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°8.0 of 17/07/2020

Project code number: APHP200375, Eudra CT 2020-001246-18

The medication substance consists in multiple Immune regulatory products

Medication number1: Anti IL-6 Receptor (Tocilizumab)

Medication number2: Dexamethasone

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

APHP

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

Version N°8.0 of 17/7/2020

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

Principal Investigator

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The study was approved by the Ethic committee (CPP) of IDF VI on09/07/2020 and authorized by the ANSM on 15/07/2020

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 favorable 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 randomized 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 performing 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 randomized 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. More than 30 subjects will be used as controls. 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. Randomization will be centralized and thus will be completely independent from patients and physicians participating in the study ensuring allocation concealment.
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 annex 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 8. AME patients (CORIMUNO-19 cohort and research). In accordance with the provisions of article L1121-8-1 of the Public Health Code. **Exclusion Criteria for the cohort:** 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. 1. 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). 2. 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 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. 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 – TOCIDEX (TOCI + Dexamethasone Versus Dexamethasone)
Rationale for using Tocilizumab + Dexamethasone and Dexamethasone in severe patients infected with COVID-19	**CORIMUNO-19 - TOCIDEX** The SRAS-CoV-S protein induces direct up-regulation of IL-6, IL-1 and TNFα, some of the most potent pro-inflammatory cytokines. Dexamethasone (DXM) is a steroid with a high anti-inflammatory activity. In the RECOVERY study, 2104 patients randomly allocated to receive dexamethasone were compared with 4321 patients concurrently allocated to usual care. Overall, 454 (21.6%) patients allocated dexamethasone and 1065 (24.6%) patients allocated usual care died within 28 days (age-adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; P<0.001). The proportional and absolute mortality rate reductions varied significantly depending on level of respiratory support at randomization (test for trend p<0.001): Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14). Therefore, in patients hospitalized with COVID-19, DXM reduced 28-day mortality among those receiving invasive mechanical ventilation or oxygen support at randomization, but not among patients not receiving respiratory support. These data provide strong evidence that DXM could become the SOC, since it is the only drug tested in a randomized way that showed improvement of survival. 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 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.

	In our previous study that randomized TCZ versus standard of Care (SOC), we have shown that TCZ was superior to SOC. 131 patients were randomized to receive SOC (n=67) or SOC + TCZ (n=64). The posterior probability of a reduction of non-invasive or mechanical ventilation or death at day 14 with TCZ was 95.0%, thus achieving predefined efficacy threshold (posterior median hazard ratio (HR) [90% credible interval], 0.58 [0.33-1.00]). Reduction of mechanical ventilation or death was of the same magnitude: HR [90% CrI], 0.58 [0.30-1.09]. With a median of follow-up of 28 days, seven deaths (11.1%) were observed in the TCZ group and 11 (16.4%) in the SOC group. No increase in serious adverse events was observed in the TCZ arm. In addition, none of the patients who received the combination of DXM + TCZ (n=10) experienced either death or ventilation support, suggesting that this combination might improve results obtained with TCZ. Interestingly, no increase of infectious events was observed. Therefore, based on these two studies, we could define a new SOC with DXM and test whether or not the combination of DXM and TCZ improve outcome of patients with severe COVID-19.
Diagnosis and inclusion and Exclusion criteria for the Tocilizumab trial	**Inclusion Criteria for the TOCI-DEX trial:** 1. Patients included in the CORIMUNO-19 cohort 2. Patients belonging to the following group: - *Group 1: Cases meeting all of the following criteria* • *Requiring more than 3L/min of oxygen* • *WHO progression scale = 5* • *No NIV or High flow* **Exclusion Criteria for the TOCIDEX trial:** ● Patients with exclusion criteria to the CORIMUNO-19 cohort. ● Known hypersensitivity to Tocilizumab or to any of their excipients. ● Known hypersensitivity to Dexamethasone or to any of their excipients. ● Pregnancy ● Current documented bacterial infection ● certain evolving viral diseases (especially active herpes, chickenpox or shingles), ● psychotic states still not controlled by treatment, ● live vaccines, ● 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) $\leq 1.0 \times 10^9$/L ○ Haemoglobin level: no limitation ○ Platelets (PLT) < 50 G /L ○ SGOT or SGPT > 5N

<table>
<tr><td>Randomisation and Treatment procedures</td><td>Within this group all consecutive patients meeting the inclusion criteria will be randomized 1:1 either in the TCZ + DXM arm or in the new defined standard of care (Soc) control arm containing DXM in a set of 60 patients in total (30 in the TCZ + DXM arm, 30 in the control DXM arm). Then the inclusions will stop to allow inclusions in other subtrials of the protocol and interim analysis.

If the interim analysis indicates to continue the subtrial, a new set of 60 patients will be included on the same basis (30 in the TCZ + DXM arm, 30 in the control DXM arm).

Inclusions of new sets will stop when statistical analyses conclude on futility or efficacy or by DSMB decision.</td></tr>
<tr><td>Duration of follow-up</td><td>90 days</td></tr>
<tr><td>Criteria for efficacy</td><td>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 WHO progression scale, oxygenation, mechanical and supportive ventilation (Optiflow and NIV). For patients who are eligible for an intervention trial (in both the intervention and control arms), this daily measurement will include trial-specific measures related to the trial outcomes of interest.

Primary endpoints:

Survival without needs of ventilator utilization (including Non-invasive ventilation and Optiflow) at day 14. Thus, events considered are needing ventilator utilization (including Non-Invasive Ventilation, or Optiflow NIV), or death. New DNR order will be considered as an event at the date of the DNR.

Secondary Endpoint:

1. WHO Ordinal Scale at day 7 and day 14

The scale is defined as follow:

<table>
<tr><td>OMS Progression scale</td><td>Descriptor</td><td>Score</td></tr>
<tr><td>Uninfected</td><td>Uninfected; non viral RNA detected</td><td>0</td></tr>
<tr><td>Ambulatory</td><td>Asymptomatic; viral RNA detected</td><td>1</td></tr>
<tr><td>Ambulatory</td><td>Symptomatic; Independent</td><td>2</td></tr>
<tr><td>Ambulatory</td><td>Symptomatic; Assistance needed</td><td>3</td></tr>
<tr><td>Hospitalized : mild disease</td><td>Hospitalized; No oxygen therapy</td><td>4</td></tr>
<tr><td>Hospitalized : mild disease</td><td>Hospitalized; oxygen by mask or nasal prongs</td><td>5</td></tr>
</table></td></tr>
</table>

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

2. Overall survival at 14, 28, 60 and 90 days
3. Survival without needs of mechanical ventilation at day 14.
4. Cumulative incidence of discharge alive at 14 and 28 days
5. Cumulative incidence of oxygen supply independency at 14 and 28 days

Exploratory outcomes;
Biological parameters improvement including CRP, neutrophil and lymphocytes counts

Criteria of safety

- Number of serious adverse events (SAEs)
- Number of Grade 3 and 4 AEs.
- Investigational medication discontinuation (for any reason)

Statistical Method	Bayesian monitoring analysis of the trial will be used. The primary outcome will be therefore analyzed using a Bayesian Cox model adjusted for age. The treatment effect will be summarized in terms of hazard ratio (HR) for the experimental vs. control arm. After inclusion of 30 patients in each arm, several posterior probabilities will be calculated: 1) posterior probability of benefit P1 = P(HR < 1 | data) ; 2) posterior probability of at least a fair benefit P2 = P(HR < 0.8 | data), 3) posterior probability of inefficacy or harm P3 = P(HR > 1 | data). At the interim analysis, the trial can be stopped for futility if P2 < 0.10 or P3 > 0.80, If P1 > 0.99, the trial can be stopped for efficacy. If the trial continues recruitment, 30 additional patients are recruited per arm, and a final analysis is conducted with **efficacy boundaries P1 > 0.95 or P2 > 0.80**. Decision boundaries are non-binding, and the DSMB can recommend continuing recruitment after the inclusion of a total of 120 participants, if the efficacy boundaries are not crossed but results are deemed promising. In that case, 60 additional patients should be included, but this number is indicative and may be revised by the DSMB based on the observed results.

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. Antiviral agents including hydroxychloroquine and azithromycine, protease inhibitors (lopinavir/ritonavir) alone or in combination, interferon are currently tested. However, the severe and critically ill patients display high inflammatory state.

Common symptoms of a person infected with coronavirus include respiratory symptoms, fever, cough, shortness of breath, and dyspnea. Case severity and mortality substantially increase with

age. Comorbidities, particularly the presence of cardiovascular diseases are an aggravating factor (5).

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 (12). COVID-19 pneumonia manifests with chest computed Tomography (CT) imaging abnormalities, even in asymptomatic patients (13-16). On hospital admission, abnormalities in chest CT images were detected among all patients. Complications included acute respiratory distress syndrome (29% cases), acute cardiac injury (12%) and secondary infection (10%).

The reason the marked heterogeneity in individual sensitivity to COVID-19 NCP and the potential roles of ageing and comorbidities is currently unknown.

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.

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 has shown a reduction of 4 days of hospital stay but did not improve survival., Other antiviral agents including hydroxychloroquine and azithromycine, protease inhibtors (lopinavir/ritonavir) alone or in combination, interferon are currently tested, but prelinary results are negative for all these drugs or combinations, leading to stopping the arms including these drugs in the large RECOVERY and SOLIDARITY trials. However, the severe and critically ill patients display high inflammatory state. While most people with COVID-19 develop only mild or uncomplicated illness, approximately 10 to 15% 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) . In severe cases, infection can cause pneumonia, severe acute respiratory syndrome, kidney failure, and even death (2). 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. Death results from respiratory failure and is associated in a substantial percentage of patients with an inflammatory syndrome and a cytokine storm (17) with acute respiratory distress syndrome (ARDS) and features of macrophage activation syndrome/hemophagocytic lymphohistiocytosis (HLH) that should be better defined.

The innate immunity is the first line of defense that recognizes infection and initiates the process of pathogen clearance and tissue repair.

Such severe clinical condition displayed by some of the patients affected with COVID-19 pneumonia are strongly reminiscent of previous and recent epidemic cases of respiratory failure associated to related coronarovirus such as the MERS-CoV, SARS-CoV.

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 (13-16). On hospital admission, abnormalities in chest CT images were detected among all patients. Complications included acute respiratory distress syndrome (29% cases), acute cardiac injury (12%) and secondary bacterial 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 . Theses 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, sTREM-1, or VEGF, Endothelin-1, Granzymes, Complement C5a…and this list is far to be exhaustive (17-32).

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 (32, 33). 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 Canakinumab an anti-IL-1β antibody, Anakinra an IL-1 trap, Secukinumab an antibody targeting IL-17A, antikinases compounds such as Abl, SYK or JAK inhibitors, or Tocilizumab and Sarilumab, two monoclonal antibodies targeting IL-6R, TREM-1 inhibitors etc. All these compounds could be used in adjunct therapy or in combination with anti-viral therapies including Remdesivir, Lopinavir–Ritonavir, interferon beta‑1β, or ribavirin (34)(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)(35), or these that block the SARS-CoV/MERS-CoV early entry and/or post entry events (Imatinib (36)) 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 (37, 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 (21).

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)(41). 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.

Therefore, we conducted CORIMUNO-TOCI trial to evaluate the tolerance and the efficacy on COVID-19 pneumopathy of tocilizumab (TCZ), an anti-human IL-6 receptor monoclonal antibody that inhibits signal transduction by binding sIL-6R and mIL-6R (see below 2.2.3.).

2.1.1 **Dexamethasone : Rationale for the use and mechanism of action**

In the absence of reliable evidence from large-scale randomized clinical trials, there is great uncertainty about the effectiveness of corticosteroids in COVID-19. Prior to RECOVERY, many COVID-19 treatment guidelines stated that corticosteroids were either ‘contraindicated’ or ‘not recommended’ (47, 48) although in China, corticosteroids are recommended for severe cases (49). Practice has varied widely across the world: in some series, as many as 50% of cases were treated with corticosteroids (10, 50). Likewise, we observed that use of corticosteroids was part of usual care in Paris area in the CORIMUNO-19 trials.

Meanwhile, the results of a large randomized controlled trial of dexamethasone (DXM) recently underscored the significant clinical benefit of anti-inflammatory actions of corticosteroids in patients hospitalized with COVID-19 and requiring oxygen support.

