclusion, participants in this research will be identified as follows by a unique identifier corresponding to the Site number (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

4.4. Inclusion and exclusion criteria in the cohort

Inclusion Criteria for the cohort:

- Laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen and/or CT Scan prior to randomization (Following typical radiological findings (ground glass abnormalities, and absence of lymphadenopathy, pleural effusion, pulmonary nodules, lung cavitation)
- Hospitalized patients

- Illness of any duration and severity (mild, moderate, severe, critical, see annexe 1), with symptoms (fever, cough, respiratory difficulties, shortness of breath), and at least one of the following:
    - Radiographic infiltrates by imaging (CT scan)
    - Clinical assessment (evidence of rales/crackles on exam) AND SpO2≤94% on room air
    - SpO2≤97 % with O2 ≥ 5L/min.
    - Requiring mechanical ventilation
    - With any comorbidities (TBD such as acute kidney injury, cardiovascular condition, pulmonary disease, obesity, high blood pressure, diabetes, chronic kidney diseases, haematological diseases, solid cancer, sickle cell diseases, autoimmune and auto-inflammatory, pregnant women, HIV infected, etc)
- Male or female adult ≥ 18 years of age at time of enrolment
- Patients must be able and willing to comply with study visits and procedures.
- Patient agrees to the collection of oropharyngeal and nasal swabs and venous blood per protocol
- Written informed consent provided by the patient or alternatively by next-of-kin prior to any protocol-specific procedures.

Exclusion Criteria for the cohort:

Participation in another clinical trial is not an exclusion criteria depending on the medication. ***Patients included in the antiviral REACTING trial are not excluded as well as patients from COVIDICUS trial.***

Severe cardiovascular disease including acute myocardial infarction, unstable angina pectoris, coronary revascularization procedure, congestive heart failure of NYHA Class III or IV, stroke, including a transient ischemic attack, edema of cardiac origin and left ventricular ejection fraction ≤ 50% are not excluded and should be discussed in each therapeutic arm.

- Patients with any condition that the physician judges could be detrimental to the patient participating in this study; including any clinically important deviations from normal

clinical laboratory values or concurrent medical conditions (active infection diseases such as severe bacterial infections, aspergillosis, tuberculosis, depending on the tested medication).

- Absence of Health Insurance
- Subject protected by law under guardianship or curatorship

4.5. Endpoints

A core set of clinical measures will be recorded daily the first 2 weeks and then every week.

- The core measures include measures of OMS progression scale, oxygenation, mechanical ventilation. These measures will allow us to classify the patient's state according to the WHO Clinical Progression Scale.
- All-cause mortality at hospital discharge or 60 days and time to hospital discharge will be also recorded.

These core set of clinical measures are aimed to be used as outcomes in trials nested within the cohort

4.6. Other data collected in the cohort

For the inclusion of women of childbearing age, a pregnancy test is done at baseline before the administration of the investigational medicinal product.

Data collected in the cohort are part of routine care (standard care for patients with COVID-19) will be recorded. Among these parameters we could cite:

Baseline

- Complete medical history and physical examination with record of vital signs (within one month) including O2 saturation by finger oximeter
- Viral load
- Concomitant medications
- CBC with differential (including lymphocytes and neutrophils, platelets)
- Blood group phenotype
- Clinical chemistry (to include sodium, potassium, chloride, CO_2, glucose, calcium, BUN, creatinine, Vitamine D)
- AST, ALT, total bilirubin, alkaline phosphatase, total protein and albumin, ferritin
- CRP, high sensitivity troponin, CPK, Myoglobin, PCT (procalcitonin)
- Coagulation panel including D-Dimers, fibrinogen , IL-6
- CH50, C3, C4

- Urine analysis (pH, glucose, erythrocytes, leukocytes, protein, albumin, nitrite, creatinine)
- Electrocardiogram
- Blood gas
- Cardiac ultrasound (optional)
- CT scan of thorax
- Collection of frozen blood samples performed for care
- Biobanking according to the local facilities (Annexe 3)

Everyday, Every week

Physical examination with record of vital signs (until discharge) including O2 saturation by finger oximeter

- Medications taken by the patient

Biological tests

- CBC with differential (including lymphocytes and neutrophils, platelets)

- Clinical chemistry (to include sodium, potassium, chloride, CO_2, glucose, calcium, BUN, creatinine)
- AST, ALT, total bilirubin, alkaline phosphatase, total protein and albumin, ferritin
- CRP, high sensitivity troponin, CPK, Myoglobin, PCT (procalcitonin)
- Coagulation panel including D-Dimers, fibrinogen , IL-6
- CH50, C3, C4 (every weeks)
- Urine analysis (pH, glucose, erythrocytes, leukocytes, protein, albumin, nitrite, creatinine)
- Electrocardiogram (ECG)
- Blood gas
- Cardiac ultrasound (optional)
- CT scan of thorax (at least once a week and on demand)

Every weeks or in case of significant clinical change

- Viral load
- Biobanking according to the local facilities (Annexe 3)

At hospital discharge

- Medications taken by the patient
- Viral load
- CBC with differential (including lymphocytes and neutrophils, platelets)
- Clinical chemistry (to include sodium, potassium, chloride, CO_2, glucose, calcium, BUN, creatinine)
- AST, ALT, total bilirubin, alkaline phosphatase, total protein and albumin, ferritin
- CRP, high sensitivity troponin, CPK, Myoglobin, PCT (procalcitonin)
- Coagulation panel including D-Dimers, fibrinogen , IL-6
- Urine analysis (pH, glucose, erythrocytes, leukocytes, protein, albumin, nitrite, creatinine)
- Electrocardiogram (ECG)
- Blood gas
- Cardiac ultrasound (optional)
- CT scan of thorax
- Biobanking according to the local facilities (Annexe 3)

At day 90 after inclusion in the cohort

· Physical examination with record of vital signs including O2 saturation by finger oximeter
· Medications taken by the patient
· CBC with differential (including lymphocytes and neutrophils, platelets)
· Clinical chemistry (to include sodium, potassium, chloride, CO_2, glucose, calcium, BUN, creatinine)
· AST, ALT, total bilirubin, alkaline phosphatase, total protein and albumin, ferritin
· CRP
· Coagulation panel including D-Dimers, fibrinogen , IL-6
· Urine analysis (pH, glucose, erythrocytes, leukocytes, protein, nitrite, creatinine)
· Electrocardiogram (ECG)
· Blood gas and pulmonary function tests
· Cardiac ultrasound (optional)
· CT scan of thorax
- Biobanking according to the local facilities (Annexe 3)

4.7. Biobanking (cf Annexe 3)

During the study, the samples (plasma, serum, DNA, RNA, cells and urine) taken will be stored in a biological sample collection at the local laboratory of each centre. Use of samples will be coordinated by a scientific advisory board chaired by Dr Pierre-Louis Tharaux, in order to be centrally analysed.

At the end of the study, the samples may be used for further analysis useful for investigation of the condition, in light of advances in scientific knowledge, provided the participant is informed and does not oppose this, as stated in the information note/consent form. The sample collection will be declared to the ministry of research and to the director of the competent regional healthcare authority (Article L. 1243-3 of the *Code de la Santé Publique* [French Public Health Code]).

4.8. Standard of care provided for all patients in the cohort

All patients in the cohort will receive standard care. This care may evolve over time. At the beginning of the study, the standard care consists of supportive therapy, oral or IV rehydratation, antimicrobial therapy, O2 therapy. In severe and critically ill patients, although its benefit is not yet fully demonstrated, corticosteroids may be used (methylprednisolone 1 mg/kg daily intravenously for 5 days, followed by 40 mg daily for 3 days and, lastly, 10 mg daily for 2 days, or dexamethasone 20 mg daily intravenously for 5 days, followed by 10 mg daily for 3 days and lastly 5 mg daily for 2 days). In this group of patients in case of hypoxia refractory to mechanical ventilation ECMO might be considered.

4.9. Flowchart

Study Flow Chart	Screening D-1 / D1	Baseline D1	D2-D15	D3	D15-D89	D28	D90	At Discharge
Eligibility								
Informed consent [1]	X[2]							
Medical history Comorbidities	X	X[2]						
Demography	X	X[2]						
Clinical status	X	X[2]	Every day		Every week or in case of significant change	X	X	X
Concomitant medications	X	X[2]	Every day		Every week or in case of significant change	X	X	X
HIV, hepatitis B, hepatitis C and tuberculosis	X	X[2]						
Viral load SARS-CoV-2 by PCR, Oropharyngeal swab	X	X[2]	Every week or in case of significant change		Every week or in case of significant change	X	X	X
SpO_2 finger oximeter	X	X[2]	Every day		Every week or in case of significant change	X	X	X
PaO2/FiO2	X	X[2]	Every day		Every week or in case of significant change	X	X	X
Thorax CT scan	X	X[2]	At least every week and on demand		Every week or in case of significant change	X	X	X
Study Intervention								
Randomization		X						
Study 1 :Tocilizumab : 8mg/kg by 1hr i.v. infusion		X		X				
Study 2 Sarilumab: 8mg/kg by 1hr i.v. infusion		X						
New study : to be modified if new treatment								
Study Procedures								
ECG	X	X[2]	On demand			If hospitalized	If hospitalized	X
Cardiac ultrasound (optional)		X[2]	On demand			If hospitalized	If hospitalized	X
Haematology and Biochemistry	X	X[2]	Every day		Every week or in case of significant change	If hospitalized	If hospitalized	X
CRP, high sensitivity troponin, CPK, Myoglobin, PCT (procalcitonin)		X[2]	Every day		Every week or in case of significant change	If hospitalized	If hospitalized	X
Coagulation panel including D-Dimers, fibrinogen , IL-6		X[2]	Every day		Every week or in case of significant change	If hospitalized	If hospitalized	X
Complement total blood test CH50, C3, C4		X[2]	Every week		Every week or in case of significant change			
Urine		X[2]	Every day		Every week or in case of significant change	If hospitalized	If hospitalized	X
Blood gas		X[2]	Every day		Every week or in case of significant change			

NT proBNP and Troponin T		X[2]	On demand		On demand	If hospitalized	If hospitalized	X
Sampling blood for care		X[2]	X		X			
Biobanking		X[2]	Every week or in case of significant change[6]		Every week or in case of significant change			
Ancillary studies[7]		X						
Adverse event(s) [3]	X	X[2]	Every day		X	X	X	X

(1) Patient will have to sign informed consent form for the study before any study procedures.
(2) Baseline assessments should be performed prior to IMP administration
(3) In case of severe neutropenia or skin toxicity, blood sample can be drawn any time from AE onset
(4) Additional administration(s) (one additional infusion at 24h) are evaluated on the basis of patient's response to TCZ 8-12 hours apart, in case of: - Absence/poor clinical improvement (decrease in oxygen supply by 50%) or clinical worsening and/or - Failure in reduction of 50% baseline C-reactive protein (a reliable surrogate marker of IL-6) or failure in normalization and/or - Failure in reduction in D-dimer, fibrinogen or ferritin levels.G
(5) In case of response after three weeks, a second could be discussed in case of relapse or progression of clinical, radiological and biological parameters. In case of absence of response after 48 hours, a second infusion could be realized
(6) Biobanking is also possible on various time according to the local center
(7) Study that need to be performed in fresh samples

5. TRIALS WITHIN THE COHORT

The cohort is specifically designed to conduct trials within cohorts.

