# Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1) : a randomised controlled trial

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THE LANCET
Respiratory Medicine

## Supplementary appendix 2

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: The CORIMUNO-19 Collaborative group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. *Lancet Respir Med* 2021; published online Jan 22. http://dx.doi.org/10.1016/S2213-2600(20)30556-7.

# Supplementary Appendix

# Effect of Anakinra vs Usual Care in Adults Hospitalized With COVID-19 and Mild-to-Moderate Pneumonia: A Randomized Clinical Trial

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*All these people are registered as collaborators

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DSMB1 resigned because of differences between the investigators and sponsors and the DSMB with regard to the management of the protocol and the communication of the results. No issues of subject safety or data integrity were raised.
AP-HP, as sponsor of the study, and investigators accepted the resignation of the initial DSMB1 on April 30, 2020 and appointed a new DMC on May 1, 2020, which was approved by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) on May 3, 2020.

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We thank for their support people having participated to the study by different aspects

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## Supplementary Methods

### Trial oversight

The trial was approved nationally by the ethics committee on March 23, 2020 (file #20.03.20.56342, CPP Île De France VI, amendment 26-20 on April 1, 2020, EudraCT: 2020-001246-18), by the French Medical Products Agency and by the Commission Nationale Informatique et Liberté. Written informed consent was obtained from all patients or from the patient's legal representative if the patient was too unwell to provide consent for entering the CORIMUNO Cohort. In this consent, patients were made aware that a number of trials may occur via the cohort, and that they will likely be offered to participate in some of them. A specific additional written consent was obtained from eligible patients who were randomly selected to be offered ANA and accept the offer to participate. The cohort and trial were conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. An executive coordination committee, was responsible for the design, conduct, and reporting of the trial. An independent data and safety monitoring board oversaw all CORIMUNO trials once a week.

### Data sources

All information required by the protocol had to be entered in the electronic case report forms used for the whole CORIMUNO-19 cohort. Research nurses, clinical research assistants and investigators used the patient's hospital records and all relevant hospital information systems (Laboratory, Radiology, Pharmacy Information System and Patients) to capture data from day 0 to day 14. A core set of clinical measures was recorded daily the first 2 weeks and then every week. The core measures included key clinical events such as changes in oxygen-support requirements (ambient air, low-flow oxygen, nasal high-flow oxygen, non-invasive positive pressure ventilation [NIPPV], invasive mechanical ventilation, and extracorporeal membrane oxygenation [ECMO], organ failures). These measures allowed classifying the patient's state according to the WHO 10 points-Clinical Progression Scale. Reported adverse events, including those leading to discontinuation of treatment, serious adverse events, time to hospital discharge and death were also recorded. In addition, biological measures routinely prescribed for care were collected. Clinical end-points for discharged patients were obtained by contacting the patients or first-degree relatives by telephone at day 14 and day 28.

### Patients

Patients entering the CORIMUNO-19 cohort were hospitalized male and female patients 18 years of age or older with a SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen < 72 hours and/or CT Scan prior to inclusion with typical radiological findings (ground glass abnormalities, and absence of lymphadenopathy, pleural effusion, pulmonary nodules, lung cavitation) and illness of any duration and severity with symptoms (fever, cough, respiratory difficulties, shortness of breath), and at least one of the following: i) Radiographic infiltrates by imaging (CT scan), ii) Clinical assessment (evidence of rales/crackles on exam or respiratory rate > 25/min) AND SpO2 ≤ 94% on room air, iii) SpO2 ≤ 97 % with O2 > 5L/min or Respiratory rate ≥ 30/min, iv) Requiring mechanical ventilation. Patients with comorbidities 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 were not excluded.
Eligible patients for CORIMUNO-ANA-1 were patients with serum CRP serum level > 25 mg/L not requiring ICU at admission with moderate and severe pneumonia according to the WHO Criteria of severity of COVID pneumonia, i.e. requiring oxygen by mask or nasal prongs : i) Moderate cases showing fever and respiratory symptoms with radiological findings of pneumonia and Requiring between 3L/min and 5L/min of oxygen to maintain an Oxygen saturation (SaO2) of 97% or more , ii) Severe cases meeting any of the following criteria: Respiratory distress (30 breaths/ min or more); Oxygen saturation of 93% or less at rest in ambient air or Oxygen saturation of 97 % or less with O2 > 5L/min; a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) (Pao2:Fio2) at or below 300 mmHg. Exclusion criteria included known hypersensitivity to Anakinra or any of its excipients, pregnancy, current documented bacterial infection, patients with any of following laboratory results out of the ranges detailed below at screening: absolute neutrophil count (ANC) ≤ $1{\cdot}0 \times 10^9$/L or less, platelets (PLT) < 50 G/L, serum glutamic-oxaloacetic transaminase (SGOT) or serum glutamic-pyruvic transaminase (SGPT) > 5N, or severe renal insufficiency as represented by an estimated glomerular filtration rate(eGFR) < 30 mL/min.

### Ten-points WHO ordinal clinical progression scale

WHO ordinal clinical progression scale (WHO-CPS) consisted of the following categories: 0, Uninfected; 1, Asymptomatic; viral RNA detected ; 2, Symptomatic; Independent ; 3, not hospitalized with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 3, Symptomatic; Assistance needed; 4, hospitalized, not requiring oxygen; 5, hospitalized, requiring oxygen by mask or nasal prongs; 6, hospitalized,

requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 7, hospitalized, requiring Intubation and Mechanical ventilation, pO2/FIO2 u150 OR SpO2/FIO2 ≥ 200; 8, hospitalized, requiring Mechanical ventilation, (pO2/FIO2<150 OR SpO2/FIO2 < 200) OR vasopressors (norepinephrine less than 0.3 microg/kg/min); 9, Mechanical ventilation, pO2/FIO2 < 150 AND vasopressors (norepinephrine more than 0.3 microg/kg/min), OR Dialysis OR ECMO hospitalized, requiring; 10, Dead.

**Data quality monitoring**

Data quality monitoring was performed in accordance with the study monitoring plan as for any studies sponsored by Assistance Publique - Hôpitaux de Paris (APHP). This monitoring was performed under the supervision of one clinical research unit officially representing the APHP sponsor (Clinical Trial Unit, CTU, Unité de Recherche Clinique Saint-Louis). This monitoring plan was elaborated in collaboration with the statistical team and the data managers of the CTU according to the protocol and the expected risks for patients. Data quality monitoring included both remote data monitoring (during the containment period in France) and on-site monitoring. During the main phase of the pandemic in Paris, study monitors were not allowed to go on-site and reviewed remotely the status of electronic case report form pages via web-access, to ensure that consents were valid, forms were being completed per instructions and queries were being resolved correctly. Predefined set of consistency checks predefined were ran by the data manager of the clinical research unit and by the statistical team in an attempt to further validate the data and raised queries that were issued directly on the study database. The on-site monitoring was performed secondarily by trained dedicated staff independent of the site investigators from all APHP clinical research units. Remote monitoring was performed. On-site monitoring included 100% source data verification performed for all patients recruited at every site for all critical data points as specified below.
All “consent” & “consent withdrawn” documents were verified to ensure these were completed in accordance with the ethics committee approved requirements and, if consent was withdrawn, this was documented appropriately. All “Do-not resuscitate orders” were also verified and documented. They verified that all inclusion criteria were fulfilled and no exclusions were present at the time of randomization. They verified also that the primary outcomes were correctly measured. They checked especially the OMS scores at all days between day one and day 14 and at Day 28, the type and start and stop dates of ventilation (high flow, non-invasive ventilation, mechanical ventilation), the dates and causes of deaths, the dates of discharges. Source data verification was also performed on the relevant case report form sections for any trial participants where Serious Adverse Events were reported. In addition, the following case report form sections were also verified for 100% of patients at each site: 1. Baseline form: comorbidities, baseline physiology, other treatments received at baseline, SpO2, PaO2, and FiO2. 2. Daily data form: all oxygen-related variables. 3. Discharge and death form: ICU and hospital discharge date and time. 4. Adverse event form: all questions on the form. 5. Protocol violations for anakinra therapeutic scheme. 6. Concomitant treatments received.