In the RECOVERY study, 2104 patients randomly allocated to receive dexamethasone were compared with 4321 patients concurrently allocated to usual care. Overall, 454 (21.6%) patients allocated dexamethasone and 1065 (24.6%) patients allocated usual care died within 28 days (age- adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; P<0.001). The proportional and absolute mortality rate reductions varied significantly depending on level of respiratory support at randomization (test for trend p<0.001): Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14).
Thus, this study (https://doi.org/10.1101/2020.06.22.20137273) was the first and the only one to demonstrate an efficacy to improve overall survival of COVID-19. Therefore, DXM should become the SOC of CORIMUNO-19 studies.

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

Tocilizumab (TCZ)(ROACTEMRA®) is an anti-human IL-6 receptor monoclonal antibody that inhibits signal transduction by binding sIL-6R and mIL-6R (51). The main approved indication is for rheumatoid arthritis, in association or not with methotrexate (52). 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 (53-58), including with high production in the lungs (59).

2.2.3. 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(60). 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.

Several observational studies have suggested a possible efficacy of TCZ in moderate, severe or critical patients with SARS-CoV2 infection. A first study conducted in China on 21 severe cases showed an improvement of the clinical and radiological outcome in 19 out the 21 patients (www.chinaxiv.org/user/download.htm?id=30387&filetype=pdf). In 30 patients with severe COVID-19 treated in one hospital in France, TCZ decreased by 33% (compared with weighted historical controls) the risk of mechanical ventilation, nonetheless, comorbidities were not balanced between groups. In a large retrospective study from Italy, which has compared 179 patients with severe or critical COVID-19 pneumonia treated with TCZ to 365 historical controls, TCZ treatment was associated with a 39% reduced risk of invasive mechanical ventilation or death, in spite of an increased risk of new severe infections (13% vs 4%).

In the CORIMUNO study (unpublished data see Appendix 1), we have randomized 131 patients to receive usual care (n=67) or usual care + TCZ (n=64). The posterior probability of a reduction of non-invasive or mechanical ventilation or death at day 14 with TCZ was 95.0%, thus achieving predefined efficacy threshold (posterior median hazard ratio (HR) [90% credible interval], 0.58 [0.33-1.00]). Reduction of mechanical ventilation or death was of the same magnitude: HR [90% CrI], 0.58 [0.30-1.09]. With a median of follow-up of 28 days, seven deaths (11.1%) were observed in the TCZ group and 11 (16.4%) in the SOC group. No increase in serious adverse events was observed in the TCZ arm.

In addition, none of the patients who received the combination of DXM + TCZ (n=10) experienced either death or ventilation support, suggesting that this combination might improve results obtained with TCZ. Interestingly, no increase of infectious events was observed.

Therefore, based on these results, we could define a new SOC with DXM and test whether or not the combination of DXM and TCZ improves outcome of patients with severe COVID-19.

2.3. 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 (61) with no significant gender differences. The potential effect of anti-viral drugs may occur soon after infection. The rationale of immune-modulators is to act later in patients with moderate, severe or critical disease, requiring oxygen support or ventilation. In RECOVERY the benefit of DXM was seen in the two later groups of patients, in CORIMUNO, TCZ was found effective in the subgroup of patients requiring oxygen support but not ventilation.

Thus, the CORIMUNO cohort, mainly dedicated to test immune modulators, will include patients with moderate, severe or critical COVID-10 pneumonia requiring oxygen support or NVI, high flow or mechanical ventilation.

3. OBJECTIVES OF THE COHORT

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 ventilation support including mechanical ventilation, NVI or optiflow for the group of WHO class 5 patients and to decrease the time of mechanical ventilation for the WHO class 6 and above patients.

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 below or above WHO class 5, 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 (62-64) 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

More than 10 hospitals have already agreed to participate: Cayenne, Bichat, Saint Louis-Lariboisière, Georges-Pompidou European Hospital (HEGP), Cochin-Hotel Dieu, Necker, Pitié-Salpêtrière, Kremlin-Bicêtre, CHU Strasbourg, CHU Lille, Institut Gustave Roussy (IGR), Mayotte, Cayenne, Kourou, Saint Laurent.

4.3. Study population

The study will include potentially all patients with confirmed COVID-19 infection by PCR and/or CT-scan and moderate or severe pneumonia.

- Illness of any duration and severity, with symptoms (fever or cough or respiratory difficulties or 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 NVI, high flow or 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

- AME patients (CORIMUNO-19 cohort and research). In accordance with the provisions of article L1121-8-1 of the Public Health Code.

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).
- 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

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, urea, creatinine, Vitamin D)
- AST, ALT, total bilirubin, alkaline phosphatase, total protein and albumin, ferritin
- CRP, high sensitivity troponin, CPK,
- Coagulation panel including D-Dimers, fibrinogen
- Dipstick urinalysis (pH, glucose, erythrocytes, leukocytes, protein, albumin, nitrite, creatinine)
- Electrocardiogram
- Cardiac ultrasound (optional)
- CT scan of thorax
- Collection of frozen blood samples performed for care
- Optional biobanking according to the local facilities (Annexe 3)

D4, D7, D14, D28 (or at hospital discharge)

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
- Coagulation panel including D-Dimers, fibrinogen, IL-6
- Dipstick urinalysis (pH, glucose, erythrocytes, leukocytes, protein, albumin, nitrite, creatinine) (optional)
- Electrocardiogram (ECG) (optional)
- Blood gas (optional)

- Cardiac ultrasound (optional)
- CT scan of thorax (optional)

Every week or in case of significant clinical change or at hospital discharge

- Viral load (optional)
- Biobanking according to the local facilities

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

· CT scan of thorax (optional)

- Biobanking according to the local facilities

4.7. Biobanking

When possible only, the samples (plasma, serum, DNA, RNA, cells and urine) taken during the study, 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 coherently analyzed *to identify subgroups of patients and assess biological responses to therapies for the purpose of the CORIMUNO-19 trials*.

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, providing 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 of care. This care may evolve over time. At the beginning of the study, the standard care consists of supportive therapy,

- oral or IV rehydratation,
- O2 therapy.

- DEXAMETHASONE Up to 85 mg over a 10 days period. 10 mg once daily (intravenous) on day 1 to day 5, then 5 mg per day on day 6 to day 10 and finally 2.5mg per day on day 11 to day 14 or until discharge if sooner.
- Low salt diet.

- HIGH DOSE ANTICOAGULANT PROPHYLAXIS for venous thromboembolism For example: Si Cl > 30 mL/min HBPM prophylaxis (Lovenox 0,4 sc once daily); For Cl 20 to 30 Innohep 4500 UI anti-Xa x1 sc; For Cl<30 : Calciparine 5000 UI anti-Xa x2 sc
- ANTIMICROBIIAL THERAPY (3^{rd} generation cephalosporin and macrolide) if suspicion of bacterial infection, guided by antibiograms and according to local policy. For example, Cefotaxime 1 gx3/d or ceftriaxone 1g/d during 7 days. If BMC>30 kg/m2 increased to Cefotaxime 2 gx3/d or ceftriaxone 2g/d during 7 days and Azithromycine 500 mg /d D1 then à 250 mg/j D2-D5

- In the group of critically ill 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. COMPARISON OF TOCILIZUMAB plus DEXAMETHASONE vs DEXAMETHASONE (New standard of care) FOR PATIENTS WITH COVID-19 : CORIMUNO-19- TOCIDEX

6.1. Investigational medicinal product(s)

6.1.1. ROACTEMRA® 20mg/mL, 80 mg, 200 mg et 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.

As reported in the CORIMUNO-19-TOCI study, we will use the posology of 8 mg/kg intravenously infused over an hour. In the case of patients weighing 100 kg or more, considering 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)) will be administrated 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
-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) 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 could be realized at day 3 (D3) 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. Their effect 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 co-administering **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 treatments have to be used with caution:

- AVK (antivitamine K drugs)
- Cyclosporin
- Theophylline
- Oral contraception

- Lovastatin
- Atorvastatin

6.1.3. **Supply of the investigational centers**

ROACTEMRA® will be specifically provided by the sponsor in the context of the COVID 19 pandemic.
ROACTEMRA® will be supplied free of charge by ROCHE and labelled by the Clinical trial department (CTD) of AGEPS (Pharmaceutical establishment of AP-HP) or by hospital pharmacist in DOM-TOM.

The CTD of AGEPS will send **ROACTEMRA®** on centers except for the center of DOM-TOM which will receive **ROACTEMRA®** directly from ROCHE.

The drugs will be dispensed by the hospital pharmacies to the care units on the basis of a specific research prescription.

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

Storage:
Store the vial in the refrigerator (2 ° C to 8 ° C). Do not freeze.
Keep the vial 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 case of absence of improvement at D3 (absence of decrease of at least 50% of oxygen requirement), a second IV infusion of TCZ will be realized at a fixed dose of 400 mg.

The hospital pharmacist or clinical research nurses will be responsible for the preparation of tocilizumab infusion bags and their labelling with compulsory clinical trials items. 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. Standard of Care with DEXAMETHASONE

Standard of care will consist of anticoagulants and antibiotics according to local policy (see above).

Adapted from the RECOVERY protocol* and available vial dosing, DXM will be administered at the following dose: DXM 10 mg once daily (IV) for the first five days (day 1 to day 5) then 5 mg per day (IV, day 6 to day 10), then 2.5 mg for up to 4 days (day 11 to day 14), or until oxygen supply independency if sooner, either alone or in combination with TOCILIZUMAB.
*In RECOVERY, the daily dose was 6 mg and the median duration of treatment was 6 days, leading to a median total dose of 36 mg.
We use a higher dose up to a total of 85 mg over 14 days to avoid any phenomenon of inflammation rebound and to have a better initial control. However, in case of earlier improvement with normalization of CRP and oxygen requirement, DXM might be stopped. This increase dose is based on the previous experience in TOCI1 protocol of CORIMUNO, and COCORICO emulated protocol.

Dexamethasone will be provided by the hospital pharmacies.
It will be dispensed to the care units on the basis of a specific research prescription.
Depending on local organization, local pharmacist or care givers will be in charge of accountability and traceability of the dexamethasone.

- Antibiotics in case of bacterial pneumonia according to local policy

- High dose anticoagulant prophylaxis for venous thromboembolism according to local policy

6.3. Inclusion/Exclusion criteria for the nested trial

Inclusion Criteria:

1. Patients included in the CORIMUNO-19 cohort

2. Patients belonging to the following group:

    - Requiring more than 3L/min of oxygen
    - WHO progression scale = 5
    - No NIV or High flow

Exclusion Criteria:

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

- Pregnancy
- Current documented bacterial infection not controlled by antibiotics.
- certain evolving viral diseases (especially active herpes, chickenpox, shingles),
- psychotic states still not controlled by treatment,
- live vaccines in the previous 4 weeks,
- Active tuberculosis or disseminated strongyloidiasis
- 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

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:

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's 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.

Primary Endpoints

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.

Secondary Endpoints

1. WHO ordinal scale at day 7 and day 14 (see definition below)

WHO/OMS Ordinal 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 Dialysis OR ECMO	9
Death	Dead	10

2. Overall survival at 14, 28, 60 and 90 days
3. Survival without needs of mechanical ventilation at day 1; New DNR order (if given after the inclusion of the patient) will be considered as an event at the date of the DNR.
4. Cumulative incidence of discharge alive at 14 and 28 days
5. Cumulative incidence of oxygen supply independency at 14 and 28 days

Exploratory outcomes;
Biological parameters improvement including CRP, neutrophil and lymphocytes counts.

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.
- **Monitoring of serum procalcitonin (PCT) and C-reactive protein (PCR) will be done at D0, D3, D7, D10 and D14**

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 and Dexamethasone.
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.

However, in the CORIMUNO study TCZ both alone or in combination with steroids, including DXM did not show any increase of 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.

For Dexamethasone: The most common adverse events include immunosuppressive effects with the risk of infections (sceptiecemia, tuberculosis, fungi infections, chicken pox, zoster herpes, measles, amoebiasis, strongyloidosis, candida, cryptococcus, mycobacteria, Nocardia, Pneumocystis, toxoplasma), eye disorders (glaucoma, infections, corneal perforation), electrolytes disturbances, adrenal suppression, diabetes, peptic ulcers, hypersensitivity, psychiatric reactions.

7. RECORDING AND REPORTING ADVERSE EVENTS

7.1. 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 a 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.

7.2. 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*
    - *Serious: 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

7.2.1. 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 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 clinical complication (defined accordingly to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE).
The sponsor will particularly monitor haematological abnormalities (grade > 3), serious liver damage (DILI, hepatic insufficiency and isolated increased of hepatic enzymes > grade 4), serious infections (Bacterial, Fungal) and hypersensitivity reactions.
Isolated biological disturbance without clinical complication or organ damage must notify to the sponsor if the grade CTCAE is > to grade 3

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

7.2.2. 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, 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

7.2.3. 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)

.