These trials are randomized, controlled adaptive trials, with frequent interim monitoring to facilitate the following: dropping of poorly performing arms, introduction of new candidate therapies and modification of current optimized standard-of-care (oSOC).

In its simplest iteration, the study can be viewed as a series of 2-arm comparisons whereby the superior treatment, if identified, from each pairwise comparison becomes the basis of the new supportive care backbone (hence the term "optimized SOC", or oSOC, to describe this potentially evolving backbone) common to each future arm of the study and against which additional investigational interventions may then be added to the protocol, tested and compared: Arm A: optimized SOC alone Arm B: Investigational treatment X + optimized SOC.

- If this pairwise comparison shows the superiority of Arm B over Arm A, then investigational treatment X featured in Arm B will be incorporated into the new oSOC common to each future arm of the study (assuming adequate drug supply exists to permit this).
- Conversely, if a given pairwise comparison of Arm A versus Arm B fails to yield a clear statistical winner in terms of the primary endpoint, then subsequent pairwise comparisons will not incorporate the "failed" intervention featured in current Arm B into the new oSOC backbone.

5.1. Adding new trials in the cohort

The choice of which experimental treatments may be studied in trials nested in the cohort and the order in which they are to be studied will be made by the scientific committee of the cohort, which is composed of a panel of physicians with expertise in the care and management of patients with Covid-19 infection.

5.2. Clinical trial process

- Trials with non overlap of the targeted population i.e. with inclusion and exclusion criteria leading to distinct groups will be driven in parallel. Thus, patients of the cohort will be randomized in the trial corresponding to their characteristics.
- Trials with overlap of the targeted population will be driven sequentially. A first set of patients will be included in the first trial (A). After inclusion of the predefined number

of patients in the i^{th} set, the set $(i+1)^{th}$ set of patients will be included in one (B) of the other trials with the overlapped targeted population. This allows to run the interim analyses of trial A on the *i*-th set and to continue to include patients in trials B. After the results of the interim analysis it will be decided to continue or not the trial A and potentially to come back to trial A or not for the $(i+2)^{th}$ set of patients

The sample of the sets will depend of each trial.

Inclusions of new sets will stop when statistical analyses conclude on futility or efficacy or by DSMB decision.

5.3. Methodological elements of trials nested in the cohort

Trials nested in the cohorts may involve:

- All patients of the cohort
- OR a subpopulation of patients with specific eligibility criteria (e.g., patients in ICU, patients with a specific biomarker, etc.)

Endpoints of the trials may involve:

- The endpoints regularly collected in the cohort (see section 4.4)
- OR specific endpoints collected for the given trial

Interventions may be of any type (e.g., medications, non pharmacological treatments, organisation of care…). According to the cmRCT design, a random sample of patients is selected among all patients eligible for the trial and is proposed the intervention. Their outcome is compared to patients who did not receive the intervention.

All elements of trials will be defined in specific dedicated protocols.
Patients who will be proposed for the intervention will provide a new consent, specific for the trial. Patients who serve as controls will not provide a new consent, according to the cmRCT design.

5.4. Termination and exit rules for trials nested in the cohort

The patient can prematurely terminate the research any time. If consent is withdrawn, none of the participant's data may be used unless the participant states in writing that he/she does not object to the said use of the data. In practice, the participant is excluded from the research.

The investigator can temporarily or permanently end a participant's participation in the study for any reason that affects the participant's safety or would be in the participant's best interests.

The case report form (CRF) must list the various reasons for ending participation in the research:

- Ineffective treatment
- Adverse reaction
- Other medical problem
- Participant's personal reasons
- Explicit withdrawal of consent

5.5. Monitoring subjects after the premature termination of treatment

Ending a participant's inclusion does not affect the normal management of the participant's illness in any way.

The Data and Safety Monitoring Board (DSMB) may specify and/or validate the study monitoring procedures.

In case of serious adverse events, the investigator must notify the sponsor and monitor the subject until complete resolution of any clinical symptoms or until the final treatment phase in the case of life threatening conditions.

5.6. Decision of a new trial nested in the cohort

Any decision of performing a new trial within the cohort would be approved by the scientific committee and the sponsor. The project would be then submitted to the CPP and ANSM.

5.7. Full or partial cancellation of a trial nested in the cohort

The sponsor (AP-HP) or the competent authority (ANSM) can prematurely terminate all or part of the research (whether temporarily or permanently) when recommended by the DSMB in the following situations:

If suspected unexpected serious adverse reactions (SUSARs) are observed in patients being treated which prompt reassessment of the study's benefit-risk ratio

Excessive toxicity observed in an interim analysis

Unexpected facts or new information about the product in the light of which the study's objectives are unlikely to be achieved may prompt the sponsor (AP-HP) or the competent authority (ANSM) to terminate the research prematurely

The sponsor (AP-HP) reserves the right to permanently suspend inclusions at any time if it appears that the inclusion objectives are not being met.

If the research is terminated prematurely, the decision and accompanying justification will be transmitted by the sponsor to the competent authority and the CPP within two weeks, along with recommendations from the DSMB.

6. FIRST NESTED TRIAL : EFFICACY OF TOCILIZUMAB FOR PATIENTS WITH COVID-19

6.1. Investigational medicinal product(s)

6.1.1. ROACTEMRA® 20mg/mL, 20mL (400mg)

Tocilizumab (TCZ), ROACTEMRA® is an anti-human IL-6 receptor monoclonal antibody that inhibits signal transduction by binding sIL-6R and mIL-6R. The main approved indication is for rheumatoid arthritis, in association or not with methotrexate. TCZ is also approved in the treatment of juvenile inflammatory arthritis and in the treatment of refractory giant cell arteritis. Interestingly, this later indication concerns aged patients and, in this population, the safety profile was the same as in younger patients. In 2017, the U.S. Food and Drug Administration approved TCZ for the treatment of cytokine release syndrome (CRS) consisting in a systemic inflammatory response caused by the massive release of pro-inflammatory cytokines in response to iatrogenic (e.g. CAR-t therapies) or infective stimuli.

Clinical trials on TCZ efficacy and safety for COVID-19 treatment are underway in China (A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19) [Registration number: ChiCTR2000029765 / date of Registration: 2020-02-13) and about to start in Italy]. In China TCZ was recently approved for patients affected by severe SARS-CoV-2 pulmonary complications by the National Health Commission of the People's Republic of China. Preliminary data from an observational study conducted in China on 21 severe cases receiving TCZ, showed an improvement of the clinical and radiological outcome.

Although the optimal dose and schedule of TCZ for treatment of CRS is not known, the intended posology is 8 mg/kg intravenously infused over an hour. In the case of patients weighing 100 kg or more, taking into account the PK / PD elements given in the SmPC, the dosage is limited to 800 mg max.

Additional administration(s) (one additional infusion at day 3 (D3)) are evaluated on the basis of patient's response to TCZ 8-12 hours apart, in case of:

- Absence/poor clinical improvement (decrease in oxygen supply by 50%) or clinical worsening and/or
- Failure in reduction of 50% baseline C-reactive protein (a reliable surrogate marker of IL-6) or failure in normalization and/or
- Failure in reduction in D-dimer, fibrinogen or ferritin levels.

Dosage adjustment is required in relation to blood parameters of liver function and blood count according to the indications specified in the patient package insert. It is advisable monitoring of the following blood parameters (full blood count including platelet count, ALT/AST, LDH, fibrinogen, D-dimer, ferritin, C-reactive protein and IL-6) at different time points: immediately before 1st infusion, immediately before 2nd infusion, 24h after 2nd infusion, 36h after 2nd infusion.

In case of absence of response after 48 hours, a second infusion of TCZ could be realized at day 3 (D3). This second dose is fixed at 400mg.

6.1.2. **Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including rescue medications**

The medical staff is expected to monitor patients and administer any drug required for the treatment and/or prevention of all the usual complications that can develop in this setting. For all additional treatments, the SCP must have been obtained from the EMA website (http://www.ema.europa.eu/ema/), or from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php), or http://base-donnees-publique.medicaments.gouv.fr

Interactions with CYP450 Substrates Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6 :

Inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Its effects on CYP2C8 or transporters is unknown. In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of **ROACTEMRA®**, respectively. The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index,

where the dose is individually adjusted. Upon initiation or discontinuation of **ROACTEMRA®**, in patients being treated with these types of medicinal products, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) and the individual dose of the medicinal product adjusted as needed. Exercise caution when coadministering **ROACTEMRA®** with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Thus the following treatment are prohibited :

- AVK
- cyclosporin
- theophylline
- Oral contraception
- lovastatin
- atorvastatin

6.1.3. **Supply of the investigational centers**

ROACTEMRA® will be specifically supplied by the sponsor to hospital pharmacies. **ROACTEMRA®** vials are subject to regulatory counter-labeling with research mentions. Hospital pharmacies will provide care units on the basis of a specific research prescription.

Origin : Specialty with marketing authorization in UE/France, marketed in France.

Storage :
Store the bottle in the refrigerator (2 ° C to 8 ° C). Do not freeze.
Keep the bottle in the outer carton in order to protect from light.
For the storage conditions of the diluted medicinal product, please refer to the SmPC.

6.1.4. **Posology and drugs administration**

Treatment includes the administration on day 1 (D1) of an infusion of **ROACTEMRA®** 8 mg / kg with a maximum dose of 800 mg for all patients weighing 100 kg or more.
In the absence of a clinical response, a second fixed dose of 400 mg of **ROACTEMRA®** will be administered on day 3 (D3).
For the terms of dilution and reconstitution, please refer to the SmPC.

6.1.5. Traceability in investigational centers

In accordance with the rules of Good Practices and to track the treatment given to each patient, all the information related to the treatment will be collected on a traceability sheet (Preparation, Dispensation, Date of administration, Time of administration, Batch number and expiry date, and Dose administered).

6.1.6. Methods for monitoring compliance with the treatment

To track the treatment given to each patient, all the information related to the treatment will be collected on a traceability sheet. This sheet will be prospectively and exhaustively monitored by clinical research assistants during the study. In case of deviations from the protocol there will be reminders to the centers and regular checks.

6.2. Control

Control patients will receive the best standard of care.