**Statistical Methods**

The trial was planned to provide rapid information of the clinical efficacy of TCZ in the setting of the COVID-19 public health emergency, with very limited prior information on clinical outcomes in the trial population. To maximize information from limited data generated, while allowing rapid decision, a Bayesian monitoring of the trial based on the co-primary outcomes was used. The original sample size was set at 120, with an interim analysis when 60 had reached day 4, and a provision to increase the sample size to 180 in case of promising, though not formally conclusive, results at the final analysis. Interim analyses were then presented weekly to the Data Safety Monitoring Board of the CORIMUNO-19 cohort. Non-binding stopping rules for efficacy and futility were indicated in the protocol. The treatment effect was expressed in terms of absolute risk difference (ARD) for the day 4 outcome and hazard ratio (HR) for the day 14 outcome. Posterior probabilities of ARD < 0 and HR < 1 were computed, representing the posterior probability of efficacy. If these probabilities were > 0·99 at the interim analysis and > 0·95 at the final analysis, the treatment could be considered as showing efficacy. We also computed the posterior probabilities of ARD <-5·5% and HR < 0·85, both denoting a similar reasonable effect under the assumption of a 50% event rate at time of analysis. If these posterior probabilities were lower than 0·20, the trial might be stopped for futility. With one interim analysis, analytical evaluation for binary outcomes and numerical evaluation for censored outcomes showed that this design controlled for a frequentist one sided 5% type I error rate.
Primary efficacy analysis was performed on an intention-to-treat basis and included all the patients who had undergone randomization, analysed in the arm they were allocated to. One patient was excluded after consent withdrawal and explicit request that the data would not be used for analysis. According to European Data protection regulation, it is not possible to keep such data, and they were erased accordingly.
For the day 4 outcome, missing data were considered as failure for the primary analysis (no missingness occurred). The posterior distributions of the difference in outcome rate was computed analytically, and the posterior distribution of the odds ratio adjusted for age and centre (as a random effect) was obtained using Monte Carlo Markov chains (MCMC).

For the day 14 primary outcome, patients discharged alive before day 14 without information on respiratory status at day 14 were considered as being alive without need for ventilation at day 14 (or maximum theoretical follow-up if shorter than 14 days).
The protocol specified that new Do-Not-Resuscitate (DNR) orders were to be considered as events. The precise definition of a "new DNR order" was a DNR order posterior to the date of randomization and that had been noted as having been effectively used to limit care in the patient medical records.
Survival without ventilation was portrayed by Kaplan–Meier plots. The posterior distribution of the hazard ratio was calculated by a Bayesian Cox proportional-hazards model estimated using Monte Carlo Markov Chains, adjusted for age at inclusion and centre (as a random effect).
Posterior distributions were summarized by the median value and 90% and 95% credible intervals. The 90% level matches the 0·95 posterior probability threshold for efficacy, and the 95% level is more usual. For each Bayesian analysis, four different chains with different starting values were used, with a burn-in of 10,000 iterations, and 100,000 additional iterations with a thinning interval of 10, leading to keeping 10,000 values per chain, 40,000 in total. The convergence of the MCMC samples was assessed using the Gelman-Rubin statistic and by visual inspection of the trace of coefficients. For the primary analyses, a non-informative flat prior distribution for the log HR was used, as a Gaussian distribution with mean 0 and variance $10^6$. More details on the Bayesian analyses are presented in the Statistical Analysis Plan, including the use of different prior distributions for the analysis of survival without need for ventilation.
An analysis only accounting for mechanical ventilation (and not non-invasive ventilation or high flow) was added as a sensitivity analysis. Preplanned subgroup analyses according to antivirals at baseline and post-hoc subgroup analyses according to corticosteroid therapies at baseline were performed using a frequentist approach.
Survival up to day 14 and day 28 was analysed using a Cox proportional hazards model adjusted for age and centre (as a random effect). Time to discharge and time to oxygen supply independency were analysed in a competing risks framework using Fine-Gray models adjusted for age and centre (as a random effect), death being the competing event. The WHO ordinal scale was analysed using a Bayesian proportional odds models comparing the distribution of ordinal scores at day 4, 7 and 14, adjusted for age and centre, and a longitudinal version of the model with a time effect and a random subject effect to analyse all scores up to day 14.
Because the statistical analysis plan did not include a provision for correcting for multiplicity in tests for secondary outcomes, results are reported as point estimates and 95% confidence intervals. These intervals should not be used to infer definitive treatment effects for secondary outcomes. Statistical analyses were conducted with SAS software, version 9.4 (SAS Institute), R version 3.6.1 and JAGS version 4.3.0.

## Supplementary Results

**Table S1. Treatments received before and after randomisation, until day 14.**
Values are n (%).

| | Anakinra (n=59) | | | Usual care (n=55) | | |
|---|---|---|---|---|---|---|
| | **Before randomisation** | **After randomisation** | **Any time** | **Before randomisation** | **After randomisation** | **Any time** |
| Anticoagulants | 33 (59%) | 37 (63%) | 53 (90%) | 29 (53%) | 33 (60%) | 49 (89%) |
| Azithromycine | 11 (19%) | 13 (22%) | 21 (36%) | 14 (25%) | 15 (27%) | 26 (47%) |
| Hydroxychloroquine | 2 (3%) | 1 (2%) | 3 (5%) | 4 (7%) | 5 (9%) | 9 (16%) |
| Antibiotics | 37 (63%) | 34 (58%) | 52 (88%) | 34 (62%) | 28 (51%) | 48 (87%) |
| Antiviral drugs | 1 (2%) | 1 (2%) | 2 (3%) | 2 (4%) | 3 (5%) | 4 (7%) |
| Lopinavir-ritonavir or lopinavir | 1 (2%) | 1 (2%) | 2 (3%) | 2(4%) | 3 (5%) | 4 (7%) |
| Immuno-modulators | 0 (0%) | 1* (2%) | 1* (2%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Corticosteroids | 7 (12%) | 27 (46%) | 30 (51%) | 8 (15%) | 26 (47%) | 29 (53%) |
| Dexamethasone | 1 (2%) | 6 (10%) | 6 (10%) | 0 (0%) | 4 (7%) | 4 (7%) |
| Prednisone/prednisolone | 3 (5%) | 10 (17%) | 11 (19%) | 5 (9%) | 10 (18%) | 13 (24%) |
| Methylprednisolone | 2 (3%) | 12 (20%) | 14 (24%) | 2 (4%) | 9 (16%) | 10 (18%) |
| Hydrocortisone** | 1 (2%) | 4 (7%) | 5 (8%) | 1 (2%) | 6 (11%) | 6 (11%) |
| Other | 0 (0%) | 4 (7%) | 4 (7%) | 0 (0%) | 1 (2%) | 1 (2%) |

* Tocilizumab (n=1)
** or hydrocortisone hemisuccinate

**Table S2. Detailed analysis of the day 4 co-primary outcome.**
In the protocol, the D4 primary outcome is defined as a WHO-CPS score ≤ 5 at day 4, and patients with a new DNR at, or before, day 4 where considered as with a WHO-CPS score > 5. Results are presented as proportions with a WHO-CPS score > 5, so that an effective treatment would result in a risk reduction. Odds ratios are adjusted on age and centre.