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).

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

The investigator notifies the sponsor without delay of all the serious adverse events listed in the corresponding section:

- Starting from the date on which the subject begins treatment with tocilizumab or dexamethasone
- Throughout the whole follow-up period intended by the trial (90 days)
- Indefinitely, if the SAE is likely to be due to the investigational medicinal product 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)

7.4. 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 by e-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.

7.5. Role of the sponsor

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

7.5.1. 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 SCP for each drug.

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), 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.

7.5.2. **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.

7.5.3. **Annual safety report : NA**

Duration of research less than 1 year.

8. SPECIFIC COMMITTEES FOR THE STUDY

8.1. 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:
Pr Deepak L Bhatt (Chair),
Pr Cristina Mussini,
Pr Patrick Yeni,
Pr Galea Sandros,
Pr Kevin Winthrop,
Pr Frank Harrel.

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.

8.2. Steering Committee

The CORIMUNO-19 study group is shown in Appendix 1

9. DATA MANAGEMENT

9.1. 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)

9.2. 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.

9.3. 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.

9.4. Data processing and storage of documents and data

9.4.1. 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.

9.4.2. 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.

9.4.3. 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.

10. STATISTICAL ASPECTS

10.1. 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. 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. The methods outlined thereafter describe the specific methods for statistical monitoring and analysis of the TOCIDEX trial.

For the CORIMUNO-19-TOCIDEX trial, individuals in the cohort eligible in the participating centers are randomized 1:1 until a predefined sample size is reached. An interim analysis is performed at mid-trial, but inclusions are not frozen to wait for the interim analysis. Accordingly, the interim analysis can be skipped if too many patients are already recruited at the scheduled time of the interim analysis, in order to avoid issues associated with overrunning (such as conflicting interim and final analyses).

The interim analysis will take place when 60 patients have reached day 7 follow-up and will consider all patients recruited by that time (the use of methods for censored observations will accommodate differential follow-up). The results of the interim analysis will be communicated to the DSMB to decide upon study termination or continuation. When the primary outcome has been analyzed (after the trial recruitment is stopped and all patients have reached day 14 follow-up), the primary analysis will be carried out and, after review by the DSMB and upon its recommendation, may be communicated to investigators or the public.

The methods outlined thereafter describe the principles for analyzing the trial.

One crucial feature of CORIMUNO-19 trials 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. With a Bayesian approach, standard definition of type I and II error probabilities do not apply. Rather, operating characteristics of the design may be derived. However, since sample size calculations for Bayesian survival trials are not straightforward, a first estimate of the sample size has been based of frequentist (i.e. non-Bayesian) considerations.

The analysis will rely on computing the posterior distribution of the hazard ratio (HR) between the experimental and control arms for the time-to-event primary outcome, adjusted for age. Additional adjustment for relevant prognostic factors may also be considered, in particular if randomization stratification factors are used. . These posterior distribution of the HR will be graphically displayed, and summarized by its medians and 90% credible interval (the Bayesian counterparts of confidence intervals). Moreover, posterior probabilities of HR < 1 and HR < 0.8 will be presented.

In a Bayesian analysis, the specification of the prior distribution is crucial. For the CORIMUNO-19-TOCIDEX trial, 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 10^2. This prior distribution ensures very little influence of our prior opinion on conclusions. The sensitivity to this prior distribution will be evaluated by using different prior distributions: two sceptic priors centered on 0 with variance set so that a P(HR < 0.5) = P(HR > 2) = 0.05 (SD 0.975) or P(HR < 0.5) = P(HR > 2) = 0.025 (SD 0.82), and two enthusiastic informative priors centered on a log HR of log 0.8 and log 0.6, and SD 0.975. Other prior distributions will possibly be defined according to possible results of other trials with tocilizumab.

Baseline characteristics will be described with summary statistics, namely frequencies and percentages, or medians and interquartile ranges (IQR). Secondary and safety outcomes will be analyzed in a frequentist framework, except for WHO scores, which will be analyzed with a Bayesian proportional odds model. 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.

10.2. Statistical criteria for termination of the study

The primary outcome will be analyzed using a Bayesian Cox model adjusted for age. The treatment effect will be summarized in terms of hazard ratio (HR) for the experimental vs. control arm.

After inclusion of 30 patients in each arm, several posterior probabilities will be calculated: 1) posterior probability of benefit P1 = P(HR < 1 | data) ; 2) posterior probability of at least a fair

benefit P2 = P(HR < 0.8 | data), 3) posterior probability of inefficacy or harm P3 = P(HR > 1 | data).

At the interim analysis, the trial can be stopped for futility if P2 < 0.10 or P3 > 0.80, If P1 > 0.99, the trial can be stopped for efficacy. If the trial continues recruitment, 30 additional patients are recruited per arm, an final analysis is conducted with efficacy boundaries P1 > 0.95 or P2 > 0.80. The probabilities and boundaries have been adapted from the Statistical Design and Analysis Plan for Sequential Parallel-Group RCF for COVID-19 (Harrell & Lindsell, 2020. http://hbiostat.org/proj/covid19/bayesplan.html).

Decision boundaries are non-binding, and the DSMB can recommend continuing recruitment after the inclusion of a total of 120 participants, if the efficacy boundaries are not crossed but results are deemed promising. In that case, 60 additional patients should be included, but this number is indicative and may be revised by the DSMB based on the observed results.

10.3. Number of participants and justification

As indicated in the previous paragraph, the total number of participants will be comprised between 60 and 180, with a balance between arms. The target sample size is 120 (60 per arm), but the trial can be stopped after inclusion of 60 participants, or increased up to a maximum of 180.

In a frequentist analysis, a sample size of 120 patients (target sample size) insures a power >90% to detect a decrease in day 14 event rate from 30% to 10% (HR 0.30), and sample size of 180 patients (maximum sample size after possible increase) insures a power of 80% to detect a decrease in day 14 event rate from 30% to 15% (HR 0.46).

10.4. Anticipated level of statistical significance

The trial is not designed for frequentist statistical testing at a predefined level of statistical significance. Rather, a Bayesian approach is used, which computes chances about unknown parameter values such as treatment effects and not chances about data. It is therefore possible to compute all of the probabilities listed above as often as desired, without penalty (Statistical Design and Analysis Plan for Sequential Parallel-Group RCF for COVID-19; Harrell & Lindsell, 2020. http://hbiostat.org/proj/covid19/bayesplan.html).

10.5. Subject replacement strategy

No subject replacement is planned.

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

We do not expect missing data for the primary outcome, which is analyzed as a time-to-event censored variable. However, patients discharged alive with missing follow-up will be considered as alive without need for ventilation support (either NIV, high flow or invasive ventilation)up to day 14. No imputation will be used for other secondary efficacy and safety outcomes.

10.7. 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.

10.8. Choice of individuals to be included in the analyses

All primary analyses will be performed in both Intention To Treat (ITT). Patients will be analyzed 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.

11. 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.

11.8.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**

11.9. 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

11.10. 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.

11.11. 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.

11.12. 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.

11.13. 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.

11.14. Pharmacist's declaration of responsibility

Depending on the location of the centers, the supply of experimental drugs will be managed by ROCHE (for the French overseas departments and territories) or AGEPS (for mainland France) on the basis of a quality agreement referring to GMP/GDP.

12. ETHICAL AND LEGAL CONSIDERATIONS

12.8. 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.

<u>Other general aspect of the consent process</u>

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.

12.9.Authorisation for the research location

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

12.10. Legal obligations

12.10.1. 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.

12.10.2. 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.

12.10.3. 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.

12.10.4. 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 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, has signed a declaration of compliance with this "Reference Methodology" Adapt based on the internal procedures of the entity managing the data.

12.10.5. 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.

12.10.6. 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.

12.10.7. 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

13. FUNDING AND INSURANCE

13.8.Sources of funding for the trial

National PHRC (Ministry of Health)

13.9.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.

14. 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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16. LIST OF ADDENDA

Liste des centres :

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.

Full name	**Address of the study location**	**Telephone / e-mail**

List of the team
Serious Adverse Events report form

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)

Appendix 1

Details of the CORIMUNO-19 Collaborative Group

Writing Committee
Olivier Hermine*, Xavier Mariette*, Pierre-Louis Tharaux*, Maxime Dougados, Matthieu Resche-Rigon, Raphael Porcher§, Philippe Ravaud§,
*, § equal contribution

Coordination Committee
Olivier Hermine, Xavier Mariette, Philippe Ravaud, Pierre-Louis Tharaux, Maxime Dougados, Raphael Porcher, Matthieu Resche-Rigon, Serge Bureau, Annick Tibi

Scientific Committee
Olivier Hermine, Valérie Pourchet-Martinez, Karine Lacombe, Joseph Emmerich, Matthieu Mahevas, Jacques Cadranel , Frédéric Schlemmer, Muriel Fartoukh, Frédéric Pene, Bertrand Guidet, Elie Azoulay, Pierre Louis Tharaux, Philippe Ravaud, Xavier Mariette, Yazdan Yazdanpanah , Marc Humbert, Maxime Dougados, Matthieu Resche-Rigon, Annick Tibi, Serge Bureau

Methodology and statistics
Responsible for methodology : Philippe Ravaud,
Raphael Porcher, Gabriel Baron, Elodie Perrodeau

Data Monitoring Committee-1*
Sylvie Chevret (chair), Laurent Bertoletti, Arnaud Bourdin, Ari Chaouat, Bruno Giraudeau
* The Data Monitoring Committee-1 resigned on May 2, 2020 following communication of preliminary results through a press release on April, 27, 2020

Data Monitoring Committee-2*
Deepak L Bhatt (Chair), Cristina Mussini, Patrick Yeni, Galea Sandros, Kevin Winthrop, Frank Harrel
* The first meeting of Data Monitoring Committee 2 hold on May 9, 2020

CORIMUNO-19 Central Coordinating Office: DRCI – AP-HP
Responsible for the sponsor: Serge Bureau
Damien Vanhoye, Cécile Kedzia, Coralie Villeret, Joséphine Braun, Didier Bouton, Riad Baameur, Emmanuelle Liegey, Amel Ouslimani, Isabelle Vivaldo, Lauren Demerville, Zouleikha Bentoumi, Anne Gysembergh-Houal, Alexandre Bourgoin, Sarra Dalibey, Hélène Brocvielle, Florent Viguier , Katya Touat, Céline Le Galludec, Stephany Pong, Jeremy Combet, Aymen Rabai, Sana Bouriche, Yousra Labidi, Sofiane Mokrani, Valentin Hosansky, René Bun, Ferhat Chikhi, Sofya Mortaki, Laure Plat , Nesine Mechouar, Toufik Taib, Priscilla Andriamiandrisoa, Anne Noah, Julie Tequi-Lebras, Christine Figuerola, Sabrina Leveau

CORIMUNO-19 platform trials Coordinating Office: DRCI – URC Lariboisière / Fernand Widal / Saint Louis

Clinical Trial Unit Lead: Matthieu Resche-Rigon
Trial logistics: Maxime Dougados
Nabil Raked, Stéphanie Alary, Samir Hamiria, Pernelle Vauboin, Thinhinane Bariz, Dhiaa Meriem Hai, Hala Semri, Moustafa Benafla, Saskia Flamand, Lakhdar Mameri, Mohamed Belloul, Claire Pacheco, Anouk Walter-Petrich, Emilia Stan, Souad Benarab, Corine Nyanou

Drug supply: AGEPS – AP-HP
Pharmacy lead: Annick Tibi
Robin Charreteur, Céline Dupré, Kévin Cardet, Blandine Lehmann, Kamyl Baghli

REACTING Group (Coordination between AP-HP, Insem and Universities)
Chair: Yazdan Yazdanpanah
Claire Madeleine, Eric D'Ortenzio, Oriane Puechal, Caroline Semaille

Local clinical centers CORIMUNO-19 trials staff (listed in order of the number of patients randomized per site in the totality of CORIMUNO-19 trials)

Tocilizumab in adults hospitalized with moderate or severe Covid-19 pneumonia: an open randomized study

CORIMUNO study group on behalf of the AP-HP / Universities / Inserm COVID-19 research collaboration *

Abstract (249 words; maxi: 250)

Background

COVID-19-infected patients can develop severe pneumonia associated with a cytokine storm including an elevation of interleukin 6 (IL-6).