6.3. Inclusion/Exclusion criteria for the nested trial

Inclusion Criteria:

1. Patients included in the CORIMUNO-19 cohort

2. Patients belonging to one of the 2 following groups:

*- Group 1: patients **not requiring ICU** at admission with moderate and severe pneumopathy according to the WHO **Criteria of severity of COVID pneumopathy.***

Moderate cases

Cases meeting all of the following criteria:

- Showing fever and respiratory symptoms with radiological findings of pneumonia.
- Requiring between 3L/min and 5L/min of of oxygen to maintain SpO2 >97%

Severe cases

Cases meeting any of the following criteria:

- Respiratory distress (≧30 breaths/ min);
- Oxygen saturation≤93% at rest in ambient air; or Oxygen saturation ≤97 % with O2 > 5L/min.
- PaO2/FiO2≦300mmHg

*- Group 2: patients **requiring ICU** based on **Criteria of severity of COVID pneumopathy.***

- Respiratory failure and requiring mechanical ventilation
- No do-not-resuscitate order (DNR order)

Exclusion Criteria:

- Patients with exclusion criteria to the CORIMUNO-19 cohort.
- Known hypersensitivity to Tocilizumab or to any of their excipients.
- Pregnancy
- Current documented bacterial infection.
- Patient with any of following laboratory results out of the ranges detailed below at screening should be discussed depending of the medication:
    - Absolute neutrophil count (ANC) ≤ 1.0 x 10^9/L
    - Haemoglobin level: no limitation
    - Platelets (PLT) < 50 G /L
    - SGOT or SGPT > 5N

The primary endpoint and secondary endpoints will depend on the group of patients and tested medication.

6.4. Endpoints for the trial

6.4.1. Efficacy endpoints

Measures

A core set of clinical measures will be recorded daily the first 2 weeks and then every week. The core measures include measures of OMS progression scale, oxygenation, mechanical ventilation. For patients who are eligible for an intervention trial (in both the intervention and control arms), this days measurement will include trial-specific measures related to the trial outcomes of interest.

Primary and secondary endpoints:

The primary endpoint and secondary endpoints will depend on the group of patients and tested medication.

Groups will be redefined as follow :

- Group 1: Cases meeting all of the following criteria
    - Requiring more than 3L/min of oxygen
    - OMS/WHO progression scale = 5
    - No NIV or High flow

- Group 2: Cases meeting all of the following criteria

    - Respiratory failure AND (requiring mechanical ventilation OR NIV OR High flow)
    - WHO progression scale >=6
    - No do-not-resuscitate order (DNR order)

For the group 1 of patients *not requiring ICU*:

Co Primary Endpoints

1. Survival without needs of ventilator utilization (including non invasive ventilation and high flow) at day 14. Thus, events considered are needing ventilator utilization (including Non Invasive Ventilation, NIV or high flow), or death. New DNR order (if given after the inclusion of the patient) will be considered as an event at the date of the DNR.
2. Early endpoint : proportion of patients alive without non-invasive ventilation of high low at day 4 (WHO progression scale ≤ 5). A patient with new DNR order at day 4 will be considered as with a score > 5.

OMS Progression scale	Descriptor	Score
Uninfected	Uninfected; non viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
Ambulatory	Symptomatic; Independent	2
Ambulatory	Symptomatic; Assistance needed	3
Hospitalized : mild disease	Hospitalized; No oxygen therapy	4
Hospitalized : mild disease	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized : severe disease	Hospitalized; oxygen by NIV or High flow	6
Hospitalized : severe disease	Intubation and Mechanical ventilation, pO2/FIO2>=150 OR SpO2/FIO2>=200	7
Hospitalized : severe disease	Mechanical ventilation, (pO2/FIO2<150 OR SpO2/FIO2<200) OR vasopressors (norepinephrine >0.3 microg/kg/min)	8
Hospitalized : severe disease	Mechanical ventilation, pO2/FIO2<150 AND vasopressors (norepinephrine >0.3 microg/kg/min), OR	9

	Dialysis OR ECMO	
Death	Dead	10

Secondary end-points will be OMS progression scale at 4, 7 and 14 days, overall survival at 14, 28 and 90 days, time to discharge, time to oxygen supply independency, time to negative viral excretion.
Biological parameters improvement:
Estimated GFR, CRP, myoglobin, CPK, cardiac troponin, ferritin, lactate, cell blood count, liver enzymes, LDH, D-Dimer, albumin, fibrinogen, triglycerides, coagulation tests, urine electrolyte, creatinuria, proteinuria, uricemia, IL6, procalcitonin, immunophenotype (Annexe 2), and exploratory tests (Annexe 3).

For the group 2 of patients *requiring ICU*:

Co Primary Endpoints

1. Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14 if patients have been intubated before day 14 ; or removal of NIV or high flow (for > 48h) if they were included under oxygen by NIV or High flow (score 6) and remained without intubation. Death or new DNR order (if given after the inclusion of the patient) will be considered as a competing event.
2. Early end point : proportion of patients with a decrease of WHO score of at least 1 point at day 4.

Secondary end points will be OMS progression scale at 4, 7 and 14 days, overall survival at 14, 28 and 90 days, the 28-day ventilator free-days, the evolution of PaO2/FiO2 ratio, respiratory acidosis at day 4 (arterial blood pH of <7.25 with a partial pressure of arterial carbon dioxide [$Paco_2$] of ≥60 mm Hg for >6 hours), time to oxygen supply independency, duration of hospitalization, time to negative viral excretion, time to ICU and hospital discharge.

Biological parameters improvement (estimated GFR, CRP, cardiac troponin, urine electrolyte and creatinine, proteinuria, uricemia, IL6, myoglobin, KIM-1, NGAL, CPK, ferritin, lactate, cell blood count, liver enzymes, LDH, D-Dimer, albumin, fibrinogen, triglycerides, coagulation tests (including activated partial thromboplastin time), procalcitonin, immunophenotype (Annexe 2), and exploratory tests (Frozen samples Annexe 3). Rate of renal replacement therapy, ventilation parameters.

For each comorbidities group secondary criteria will be specifically addressed:

For each tested medication, specific markers of efficacy and safety may be used and will be defined.

6.4.2. **Safety endpoints**

In the setting of COVID-19 NCP and short term immunomodulatory therapy, we will monitor major safety endpoints: blood cells and platelets counts and liver transaminases, frequently, every three days systematically.

- **Neutrophil count**

  Treatment with Tocilizumab (Actemra) or Sarilumab (Kevzara) was associated with a higher incidence of decrease in ANC. Decrease in ANC was not associated with higher incidence of infections, including serious infections.

  - In patients who develop an ANC less than 0.5 x 10_9/L, treatment with Tocilizumab or Sarilumab should be discontinued.
  - Neutrophil count should be monitored 4 to 8 weeks after start of therapy and according to clinical judgment thereafter. For recommended dose modifications based on ANC results.

- **Platelet count**

  Treatment with Tocilizumab or Sarilumab was associated with a reduction in platelet counts in clinical studies.

  - In patients who develop a platelet count less than 50 x 10_3/ µL, treatment with Tocilizumab or Sarilumab should be discontinued.
  - Platelet count should be monitored 4 to 8 weeks after start of therapy and according to clinical judgment thereafter.

- **Liver enzymes**

  Treatment with Tocilizumab was associated with a higher incidence of transaminase elevations.

  - Initiating treatment with Tocilizumab is not recommended in patients with elevated transaminases, ALT or AST greater than 1.5 x ULN for chronic therapies. However, given the emergency situation due to COVID-19, we still propose the use of these treatments.

- In patients who develop elevated ALT greater than 5 x ULN, treatment with Tocilizumab should be discontinued

- **Hypersensitivity reactions**: monitoring of occurrence of skin rashes, drop of blood pressure, ventilatory asynchronization. At the time of treatment injection.

6.5. Specific data to be collected for this trial

None

6.6. Expected benefits and risks

The clinical benefit is globally to prevent death in all patient groups.

Other benefits are to:

- blunt not only the pneumopathy-induced damage but also other COVID-19-associated injuries such as acute kidney injury (AKI), myocarditis, secondary bacterial infections.
- shorten the duration of hospital stay with minimization of physical (hospital acquired pressure ulcers, increased morbidity and mortality associated with nosocomial infections), psychological and economic complications related with prolonged stay.
- Shortening the hospital stay fosters not only individual clinical benefit but also collective clinical benefit through facilitation of collective access to caregivers.
- limit long term sequelae, in particular lung fibrosis and chronic kidney disease secondary to acute kidney injury (markedly prevalent in about 20% of individuals with ARDS).

The risks pertain to potential adverse effects of Tocilizumab

There are currently no known published reports of IL-6R antagonists for infectious sepsis or pneumonia. Because IL-6 contributes to host defense against bacterial and viral pathogens, there is a concern that IL-6 inhibition may exacerbate infections thus delaying recovery from sepsis.

For Tocilizumab: The most common adverse events (at least 5%) seen in TCZ/ ROACTEMRA-IV treated patients in a 12-week controlled portion of a study were: upper respiratory tract infection, headache, nasopharyngitis and diarrhea.

Risks exist of rare but severe hepatotoxicity, reactivation of latent tuberculosis, gastrointestinal perforations, neutropenia, with special risk In patients who develop an ANC less than 500 per

mm3. Treatment with TCZ/ACTEMRA was associated with a reduction in platelet counts. Hypersensitivity reactions, including anaphylaxis.

6.7. Sketch of statistical methods

The detailed statistical methods are identical for both subtrials, and presented in paragraph 11. A sketch of methods is given here.

To maximize information from limited data generated, while allowing rapid decision, a Bayesian monitoring of the trial based on tco-primary outcomes will be used. The overall strategy has been determined so as to control for a frequentist one sided 5% type I error rate. The following methods pertain to the conduct and analysis of the subtrial in a given group of patients (group I or group II), that are analyzed separately with different primary outcomes, but conducted simultaneously (with stratified randomization) for logistical reasons. The total sample size will be 120 (60 in each arm) at the interim analysis, and 240 (120 per arm) at the second analysis.

Since it is not possible to determine in advance how many patients will be recruited in each stratum, the sample sizes used for the following calculations are indicative, considering equally sized strata (groups). At the interim analysis, two posterior probabilities will be calculated: 1) the posterior probability of a lower event rate in the experimental than in the control arm (posterior probability of efficacy) and 2) the posterior probability of achieving at least a predefined effect corresponding to a hazard ratio of 0.85 (for time-to-event primary outcomes) or a risk difference of 5.5% (for binary co-primary outcomes) (posterior probability of sufficient efficacy). If the posterior probability of sufficient efficacy is less than 0.20, the trial can be stopped for futility. If the posterior probability of efficacy is higher than 0.99, the trial can be stopped for efficacy. Otherwise, the trial will continue with inclusion of additional patients, as predefined, and a final analysis is conducted with decision boundary at a posterior probability of efficacy > 0.95. Decision boundaries are non-binding, and the DSMB can recommend continuing recruitment, in the whole population or a subgroup. Final decision boundaries are then readapted to control for a one-sided type I error rate close to 5%. If the strata (groups I or II) are equally sized, the interim analysis should occur after 60 patients, and the second one with 120. This design (with only two stages) has then type I error rate 0.047 if event rates are 50% in each arm, and power 0.972 to detect a decrease from 0.50 to 0.20 and 0.739 to detect a decrease from 0.50 to 0.30.