| | **Anakinra (n=59)** | **Usual care (n=55)** | **Risk difference** | **Adjusted odds ratio** |
|---|---|---|---|---|
| N (%) WHO > 5 | 21 (36%) | 21 (38%) | | |
| Posterior Median | 35·9% | 38·5 | –2·5% | 0·90 |
| 90% CrI | | | –17·1 to +12·0 | 0·47 to 1·73 |
| 95% CrI | 24·6 to 48·4 | 26·5 to 51·5 | –19·8 to +14·8 | 0·41 to 1·96 |
| Posterior probabilities | | | | |
| *P*(any benefit)* | | | 0·612 | 0·604 |
| *P*(moderate or greater benefit)** | | | 0·369 | 0·442 |

CrI: Credible interval
* *P*(any benefit): *P*(RD < 0) or *P*(OR < 1)
** *P*(moderate or greater benefit): *P*(RD < 5·5%) or *P*(OR < 0·85)

**Table S3. Details of events for the day 14 co-primary outcome.**

| | **Anakinra (n=59)** | **Usual care (n=55)** |
|---|---|---|
| Number of events | 28 | 28 |
| Events | | |
| Non-invasive ventilation/high flow | 19 | 17 |
| *Then invasive ventilation (then death)* | *5 (3)* | *5 (2)* |
| *Then death* | *7* | *3* |
| Invasive ventilation (then death) | 5 (1) | 3 (1) |
| Death | 2 | 6 |
| Do-not-resuscitate order (then death) | 2 (2) | 2 (2) |
| Cumulative incidence at day 14 (95% CI) | 47% (33 to 59) | 51% (36 to 62) |
| Difference (95% CI) | –3% (–22 to +15) | |

CI: confidence interval

**Table S4. Sensitivity analysis for the day 14 co-primary outcome.**
Summary of the posterior distribution, frequentist analysis and definition of the outcome as need for mechanical ventilation or death. Hazard ratios (HRs) are adjusted on age and centre. A HR < 1 is in favour of anakinra.

| Parameter | Bayesian adjusted analysis (primary analysis) | Bayesian unadjusted analysis | Frequentist analysis | Bayesian adjusted analysis of time to mechanical ventilation or death |
|---|---|---|---|---|
| Median posterior HR | 0·97 | 0·94 | 0·96 | 0·94 |
| 90% CrI | 0·62 to 1·52 | 0·60 to 1·47 | 0·62 to 1·50 | 0·55 to 1·64 |
| 95% CrI | 0·57 to 1·66 | 0·55 to 1·60 | 0·57 to 1·63 | 0·49 to 1·92 |
| Posterior probabilities | | | | |
| *P*(HR < 1) | 0·545 | 0·594 | | 0·567 |
| *P*(HR < 0·95) | 0·471 | 0·520 | | 0·508 |
| *P*(HR < 0·85) | 0·317 | 0·356 | | 0·375 |
| *P*(HR < 0·8) | 0·241 | 0·276 | | 0·309 |
| *P*-value | | | 0·44 | |

HR: hazard ratio; CrI: credible interval
* For the frequentist analysis, the point estimate of the hazard ratio is given, with 90% and 95% confidence intervals instead of credible intervals. Posterior probabilities are not relevant, but a one-sided *p*-value is given instead.

**Table S5. Numbers of patients in each WHO scale until day 14.**

| | Day 1 | | Day 4* | | Day 7 | | Day 14 | |
|---|---|---|---|---|---|---|---|---|
| | Anakinra | Usual care | Anakinra | Usual care | Anakinra | Usual care | Anakinra | Usual care |
| No. randomised | 59 | 55 | 59 | 55 | 59 | 55 | 59 | 55 |
| No. scores | 59 | 55 | 59 | 55 | 54 | 53 | 56 | 53 |
| No. missing | 0 | 0 | 0 | 0 | 5 | 2 | 3 | 2 |
| WHO-CPS score | | | | | | | | |
| 0 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 9 (16%) | 1 (2%) |
| 1 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 3 (5%) | 4 (8%) |
| 2 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 6 (11%) | 9 (17%) |
| 3 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (4%) | 3 (6%) |
| 4 | 0 (0%) | 0 (0%) | 3 (5%) | 0 (0%) | 8 (15%) | 5 (9%) | 4 (7%) | 4 (8%) |
| 5 | 59 (100%) | 55 (100%) | 36 (61%) | 35 (64%) | 23 (43%) | 26 (49%) | 12 (21%) | 13 (25%) |
| 6 | 0 (0%) | 0 (0%) | 13 (22%) | 13 (24%) | 8 (15%) | 7 (13%) | 3 (5%) | 1 (2%) |
| 7 | 0 (0%) | 0 (0%) | 1 (2%) | 3 (5%) | 3 (6%) | 2 (4%) | 2 (4%) | 2 (4%) |
| 8 | 0 (0%) | 0 (0%) | 5 (8%) | 1 (2%) | 6 (11%) | 2 (4%) | 6 (11%) | 3 (6%) |
| 9 | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 2 (4%) | 0 (0%) | 0 (0%) |
| 10 | 0 (0%) | 0 (0%) | 1 (2%) | 2 (4%) | 5 (9%) | 9 (17%) | 9 (16%) | 13 (25%) |

* Differences with day 4 primary outcome are due to DNR orders that are considered as a CPS score > 5 for the binary outcome, while observed scores on day 4 are presented here.

**Table S6. Overall survival at pre-specified timepoints.**
Hazard ratios (HRs) are adjusted on age and centre.

| | Anakinra (n=59) | | Usual care (n=55) | | |
|---|---|---|---|---|---|
| Timepoint | N deaths | OS (95% CI) | N deaths | OS (95% CI) | Adjusted HR (95% CI) |
| Day 14 | 9 | 85% (76 to 94) | 13 | 76% (66 to 88) | 0·56 (0·23 to 1·39) |
| Day 28 | 13 | 78% (68 to 89) | 13 | 76% (66 to 88) | 0·77 (0·33 to 1·77) |
| Day 90 | 16 | 72% (61 to 84) | 15* | 72% (62 to 85) | 0·97 (0·46 to 2·04) |

OS: overall survival; HR: hazard ratio; CI: confidence interval
* One patient died on day 91, and is not counted among the 15.