Methods

We have initiated a cohort of multiple randomized controlled trials open-label of immune modulatory drugs in COVID-19 patients with moderate, severe or critical pneumonia (CORIMUNO-19). In the present trial, patients with moderate or severe pneumonia requiring oxygen (>3 L/mn, WHO class 5) but no ventilation were randomly assigned to receive standard of care (SOC) or SOC + tocilizumab (TCZ) 8mg/kg IV at day 1 possibly repeated at day 3. Primary outcomes were the time from randomization

to non-invasive or mechanical ventilation support or death measured at day 4 and day 14, and were analyzed using Bayesian methods on an intent-to-treat basis.

Results

131 patients were randomized to receive SOC (n=67) or SOC + TCZ (n=64). The posterior probability of a reduction of non-invasive or mechanical ventilation or death at day 14 with TCZ was 95.0%, thus achieving predefined efficacy threshold (posterior median hazard ratio (HR) [90% credible interval], 0.58 [0.33-1.00]). Reduction of mechanical ventilation or death was of the same magnitude: HR [90% CrI], 0.58 [0.30-1.09]. With a median of follow-up of 28 days, seven deaths (11.1%) were observed in the TCZ group and 11 (16.4%) in the SOC group. No increase in serious adverse events was observed in the TCZ arm.

Conclusion

In patients with COVID-19 pneumonia receiving oxygen support, TCZ was able to reduce the need for non-invasive or mechanical ventilation. (Funded by PHRC, ClinicalTrials.gov number, NCT04331808).

Table 1. Demographic, clinical, biological characteristics at baseline. Values are median [interquartile range] unless stated otherwise.

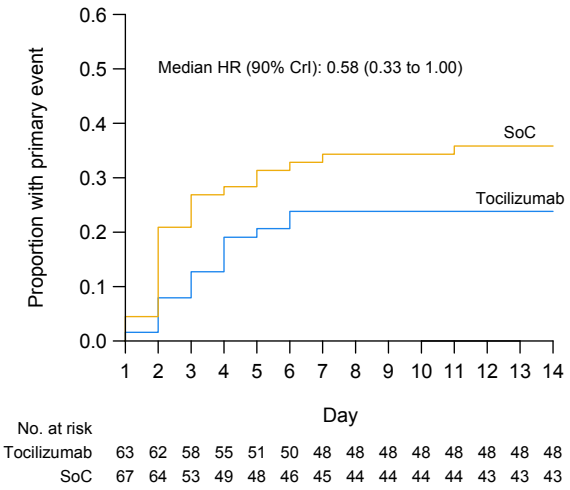
	Tocilizumab (N=63)	**SoC (N=67)**
Age (years)	64.0 [57.1-74.3]	63.3 [57.1-72.3]
Male, n/N (%)	44/63 (70%)	44/67 (66%)
Weight (kg)	80.0 [70.0-90.0]	78.0 [70.0-90.0] (n=55)
WHO score (0-10) = 5, n/N (%)	63/63 (100%)	67/67 (100%)
Temperature (°C)	37.3 [36.8-38.2]	37.9 [37.0-38.6]
Respiratory rate (breaths / min)	24.0 [22.0-30.0] (n=56)	26.0 [24.0-30.0] (n=57)
Flow (L/min)	5.0 [3.0-8.0]	5.0 [3.0-6.0]
SpO2 (%)	95.0 [93.0-96.0]	95.0 [93.0-97.0]
Time from symptoms onset to randomization (days)	10.0 [7.0-13.0] (n=62)	10.0 [8.0-13.0] (n=66)
Co-existing conditions, n/N (%)		
Chronic cardiac disease	20/61 (33%)	20/67 (30.0%)
Diabetes	20/61 (33%)	23/67 (34%)
Chronic kidney disease (stage 1 to 3)	5/61 (8%)	12/67 (18%)

	Tocilizumab (N=63)	SoC (N=67)
Asthma	5/61 (8%)	3/67 (5%)
Chronic pulmonary disease (not asthma)	3/61 (5%)	3/67 (5%)
Active malignant neoplasm	4/61 (7%)	5/67 (8%)
Smoking		
- **No**	55/61 (90%)	62/67 (93%)
- **Current**	1/61 (2%)	2/67 (3%)
- **Former**	5/61 (8%)	3/67 (4%)
Laboratory values		
C-reactive protein (CRP) (mg/L)	119.5 [74.5-219.5] (n=56)	127.0 [84.0-171.0] (n=63)
D-Dimer (µg/L)	869 [524-1380] (n=50)	1250 [780-1812] (n=50)
Neutrophil count (G/L)	4.9 [3.9-7.5] (n=60)	5.1 [3.4-6.6] (n=63)
Lymphocyte count (G/L),	1.0 [0.7-1.4] (n=60)	1.1 [0.6-1.2] (n=60)
Lymphocytes to neutrophils ratio	0.2 [0.1-0.3] (n=48)	0.2 [0.1-0.3] (n=40)
Hemoglobin (g/dL)	12.8 [11.9-13.8] (n=62)	12.3 [10.9-13.4] (n=65)
Platelet count (g/L)	230 [187-324] (n=62)	226 [163-286] (n=65)
ALT / SGPT (IU/L)	40.0 [30.0-67.0] (n=57)	35.0 [22.0-55.0] (n=62)
AST / SGOT (IU/L)	50.0 [34.0-66.0] (n=58)	55.0 [36.0-74.0] (n=62)
Albumin (g/L)	30.0 [27.0-36.0] (n=43)	32.2 [28.0-36.0] (n=42)
Creatinine (µmol/L)	71.0 [56.0-87.0] (n=61)	75.0 [59.5-119.5] (n=64)
Ferritin (mg/L)	1292 [424-2484] (n=43)	1070 [563-1790] (n=46)
LDH (IU/L)	401 [313-582] (n=46)	434 [351-558] (n=51)
CPK (IU/L)	136.0 [48.0-284.0] (n=42)	105.0 [67.0-236.0] (n=41)

ALD denotes alanine aminotransferase, AST aspartate aminotransferase, LDH Lactate dehydrogenase, CPK *creatine phosphokinase.*

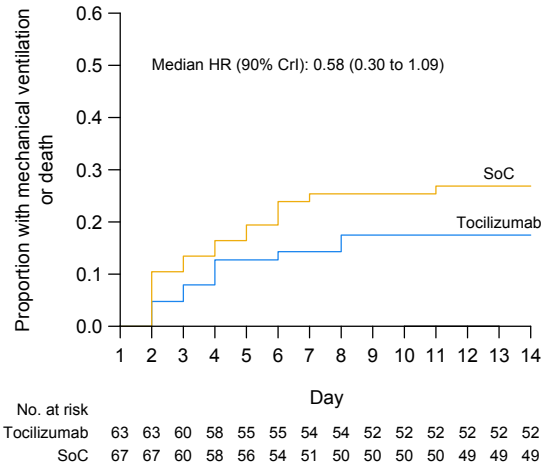
Figure 1

A



Parameter	Value
Median HR	0.58
90% CrI	0.33 to 1.00
95% CrI	0.30 to 1.11
P(HR < 1)	0.950
P(HR < 0.95)	0.931
P(HR < 0.85)	0.874
P(HR < 0.8)	0.831

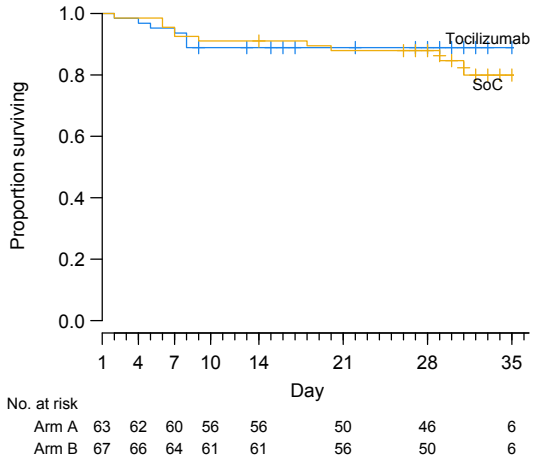
B



Parameter	Value

Median HR	0.60
90% CrI	0.35 to 1.03
95% CrI	0.31 to 1.14
P(HR < 1)	0.942
P(HR < 0.95)	0.920
P(HR < 0.85)	0.850
P(HR < 0.8)	0.803

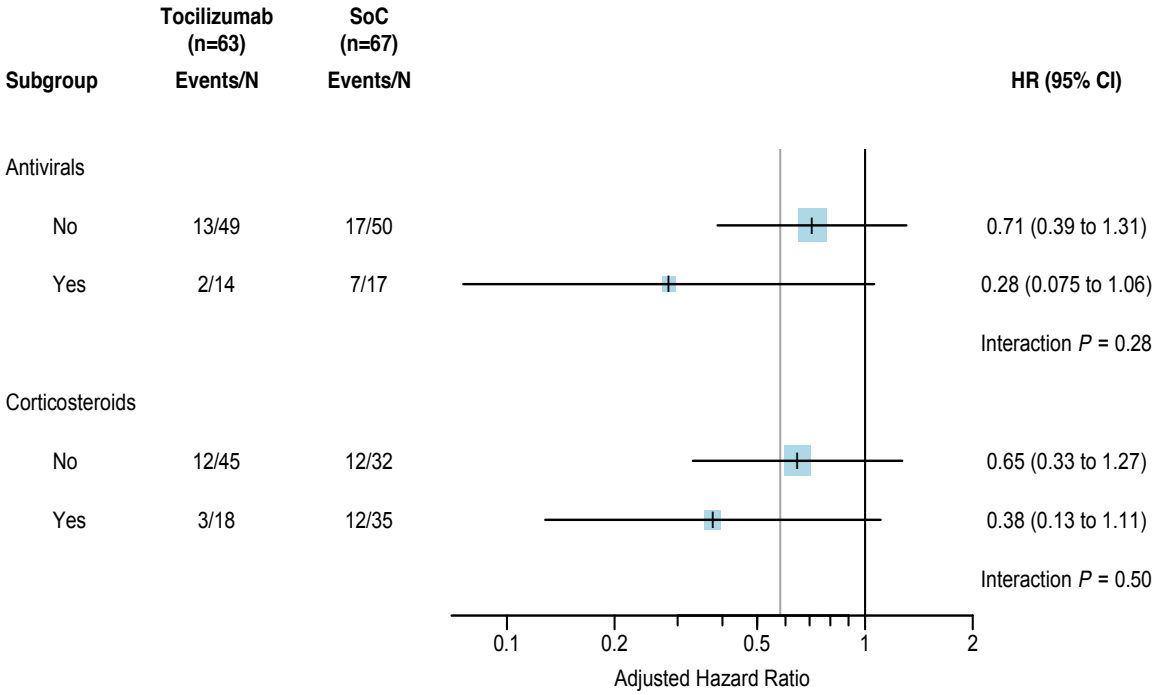
C



Parameter	Value
Median HR	0.58
90% CrI	0.30 to 1.09
95% CrI	0.26 to 1.23
P(HR < 1)	0.925
P(HR < 0.95)	0.903
P(HR < 0.85)	0.844
P(HR < 0.8)	0.804

Figure 1 Proportion of patients with occurrence of the primary event.

Kaplan Meier cumulative estimates of probability of **(A)** death or ventilation support (mechanical ventilation, Optiflow™ or non-invasive ventilation), **(B)** death or mechanical ventilation, **(C)** death in Tocilizumab (TCZ) group compared with the standard of care group (SOC). Events occurring on day 1 occurred on the same day as, but after, randomization. HR=Hazard ratio.



- 10 patients with TCZ + DXM → 0 event
- 17 patients with SOC + DXM → 6 events

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°10.0 of 10/11/2020

Project code number: APHP200375, Eudra CT 2020-001246-18

The medication substance consists in multiple Immune regulatory products

Medication number1: Anti IL-6 Receptor (Tocilizumab)

Medication number2: Dexamethasone

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

APHP

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

Version N°10.0 of 10/11/2020

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
Hospital Necker Enfants Malades
149, Rue de Sèvres - 75743 Paris Cedex 15

Date: ……/……/……..
Signature:

Sponsor

Assistance Publique – Hôpitaux de Paris
Département de la Recherche Clinique et du Développement
Hospital Saint Louis
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Date: ……/……/……..
Signature:

The study was approved by the Ethic committee (CPP) of IDF VI on09/07/2020 and authorized by the ANSM on 15/07/2020

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 favorable 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 randomized 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 performing 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 randomized 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. More than 30 subjects will be used as controls. 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. Randomization will be centralized and thus will be completely independent from patients and physicians participating in the study ensuring allocation concealment.
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 2 000 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 annex 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 8. AME patients (CORIMUNO-19 cohort and research). In accordance with the provisions of article L1121-8-1 of the Public Health Code. **Exclusion Criteria for the cohort:** 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. 1. 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). 2. 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 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. 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 – TOCIDEX (TOCI + Dexamethasone Versus Dexamethasone)
Rationale for using Tocilizumab + Dexamethasone and Dexamethasone in severe patients infected with COVID-19	**CORIMUNO-19 - TOCIDEX** The SRAS-CoV-S protein induces direct up-regulation of IL-6, IL-1 and TNFα, some of the most potent pro-inflammatory cytokines. Dexamethasone (DXM) is a steroid with a high anti-inflammatory activity. In the RECOVERY study, 2104 patients randomly allocated to receive dexamethasone were compared with 4321 patients concurrently allocated to usual care. Overall, 454 (21.6%) patients allocated dexamethasone and 1065 (24.6%) patients allocated usual care died within 28 days (age-adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; P<0.001). The proportional and absolute mortality rate reductions varied significantly depending on level of respiratory support at randomization (test for trend p<0.001): Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14). Therefore, in patients hospitalized with COVID-19, DXM reduced 28-day mortality among those receiving invasive mechanical ventilation or oxygen support at randomization, but not among patients not receiving respiratory support. These data provide strong evidence that DXM could become the SOC, since it is the only drug tested in a randomized way that showed improvement of survival. 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 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.