7. SECOND NESTED TRIAL : EFFICACY OF SARILUMAB FOR PATIENTS WITH COVID-19

7.1. Investigational medicinal product(s)

7.1.1. KEVZARA® 200mg, Pre-filled syringe

Sarilumab (KEVZARA®) is a human monoclonal antibody (IgG1 subtype) that specifically binds to both soluble and membrane-bound IL-6 receptors (IL-6Ra). Sarilumab is currently approved for treatment in patients with RA at 200 mg Q2W (SC) [with down dosing to 150 mg Q2W (SC) for certain laboratory changes]. Sarilumab is highly similar to tocilizumab and there is reported evidence that IV treatment with 400 mg of tocilizumab (Actemra®), an anti-IL-6R monoclonal antibody (mAb), provides a clinically meaningful improvement in clinical symptoms that are thought to be mediated by cytokine release in patients with severe or critical COVID-19 infection.

Sarilumab is currently approved at 200 mg Q2W (SC) for the treatment of rheumatoid arthritis in multiple countries. In this protocol involving critically ill patients, it is preferable to use an IV injection. While there is limited experience in the use of sarilumab by IV infusion, the choice of the dose the use of sarilumab to be given by the IV route in this setting is supported by the high degree of bio-similarity of sarilumab to tocilizumab including a number of similarities in clinically observed pharmacokinetics, pharmacodynamics (to include safety, and PD endpoints). Based on available data, on a per mg basis, tocilizumab and sarilumab behave comparably in vivo with respect to potency, PK, PD, efficacy, and safety. Thus, the safety of sarilumab at doses as high as 400 mg IV can be extrapolated from the experience with similar and even higher doses of tocilizumab. Thus, it will be an IV dose of 400 mg of sarilumab in a 1 hour-infusion that will be given in this study.

Regarding the methods of administration of **KEVZARA®**, we rely on the recommendations made by the SANOFI-AVENTIS laboratory in the particular context of the COVID-19 epidemic (cf. Corona Virus (COVID-19) Sarilumab IV ** Information for Research purposes only **).

7.1.2. **Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including rescue medications**

There are no prohibited treatments. The medical staff is expected to monitor patients and administer any drug required for the treatment and/or prevention of all the usual complications that can develop in this setting. For all additional treatments, the SCP must have been obtained from the EMA website (http://www.ema.europa.eu/ema/), or from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php), or http://base-donnees-publique.medicaments.gouv.fr

7.1.3. Supply of the investigational centers

KEVZARA® will not be specifically provided by the sponsor in the context of the COVID 19 pandemic. The drugs will be provided by the hospital pharmacies to the care units on the basis of a specific research prescription.

Origin : Origin : Specialty with marketing authorization in UE/France, marketed in France.

Storage :
Store in the refrigerator (between 2 ° C and 8 ° C). Do not freeze.
The pre-filled syringe should be stored in the original package in order to protect from light.
After reconstitution, administer immediately.

7.1.4. Posology and drugs administration

Treatment consists of the administration of a single 400 mg dose of Sarilumab IV.
The treatment will be administered as a slow IV infusion over a period of one hour, as indicated on the brochure provided by SANOFI GENZYME (Corona Virus COVID-19 Sarilumab (**KEVZARA**®) IV Information for research purpose only).
The solution should not be used if it is cloudy, discolored or contains particles, or if any part of the injection device appears damaged.
The contents of the 2 syringes of **KEVZARA**® 200mg must be diluted in a bag without DEHP of 100 mL of 0.9% NaCl.
In the absence of a clinical response, a second dose of **KEVZARA®** will be administered on day 3 (D3).
Administration should be performed using a DEHP-free infusion kit equipped with a 0.2µm PES filter.

7.1.5. Traceability in investigational centers

In accordance with the rules of Good Practices and to track the treatment given to each patient, all the information related to the treatment will be collected on a traceability sheet (Preparation, Dispensation, Date of administration, Time of administration, Batch number and expiry date, and Dose administered).

7.1.6. Methods for monitoring compliance with the treatment

To track the treatment given to each patient, all the information related to the treatment will be collected on a traceability sheet. This sheet will be prospectively and exhaustively monitored by clinical research assistants during the study. In case of deviations from the protocol there will be reminders to the centers and regular checks.

7.2. Control

Control patients will receive the best standard of care.

7.3. Inclusion/Exclusion criteria for the nested trial

Inclusion Criteria:

1. Patients included in the CORIMUNO-19 cohort

2. Patients belonging to one of the 2 following groups:

- *Group 1: patients **not requiring ICU** at admission with moderate and severe pneumopathy according to the WHO **Criteria of severity of COVID pneumopathy.***

Moderate cases

Cases meeting all of the following criteria:

- Showing fever and respiratory symptoms with radiological findings of pneumonia.
- Requiring between 3L/min and 5L/min of oxygen to maintain SpO2 >97%

Severe cases

Cases meeting any of the following criteria:

- Respiratory distress (≧30 breaths/ min);
- Oxygen saturation≤93% at rest in ambient air; or Oxygen saturation ≤97 % with O2 > 5L/min.
- PaO2/FiO2≦300mmHg

- *Group 2: patients **requiring ICU** based on **Criteria of severity of COVID pneumopathy.***

- Respiratory failure and requiring mechanical ventilation
- No do-not-resuscitate order (DNR order)

Exclusion Criteria:

- Patients with exclusion criteria to the CORIMUNO-19 cohort.
- Known hypersensitivity to Sarilumab or to any of their excipients.

- Pregnancy
- Current documented bacterial infection
- Patient with any of following laboratory results out of the ranges detailed below at screening should be discussed depending of the medication:
    - Absolute neutrophil count (ANC) ≤ 1.0 x 10^9/L
    - Haemoglobin level: no limitation
    - Platelets (PLT) < 50 G /L
    - SGOT or SGPT > 5N

The primary endpoint and secondary endpoints will depend on the group of patients and tested medication.

7.4. Endpoints for the trial

7.4.1. Efficacy endpoints

Measures

A core set of clinical measures will be recorded daily the first 2 weeks and then every week. The core measures include measures of OMS progression scale, oxygenation, mechanical ventilation. For patients who are eligible for an intervention trial (in both the intervention and control arms), this day measurement will include trial-specific measures related to the trial outcomes of interest.

Primary and secondary endpoints:

The primary endpoint and secondary endpoints will depend on the group of patients and tested medication.

Groups will be redefined as follow :

- Group 1: Cases meeting all of the following criteria
    - Requiring more than 3L/min of oxygen
    - OMS/WHO progression scale = 5
    - No NIV or High flow

- Group 2: Cases meeting all of the following criteria

    - Respiratory failure AND (requiring mechanical ventilation OR NIV OR High flow)
    - WHO progression scale >=6
    - No do-not-resuscitate order (DNR order)

For the group 1 of patients *not requiring ICU*:

Co Primary Endpoints

1. Survival without needs of ventilator utilization (including non invasive ventilation and high flow) at day 14. Thus, events considered are needing ventilator utilization (including Non Invasive Ventilation, NIV or high flow), or death. New DNR order (if given after the inclusion of the patient) will be considered as an event at the date of the DNR.
2. Early endpoint : proportion of patients alive without non-invasive ventilation of high low at day 4 (WHO progression scale ≤ 5). A patient with new DNR order at day 4 will be considered as with a score > 5.

OMS Progression scale	Descriptor	Score
Uninfected	Uninfected; non viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
Ambulatory	Symptomatic; Independent	2
Ambulatory	Symptomatic; Assistance needed	3
Hospitalized : mild disease	Hospitalized; No oxygen therapy	4
Hospitalized : mild disease	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized : severe disease	Hospitalized; oxygen by NIV or High flow	6
Hospitalized : severe disease	Intubation and Mechanical ventilation, pO2/FIO2>=150 OR SpO2/FIO2>=200	7
Hospitalized : severe disease	Mechanical ventilation, (pO2/FIO2<150 OR SpO2/FIO2<200) OR vasopressor	8
Hospitalized : severe disease	Mechanical ventilation, pO2/FIO2<150 AND vasopressors, OR Dialysis OR ECMO	9
Death	Dead	10

Secondary end-points will be OMS progression scale at 4, 7 and 14 days, overall survival at 14, 28 and 90 days, time to discharge, time to oxygen supply independency, time to negative viral excretion.
Biological parameters improvement:
Estimated GFR, CRP, myoglobin, CPK, cardiac hs troponin, ferritin, lactate, cell blood count, liver enzymes, LDH, D-Dimer, albumin, fibrinogen, triglycerides, coagulation tests, urine electrolyte, creatinuria, proteinuria, uricemia, IL-6, procalcitonin, immunophenotype (Annexe 2), and exploratory tests (Annexe 3).

For the group 2 of patients *requiring ICU*:

Co Primary Endpoints

1. Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14 if patients have been intubated before day 14 ; or removal of NIV or high flow (for > 48h) if they were included under oxygen by NIV or High flow (score 6) and remained without intubation. Death or new DNR order (if given after the inclusion of the patient) will be considered as a competing event.
2. Early end point : proportion of patients with a decrease of WHO score of at least 1 point at day 4.

Secondary end points will be OMS progression scale at 4, 7 and 14 days, overall survival at 14, 28 and 90 days, the 28-day ventilator free-days, respiratory acidosis at day 4 (arterial blood pH of <7.25 with a partial pressure of arterial carbon dioxide [$Paco_2$] of ≥60 mm Hg for >6 hours), the evolution of PaO2/FiO2 ratio, time to oxygen supply independency, duration of hospitalization, time to negative viral excretion, time to ICU and hospital discharge.

Biological parameters improvement (estimated GFR, CRP, cardiac troponin, urine electrolyte and creatinine, proteinuria, uricemia, IL6, myoglobin, KIM-1, NGAL, CPK, ferritin, lactate, cell blood count, liver enzymes, LDH, D-Dimer, albumin, fibrinogen, triglycerides, coagulation tests (including activated partial thromboplastin time), procalcitonin, immunophenotype (Annexe 2), and exploratory tests (Frozen samples Annexe 3). Rate of renal replacement therapy, ventilation parameters.

For each comorbidities group secondary criteria will be specifically addressed:

For each tested medication, specific markers of efficacy and safety may be used and will be defined.