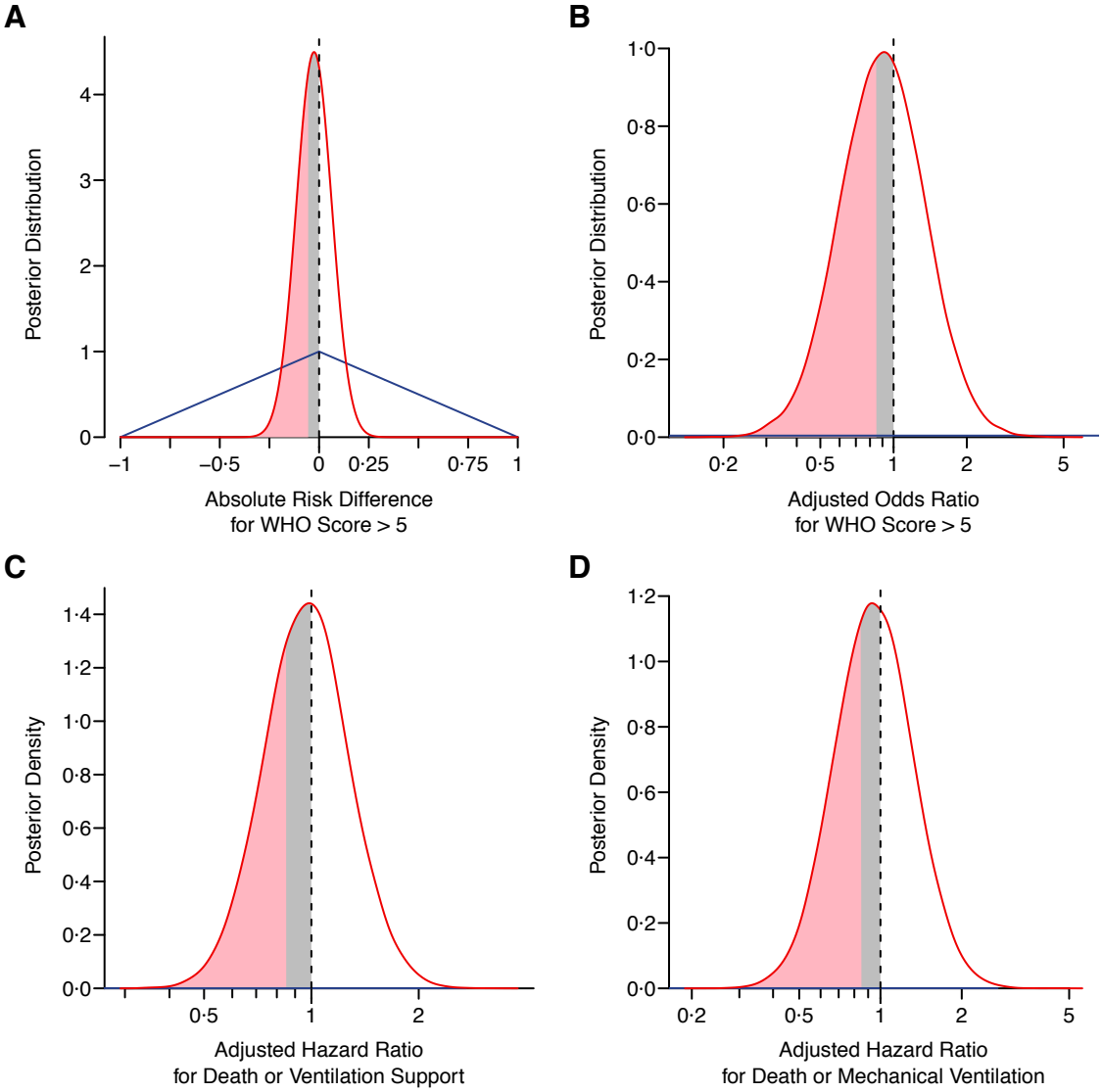


**Figure S1. Posterior distributions.**

The plots give the posterior (red line) and minimally informative prior (blue line) distribution of parameters in Bayesian analyses for the absolute risk difference of WHO > 5 at D4 (panel A), the adjusted odds ratio of WHO > 5 (panel B), the adjusted hazard ratio for death or ventilation support (mechanical ventilation, high-flow or non-invasive ventilation) (panel C), and the adjusted hazard ratio for death or mechanical ventilation (panel D). The black dashed lines indicate no treatment effect. The red shaded regions show the posterior probabilities of ARD < -5·5%, OR < 0·85 or HR < 0·85 (moderate or greater effect) and the grey shaded plus the red shaded regions the posterior probabilities of ARD < 0, OR < 1 or HR < 1 (any effect).

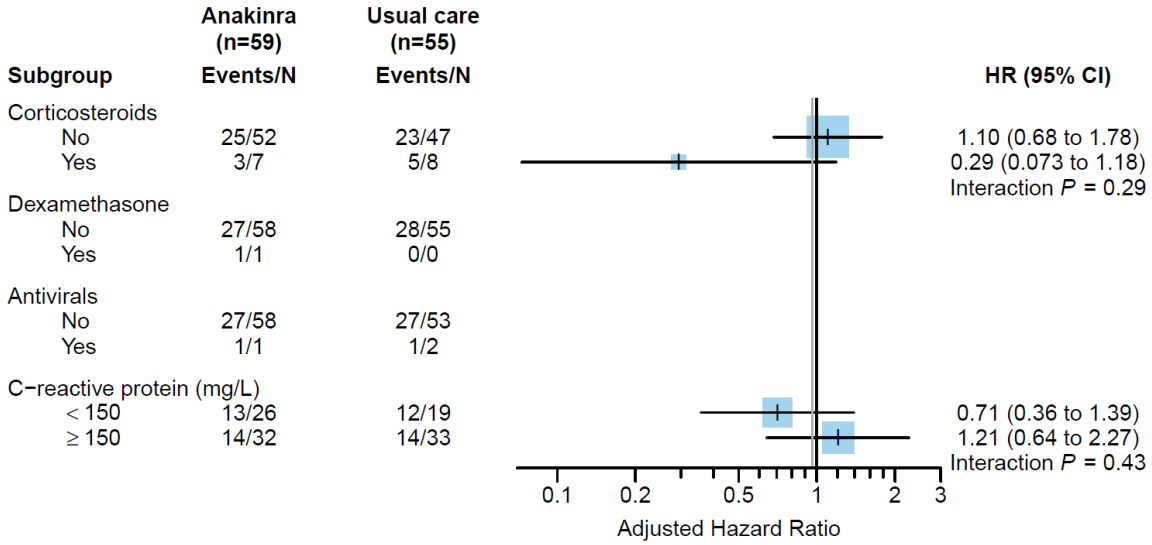


**Figure S2. Subgroup analyses for the day 14 co-primary outcome.**

Results presented are adjusted hazard ratios for death or ventilation support (mechanical ventilation, high-flow or non-invasive ventilation). Dexamethasone and antivirals were given at baseline to too few patients for subgroup analyses to be performed.