	In our previous study that randomized TCZ versus standard of Care (SOC), we have shown that TCZ was superior to SOC. 131 patients were randomized to receive SOC (n=67) or SOC + TCZ (n=64). The posterior probability of a reduction of non-invasive or mechanical ventilation or death at day 14 with TCZ was 95.0%, thus achieving predefined efficacy threshold (posterior median hazard ratio (HR) [90% credible interval], 0.58 [0.33-1.00]). Reduction of mechanical ventilation or death was of the same magnitude: HR [90% CrI], 0.58 [0.30-1.09]. With a median of follow-up of 28 days, seven deaths (11.1%) were observed in the TCZ group and 11 (16.4%) in the SOC group. No increase in serious adverse events was observed in the TCZ arm. In addition, none of the patients who received the combination of DXM + TCZ (n=10) experienced either death or ventilation support, suggesting that this combination might improve results obtained with TCZ. Interestingly, no increase of infectious events was observed. Therefore, based on these two studies, we could define a new SOC with DXM and test whether or not the combination of DXM and TCZ improve outcome of patients with severe COVID-19.
Diagnosis and inclusion and Exclusion criteria for the Tocilizumab trial	**Inclusion Criteria for the TOCI-DEX trial:** 1. Patients included in the CORIMUNO-19 cohort 2. Patients belonging to the following group: - *Group 1: Cases meeting all of the following criteria* • *Requiring ≥ 3L/min of oxygen* • *WHO progression scale = 5* • *No NIV or High flow* **Exclusion Criteria for the TOCIDEX trial:** ● Patients with exclusion criteria to the CORIMUNO-19 cohort. ● Known hypersensitivity to Tocilizumab or to any of their excipients. ● Known hypersensitivity to Dexamethasone or to any of their excipients. ● Pregnancy ● Current documented bacterial infection ● certain evolving viral diseases (especially active herpes, chickenpox or shingles), ● psychotic states still not controlled by treatment, ● live vaccines, ● 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

<table>
<tr><td>Randomisation and Treatment procedures</td><td>Within this group all consecutive patients meeting the inclusion criteria will be randomized 1:1 either in the TCZ + DXM arm or in the new defined standard of care (Soc) control arm containing DXM in a set of 60 patients in total (30 in the TCZ + DXM arm, 30 in the control DXM arm). Then the inclusions will stop to allow inclusions in other subtrials of the protocol and interim analysis.

If the interim analysis indicates to continue the subtrial, a new set of 60 patients will be included on the same basis (30 in the TCZ + DXM arm, 30 in the control DXM arm).

Inclusions of new sets will stop when statistical analyses conclude on futility or efficacy or by DSMB decision.</td></tr>
<tr><td>Duration of follow-up</td><td>90 days</td></tr>
<tr><td>Criteria for efficacy</td><td>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 WHO progression scale, oxygenation, mechanical and supportive ventilation (Optiflow and NIV). For patients who are eligible for an intervention trial (in both the intervention and control arms), this daily measurement will include trial-specific measures related to the trial outcomes of interest.

Primary endpoints:

Survival without needs of invasive ventilation at day 14. Thus, events considered are mechanical (invasive) ventilation or death. A new DNR order will be considered as an event at the actual date of care limitation.

Secondary Endpoint:

1. WHO Ordinal Scale at day 7 and day 14

The scale is defined as follow:

<table>
<tr><td>OMS Progression scale</td><td>Descriptor</td><td>Score</td></tr>
<tr><td>Uninfected</td><td>Uninfected; non viral RNA detected</td><td>0</td></tr>
<tr><td>Ambulatory</td><td>Asymptomatic; viral RNA detected</td><td>1</td></tr>
<tr><td>Ambulatory</td><td>Symptomatic; Independent</td><td>2</td></tr>
<tr><td>Ambulatory</td><td>Symptomatic; Assistance needed</td><td>3</td></tr>
<tr><td>Hospitalized : mild disease</td><td>Hospitalized; No oxygen therapy</td><td>4</td></tr>
<tr><td>Hospitalized : mild disease</td><td>Hospitalized; oxygen by mask or nasal prongs</td><td>5</td></tr>
</table></td></tr>
</table>

	<table><tr><td>Hospitalized : severe disease</td><td>Hospitalized; oxygen by NIV or High flow</td><td>6</td></tr><tr><td>Hospitalized : severe disease</td><td>Intubation and Mechanical ventilation, pO2/FIO2>=150 OR SpO2/FIO2>=200</td><td>7</td></tr><tr><td>Hospitalized : severe disease</td><td>Mechanical ventilation, (pO2/FIO2<150 OR SpO2/FIO2<200) OR vasopressors (norepinephrine >0.3 microg/kg/min)</td><td>8</td></tr><tr><td>Hospitalized : severe disease</td><td>Mechanical ventilation, pO2/FIO2<150 AND vasopressors (norepinephrine >0.3 microg/kg/min), OR Dialysis OR ECMO</td><td>9</td></tr><tr><td>Death</td><td>Dead</td><td>10</td></tr></table> 2. Overall survival at 14, 28, 60 and 90 days 3. Survival without needs of ventilator utilization (including non-invasive ventilation and Optiflow) at day 14. 4. Cumulative incidence of discharge alive at 14 and 28 days 5. Cumulative incidence of oxygen supply independency at 14 and 28 days Exploratory outcomes; Biological parameters improvement including CRP, neutrophil and lymphocytes counts
Criteria of safety	● Number of serious adverse events (SAEs) ● Number of Grade 3 and 4 AEs. ● Investigational medication discontinuation (for any reason)

Statistical Method	Bayesian monitoring analysis of the trial will be used. The primary outcome will be therefore analyzed using a Bayesian Cox model adjusted for age. The treatment effect will be summarized in terms of hazard ratio (HR) for the experimental vs. control arm. The maximum sample size if fixed as 660 patients (330 per arm). After inclusion of every 60 patients (on average 30 in each arm), starting when the first 60 patients have valid data for at least 7 days of follow-up, several posterior probabilities will be calculated: 1) posterior probability of benefit P1 = P(HR < 1 | data) ; 2) posterior probability of at least a fair benefit P2 = P(HR < 0.8 | data), 3) posterior probability of inefficacy or harm P3 = P(HR > 1 | data). At each of these interim analyses, the following actions are triggered: • Stop with evidence for efficacy if $P_1 > 0.95$ ($P_1 > 0.99$ at the first analysis because we consider that there is a need for very convincing evidence if the sample size is very limited, and this was already planned in the previous version of the protocol); • Stop for futility if $P_2 < 0.10$ or $P_3 > 0.80$; • Stop with evidence for efficacy if $P_2 > 0.80$ (only actionable when at least 180 patients have been randomized, i.e. starting from the third analysis). Decision boundaries are non-binding, and the DSMB can recommend continuing recruitment or stopping for other reasons.

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. Antiviral agents including hydroxychloroquine and azithromycine, protease inhibitors (lopinavir/ritonavir) alone or in combination, interferon are currently tested. However, the severe and critically ill patients display high inflammatory state.

Common symptoms of a person infected with coronavirus include respiratory symptoms, fever, cough, shortness of breath, and dyspnea. Case severity and mortality substantially increase with

age. Comorbidities, particularly the presence of cardiovascular diseases are an aggravating factor (5).

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 (12). COVID-19 pneumonia manifests with chest computed Tomography (CT) imaging abnormalities, even in asymptomatic patients (13-16). On hospital admission, abnormalities in chest CT images were detected among all patients. Complications included acute respiratory distress syndrome (29% cases), acute cardiac injury (12%) and secondary infection (10%).

The reason the marked heterogeneity in individual sensitivity to COVID-19 NCP and the potential roles of ageing and comorbidities is currently unknown.

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.

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 has shown a reduction of 4 days of hospital stay but did not improve survival., Other antiviral agents including hydroxychloroquine and azithromycine, protease inhibtors (lopinavir/ritonavir) alone or in combination, interferon are currently tested, but prelinary results are negative for all these drugs or combinations, leading to stopping the arms including these drugs in the large RECOVERY and SOLIDARITY trials. However, the severe and critically ill patients display high inflammatory state. While most people with COVID-19 develop only mild or uncomplicated illness, approximately 10 to 15% 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) . In severe cases, infection can cause pneumonia, severe acute respiratory syndrome, kidney failure, and even death (2). 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. Death results from respiratory failure and is associated in a substantial percentage of patients with an inflammatory syndrome and a cytokine storm (17) with acute respiratory distress syndrome (ARDS) and features of macrophage activation syndrome/hemophagocytic lymphohistiocytosis (HLH) that should be better defined.

The innate immunity is the first line of defense that recognizes infection and initiates the process of pathogen clearance and tissue repair.

Such severe clinical condition displayed by some of the patients affected with COVID-19 pneumonia are strongly reminiscent of previous and recent epidemic cases of respiratory failure associated to related coronarovirus such as the MERS-CoV, SARS-CoV.

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 (13-16). On hospital admission, abnormalities in chest CT images were detected among all patients. Complications included acute respiratory distress syndrome (29% cases), acute cardiac injury (12%) and secondary bacterial 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 . Theses 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, sTREM-1, or VEGF, Endothelin-1, Granzymes, Complement C5a…and this list is far to be exhaustive (17-32).

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 (32, 33). 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 Canakinumab an anti-IL-1β antibody, Anakinra an IL-1 trap, Secukinumab an antibody targeting IL-17A, antikinases compounds such as Abl, SYK or JAK inhibitors, or Tocilizumab and Sarilumab, two monoclonal antibodies targeting IL-6R, TREM-1 inhibitors etc. All these compounds could be used in adjunct therapy or in combination with anti-viral therapies including Remdesivir, Lopinavir–Ritonavir, interferon beta‑1β, or ribavirin (34)(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)(35), or these that block the SARS-CoV/MERS-CoV early entry and/or post entry events (Imatinib (36)) 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 (37, 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 (21).

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)(41). 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.

Therefore, we conducted CORIMUNO-TOCI trial to evaluate the tolerance and the efficacy on COVID-19 pneumopathy of tocilizumab (TCZ), an anti-human IL-6 receptor monoclonal antibody that inhibits signal transduction by binding sIL-6R and mIL-6R (see below 2.2.3.).

2.1.1 Dexamethasone : Rationale for the use and mechanism of action

In the absence of reliable evidence from large-scale randomized clinical trials, there is great uncertainty about the effectiveness of corticosteroids in COVID-19. Prior to RECOVERY, many COVID-19 treatment guidelines stated that corticosteroids were either ‘contraindicated’ or ‘not recommended’ (47, 48) although in China, corticosteroids are recommended for severe cases (49). Practice has varied widely across the world: in some series, as many as 50% of cases were treated with corticosteroids (10, 50). Likewise, we observed that use of corticosteroids was part of usual care in Paris area in the CORIMUNO-19 trials.

Meanwhile, the results of a large randomized controlled trial of dexamethasone (DXM) recently underscored the significant clinical benefit of anti-inflammatory actions of corticosteroids in patients hospitalized with COVID-19 and requiring oxygen support.

In the RECOVERY study, 2104 patients randomly allocated to receive dexamethasone were compared with 4321 patients concurrently allocated to usual care. Overall, 454 (21.6%) patients allocated dexamethasone and 1065 (24.6%) patients allocated usual care died within 28 days (age- adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; P<0.001). The proportional and absolute mortality rate reductions varied significantly depending on level of respiratory support at randomization (test for trend p<0.001): Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14).
Thus, this study (https://doi.org/10.1101/2020.06.22.20137273) was the first and the only one to demonstrate an efficacy to improve overall survival of COVID-19. Therefore, DXM should become the SOC of CORIMUNO-19 studies.