7.4.2. **Safety endpoints**

In the setting of COVID-19 NCP and short term immunomodulatory therapy, we will monitor major safety endpoints: blood cells and platelets counts and liver transaminases, frequently, every three days systematically.

- **Neutrophil count**

  Treatment with Sarilumab (Kevzara) was associated with a higher incidence of decrease in ANC. Decrease in ANC was not associated with higher incidence of infections, including serious infections.

  - In patients who develop an ANC less than 0.5 x 10_9/L, treatment with Tocilizumab or Sarilumab should be discontinued.
  - Neutrophil count should be monitored 4 to 8 weeks after start of therapy and according to clinical judgment thereafter. For recommended dose modifications based on ANC results.

- **Platelet count**

  Treatment with Sarilumab was associated with a reduction in platelet counts in clinical studies.

  - In patients who develop a platelet count less than 50 x 10_3/ µL, treatment with Sarilumab should be discontinued.
  - Platelet count should be monitored 4 to 8 weeks after start of therapy and according to clinical judgment thereafter.

- **Liver enzymes**

  Treatment with Sarilumab was associated with a higher incidence of transaminase elevations.

Initiating treatment with Sarilumab is not recommended in patients with elevated transaminases, ALT or AST greater than 1.5 x ULN for chronic therapies. However, given the emergency situation due to COVID-19, we still propose the use of these treatments.
In patients who develop elevated ALT greater than 5 x ULN, treatment with Sarilumab should be discontinued

- **Hypersensitivity reactions**: monitoring of occurrence of skin rashes, drop of blood pressure, ventilatory asynchronization. At the time of treatment injection.

7.5. Specific data to be collected for this trial

None

7.6. Expected benefits and risks

The clinical benefit is globally to prevent death.
Other benefits are to:

- blunt not only the pneumopathy-induced damage but also other COVID-19-associated injuries such as acute kidney injury (AKI), myocarditis, secondary bacterial infections.
- shorten the duration of hospital stay with minimization of physical (hospital acquired pressure ulcers, increased morbidity and mortality associated with nosocomial infections), psychological and economic complications related with prolonged stay.
- Shortening the hospital stay fosters not only individual clinical benefit but also collective clinical benefit through facilitation of collective access to caregivers.
- limit long term sequelae, in particular lung fibrosis and chronic kidney disease secondary to acute kidney injury (markedly prevalent in about 20% of individuals with ARDS).

The risks pertain to potential adverse effects of Sarilumab.
There are currently no known published reports of IL-6R antagonists for infectious sepsis or pneumonia. Because IL-6 contributes to host defense against bacterial and viral pathogens, there is a concern that IL-6 inhibition may exacerbate infections thus delaying recovery from sepsis.

Common adverse drug reactions seen in the clinical trials for Sarilumab/ Kevzara include infections (such as nasopharyngitis, upper respiratory tract infections, and urinary tract infections), neutropenia, injection-site erythema, increased low-density lipoprotein (LDL) cholesterol, and increased liver enzymes.
Severe adverse effects were hypersensitivity reactions, including anaphylaxis, upper respiratory and urinary tract infection. Patients chronically treated with sarilumab are at increased risk for developing serious and opportunistic infections. Most developed infections

while taking other immunosuppressants or disease modifying anti-rheumatic arthritis (DMARDs) with sarilumab.

The safety profile of Sarilumab is well known. While decreases in absolute neutrophil count (ANC) is seen in patients treated with sarilumab, they are reported not to be associated with increased incidence of infection or serious infections in patients with rheumatoid arthritis (Fleischmann, 2017). A clinical study of neutrophil trafficking suggested that this decrease is due to an redistribution into the marginating pool, rather than a net decrease in the neutrophil population (Lok, 2017).

Treatment with Sarilumab was associated with a higher incidence of decrease in ANC (absolute neutrophil count); a reduction in platelet counts; and transaminase elevations. In addition, gastrointestinal perforation has been reported in clinical studies, including in patients receiving corticosteroids.

7.7. Sketch of statistical methods

The detailed statistical methods are identical for both subtrials, and presented in paragraph 11. A sketch of methods is given here.

To maximize information from limited data generated, while allowing rapid decision, a Bayesian monitoring of the trial based on tco-primary outcomes will be used. The overall strategy has been determined so as to control for a frequentist one sided 5% type I error rate. The following methods pertain to the conduct and analysis of the subtrial in a given group of patients (group I or group II), that are analyzed separately with different primary outcomes, but conducted simultaneously (with stratified randomization) for logistical reasons. The total sample size will be 120 (60 in each arm) at the interim analysis, and 240 (120 per arm) at the second analysis.

Since it is not possible to determine in advance how many patients will be recruited in each stratum, the sample sizes used for the following calculations are indicative, considering equally sized strata (groups). At the interim analysis, two posterior probabilities will be calculated: 1) the posterior probability of a lower event rate in the experimental than in the control arm (posterior probability of efficacy) and 2) the posterior probability of achieving at least a predefined effect corresponding to a hazard ratio of 0.85 (for time-to-event primary outcomes) or a risk difference of 5.5% (for binary co-primary outcomes) (posterior probability of sufficient efficacy). If the posterior probability of sufficient efficacy is less than 0.20, the trial can be stopped for futility. If the posterior probability of efficacy is higher than 0.99, the trial can be stopped for efficacy. Otherwise, the trial will continue with inclusion of additional

patients, as predefined, and a final analysis is conducted with decision boundary at a posterior probability of efficacy > 0.95. Decision boundaries are non-binding, and the DSMB can recommend continuing recruitment, in the whole population or a subgroup. Final decision boundaries are then readapted to control for a one-sided type I error rate close to 5%. If the strata (groups I or II) are equally sized, the interim analysis should occur after 60 patients, and the second one with 120. This design (with only two stages) has then type I error rate 0.047 if event rates are 50% in each arm, and power 0.972 to detect a decrease from 0.50 to 0.20 and 0.739 to detect a decrease from 0.50 to 0.30.

8. RECORDING AND REPORTING ADVERSE EVENTS

8.1. Definitions

According to Article R1123-46 of the French Public Health Code:

- **Adverse event**

Any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the clinical trial or with the investigational product.

- **Adverse reaction to an investigational medicinal product**

Any adverse event occurred in a trial subject, which has **at least a possible** causal relationship with the clinical trial or with the investigational medicinal product

- **Serious adverse event or reaction**

Any adverse event or reaction that at any dose of medication, results in death, threatens the life of the research subject, requires hospitalisation or prolongs hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product, whose nature, severity, frequency or outcome is inconsistent with the safety information described in the Reference Safety Information

(summary of product characteristics, or the investigator's brochure if the product is not authorised).

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for clinical trial sponsors (ANSM):

- **Emerging safety issue**

Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.
For the clinical trials involving the first administration or use of an investigational medicinal product in healthy volunteers, any serious adverse reaction.

Examples:
a) Any clinically significant increase in the frequency of an expected serious adverse reaction
b) Suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports
c) Any new safety issue relating to the conduct of the clinical trial or the development of the investigational medicinal product that may impact the safety of the trial subjects.
Examples:

- A serious adverse event likely to be related to the interventions and the trial's diagnostic procedures and which may impact the conduct of the clinical trial,
- A significant risk on the trial subjects such as ineffectiveness of the investigational medicinal product in treating a life-threatening illness under investigation,
- Significant safety results from a recently completed non-clinical study (such as a carcinogenicity study),
- The premature termination, or temporary suspension, of a trial conducted on the same investigational medicinal product in another country, for safety reasons,
- An unexpected serious adverse reaction associated with a non-experimental medication required for the conduct of the clinical trial, (e.g. challenge agents, rescue treatment)

d) Recommendations from the Data Safety Monitoring Board (DSMB), if applicable, that may affect the safety of the trial subjects

e) Any suspected unexpected serious adverse reaction (SUSAR) reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication.

8.2. The role of the investigator

The investigator must **assess the seriousness criteria of each adverse event** and record all serious and non-serious adverse events in the case report form (CRF). The investigator must **document** serious adverse events **as thorough as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the severity** of the adverse events by using:

- either general terms:
    - *Mild: tolerated by the patient, does not interfere with daily activities*
    - *Moderate: sufficiently uncomfortable to affect daily activities*
    - *Severe: preventing daily activities*
- or a severity grading scale for adverse events, attached to the protocol: by using an adverse events rating scale developed by the International Bone Marrow Transplant Registry (IBMTR) in 1997 and as described by Cahn and coll. and assess the causal relationship between the experimental procedure and the SAE.
- or using the NCI CTCAE v5.0.

The investigator must assess the **causal relationship** between the serious adverse events and the investigational medicinal product(s) or the study procedure(s).

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not ruled out).

These terms are defined as follows (extracted from the WHO-UMC causality categories, version dated 17/04/2012).

Table: WHO-UMC causality categories (extract)

Causality term	Assessment criteria*
Certain	· Event or laboratory test abnormality, with plausible time relationship to drug intake ** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake ** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake ** · That makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with

** Or study procedures

8.2.1. Serious adverse events that require a notification without delay by the investigator to the sponsor

As per article R.1123-49 of the French Public Health Code (CSP), the investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any serious adverse event which occurs during a trial and at the latest within 24 hours as described in Article L.1121-1(1) CSP, except those which are listed in the protocol and, if applicable, in the investigator's brochure as not requiring a notification without delay.

A serious adverse event is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Any other grade III or higher severe or toxic manifestations (defined accordingly to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE).
The sponsor will particularly monitor haematological abnormalities (grade > or = 3), serious liver damage, serious infections and hypersensitivity reactions.

The investigator must notify the sponsor without delay on the day when the investigator becomes aware of these adverse events and at the latest within 24 hours, , according to the same modalities and within the same timeline as for serious adverse events (see above).

8.2.2. Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are simply recorded in the case report form.

Normal and natural course of the condition

- Scheduled inpatient hospitalisation for monitoring the condition under investigation (with no deterioration in the subject's medical condition compared to baseline)

- Inpatient hospitalisation for routine treatment or monitoring the condition under investigation, not associated with a deterioration in the subject's medical condition
- Any routine complications occurring in patients in ICU and or infected by COVID 19 (except death), especially:

  Acute cardiac injury: acute heart failure, type 1 or 2 myocardial infarction, myocarditis

  - Acute kidney injury, need for renal replacement therapy except grade 4 and 5 according CTCAE scale
  - Acute respiratory distress syndrome, requirement of mechanical ventilation (invasive or not) or an ECMO
  - Multiple organ failure except grade 5 according CTCAE scale.
  - Pulmonary embolism

8.2.3. **Special circumstances**

In utero exposure

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study and at the latest within 24 hours, even if it is not associated with an adverse event.

If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.

Adverse events during the trial possibly related with the treatments prescribed as part of the patient's standard care

The investigator must report these adverse events to the relevant regional pharmacovigilance centre, Centre Régional de Pharmacovigilance (CRPV).