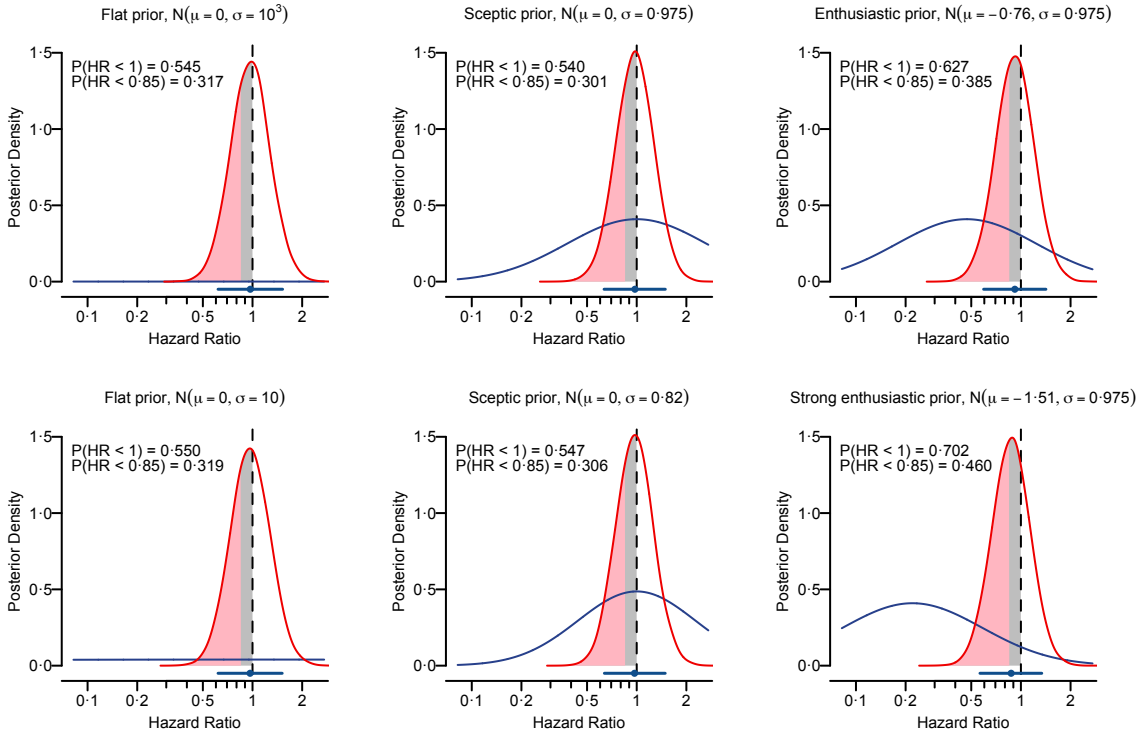


**Figure S3. Sensitivity analysis to the choice of priors in the Bayesian analysis of the day 14 co-primary outcome.**

Posterior density of the adjusted hazard ratio for the primary outcome (red line) according to different priors represented in dark blue. The dashed line indicates a HR of 1 representing no treatment effect. Posterior probabilities of HR < 0·85 (red shaded region) and of HR < 1 (grey shaded plus red shaded regions) are also presented. The priors are given for the log hazard ratio. The blue point and line present the posterior median and 90% credible interval of the HR. The flat prior N($\mu = 0$, $\sigma = 10^3$) is the minimally informative prior used in the primary analysis. Sceptic priors are determined so that high effects are unlikely, namely P(HR < 0·2) = P(HR > 5) = 0·05 ($\sigma = 0{\cdot}975$) and (HR < 0·2) = P(HR > 5) = 0·025 ($\sigma = 0{\cdot}82$). Enthusiastic priors are centred on half the log HR (–0·76) or the log HR (–1·51) reported for death or mechanical ventilation in an observational study (Huet et al. *Lancet Rheumatol* 2020;2: e393–400 400, https://doi.org/10.1016/S2665-9913(20)30164-8, which reported a hazard ratio of 0·22 in a similar population), and are informative ($\sigma = 0{\cdot}975$). In all cases, results are largely unaffected by the prior distribution, with median adjusted HR ranging from 0·873 to 0·976 despite very strong enthusiastic priors, and posterior probabilities of any effect P(HR < 1) ranging from 0·540 to 0·702.

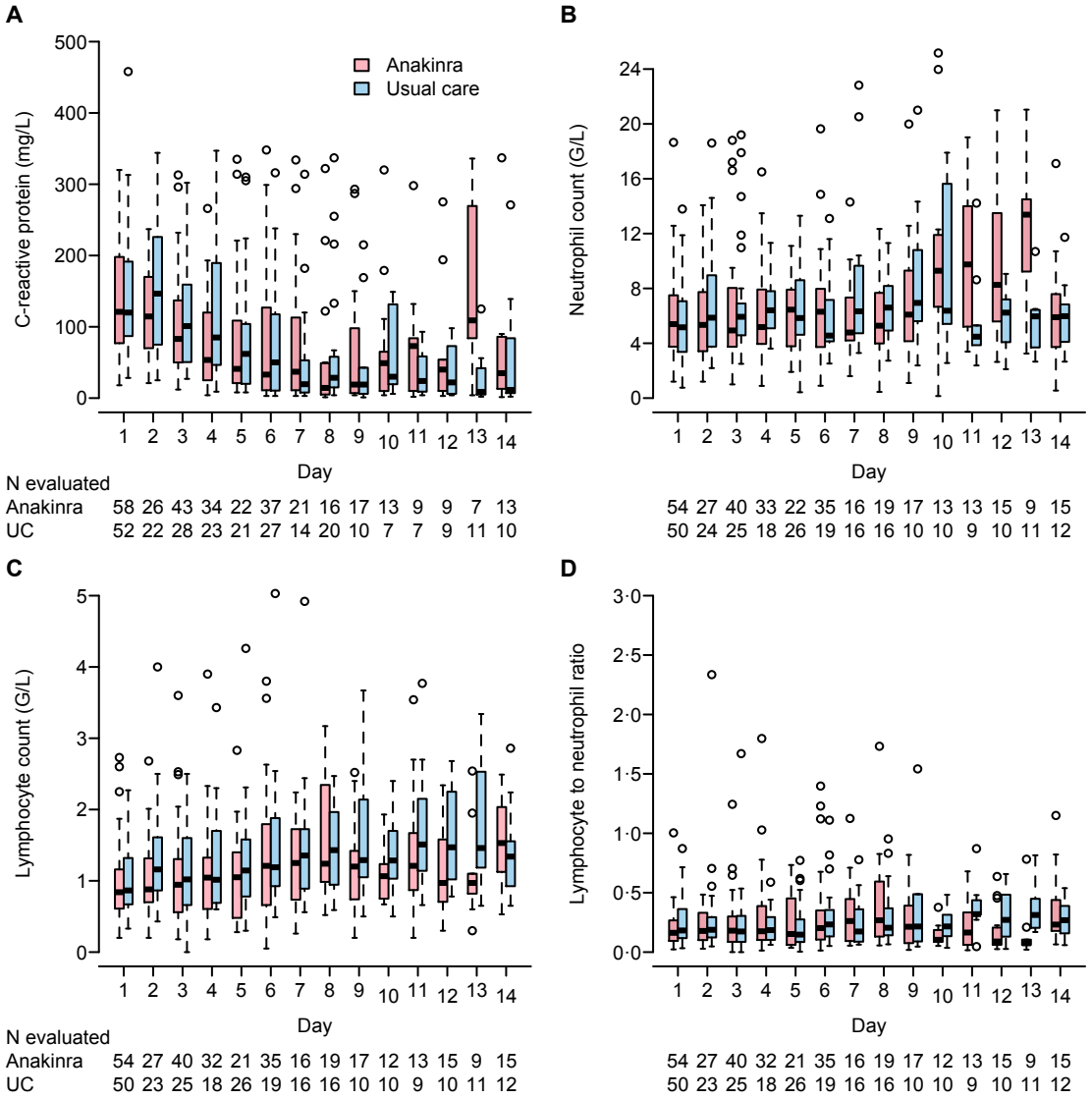


**Figure S4. Evolution of biological parameters.**

The box and whisker plots present the median (thick line) and first and third quartiles (box limits). Outer whiskers extend to the most extreme data point which is no more than 1·5 times the interquartile range from the box. Isolated points denote observations outside this range.

## Statistical Analysis Plan

Statistical Analysis Plan, Version 2.1 (21 September 2020)

# Cohort Multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients
# Efficacy of anakinra for patients with covid-19
# CORIMUNO-19-ANA

## Statistical Analysis Plan

Version 2.1

21 September 2020

Redacted by Raphaël Porcher and Gabriel Baron
Validated by Philippe Ravaud

| | |
|---|---|
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| | |
|---|---|
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# 1 Summary

| | **CORIMUNO-19-ANA** |
|---|---|
| **Rationale for using anakinra in severe patients infected with COVID-19** | **CORIMUNO-19 - ANA**<br>The SRAS-CoV-S protein induces direct up-regulation of IL-6, IL-1 and TNFα, some of the most potent pro-inflammatory cytokines<br>A recent report indicates higher serum IL1 β and IL1R α in both ICU patients and non-ICU patients with pneumonia than in healthy adults at initial assessment (6). Of note, no difference in mean IL-1β levels were found between the ICU patients and non-ICU patients with pneumonia<br>Anakinra (ANA) (Kineret®) is a recombinant human decoy IL-1Ra and therefore blocks IL-1α and IL-1β. |
| **Diagnosis and inclusion and Exclusion criteria for the CORIMUNO-19-ANA trial** | **Inclusion Criteria for the Anakinra trial:**<br>1. Patients included in the CORIMUNO-19 cohort<br>2. Patients with C-reactive protein level (CRP) > 25 mg / L the day or the day before the infusion)<br>3. Patients belonging to one of the 2 following groups:<br>- *Group 1: Cases meeting all of the following criteria*<br>• *Requiring more than 3L/min of oxygen*<br>• *10 pt WHO clinical progression scale = 5*<br>• *No NIV or High flow*<br>- *Group 2: Cases meeting all of the following criteria*<br>• *Respiratory failure AND (requiring mechanical ventilation OR NIV OR High flow)*<br>• *10 pt OMS/WHO progression scale >=6*<br>• *No do-not-resuscitate order (DNR order)*<br>**Exclusion Criteria for the Anakinra trial:**<br>1. Patients with exclusion criteria to the CORIMUNO-19 cohort.<br>2. Known hypersensitivity to Anakinra or to any of their excipients.<br>3. Pregnancy<br>4. Current documented bacterial infection<br>5. Patient with any of following laboratory results out of the ranges detailed below at screening should be discussed depending of the medication:<br>a. Absolute neutrophil count (ANC) ≤ 1.0 x $10^9$/L<br>b. Haemoglobin level: no limitation<br>c. Platelets (PLT) < 50 G /L |