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

Tocilizumab (TCZ)(ROACTEMRA®) is an anti-human IL-6 receptor monoclonal antibody that inhibits signal transduction by binding sIL-6R and mIL-6R (51). The main approved indication is for rheumatoid arthritis, in association or not with methotrexate (52). 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 (53-58), including with high production in the lungs (59).

2.2.3. 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(60). 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.

Several observational studies have suggested a possible efficacy of TCZ in moderate, severe or critical patients with SARS-CoV2 infection. A first study conducted in China on 21 severe cases showed an improvement of the clinical and radiological outcome in 19 out the 21 patients (www.chinaxiv.org/user/download.htm?id=30387&filetype=pdf). In 30 patients with severe COVID-19 treated in one hospital in France, TCZ decreased by 33% (compared with weighted historical controls) the risk of mechanical ventilation, nonetheless, comorbidities were not balanced between groups. In a large retrospective study from Italy, which has compared 179 patients with severe or critical COVID-19 pneumonia treated with TCZ to 365 historical controls, TCZ treatment was associated with a 39% reduced risk of invasive mechanical ventilation or death, in spite of an increased risk of new severe infections (13% vs 4%).

In the CORIMUNO study (unpublished data see Appendix 1), we have randomized 131 patients to receive usual care (n=67) or usual care + TCZ (n=64). The posterior probability of a reduction of non-invasive or mechanical ventilation or death at day 14 with TCZ was 95.0%, thus achieving predefined efficacy threshold (posterior median hazard ratio (HR) [90% credible interval], 0.58 [0.33-1.00]). Reduction of mechanical ventilation or death was of the same magnitude: HR [90% CrI], 0.58 [0.30-1.09]. With a median of follow-up of 28 days, seven deaths (11.1%) were observed in the TCZ group and 11 (16.4%) in the SOC group. No increase in serious adverse events was observed in the TCZ arm.

In addition, none of the patients who received the combination of DXM + TCZ (n=10) experienced either death or ventilation support, suggesting that this combination might improve results obtained with TCZ. Interestingly, no increase of infectious events was observed.

Therefore, based on these results, we could define a new SOC with DXM and test whether or not the combination of DXM and TCZ improves outcome of patients with severe COVID-19.

2.3. 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 (61) with no significant gender differences. The potential effect of anti-viral drugs may occur soon after infection. The rationale of immune-modulators is to act later in patients with moderate, severe or critical disease, requiring oxygen support or ventilation. In RECOVERY the benefit of DXM was seen in the two later groups of patients, in CORIMUNO, TCZ was found effective in the subgroup of patients requiring oxygen support but not ventilation.

Thus, the CORIMUNO cohort, mainly dedicated to test immune modulators, will include patients with moderate, severe or critical COVID-10 pneumonia requiring oxygen support or NVI, high flow or mechanical ventilation.

3. OBJECTIVES OF THE COHORT

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 ventilation support including mechanical ventilation, NVI or optiflow for the group of WHO class 5 patients and to decrease the time of mechanical ventilation for the WHO class 6 and above patients.

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 below or above WHO class 5, 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 (62-64) 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

More than 10 hospitals have already agreed to participate: Cayenne, Bichat, Saint Louis-Lariboisière, Georges-Pompidou European Hospital (HEGP), Cochin-Hotel Dieu, Necker, Pitié-Salpêtrière, Kremlin-Bicêtre, CHU Strasbourg, CHU Lille, Institut Gustave Roussy (IGR), Mayotte, Cayenne, Kourou, Saint Laurent.

4.3. Study population

The study will include potentially all patients with confirmed COVID-19 infection by PCR and/or CT-scan and moderate or severe pneumonia.

- Illness of any duration and severity, with symptoms (fever or cough or respiratory difficulties or 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 NVI, high flow or 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

- AME patients (CORIMUNO-19 cohort and research). In accordance with the provisions of article L1121-8-1 of the Public Health Code.

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).
- 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

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, urea, creatinine, Vitamin D)
- AST, ALT, total bilirubin, alkaline phosphatase, total protein and albumin, ferritin
- CRP, high sensitivity troponin, CPK,
- Coagulation panel including D-Dimers, fibrinogen
- Dipstick urinalysis (pH, glucose, erythrocytes, leukocytes, protein, albumin, nitrite, creatinine)
- Electrocardiogram
- Cardiac ultrasound (optional)
- CT scan of thorax
- Collection of frozen blood samples performed for care
- Optional biobanking according to the local facilities (Annexe 3)

D4, D7, D14, D28 (or at hospital discharge)

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
- Coagulation panel including D-Dimers, fibrinogen, IL-6
- Dipstick urinalysis (pH, glucose, erythrocytes, leukocytes, protein, albumin, nitrite, creatinine) (optional)
- Electrocardiogram (ECG) (optional)
- Blood gas (optional)

- Cardiac ultrasound (optional)
- CT scan of thorax (optional)

Every week or in case of significant clinical change or at hospital discharge

- Viral load (optional)
- Biobanking according to the local facilities

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

· CT scan of thorax (optional)

- Biobanking according to the local facilities

4.7. Biobanking

When possible only, the samples (plasma, serum, DNA, RNA, cells and urine) taken during the study, 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 coherently analyzed *to identify subgroups of patients and assess biological responses to therapies for the purpose of the CORIMUNO-19 trials*.

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, providing 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 of care. This care may evolve over time. At the beginning of the study, the standard care consists of supportive therapy,

- oral or IV rehydratation,
- O2 therapy.

- DEXAMETHASONE Up to 85 mg over a 10 days period. 10 mg once daily (intravenous) on day 1 to day 5, then 5 mg per day on day 6 to day 10 and finally 2.5mg per day on day 11 to day 14 or until discharge if sooner.
- Low salt diet.

- HIGH DOSE ANTICOAGULANT PROPHYLAXIS for venous thromboembolism For example: Si Cl > 30 mL/min HBPM prophylaxis (Lovenox 0,4 sc once daily); For Cl 20 to 30 Innohep 4500 UI anti-Xa x1 sc; For Cl<30 : Calciparine 5000 UI anti-Xa x2 sc
- ANTIMICROBIIAL THERAPY (3rd generation cephalosporin and macrolide) if suspicion of bacterial infection, guided by antibiograms and according to local policy. For example, Cefotaxime 1 gx3/d or ceftriaxone 1g/d during 7 days. If BMC>30 kg/m2 increased to Cefotaxime 2 gx3/d or ceftriaxone 2g/d during 7 days and Azithromycine 500 mg /d D1 then à 250 mg/j D2-D5

- In the group of critically ill 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. COMPARISON OF TOCILIZUMAB plus DEXAMETHASONE vs DEXAMETHASONE (New standard of care) FOR PATIENTS WITH COVID-19 : CORIMUNO-19- TOCIDEX

6.1. Investigational medicinal product(s)

6.1.1. ROACTEMRA® 20mg/mL, 80 mg, 200 mg et 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.

As reported in the CORIMUNO-19-TOCI study, we will use the posology of 8 mg/kg intravenously infused over an hour. In the case of patients weighing 100 kg or more, considering 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)) will be administrated 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
-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) 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 could be realized at day 3 (D3) 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. Their effect 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 co-administering **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 treatments have to be used with caution:

- AVK (antivitamine K drugs)
- Cyclosporin
- Theophylline
- Oral contraception

- Lovastatin
- Atorvastatin

6.1.3. **Supply of the investigational centers**

ROACTEMRA® will be specifically provided by the sponsor in the context of the COVID 19 pandemic.
ROACTEMRA® will be supplied free of charge by ROCHE and labelled by the Clinical trial department (CTD) of AGEPS (Pharmaceutical establishment of AP-HP) or by hospital pharmacist in DOM-TOM.

The CTD of AGEPS will send **ROACTEMRA®** on centers except for the center of DOM-TOM which will receive **ROACTEMRA®** directly from ROCHE.

The drugs will be dispensed by the hospital pharmacies to the care units on the basis of a specific research prescription.

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

Storage:
Store the vial in the refrigerator (2 ° C to 8 ° C). Do not freeze.
Keep the vial 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 case of absence of improvement at D3 (absence of decrease of at least 50% of oxygen requirement), a second IV infusion of TCZ will be realized at a fixed dose of 400 mg.

The hospital pharmacist or clinical research nurses will be responsible for the preparation of tocilizumab infusion bags and their labelling with compulsory clinical trials items. 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. Standard of Care with DEXAMETHASONE

Standard of care will consist of anticoagulants and antibiotics according to local policy (see above).

Adapted from the RECOVERY protocol* and available vial dosing, DXM will be administered at the following dose: DXM 10 mg once daily (IV) for the first five days (day 1 to day 5) then 5 mg per day (IV, day 6 to day 10), then 2.5 mg for up to 4 days (day 11 to day 14), or until oxygen supply independency if sooner, either alone or in combination with TOCILIZUMAB.
*In RECOVERY, the daily dose was 6 mg and the median duration of treatment was 6 days, leading to a median total dose of 36 mg.
We use a higher dose up to a total of 85 mg over 14 days to avoid any phenomenon of inflammation rebound and to have a better initial control. However, in case of earlier improvement with normalization of CRP and oxygen requirement, DXM might be stopped. This increase dose is based on the previous experience in TOCI1 protocol of CORIMUNO, and COCORICO emulated protocol.

Dexamethasone will be provided by the hospital pharmacies.
It will be dispensed to the care units on the basis of a specific research prescription.
Depending on local organization, local pharmacist or care givers will be in charge of accountability and traceability of the dexamethasone.

- Antibiotics in case of bacterial pneumonia according to local policy

- High dose anticoagulant prophylaxis for venous thromboembolism according to local policy

6.3. Inclusion/Exclusion criteria for the nested trial

Inclusion Criteria:

1. Patients included in the CORIMUNO-19 cohort

2. Patients belonging to the following group:

    - Requiring ≥ 3L/min of oxygen
    - WHO progression scale = 5
    - No NIV or High flow

Exclusion Criteria:

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

- Pregnancy
- Current documented bacterial infection not controlled by antibiotics.
- certain evolving viral diseases (especially active herpes, chickenpox, shingles),
- psychotic states still not controlled by treatment,
- live vaccines in the previous 4 weeks,
- Active tuberculosis or disseminated strongyloidiasis
- 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

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:

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's 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.

Primary Endpoints

Survival without needs of invasive ventilation at day 14. Thus, events considered are mechanical (invasive) ventilation or death. A new DNR order will be considered as an event at the actual date of care limitation.

Secondary Endpoints

1. WHO ordinal scale at day 7 and day 14 (see definition below)

WHO/OMS Ordinal 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 Dialysis OR ECMO	9
Death	Dead	10

2. Overall survival at 14, 28, 60 and 90 days
3. Survival without needs of ventilator utilization (including non-invasive ventilation and Optiflow) at day 14.
4. Cumulative incidence of discharge alive at 14 and 28 days
5. Cumulative incidence of oxygen supply independency at 14 and 28 days

Exploratory outcomes;
Biological parameters improvement including CRP, neutrophil and lymphocytes counts.

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.

- **Monitoring of serum procalcitonin (PCT) and C-reactive protein (PCR) will be done at D0, D3, D7, D10 and D14**

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 and Dexamethasone.
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.
However, in the CORIMUNO study TCZ both alone or in combination with steroids, including DXM did not show any increase of 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.

For Dexamethasone: The most common adverse events include immunosuppressive effects with the risk of infections (sceptiecemia, tuberculosis, fungi infections, chicken pox, zoster herpes, measles, amoebiasis, strongyloidosis, candida, cryptococcus, mycobacteria, Nocardia, Pneumocystis, toxoplasma), eye disorders (glaucoma, infections, corneal perforation), electrolytes disturbances, adrenal suppression, diabetes, peptic ulcers, hypersensitivity, psychiatric reactions.

7. RECORDING AND REPORTING ADVERSE EVENTS

7.1. 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 a 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.

7.2. 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*
    - *Serious: 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

7.2.1. 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 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 clinical complication (defined accordingly to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE).
The sponsor will particularly monitor haematological abnormalities (grade > 3), serious liver damage (DILI, hepatic insufficiency and isolated increased of hepatic enzymes > grade 4), serious infections (Bacterial, Fungal) and hypersensitivity reactions.
Isolated biological disturbance without clinical complication or organ damage must notify to the sponsor if the grade CTCAE is > to grade 3

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

7.2.2. 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, 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

7.2.3. 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 (unless they led to death): i.e. respiratory worsening (including desaturation, hypoxia, hypoxemia, dyspnea, cough), asthenia and/or transfer to ICU without any other etiology than COVID-19.