8.3. Period during which the investigator must send notification of SAEs to the sponsor without delay

The investigator notifies the sponsor without delay and at the latest within 24 hours of all the serious adverse events listed in the corresponding section:

- Starting from the date on which the subject signs the consent form
- Throughout the whole follow-up period intended by the trial (90 days)
- , After the end of the clinical trial, if the SAE is likely to be due to the investigational medicinal product (IMP) or to the study interventions (e.g. serious reactions that could appear at long term after exposure to the medication, such as cancers or congenital abnormalities). In that case, the investigator does not have to systematically and indefinitely collect all SAEs possibly related to the IMP, but must transmit all possible SAEs related to the IMP of which he has knowledge.

8.4. Procedures and deadlines for notifying the sponsor

The investigator should initially complete a SAE reporting form (contained in the case report form). This report must be signed by the investigator.

The investigator must complete every section of the SAE form so that the sponsor can carry out the appropriate assessment.

The initial report sent to the sponsor must be rapidly followed up by one or more additional written reports describing the course of the event and any complementary information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results of additional exams, etc.). These documents must be anonymized. In addition, the investigator must state the study acronym and the number and initials of the study participant on each paper.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has terminated his participation in the trial.

The initial report, the SAE follow-up reports and all other documents must be sent to the sponsor's safety Department bye-mail (eig-vigilance.drc@aphp.fr) to the sponsor's safety department. It is possible to send the SAE to the Safety department by fax to the sponsor's safety department, fax No. +33 (0)1 44 84 17 99 only in case of unsuccessful attempt to send the SAE by e-mail and in order to avoid duplicates.

For trials which use e-CRF

- The investigator completes the SAE report form in the e-CRF, then validates, prints and signs the form before sending it by e-mail;
- In case of failure to connect to the e-CRF, the investigator should complete, sign and send the SAE report form to the safety Department. As soon as the connection is restored, the investigator must complete the SAE report form in the e-CRF.

The investigator must comply with all requests for additional information from the sponsor.
For all questions relating to an adverse event report, the safety Department can be contacted via email at vigilance.drc@aphp.fr.
For cases of in utero exposure, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

8.5. Role of the sponsor

The sponsor, represented by its safety Department, shall continuously assess the safety of each investigational medicinal product throughout the trial.

8.5.1. **Analysis and declaration of serious adverse events**

The sponsor assesses:

- The seriousness of all reported adverse events,
- The causal relationship between these adverse events and investigational medicinal product and any other treatments,

All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.

- The expectedness assessment of the serious adverse reactions

Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.

The sponsor, acting through its safety Department, assesses the expectedness of the serious adverse reaction based on the information described below.

For serious adverse events likely to be related to the investigational medicinal product(s):

· Refer to the SPC in Appendix for each drugs.

- **For sarilumab:**

The most frequent adverse reactions observed with sarilumab in clinical studies were neutropenia, increased ALT, injection site erythema, upper respiratory infections, and urinary tract infections. The most common serious adverse reactions were infections. Refer to the SmPC of Kevzara® for more details.

- **For tocilizumab**

The most commonly reported adverse reactions observed with were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT. The most serious adverse reactions were serious infections, complications of diverticulitis, and hypersensitivity reactions. Refer to the SmPC of RoActemra® for more details.

The serious adverse events associated with the study procedures are:

Blood samples for the analyses are carried out at the same time as those necessary for the usual follow-up.

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs),) and **all expected serious adverse reactions of fatal outcome** (as requested by ANSM), within the regulatory time frame, to the ANSM (French Health Products Safety Agency).

- The sponsor must send the initial report without delay upon receipt of the unexpected serious adverse reaction if it is fatal or life-threatening, or otherwise within 15 days from receipt of any other type of unexpected serious adverse reaction;
- The sponsor must provide all relevant additional information by sending follow-up reports, within 8 calendar days following receipt.

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor must notify all the investigators about any information that could adversely affect the safety of the trial subjects.

8.5.2. **Analysis and declaration of other safety data**

This relates to any new safety data that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.

The sponsor will inform the competent authority and the Ethics committee without delay after becoming aware of the emerging safety issue and, if applicable, describe which measures have been taken.

Following the initial declaration of emerging safety issues, the sponsor will declare to ANSM any additional relevant information about the new safety issues in the form of a follow-up report, which must be sent no later than 8 days after becoming aware of the information.

8.5.3. **Annual safety report**

The sponsor must prepare once yearly throughout the trial duration an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- An analysis of safety data concerning trial subjects
- A description of the patients included in the trial (demographic profile etc.)
- A list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- Cumulative summary tabulation of all the serious adverse events that have occurred since the beginning of the clinical trial

The report must be transmitted to ANSM no later than 60 days after the anniversary date corresponding to the date of authorization of the clinical trial by ANSM.

9. SPECIFIC COMMITTEES FOR THE STUDY

9.1. Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) can be set up by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of a DSMB to the Competent Authority (ANSM) and to the Ethics committee.
A DSMB will be set up for this trial. The DSMB must hold its first meeting before the first subject is enrolled.

The members of the DSMB are:
Cristina Mussini, University of Modena, Modena, IT;

Patrick Yeni, Maladies Infectieuses, Paris, FR

Sandro Galea, School of Public Health, Boston University, Boston, MA, USA;

Kevin Winthrop, Oregon Health and Science University, Portland, OR, USA;

Deepak L Bhatt, Harvard Medical School, Boston, MA, USA;

Frank Harrell, Department of Biostatistics, Vanderbilt University School of Medicine, Nashville TN, USA.

The DSMB's principal missions and their operating procedures are described in the DSMB chart of the study. The DSMB has a consultative role. The decision concerning the conduct of the clinical trial relies on the sponsor.
The DSMB will meet at least once a week or upon request.

9.2. Steering Committee

The steering will be constituted of : Pierre-Louis Tharaux, Olivier Hermine, Xavier Mariette, Philippe Ravaud, Matthieu Resche-Rigon, Xavier Lescure, Alexandre Demoule, David Montani, Lila Boudama, Jean François Timsit, Antoine Dossier, Frédéric Pène, Damien Sène, Bruno Megarbane, Julien Poissy, (to be extended)

10. DATA MANAGEMENT

10.1. Access to data

In accordance with GCP:
- The sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures.
- The investigators will ensure the persons in charge of monitoring and auditing the clinical trial and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

10.2. Source documents

The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the trial. Source documents will be kept by the investigator, or by the hospital in the case of hospital medical records, for the statutory period.

10.3. Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of

information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code).
During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised.
Under no circumstances will the names and addresses of the subjects be shown.
The sponsor will ensure that each subject has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

10.4. Data processing and storage of documents and data

10.4.1. Identification of the person responsible and the location of the data processing management

Pr. Matthieu RESCHE-RIGON from Service BioStatistique et Information Médicale (SBIM) Hôpital Saint Louis, AP-HP, Paris will be responsible for data entry and the relevant procedures. The same goes for conducting the statistical analysis.

10.4.2. Data Entry

Data entry for data made non-identifying will be carried out on electronic media via a web browser (Cleanweb) linked to a database stored on the sponsor server.

10.4.3. Ownership of the data

Data entry for data made non-identifying will be carried out on electronic media via a web browser (Cleanweb) linked to a database stored on the sponsor server.

11. STATISTICAL ASPECTS

11.1. Planned statistical methods, including the timetable for any planned interim analyses

The CORIMUNO-19 trial is planned according to a cohort multiple Randomized Controlled Trials design. The basic idea is that individuals in the cohort eligible to a specific trial are randomised 1:1 to the first trial until a predefined sample size is reached. Then, they are

randomized to a second trial while inclusions in the first trial are frozen, waiting for the evaluation of the primary outcome and an interim analysis. Then inclusions in the first trial can be resumed, whereas inclusions in the second trial are frozen, and so on. If no other trial is available for this specific population of patients and the drug is already known (for instance if it is already marketed for another indication, and has a known safety profile), then inclusions may not stop to wait for the interim analysis results.

The methods outlined thereafter describe the principles for analysing one specific trial in one specific population (i.e. patients not requiring ICU). The trials are analysed separately in each population—or group—of patients, but are conducted simultaneously for logistical reasons. Information from previous trials or populations can be incorporated in the prior distribution (see below a description of Bayesian methods).

One crucial feature of the CORIMUNO-19 trial is to remain as flexible as possible, in an urgency context, when information may change quickly. The study therefore attempts to maximize information from limited data generated, while allowing rapid decision. This will be achieved by the use of Bayesian monitoring of the trial. While using a Bayesian approach, where standard definition of type I and II error rate do not apply, the trial is also planned to control for frequentist (i.e. non-Bayesian) error rates. In particular, the overall strategy will be to control for a frequentist one sided type I error rate close to 5% over one specific trial.

The analysis will therefore rely on computing the posterior distribution of the hazard ratio between the experimental and control arms for time-to-event co-primary outcomes and the posterior distributions of event rates in each arm for binary co-primary outcomes. From the latter, the posterior distribution of the difference in event rate will be derived. These posterior distributions will be graphically displayed, and summarized by their medians and 95% credibility intervals (the Bayesian counterparts of confidence intervals).

In a Bayesian analysis, the specification of the prior distribution is crucial. For the first trials conducted in the cmRCT, we want the conclusions to depend primarily on data from the trial, not on prior opinion. An uninformative prior for the hazard ratio will therefore be used. More precisely, the prior distribution for the log hazard ratio will be a Gaussian distribution with mean 0 and variance 10^6. For binary outcomes, let p denote the probability of outcome in a given arm; the prior distribution of p is set as a beta prior distribution with parameters 1 and 1, equivalent to a uniform distribution on the interval (0,1). This corresponds to a hypothetical situation where we would have data on two individuals treated with the corresponding arm strategy, and observing that exactly 1 of the 2 experiencing the outcome. These prior distributions ensure very little influence of our prior opinion on conclusions. For subsequent

trials where a tested agent would become oSOC, then an informative prior could be used, based on the results observed on previous trials. This prior information may translate into a different prior distribution for the baseline cumulative hazard (cumulative hazard under control strategy). This procedure will be described in future trial-specific protocols.

For now the calculations in this base protocol have been performed for a sample size of 60 individuals per arm, with interim analyses after 30. However, this may be adapted to allow continuing the trial if results are promising, though not formally achieving the predefined efficacy boundary. Additional calculations have thus been performed with the additional recruitment of 30 individuals per arm after the sample size of 60 has been reached (see below). This may also be modified in future protocols. **Moreover, it is practically unfeasible in the urgency context of COVID-19 to conduct a trial with the same experimental drug independently in the two groups of patients. Accordingly, the trial is conducted as a single trial, with randomisation stratified on the patients group.** The total sample size is therefore fixed for the whole trial at 120 (60 per arm) for the first formal interim analysis, and 240 (120 per arm) for the final analysis, but with an option to accrue 120 patients more (60 per am) depending of the recommendations of the DSMB (see below). The share of each stratum (group of patients) may not be equal, but calculations presented in the paragraph 11.2 below have been performed assuming an equal number per stratum. This will be adapted to show the properties of the design according to the observed proportion of patients in each stratum.