| | |
|---|---|
| | d. SGOT or SGPT > 5N<br>e. Severe renal insufficiency with Glomerular filtration rate < 30 ml / mn |
| **Randomisation and Treatment procedures** | **Two separate trials** are conducted and analyzed independently, one in each group of patients defined above (group 1: patients not requiring ICU, with WHO Clinical Progression Scale [WHO-CPS] 5 at inclusion) and group 2, patients requiring ICU, with a WHO-CPS of 6 or more at inclusion).<br>All consecutive patients meeting the inclusion criteria will be randomised 1:1 either in the intervention arm or control arm in a set of 120 patients in total 60 in each arm). Interim analyses are planned, but inclusions are not frozen to wait for the interim analyses.<br>Inclusions of patients will stop when statistical analyses conclude on futility or efficacy, or by DSMB decision.<br><br>In each trial patients will be randomized between<br>• **Intervention arm**: two IV infusions / day of Anakinra KINERET® 200mg (total 400 mg) at day 1 (D1), D2 and D3. In case of improvement at D4 (clinical improvement and decrease of CRP level > 50%), two IV infusions / day of Anakinra KINERET® 100mg (total 200 mg) at D4, and one IV infusion of Anakinra KINERET® 100mg (total 100 mg) at D5. In case of absence of improvement at D4, treatment will consist in additional two IV infusions / day of Anakinra KINERET® 200mg (total 400 mg) at D4, D5 and D6, followed by two IV infusions / day of Anakinra KINERET® 100mg (total 200 mg) at D7 and one IV infusion of Anakinra KINERET® 100mg (total 100 mg) at D8.<br>• **Control arm**: Best standard of care |
| ***Duration of follow-up*** | 90 days |

**Criteria for efficacy**

**Measures**

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

**Primary and secondary endpoints:**

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

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

***Co Primary Endpoints***

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

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

| | | |
|---|---|---|
| | pO2/FIO2<150 AND vasopressors (norepinephrine >0.3 microg/kg/min), OR Dialysis OR ECMO | |
| Death | Dead | 10 |

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

**For the group 2 of patients *requiring ICU*:**

***Co Primary Endpoints***

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

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

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

**Criteria of safety**

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

| | |
|---|---|
| **Statistical Method** | To maximize information from limited data generated, while allowing rapid decision, a Bayesian monitoring of the trial based on the co-primary outcomes will be used. The overall strategy has been determined so as to control for a frequentist one sided 5% type I error rate. The following methods pertain to the conduct and analysis of **each trial** (patients of group 1 or patients of group 2), that are analysed separately with different primary outcomes.<br><br>**The total sample size in each group (group 1: patients not requiring ICU and group 2: patients requiring ICU) is fixed at 120 (60 per arm) for the final analysis, with interim analysis after 60 (30 per arm)**<br><br>At the interim analysis, two posterior probabilities will be calculated: 1) the posterior probability of a lower event rate in the experimental than in the control arm (posterior probability of efficacy) and 2) the posterior probability of achieving at least a predefined effect corresponding to a hazard ratio of 0.85 (for time-to-event primary outcomes) or a risk difference of 5.5% (for binary co-primary outcomes) (posterior probability of sufficient efficacy). If the posterior probability of sufficient efficacy is less than 0.20, the trial can be stopped for futility. If the posterior probability of efficacy is higher than 0.99, the trial can be stopped for efficacy. Otherwise, the trial will continue with inclusion of additional patients, as predefined, and a final analysis is conducted with decision boundary at a posterior probability of efficacy > 0.95. Decision boundaries are non-binding, and the DSMB can recommend continuing recruitment, in the whole population or a subgroup. Final decision boundaries are then readapted to control for a one-sided type I error rate close to 5%. If the strata (groups I or II) are equally sized, the interim analysis should occur after 60 patients, and the second one with 120. This design (with only two stages) has then type I error rate 0.047 if event rates are 50% in each arm, and power 0.972 to detect a decrease from 0.50 to 0.20 and 0.739 to detect a decrease from 0.50 to 0.30. |

# 2 Analysis population

## 2.1 Flow diagram

At the final analysis of trial, a flow chart will be constructed according to the CONSORT 2010 reporting guidelines. It will describe:

- The number of eligible patients, randomized patients and the number of patients who have actually followed the study;
- The intervention arm allocated per randomization;
- Early cessation of the intervention and their causes and drop-outs;
- The number of patients excluded from the analysis.

The number of randomized but ineligible patients, if any, will also be reported, as well as the reason for ineligibility.

## 2.2 Definition of the analysis population

For interim monitoring, the analysis will be carried out according to the intention to treat (ITT) principle, i.e. each randomised participant will be analysed in the group assigned to him/her by randomisation, regardless of the actual treatment received or other protocol deviations. In particular patients randomised while not meeting eligibility criteria will be kept in the analysis. In the cmRCT design, randomisation occurs prior to offering an intervention, and some number of eligible patients who are randomly selected to be offered an intervention will not accept the offer. An intention to treat analysis could therefore dilute any treatment effects, and Relton et al. suggested using a complier average causal effect (CACE) analysis which provides unbiased estimates of the treatment effect for patients who comply with the protocol.
At the final analysis stage, the ITT will be carried out, comparing all randomised patients in the intervention arm they were allocated to as described above, but a CACE analysis will be added, using an instrumental variable approach which assumes that a patient's decision not to accept the intervention will not affect the outcome (except through the intervention actually received).
No data will be analysed for patients who have withdrawn their consent during the study and have expressed opposition to the analysis of their data. If necessary, the data concerning these patients that have been collected will be destroyed. The existence of these patients will nevertheless be documented in the study flow chart.

## 2.3 Sample size

The total sample size has been fixed for each trial at 60 (30 per arm) for the first formal interim analysis, and 120 (60 per arm) for the final analysis, but with an option to accrue 60 patients more (30 per am) depending of the recommendations of the DSMB (see below).

# 3 Analysis principles

## 3.1 General principles for analysis of outcomes

Data analysis will be blinded to treatment allocation. Accordingly, when analyses are not symmetrical (e.g. probability of a lower event rate with experimental than control), two analyses will be performed, successively considering each arm as the experimental one.
The final results will be reported according to the recommendations of CONSORT 2010.
All outcomes will be analysed in superiority analyses, and the final analyses will be adjusted for centre as a random effect (randomisation stratification). At the final analysis stage, secondary analyses will be carried out adjusting for the centre in random effects models.
One crucial feature of the 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. While using a Bayesian approach, where standard definition of type I and II error rate do not apply, the trial is also planned to control for frequentist (i.e. non-Bayesian) error rates. In particular, the overall strategy will be to control for a frequentist one sided type I error rate close to 5% over one specific trial.
The primary efficacy analyses will therefore rely on computing the posterior distribution of the hazard ratio between the experimental and control arms for time-to-event co-primary outcomes and the posterior distributions of event rates in each arm for binary co-primary outcomes. From the latter, the posterior distribution of the difference in event rate will be derived. These posterior distributions will be graphically displayed, and summarized by their medians and 95% credibility intervals (the Bayesian counterparts of confidence intervals).
For secondary efficacy and safety outcomes, frequentist (i.e. non-Bayesian) analyses will be used. No correction for multiplicity and no hierarchical testing procedures are planned in analysing secondary outcomes. These analyses will therefore be considered as exploratory in nature.