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).

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

The investigator notifies the sponsor without delay of all the serious adverse events listed in the corresponding section:

- Starting from the date on which the subject begins treatment with tocilizumab or dexamethasone
- Throughout the whole follow-up period intended by the trial (90 days)
- Indefinitely, if the SAE is likely to be due to the investigational medicinal product 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)

7.4. 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 by e-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.

7.5. Role of the sponsor

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

7.5.1. 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 SCP for each drug.

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), 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.

7.5.2. **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.

7.5.3. **Annual safety report : NA**

Duration of research less than 1 year.

8. SPECIFIC COMMITTEES FOR THE STUDY

8.1. 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:
Pr Deepak L Bhatt (Chair),
Pr Cristina Mussini,
Pr Patrick Yeni,
Pr Galea Sandros,
Pr Kevin Winthrop,
Pr Frank Harrel.

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.

8.2. Steering Committee

The CORIMUNO-19 study group is shown in Appendix 1

9. DATA MANAGEMENT

9.1. 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)

9.2. 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.

9.3. 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.

9.4. Data processing and storage of documents and data

9.4.1. 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.

9.4.2. 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.

9.4.3. 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.

10. STATISTICAL ASPECTS

10.1. 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. 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. The methods outlined thereafter describe the specific methods for statistical monitoring and analysis of the TOCIDEX trial.

For the CORIMUNO-19-TOCIDEX trial, individuals in the cohort eligible in the participating centers are randomized 1:1 until a predefined sample size is reached. Interim analyses are performed after randomization of sets of 60 patients, approximately, and inclusions are not frozen to wait for the interim analysis. Accordingly, an interim analysis can be skipped if too many patients are already recruited at the scheduled time of the interim analysis, in order to avoid issues associated with overrunning (such as conflicting interim and final analyses).

The interim analyses will begin when 60 patients have reached day 7 follow-up (with valid data for the period) and will be repeated after every 60 patients are included. They will consider all patients recruited by that time (the use of methods for censored observations will accommodate differential follow-up). The results of the interim analysis will be communicated to the DSMB to decide upon study termination or continuation. When the primary outcome has been analyzed (after the trial recruitment is stopped and all patients have reached day 14 follow-up), the primary analysis will be carried out and, after review by the DSMB and upon its recommendation, may be communicated to investigators or the public.

The methods outlined thereafter describe the principles for analyzing the trial.

One crucial feature of CORIMUNO-19 trials 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. With a Bayesian approach, standard definition of type I and II error probabilities do not apply. Rather, operating characteristics of the design may be derived. However, since sample size calculations for Bayesian survival trials are not

straightforward, a first estimate of the sample size has been based of frequentist (i.e. non-Bayesian) considerations.

The analysis will rely on computing the posterior distribution of the hazard ratio (HR) between the experimental and control arms for the time-to-event primary outcome, adjusted for age. Additional adjustment for relevant prognostic factors may also be considered, in particular if randomization stratification factors are used (e.g. center). These posterior distribution of the HR will be graphically displayed, and summarized by its medians and 90% credible interval (the Bayesian counterparts of confidence intervals). Moreover, posterior probabilities of HR < 1 and HR < 0.8 will be presented.

In a Bayesian analysis, the specification of the prior distribution is crucial. For the CORIMUNO-19-TOCIDEX trial, 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 10^2. This prior distribution ensures very little influence of our prior opinion on conclusions. The sensitivity to this prior distribution will be evaluated by using different prior distributions: two sceptic priors centered on 0 with variance set so that a P(HR < 0.5) = P(HR > 2) = 0.05 (SD 0.975) or P(HR < 0.5) = P(HR > 2) = 0.025 (SD 0.82), and two enthusiastic informative priors centered on a log HR of log 0.8 and log 0.6, and SD 0.975. Other prior distributions will possibly be defined according to possible results of other trials with tocilizumab.

Baseline characteristics will be described with summary statistics, namely frequencies and percentages, or medians and interquartile ranges (IQR). Secondary and safety outcomes will be analyzed in a frequentist framework, except for WHO scores, which will be analyzed with a Bayesian proportional odds model. 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.

10.2. Statistical criteria for termination of the study

The primary outcome will be analyzed using a Bayesian Cox model adjusted for age. The treatment effect will be summarized in terms of hazard ratio (HR) for the experimental vs. control arm.

At each interim analysis, the following posterior probabilities are calculated:

- Posterior probability of benefit $P_1 = P(HR < 1 \mid data)$;
- Posterior probability of at least a fair benefit $P_2 = P(HR < 0.8 \mid data)$;
- Posterior probability of inefficacy or harm $P_3 = P(HR > 1 \mid data)$.

At each analysis, the following actions are triggered according to the thresholds given below, adapted from the Statistical Design and Analysis Plan for Sequential Parallel-Group RCF for COVID-19 (Harrell & Lindsell, 2020. http://hbiostat.org/proj/covid19/bayesplan.html):

- Stop with evidence for efficacy if $P_1 > 0.95$ ($P_1 > 0.99$ at the first analysis because we consider that there is a need for very convincing evidence if the sample size is very limited, and this was already planned in the previous version of the protocol);
- Stop for futility if $P_2 < 0.10$ or $P_3 > 0.80$;
- Stop with evidence for efficacy if $P_2 > 0.80$ (only actionable when at least 180 patients have been randomized, i.e. starting from the third analysis).

Decision boundaries are non-binding, and the DSMB can recommend continuing recruitment or stopping the trial depending on other evidence.

10.3. Number of participants and justification

A maximum of 660 patient can be recruited in the trial, with a balance between arms.

In a frequentist analysis, a sample size of 634 patients insures a power >80% to detect a decrease in day 14 event rate from 25% to 17% (HR 0.65), using a one-sided 5% type I error rate (as a parallel for the $P_1 > 0.95$ decision rule in the Bayesian analysis). Given data are analyzed after inclusion of every 60 patients, the maximum sample size has been increased to 660.

10.4. Anticipated level of statistical significance

The trial is not designed for frequentist statistical testing at a predefined level of statistical significance. Rather, a Bayesian approach is used, which computes chances about unknown parameter values such as treatment effects and not chances about data. It is therefore possible to compute all of the probabilities listed above as often as desired, without penalty (Statistical Design and Analysis Plan for Sequential Parallel-Group RCF for COVID-19; Harrell & Lindsell, 2020. http://hbiostat.org/proj/covid19/bayesplan.html).

10.5. Subject replacement strategy

No subject replacement is planned.

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

We do not expect missing data for the primary outcome, which is analyzed as a time-to-event censored variable. However, patients discharged alive with missing follow-up will be considered as alive without need for ventilation support (either NIV, high flow or invasive ventilation) up to day 14. No imputation will be used for other secondary efficacy and safety outcomes.

10.7. 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.

10.8. Choice of individuals to be included in the analyses

All primary analyses will be performed in both Intention To Treat (ITT). Patients will be analyzed 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.

11. 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.

11.8.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**

11.9. 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

11.10. 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.

11.11. 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.

11.12. 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.

11.13. 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.

11.14. Pharmacist's declaration of responsibility

Depending on the location of the centers, the supply of experimental drugs will be managed by ROCHE (for the French overseas departments and territories) or AGEPS (for mainland France) on the basis of a quality agreement referring to GMP/GDP.

12. ETHICAL AND LEGAL CONSIDERATIONS

12.8. 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.

<u>Other general aspect of the consent process</u>

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.

12.9.Authorisation for the research location

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

12.10. Legal obligations

12.10.1. 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.

12.10.2. 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.

12.10.3. 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.

12.10.4. 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 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, has signed a declaration of compliance with this "Reference Methodology" Adapt based on the internal procedures of the entity managing the data.

12.10.5. 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.

12.10.6. 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.

12.10.7. 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

13. FUNDING AND INSURANCE

13.8.Sources of funding for the trial

National PHRC (Ministry of Health)

13.9.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.

14. 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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16. LIST OF ADDENDA

Liste des centres :

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.

Full name	**Address of the study location**	**Telephone / e-mail**

List of the team
Serious Adverse Events report form

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)

Appendix 1

Details of the CORIMUNO-19 Collaborative Group

Writing Committee
Olivier Hermine*, Xavier Mariette*, Pierre-Louis Tharaux*, Maxime Dougados, Matthieu Resche-Rigon, Raphael Porcher§, Philippe Ravaud§,
*, § equal contribution

Coordination Committee
Olivier Hermine, Xavier Mariette, Philippe Ravaud, Pierre-Louis Tharaux, Maxime Dougados, Raphael Porcher, Matthieu Resche-Rigon, Serge Bureau, Annick Tibi

Scientific Committee
Olivier Hermine, Valérie Pourchet-Martinez, Karine Lacombe, Joseph Emmerich, Matthieu Mahevas, Jacques Cadranel , Frédéric Schlemmer, Muriel Fartoukh, Frédéric Pene, Bertrand Guidet, Elie Azoulay, Pierre Louis Tharaux, Philippe Ravaud, Xavier Mariette, Yazdan Yazdanpanah , Marc Humbert, Maxime Dougados, Matthieu Resche-Rigon, Annick Tibi, Serge Bureau

Methodology and statistics
Responsible for methodology : Philippe Ravaud,
Raphael Porcher, Gabriel Baron, Elodie Perrodeau

Data Monitoring Committee-1*
Sylvie Chevret (chair), Laurent Bertoletti, Arnaud Bourdin, Ari Chaouat, Bruno Giraudeau
* The Data Monitoring Committee-1 resigned on May 2, 2020 following communication of preliminary results through a press release on April, 27, 2020

Data Monitoring Committee-2*
Deepak L Bhatt (Chair), Cristina Mussini, Patrick Yeni, Galea Sandros, Kevin Winthrop, Frank Harrel
* The first meeting of Data Monitoring Committee 2 hold on May 9, 2020

CORIMUNO-19 Central Coordinating Office: DRCI – AP-HP
Responsible for the sponsor: Serge Bureau
Damien Vanhoye, Cécile Kedzia, Coralie Villeret, Joséphine Braun, Didier Bouton, Riad Baameur, Emmanuelle Liegey, Amel Ouslimani, Isabelle Vivaldo, Lauren Demerville, Zouleikha Bentoumi, Anne Gysembergh-Houal, Alexandre Bourgoin, Sarra Dalibey, Hélène Brocvielle, Florent Viguier , Katya Touat, Céline Le Galludec, Stephany Pong, Jeremy Combet, Aymen Rabai, Sana Bouriche, Yousra Labidi, Sofiane Mokrani, Valentin Hosansky, René Bun, Ferhat Chikhi, Sofya Mortaki, Laure Plat , Nesine Mechouar, Toufik Taib, Priscilla Andriamiandrisoa, Anne Noah, Julie Tequi-Lebras, Christine Figuerola, Sabrina Leveau

CORIMUNO-19 platform trials Coordinating Office: DRCI – URC Lariboisière / Fernand Widal / Saint Louis

Clinical Trial Unit Lead: Matthieu Resche-Rigon
Trial logistics: Maxime Dougados
Nabil Raked, Stéphanie Alary, Samir Hamiria, Pernelle Vauboin, Thinhinane Bariz, Dhiaa Meriem Hai, Hala Semri, Moustafa Benafla, Saskia Flamand, Lakhdar Mameri, Mohamed Belloul, Claire Pacheco, Anouk Walter-Petrich, Emilia Stan, Souad Benarab, Corine Nyanou

Drug supply: AGEPS – AP-HP
Pharmacy lead: Annick Tibi
Robin Charreteur, Céline Dupré, Kévin Cardet, Blandine Lehmann, Kamyl Baghli

REACTING Group (Coordination between AP-HP, Insem and Universities)
Chair: Yazdan Yazdanpanah
Claire Madeleine, Eric D'Ortenzio, Oriane Puechal, Caroline Semaille

Local clinical centers CORIMUNO-19 trials staff (listed in order of the number of patients randomized per site in the totality of CORIMUNO-19 trials)

Tocilizumab in adults hospitalized with moderate or severe Covid-19 pneumonia: an open randomized study

CORIMUNO study group on behalf of the AP-HP / Universities / Inserm COVID-19 research collaboration *

Abstract (249 words; maxi: 250)

Background

COVID-19-infected patients can develop severe pneumonia associated with a cytokine storm including an elevation of interleukin 6 (IL-6).