Baseline characteristics will be described with summary statistics, namely frequencies and percentages, or medians and interquartile ranges (IQR). Secondary and safety outcomes will be analysed in a frequentist framework. Final analysis will account for randomization stratification factors. All the analyses will be described in a statistical analysis plan (SAP) that will be written and signed before freezing of the database.

At the end of the study subgroup analyses will be performed according to antiviral therapies. Moreover interactions between experimental treatments and antiviral therapies will explored and tested.

Statistical analyses will be performed using the R statistical package version 3.6.1 or later (The R Foundation for Statistical Computing, https://www.R-project.org/).

11.2. Statistical criteria for termination of the study

This section describes the Bayesian monitoring of the trial in the base protocol. The strategy is planned similarly for all trials in the cmRCT, but control event rates and therefore the number

of interim analyses, decision boundaries and the sample sizes will be adapted for each trial. In each trial, we defined two co-primary outcomes, one time-to-event outcome evaluated up to day 14, and an early success outcome evaluated on day 4. Methods for trial monitoring have been developed for the early outcome because (1) short-term outcomes are obtained more quickly so are easier for early interim decision and (2) calculations of all possible outcomes are more tractable for binary outcomes. For analyses based on the hazard ratio, which allow to account for all information gathered in the trial (even for patients who do not have the entire follow-up necessary to evaluate a binary outcome), the same decision boundaries will be used. It is not expected that the properties of the boundaries would be significantly different when using the posterior distribution of the hazard ratio (identically to the use of O'Brien Fleming boundaries in frequentist trials for continuous, binary or survival outcomes). The main adaptation is to convert the timing of the interim analysis in terms of fraction of information, i.e. fraction of the total expected number of events instead of fraction of the total number of patients). More comprehensive simulation studies will be performed to describe the properties of the design in an appendix to the protocol. Also, in all what follows, we assume the "event" corresponding to the outcome being detrimental to patients, so that an effective treatment would lower the event rate, or achieve a hazard ratio $q < 1$. When the clinical definition of the outcome is opposite, then analysis will be performed on the inverse (e.g. failure instead or success, or inverse of the hazard ratio $1/q$).

Let us denote p_E and p_C the event rates in the experimental and control arms, respectively. At the interim analysis, the posterior probability of a lower event rate in the experimental than in the control arm is calculated, i.e. $P(p_E < p_C \mid \text{data})$, which we term the *posterior probability of efficacy*. The posterior probability $P(p_E < p_C - d \mid \text{data})$ is also computed, corresponding to the probability to achieve at least a d treatment effect, termed the *posterior probability of sufficient efficacy.* At each interim analysis, if the posterior probability of sufficient efficacy is less than 0.20, the trial could be stopped for futility upon decision of the DSMB (indicative and not binding futility boundary). If the posterior probability of efficacy is higher than 0.99, then the trial may be stopped for efficacy (again this boundary is not binding and the DSMB may propose to continue the accrual based on other information, such as secondary outcomes or safety). The choice of interim monitoring for futility based on the posterior probability of sufficient efficacy and not the posterior probability of efficacy is justified by the need to increase the chance of early stopping for futility when information increases, if the experimental treatment is no better than the control. Conversely, keeping a constant futility boundary on the posterior probability of efficacy would decrease the chances of early stopping

if additional analyses are performed, because under the null, as information increases, the posterior distribution of efficacy would converge to 0.5. This boundary is stricter than using a boundary on the posterior probability of efficacy (grey line on the figure 1, left panel), but this choice is justified by the need to quickly identify treatments with a large effect. The futility threshold (0.20) may be revised in future trials, if expected effects are lower.

When no stopping for futility or efficacy is decided, additional patients are recruited in each arm. At the interim analyses, the predictive probability of achieving a success after inclusion of a total of 60 patients per arm (posterior probability of efficacy > 0.95) will also be computed, and the trial can be stopped for futility if it is less than 10%. The final analysis will occur after final recruitment, and a posterior probability of efficacy higher than 0.95 will be considered as indicating efficacy.

To compute the probability of sufficient efficacy, we assumed that the hazard ratio for time-to-event outcomes should be at least 0.85, which translates to an event rate of 45.5% in the experimental arm when it is 50% in the control arm. Accordingly, d was set to 0.055 for calculations with binary outcomes. The table 1 presents the properties of the design under different scenarios, assuming 30 patients per arm have been recruited at the interim analysis, and 30 additional per arm have been recruited to reach the final analysis. The figure 1 displays the decision boundaries for the early outcome.

Table 1. Operational characteristics of the design under different scenarios.

	Failure rate p in each group			
Scenario	No effect	Very large effect	Large effect	Mild effect
Parameterizations	p_C=0.5, p_E=0.5	p_C=0.5, p_E=0.2	p_C=0.5, p_E=0.3	p_C=0.5, p_E=0.35
Corresponding hazard ratio	1	0.32	0.51	0.62
Probability of early stopping for futility	0.349	0.0017	0.023	0.057
Probability of early stopping for efficacy	0.0087	0.558	0.228	0.121

Probability of efficacy at 2nd stage	0.038	0.413	0.510	0.393
Overall probability of rejection	0.047	0.972	0.739	0.514

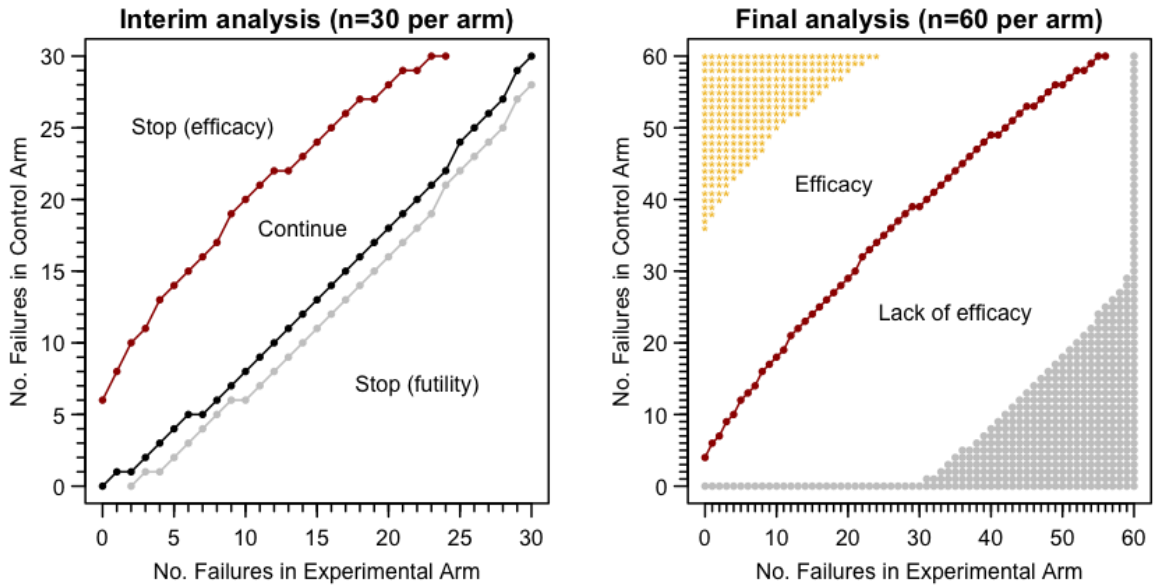

Figure 1. Decision boundaries for the interim and final analysis. Red lines indicate efficacy boundaries, and black lines futility boundaries. On the left plot, the interim analysis is performed after inclusion of 30 patients per arm, and the gray line indicate what the boundary would be if the posterior probability of efficacy was used to define futility instead of the posterior probability of sufficient efficacy. On the right plot, the final analysis after accrual of 30 more patients per arm is presented. Gloden stars indicate regions that should not occur if the decision boundaries are respected, because the trial would have been stopped for efficacy at the interim analysis. Gray points indicate regions that should not occur if the decision boundaries are respected, because the trial would have been stopped for futility at the interim analysis.

In the case the DSMB would deem results promising but not yet conclusive after inclusion of 60 individuals per arm (that we consider for illustration as a posterior probability of sufficient efficacy of 0.40 or more but a posterior probability of efficacy is of 0.97 or less), 30 additional patients per arm could be recruited, the final decision boundary could be adapted to a posterior probability of efficacy > 0.963 to control the type I error rate. The table 2 summarizes the

properties of such extension under the four previous scenarios, and illustrates that this could have an important effect on the power in scenarios where the efficacy is less than anticipated.

Table 2. Operational characteristics of the design with extension to a third stage, under different scenarios. In this example, it is assumed that the DSMB would consider results to be promising if the posterior probability of sufficient efficacy of 0.40 or more but a posterior probability of efficacy is of 0.97 or less, and the final decision boundary is set to a posterior probability of efficacy > 0.963 to control the type I error rate.

	Failure rate p in each group			
Scenario	No effect	Very large effect	Large effect	Mild effect
Parameterizations	p_C=0.5, p_E=0.5	p_C=0.5, p_E=0.2	p_C=0.5, p_E=0.3	p_C=0.5, p_E=0.35
Probability of occurrence	0.307	0.046	0.313	0.460
Probability of efficacy at 3rd stage	0.018	0.043	0.209	0.221
Overall probability of rejection	0.050	0.994	0.848	0.631

In terms of trial monitoring, it is also planned that more interim analyses would be performed, primary safety reviews, but the posterior distribution of key efficacy parameters should then also be presented to the DSMB, without formal stopping rules. This may be performed on a weekly basis, depending on the speed of inclusions, to monitor the progress of the trial.

11.3. Number of participants and justification

The total sample size is therefore fixed for the whole trial at 240 (120 per arm) for the final analysis, with interim analysis after 120 (60 per arm), and an option to accrue 120 patients more (60 per am) depending of the recommendations of the DSMB.

The calculations shown in the table 1 show that the type I error rate of the design would be 4.7% if the event rate is 0.50 in each arm, and the power to detect a decrease from 0.50 to 0.20 would be 97.2%. This trial would also have power 73.9% to detect a decrease from 0.50 to 0.30.

11.4. Anticipated level of statistical significance

The trial is not designed for frequentist statistical testing at a predefined level of statistical significance. Nevertheless, as explained above, the current decision boundaries allow to control for a frequentist type I error rate of 0.047.

11.5. Subject replacement strategy

No subject replacement is planned.

11.6. Method for taking into account missing, unused or invalid

We do not expect missing data for the primary outcome. However, were data to be missing, they will be imputed as failures for the trial monitoring. No imputation will be used for secondary efficacy and safety outcomes.