### 3.2 Participants' characteristics at inclusion

The characteristics of patients collected at inclusion will be described globally and by randomization group, using means, standard deviations, medians, interquartile intervals, minimum and maximum for quantitative variables and by their numbers and percentages by modality for qualitative variables.
The number of missing data for each variable will also be reported. No statistical tests for comparison between groups will be carried out.

### 3.3 Handling of missing or incoherent data

Given their nature and the trial settings, it is not be expected that primary outcome data would be missing. However, in the case some outcomes would be missing, binary missing outcomes will be treated as treatment failures in interim and primary final analyses, with an imputation by last value carried forward as a sensitivity analysis. For time-to-event outcomes, they will be naturally handled using methods for censored data. No imputation will be used for secondary efficacy and safety outcomes.

### 3.4 Statistical software

The analyses will be carried out using the R software version 3.6.1 or later (The R Foundation for Statistical Computing, Vienna, Austria), SAS version 9.4 or later (SAS Institute Cary, NC) and JAGS version 4.3.0 or later.

## 4 Co-primary outcome analysis

### 4.1 Definitions

Two co-primary outcomes are used for each group of patients, one short-term outcome evaluated at 4 days, primarily used for trial monitoring, and one longer-term outcome evaluated at 14 days. For numbering the days, the day of inclusion is considered as day 1.

#### *4.1.1 Group 1: patients not requiring ICU*

1) Survival without needs of ventilator utilization (including non invasive ventilation and high flow) at day 14. Thus, events considered are needing ventilator utilization (including Non Invasive Ventilation, NIV or high flow), or death. New DNR order (if given after the inclusion of the patient) will be considered as an event at the date of the DNR.

2) Early endpoint : proportion of patients alive without non-invasive ventilation of high low at day 4 (WHO progression scale ≤ 5). A patient with new DNR order at day 4 will be considered as with a score > 5.

| WHO Clinical Progression Scale (WHO-CPS) | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected; non viral RNA detected | 0 |
| Ambulatory | Asymptomatic; viral RNA detected | 1 |
| Ambulatory | Symptomatic; Independent | 2 |
| Ambulatory | Symptomatic; Assistance needed | 3 |
| Hospitalized : mild disease | Hospitalized; No oxygen therapy | 4 |
| Hospitalized : mild disease | Hospitalized; oxygen by mask or nasal prongs | 5 |
| Hospitalized : severe disease | Hospitalized; oxygen by NIV or High flow | 6 |
| Hospitalized : severe disease | Intubation and Mechanical ventilation, pO2/FIO2>=150 OR SpO2/FIO2>=200 | 7 |
| Hospitalized : severe disease | Mechanical ventilation, (pO2/FIO2<150 OR SpO2/FIO2<200) OR vasopressor (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 |

*4.1.2 Group 2: patients requiring ICU*

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

## 4.2 Trial monitoring

This section describes the Bayesian monitoring of the trial in one of the groups. Calculations have been made for a fixed sample size at the interim and final analysis (30 per arm and 60 per arm, respectively), but in practice, since the trial is conducted simultaneously in both groups, the numbers may differ. For simplicity, we did not plan to modify the decision boundaries according to the observed numbers of patients actually included in each group. Rather, the properties of the design (table 1) will be re-evaluated taking the actual numbers into account.
We defined two co-primary outcomes, one time-to-event outcome evaluated up to day 14, and an early success outcome evaluated on day 4. Methods for trial monitoring have been developed

for the early outcome because (1) short-term outcomes are obtained more quickly so are easier for early interim decision and (2) calculations of all possible outcomes are more tractable for binary outcomes. For analyses based on the hazard ratio, which allow to account for all information gathered in the trial (even for patients who do not have the entire follow-up necessary to evaluate a binary outcome), the same decision boundaries will be used. It is not expected that the properties of the boundaries would be significantly different when using the posterior distribution of the hazard ratio. Simulation studies were then performed to describe the properties of the design (table 2). Also, in all what follows, we assume the "event" corresponding to the outcome being detrimental to patients, so that an effective treatment would lower the event rate, or achieve a hazard ratio $\theta < 1$. When the clinical definition of the outcome is opposite, then analysis will be performed on the inverse (e.g. failure instead or success, or inverse of the hazard ratio $1/\theta$).

### *4.2.1 Interim analyses*

Let us denote $p_E$ and $p_C$ the event rates in the experimental and control arms, respectively. At each analysis, the posterior probability of a lower event rate in the experimental than in the control arm is calculated, i.e. $P(p_E < p_C \mid \text{data})$, which we term the *posterior probability of efficacy*. The posterior probability $P(p_E < p_C - \delta \mid \text{data})$ is also computed, corresponding to the probability to achieve at least a $\delta$ treatment effect, termed the *posterior probability of sufficient efficacy.* To compute the probability of sufficient efficacy, we assumed that the hazard ratio for time-to-event outcomes should be at least 0.85, which translates to an event rate of 45.5% in the experimental arm when it is 50% in the control arm. Accordingly, $\delta$ was set to 0.055 for calculations with binary outcomes. The specification of the prior distribution is crucial. For this first trial conducted in the cmRCT, we want the conclusions to depend primarily on data from the trial, not on prior opinion. An uninformative prior for the hazard ratio will therefore be used. More precisely, the prior distribution of $p_E$ and $p_C$ will be set as a beta prior distribution with parameters 1 and 1, equivalent to a uniform distribution on the interval (0,1). This corresponds to a hypothetical situation where we would have data on two individuals treated with each arm strategy, and observing that exactly 1 of the 2 experiencing the outcome.

For time-to-event outcomes, a Bayesian Cox model will be estimated using Markov chain Monte Carlo (MCMC) methods, using a Gaussian prior distribution with mean 0 and variance $10^6$. The posterior probability of the hazard ratio $\theta$ will be used to define posterior probability of efficacy as $P(\theta < 1)$ and the posterior probability of sufficient efficacy $P(\theta < \eta)$, with $\eta$ fixed at 0.85. The prior distributions used ensure very little influence of our prior opinion on conclusions.

### *4.2.2 Stopping rules*

At each interim analysis, if the posterior probability of sufficient efficacy is less than 0.20, the trial could be stopped for futility upon decision of the DSMB (indicative and not binding futility boundary). If the posterior probability of efficacy is higher than 0.99, then the trial may be stopped for efficacy (again this boundary is not binding and the DSMB may propose to continue the accrual based on other information, such as secondary outcomes or safety). The choice of interim monitoring for futility based on the posterior probability of sufficient efficacy and not the posterior probability of efficacy is justified by the need to increase the chance of early stopping for futility when information increases, if the experimental treatment is no better than the control. Conversely, keeping a constant futility boundary on the posterior probability of efficacy would decrease the chances of early stopping if additional analyses are performed, because under the null, as information increases, the posterior distribution of efficacy would converge to 0.5. This boundary is stricter than using a boundary on the posterior probability of efficacy (grey line on the figure 1, left panel), but this choice is justified by the need to quickly identify treatments with a large effect.

At the interim analyses, the predictive probability of achieving a success after inclusion of a total of 60 patients per arm (posterior probability of efficacy > 0.95) will also be computed for the short-term outcome, and the trial can be stopped for futility if it is less than 10%.
When no stopping for futility or efficacy is decided, additional patients are recruited in each arm. The final analysis will occur after final recruitment, and a posterior probability of efficacy higher than 0.95 will be considered as indicating efficacy.
Another option would be to continue accrual in a subgroup only (adaptive enrichment) according to the posterior probabilities in the different subgroups. If such a modification is implemented, then the SAP will be revised to accommodate such modifications.
The protocol also mentions additional interim analyses by the DSMB, without formal stopping rules. For these analyses, safety data will be presented, as well as posterior probabilities for both short-term and mid-term outcomes.