Methods

We have initiated a cohort of multiple randomized controlled trials open-label of immune modulatory drugs in COVID-19 patients with moderate, severe or critical pneumonia (CORIMUNO-19). In the present trial, patients with moderate or severe pneumonia requiring oxygen (>3 L/mn, WHO class 5) but no ventilation were randomly assigned to receive standard of care (SOC) or SOC + tocilizumab (TCZ) 8mg/kg IV at day 1 possibly repeated at day 3. Primary outcomes were the time from randomization

to non-invasive or mechanical ventilation support or death measured at day 4 and day 14, and were analyzed using Bayesian methods on an intent-to-treat basis.

Results

131 patients were randomized to receive SOC (n=67) or SOC + TCZ (n=64). The posterior probability of a reduction of non-invasive or mechanical ventilation or death at day 14 with TCZ was 95.0%, thus achieving predefined efficacy threshold (posterior median hazard ratio (HR) [90% credible interval], 0.58 [0.33-1.00]). Reduction of mechanical ventilation or death was of the same magnitude: HR [90% CrI], 0.58 [0.30-1.09]. With a median of follow-up of 28 days, seven deaths (11.1%) were observed in the TCZ group and 11 (16.4%) in the SOC group. No increase in serious adverse events was observed in the TCZ arm.

Conclusion

In patients with COVID-19 pneumonia receiving oxygen support, TCZ was able to reduce the need for non-invasive or mechanical ventilation. (Funded by PHRC, ClinicalTrials.gov number, NCT04331808).

Table 1. Demographic, clinical, biological characteristics at baseline. Values are median [interquartile range] unless stated otherwise.

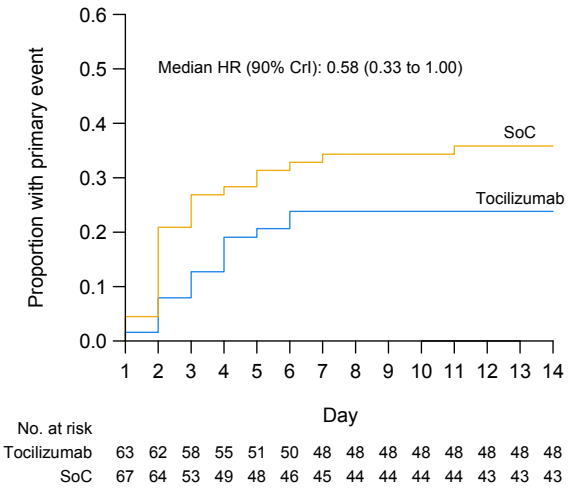
	Tocilizumab (N=63)	**SoC (N=67)**
Age (years)	64.0 [57.1-74.3]	63.3 [57.1-72.3]
Male, n/N (%)	44/63 (70%)	44/67 (66%)
Weight (kg)	80.0 [70.0-90.0]	78.0 [70.0-90.0] (n=55)
WHO score (0-10) = 5, n/N (%)	63/63 (100%)	67/67 (100%)
Temperature (°C)	37.3 [36.8-38.2]	37.9 [37.0-38.6]
Respiratory rate (breaths / min)	24.0 [22.0-30.0] (n=56)	26.0 [24.0-30.0] (n=57)
Flow (L/min)	5.0 [3.0-8.0]	5.0 [3.0-6.0]
SpO2 (%)	95.0 [93.0-96.0]	95.0 [93.0-97.0]
Time from symptoms onset to randomization (days)	10.0 [7.0-13.0] (n=62)	10.0 [8.0-13.0] (n=66)
Co-existing conditions, n/N (%)		
Chronic cardiac disease	20/61 (33%)	20/67 (30.0%)
Diabetes	20/61 (33%)	23/67 (34%)
Chronic kidney disease (stage 1 to 3)	5/61 (8%)	12/67 (18%)

	Tocilizumab (N=63)	SoC (N=67)
Asthma	5/61 (8%)	3/67 (5%)
Chronic pulmonary disease (not asthma)	3/61 (5%)	3/67 (5%)
Active malignant neoplasm	4/61 (7%)	5/67 (8%)
Smoking		
- **No**	55/61 (90%)	62/67 (93%)
- **Current**	1/61 (2%)	2/67 (3%)
- **Former**	5/61 (8%)	3/67 (4%)
Laboratory values		
C-reactive protein (CRP) (mg/L)	119.5 [74.5-219.5] (n=56)	127.0 [84.0-171.0] (n=63)
D-Dimer (µg/L)	869 [524-1380] (n=50)	1250 [780-1812] (n=50)
Neutrophil count (G/L)	4.9 [3.9-7.5] (n=60)	5.1 [3.4-6.6] (n=63)
Lymphocyte count (G/L),	1.0 [0.7-1.4] (n=60)	1.1 [0.6-1.2] (n=60)
Lymphocytes to neutrophils ratio	0.2 [0.1-0.3] (n=48)	0.2 [0.1-0.3] (n=40)
Hemoglobin (g/dL)	12.8 [11.9-13.8] (n=62)	12.3 [10.9-13.4] (n=65)
Platelet count (g/L)	230 [187-324] (n=62)	226 [163-286] (n=65)
ALT / SGPT (IU/L)	40.0 [30.0-67.0] (n=57)	35.0 [22.0-55.0] (n=62)
AST / SGOT (IU/L)	50.0 [34.0-66.0] (n=58)	55.0 [36.0-74.0] (n=62)
Albumin (g/L)	30.0 [27.0-36.0] (n=43)	32.2 [28.0-36.0] (n=42)
Creatinine (µmol/L)	71.0 [56.0-87.0] (n=61)	75.0 [59.5-119.5] (n=64)
Ferritin (mg/L)	1292 [424-2484] (n=43)	1070 [563-1790] (n=46)
LDH (IU/L)	401 [313-582] (n=46)	434 [351-558] (n=51)
CPK (IU/L)	136.0 [48.0-284.0] (n=42)	105.0 [67.0-236.0] (n=41)

ALD denotes alanine aminotransferase, AST aspartate aminotransferase, LDH Lactate dehydrogenase, CPK *creatine phosphokinase.*

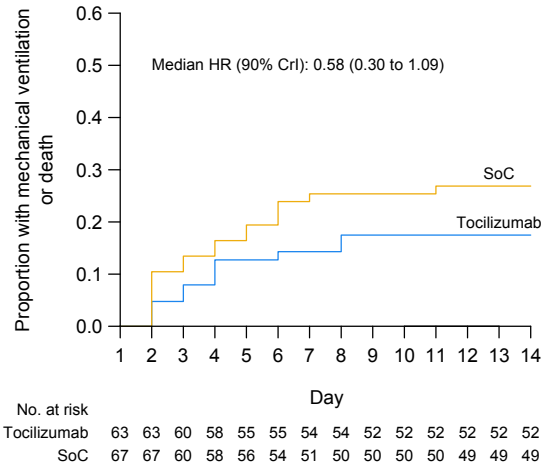
Figure 1

A



Parameter	Value
Median HR	0.58
90% CrI	0.33 to 1.00
95% CrI	0.30 to 1.11
P(HR < 1)	0.950
P(HR < 0.95)	0.931
P(HR < 0.85)	0.874
P(HR < 0.8)	0.831

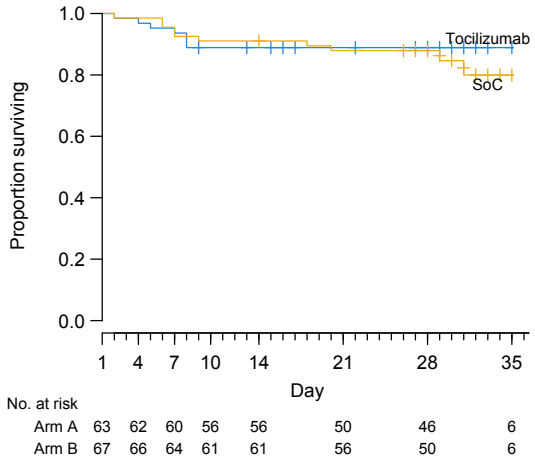
B



Parameter	Value

Median HR	0.60
90% CrI	0.35 to 1.03
95% CrI	0.31 to 1.14
P(HR < 1)	0.942
P(HR < 0.95)	0.920
P(HR < 0.85)	0.850
P(HR < 0.8)	0.803

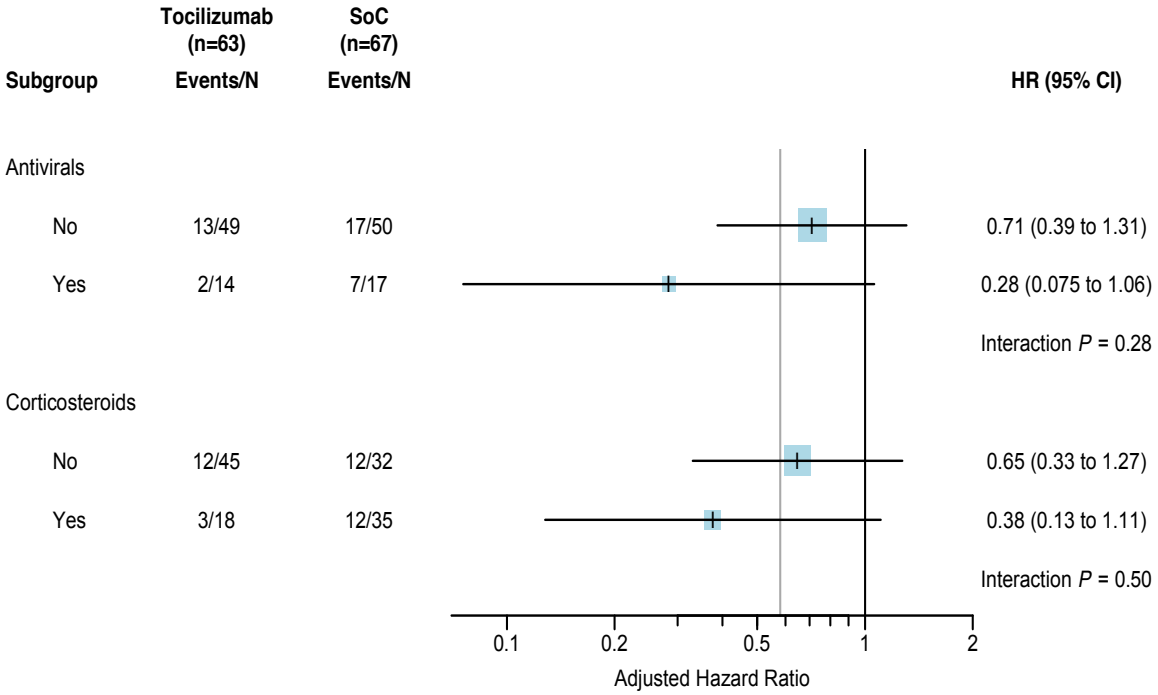
C



Parameter	Value
Median HR	0.58
90% CrI	0.30 to 1.09
95% CrI	0.26 to 1.23
P(HR < 1)	0.925
P(HR < 0.95)	0.903
P(HR < 0.85)	0.844
P(HR < 0.8)	0.804

Figure 1 Proportion of patients with occurrence of the primary event.

Kaplan Meier cumulative estimates of probability of **(A)** death or ventilation support (mechanical ventilation, Optiflow™ or non-invasive ventilation), **(B)** death or mechanical ventilation, **(C)** death in Tocilizumab (TCZ) group compared with the standard of care group (SOC). Events occurring on day 1 occurred on the same day as, but after, randomization. HR=Hazard ratio.



- 10 patients with TCZ + DXM → 0 event
- 17 patients with SOC + DXM → 6 events

COMPARATIVE TABLE OF AMENDMENTS TO THE PROTOCOL CORIMUNO-19 - TOCIDEX

N° SM (Substantial Modification)	SM 16	SM 17	SM 18
Substantial changes	Initial protocol version for Corimuno-19-Tocidex study : V8.0 of 17/07/2020	- List of CORIMUNO-19 facilities updated : addition of 046 - Hôpital Américain de Paris	**Protocol version for Corimuno-19-Tocidex study V10.0 of 10/11/2020 with the modifications below :** - Increase of patients number to be included in the COHORT CORIMUNO-19 - Increase of patients number to be included in the TOCIDEX study (see chapter 10.3) - Further details about SAE that are not to notify immediately (see chapter 7.2.3) - Correction of inclusion criteria : "Requiring **≥** 3L/min of oxygen" instead of "Requiring > 3L/min of oxygen" (see chapter 6.3) - Modification of the definition of the primary endpoint to : "Survival without needs of invasive ventilation at day 14. Thus, events considered are mechanical (invasive) ventilation or death. A new DNR order will be considered as an event at the actual date of care limitation." - List of CORIMUNO-19 centers updated : addition of 048 - Nantes