11.7. Management of modifications made to the analysis plan for the initial strategy

All the analyses will be described in a statistical analysis plan (SAP) that will be written and signed before freezing of the database), in order to accommodate any event or protocol modification that may have occurred and that would affect the way the analysis should be conducted..
We do not expect modifications of the initial analysis strategy. However, should such modifications occur after the SAP has been validated, a modified SAP would be issued. The original SAP as well as the modified SAP will be kept in the study files, with the justification for any modification.

11.8. Choice of individuals to be included in the analyses

In the classical cmRCT design, randomisation occurs prior to offering an intervention, and some number of eligible patients who are randomly selected to be offered an intervention will not accept the offer. An intention to treat analysis could therefore dilute any treatment effects. Relton et al. suggested using a complier average causal effect (CACE) analysis which provides unbiased estimates of the treatment effect for patients who comply with the protocol. Thus, for al trials where only patients in the intervention arm are offered the intervention, all primary analyses will be performed in both Intention To Treat (ITT) and CACE basis. For CACE analyses, an instrumental variable approach to the analysis, which assumes that a patient's decision not to accept the intervention will not affect the outcome (except through the intervention actually received). For the ITT analysis, patients will be analysed according to the treatment arm they were randomized to (i.e. offer or no offer group), even if the participant did not accept the intervention.

12. QUALITY CONTROL AND ASSURANCE

Every clinical study managed by AP-HP is ranked according to the projected risk incurred by the study participants using a classification system specific to AP-HP-sponsored clinical trials.

12.1. General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the trial. The sponsor must have a quality assurance system for monitoring the implementation of the study at the research centres.

For this purpose, the sponsor shall appoint Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study sites, after completing their initial visits. The purpose of monitoring the study, as defined in the Good Clinical Practices, is to verify that:

- The research subjects are safe, protected and their rights are being met
- The data being recorded is accurate, complete and consistent with the source documents
- The study is carried out in accordance with the current version of the protocol, with GCP and with all statutory and regulatory requirements.

Strategy for site opening

The strategy for opening the sites is determined using the tailored monitoring plan.

Scope of site monitoring

In the case of this risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: level **B**

12.2. Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

12.3. Case Report Form

Electronic CRF:

All information required by the protocol must be entered in the case report forms. The data must be collected as and when it is obtained, and clearly recorded in these case report forms. Any missing data must be coded.

Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given instructions for using this tool.

Using on-line case report forms means the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, there are consistency checks to ensure the data are verified immediately upon being entered. The investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

12.4. Management of non-compliances

Any events that occur as a result of the investigator or any other individual involved in conducting the study failing to comply with the protocol, standard operating procedures, good clinical practice or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

The sponsor has its own procedures for managing these non-compliances.

12.5. Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the basis of medical secrecy.

An audit can be carried out at any time by independent individuals appointed by the sponsor. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the trial agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study.

12.6. Principal Investigator's declaration of responsibility

Before starting the trial, each investigator will give the sponsor’s representative a signed and dated copy of his/her curriculum vitæ and RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will agree to comply with legislation and to conduct the trial in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a declaration of responsibility (standard DRCD document), which will be sent to the sponsor's representative.

The investigators and their co-workers will sign a delegation form specifying each person's role.

12.7. Pharmacist's declaration of responsibility

Production problems must be recorded according to the Manufacturing unit (LTCG) procedures.

13. ETHICAL AND LEGAL CONSIDERATIONS

13.1. Methods for informing and obtaining consent from the research participants

The study will be conducted in compliance with the principles of the Declaration of Helsinki (2008) and other major ethical guidelines.

Information and consent process specific to cmRCT design

The process for informing patients and obtaining their consent in a cmRCT is conducted in 2 steps:

a. Participants are invited to participate in a cohort study.

In the cmRCT design, individuals first consent to participate in a cohort. The local recruiting physician will explain the nature and purpose of the COVID Cohort and provide the participants with a copy of the consent and information sheet. Participants will be informed that agreeing to participate in the COVID Cohort will involve (1) giving permission to the research staff to use their medical record to complete the COVID baseline Medical Data form; (2) giving permission for COVID investigators to propose them an intervention that is being evaluated in any COVID intervention trials embedded in the cohort; (3) giving permission for their data to be used for comparison purposes in any COVID intervention trials embedded in the cohort.

Patients will be informed that participation in the COVID Cohort will not affect their usual care in any way. They will also be informed that only patients who are randomly selected to be offered an intervention will be contacted about the intervention. Finally, it is explained that patients' current consent is only for participation in the COVID Cohort, and that separate consent will be sought for participation in a particular COVID intervention.

b. Participants are invited to receive the intervention / treatment tested in a COVID trial

When patients are eligible to participate in a COVID embedded trial, they will be contacted by the local recruiting physician who will describe the intervention/treatment evaluated with its risk and benefit and provide the participants with a copy of the consent and information sheet. Patients will be informed that their participation will not affect their usual care in any way.

Other general aspect of the consent process

In accordance with Article L1122-1-1 of the French Code of Public Health, biomedical research may only be initiated after the participant has been provided with comprehensive study information (as set out in Article L.1122-1) and has given his/her prior, written, informed consent.

The participant's written, informed consent shall be obtained by the investigator (or a physician representing the investigator) during the selection visit, before inclusion of the participant in the research. After the receipt of study information, the participant will be given time if needed to consider his/her participation before being asked to sign the consent form. Copies of the study information sheet and the consent form (signed and dated by the research participant and by the investigator or the physician representing the investigator) will be given to the individual prior to his/her participation in the study. Furthermore, the methods used for obtaining the participant's consent and the methods used to provide information with the goal of obtaining consent will be specified in the participant's medical records. The investigator will keep the original signed and dated copy of the participant's consent form.

If the person is unable to give his or her written consent, consent may be obtained, in descending order of priority, from a legal representative, family member or a close relative. These persons must have no connection whatsoever to the investigator or the sponsor.

Whilst participating in this study, subjects may not take part in any other clinical study without first speaking to the doctor in charge of this trial.

13.2. Authorisation for the research location

Units participating in the study will have specific authorisation for the location if requested.

13.3. Legal obligations

13.3.1. The sponsor's role

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the *Code de la Santé Publique (French Public Health Code)*. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

13.3.2. Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants concerning a medicinal product for human use, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory requirements.

13.3.3. Request for authorisation from ANSM

Prior to starting the study, AP-HP, as sponsor, must obtains authorisation from the ANSM (French Health Products Safety Agency) for the interventional study involving human participants concerning a medicinal products for human use, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

13.3.4. Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

This research is not governed by the CNIL (French Data Protection Agency) "Reference Methodology for processing personal data used within the scope of health research" (amended MR-001). AP-HP, as sponsor of the research, must obtain approval of CNIL.

13.3.5. Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain approval from the CPP (Research Ethics Committee) and authorisation from the ANSM within the scope of their respective authorities, before the amendment can be implemented.

The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

13.3.6. Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year

following the end of the study, i.e., the end of the participation of the last participant in the study.

13.3.7. **Archiving**

Specific documents for an interventional study involving human participants concerning a medicinal product for human use will be archived by the investigator and the sponsor for *15 years* after the end of the research.

This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list) :
  - · the successive versions of the protocol (identified by the version number and its date), and any appendices
  - · the ANSM authorisations and CPP (Research Ethics Committee) decisions
  - · any correspondence
  - · the enrolment list or register
  - · the appendices specific to the research
  - · final study report
- The data collection documents

14. FUNDING AND INSURANCE

14.1. Sources of funding for the trial

National PHRC (Ministry of Health)

14.2. Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own third party liability as well as the third party liability of all the doctors involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the study participant and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the

grounds of a third party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GERLING through BIOMEDIC-INSURE, covering its own third party liability and that of any collaborator (doctor or research staff), in accordance with Article L.1121-10 of CSP.

15. PUBLICATION RULES

Mention of AP-HP affiliation for projects sponsored by AP-HP

- *If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant*
- *However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be "AP-HP"*
- *Each of these affiliations must be identified by an address and separated by a semicolon (;)*
- *The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France*

Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

- "The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l'Innovation)"

Mention of the financial backer in the acknowledgements of the text

- *If PHRC: "The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 20XX (French Ministry of Health)"*
- *If an AP-HP internal call for tenders, specify: "The study was funded by a grant from Assistance Publique – Hôpitaux de Paris"*

This study has been registered on the website http://clinicaltrials.gov/ under number *(add the registration number when the study is registered)*.

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17. LIST OF ADDENDA

Every addendum and the log of addenda versions are attached, independently of the protocol. Every addendum can be modified (change of addendum version) without modifying the version of the protocol.

-List of the team

-Serious Adverse Events report form

-Pregnancy report form

-Adverse events rating scale developed by the International Bone Marrow Transplant Registry (IBMTR) in 1997 and as described by Cahn and coll.

-The NCI CTCAE v5.0. (https://evs.nci.nih.gov/ftp1/CTCAE/About.html)

-SCP and Investigator's Brochure

The SCP must have been obtained from the EMA website (http://www.ema.europa.eu/ema/), or from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php)

-Addendum 1: CORIMUNO19-ANA protocol: Nested trial N°3: **Efficacity of anakinra in COVID19 patients**

-Addendum 2: CORIMUNO19-VIRO protocol: Nested trial N°4: **TRIAL EVALUATING EFFICACY OF SARILUMAB + AZITHROMYCIN + HYDROXYCHLOROQUINE, AND SARILUMAB alone, FOR ADULT PATIENTS HOSPITALIZED WITH MODERATE TO SEVERE COVID-19**

-Addendum 3: CORIMUNO19-ECU protocol: Nested trial N°5: **TRIAL EVALUATING EFFICACY OF ECULIZUMAB IN PATIENTS WITH COVID-19 INFECTION**

-Addendum 4: CORIMUNO19-CORIPLASM: Nested trial N°6: **EFFICACY OF CONVALESCENT PLASMA TO TREAT SARS-COV2 INFECTED PATIENTS , A NESTED TRIAL IN THE CORIMUNO-19 COHORT**

-Addendum 5: CORIMUNO19-BARI protocol: Nested trial N°7: **TRIAL EVALUATING EFFICACY OF BARICITINIB FOR PATIENTS WITH COVID-19 (JAKOVID)**

-Addendum 6: CORIMUNO19-SECU protocol: Nested trial N°8: **TRIAL EVALUATING EFFICACY OF SECUKINUMAB FOR PATIENTS WITH COVID-19**

-Addendum 7: CORIMUNO19-BEVA protocol: Nested trial N°9 : **TRIAL EVALUATING EFFICACY and SAFETY OF BEVACIZUMAB (AVASTIN®) IN PATIENTS WITH SEVERE HYPOXEMIC COVID-19, NESTED IN THE CORIMUNO-19 COHORT**