### *4.2.3 Frequentist properties of the design*

The table 1 presents the properties of the design under different scenarios. The figure 1 displays the decision boundaries for the early outcome in the case 30 patients per arm have been recruited.

**Table 1. Operational characteristics of the design under different scenarios for analysis of the binary outcome.**

| | Failure rate p in each group | | | |
|---|---|---|---|---|
| Scenario | No effect | Very large effect | Large effect | Mild effect |
| Parameterizations | $p_C$=0.5, $p_E$=0.5 | $p_C$=0.5, $p_E$=0.2 | $p_C$=0.5, $p_E$=0.3 | $p_C$=0.5, $p_E$=0.35 |
| Corresponding hazard ratio | 1 | 0.32 | 0.51 | 0.62 |
| Probability of early stopping for futility | 0.349 | 0.0017 | 0.023 | 0.057 |
| Probability of early stopping for efficacy | 0.0087 | 0.558 | 0.228 | 0.121 |
| Probability of efficacy at 2$^{nd}$ stage | 0.038 | 0.413 | 0.510 | 0.393 |
| Overall probability of rejection | 0.047 | 0.972 | 0.739 | 0.514 |

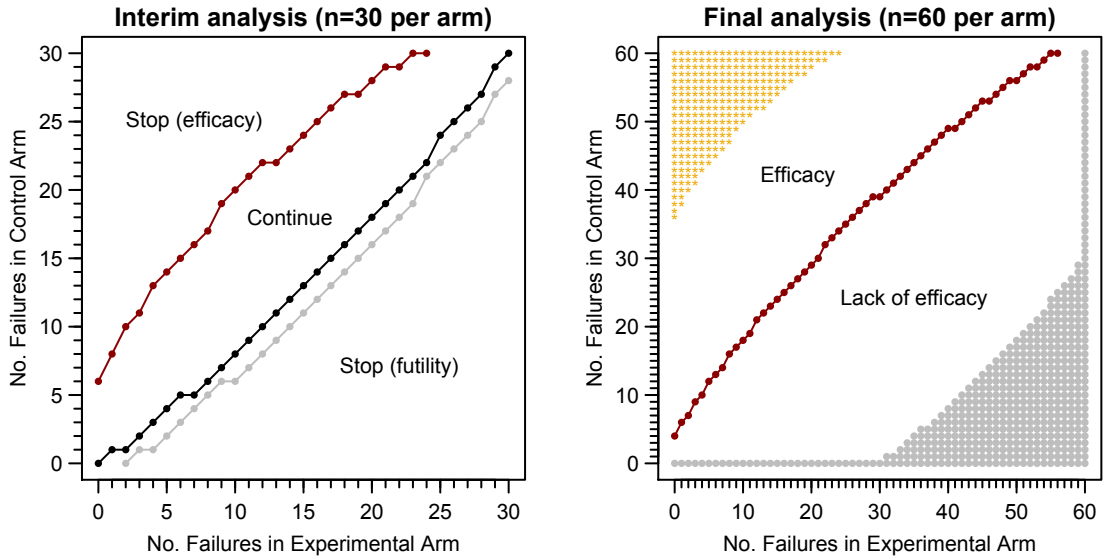


**Figure 1. Decision boundaries for the interim and final analysis.** Red lines indicate efficacy boundaries, and black lines futility boundaries. On the left plot, the interim analysis is performed after inclusion of 30 patients per arm, and the gray line indicate what the boundary would be if the posterior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

**Table 2. Operational characteristics of the design under different scenarios for analysis of the time-to-event outcome.** Results were obtained from 10,000 numerical simulation runs. We used exponential simulations, assuming a median survival with control of 14 days and accrual of 120 patients over 10 days, interim analysis at 10 days, and final analysis after 24 days (when the last patient would have attained 14 days follow-up).

| | Failure rate p in each group | | |
|---|---|---|---|
| Scenario | No effect | Very large effect | Large effect |
| Parameterizations | $p_C$=0.5, $p_E$=0.5 | $p_C$=0.5, $p_E$=0.2 | $p_C$=0.5, $p_E$=0.3 |
| Corresponding hazard ratio | 1 | 0.32 | 0.51 |
| Probability of early stopping for efficacy | 0.011 | 0.478 | 0.204 |
| Probability of efficacy at 2$^{nd}$ stage | 0.043 | 0.507 | 0.623 |
| Overall probability of rejection | 0.054 | 0.985 | 0.827 |

In the case the DSMB would deem results promising but not yet conclusive after inclusion of the final sample size (that we consider for illustration as a posterior probability of sufficient efficacy of 0.40 or more but a posterior probability of efficacy is of 0.97 or less), the protocol envisaged that 30 additional patients per arm could be recruited. The final decision boundary could be adapted to a posterior probability of efficacy > 0.963 to control the type I error rate. The table 3 summarizes the properties of such extension under the four previous scenarios, and illustrates that this could have an important effect on the power in scenarios where the efficacy is less than anticipated.

**Table 3. Operational characteristics of the design with extension to a third stage, under different scenarios.** In this example, it is assumed that the DSMB would consider results to be promising if the posterior probability of sufficient efficacy of 0.40 or more but a posterior probability of efficacy is of 0.97 or less, and the final decision boundary is set to a posterior probability of efficacy > 0.963 to control the type I error rate.

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

### *4.2.4 Presentation of results*

For unadjusted analyses, and for purpose of trial monitoring, the posterior distributions of the event rates in each group and of their difference will be graphically displayed, and summarized by their median and 95% credibility interval. Similarly, for longer-term outcomes, the posterior distribution of the hazard ratio will be displayed, and summarized by its median and 95% credibility interval. Kaplan-Meier plots or cumulative incidence of the longer-term events will also be estimated in each arm, in a frequentist approach. Posterior probabilities of efficacy and sufficient efficacy will also be presented for both short-term event rates and longer-term outcomes.

## 4.3 Final analyses

For the short-term outcome, the posterior distributions of the difference in outcome rate and the odds ratio will be computed, and summarized by their median, 90% and 95% credible intervals. The 90% level matches the 95% threshold for the posterior probability of efficacy, and the 95% levels the more usual level. The posterior distribution of odds ratio adjusted for age and centre (as a random effect) will be also estimated using MCMC and summarized in the same way.
For the long-term outcome, the posterior distribution of the hazard ratio both unadjusted and adjusted for age and centre (as a random effect) will be calculated using MCMC and summarized by their median, 90% and 95% credible intervals. For group 2, where the primary outcome is the cumulative incidence of extubation, the hazard ratio will be estimated by a Fine-Gray model (subdistribution hazard ratio).
Frequentist analysis will be also presented for both outcomes, only for the adjusted analyses, using a logistic model, a Cox model and a Fine-Gray model, respectively.

### *4.3.1 Settings for Monte Carlo Markov Chain Bayesian analyses*

The initial protocol specified using Gaussian prior distributions with mean 0 and variance $10^6$ for the log hazard ratio. For adjusted analyses, the prior for the log hazard ratio for age is also a Gaussian prior, with mean 0 and variance $10^6$. Four different chains with different starting values will be run, with a burn-in of 10,000 iterations, and 100,000 additional iterations and a thinning interval of 10, leading to keeping 10,000 values per chain, 40,000 in total. The convergence of the models will be assessed using the Gelman-Rubin statistic and by visual inspection of the trace of coefficients
As a sensitivity analysis, we investigated different prior distribution, with a flat prior with smaller variance ($10^2$) which makes less likely unrealistic treatment effects, two sceptic priors centred on 0 with variance set so that a P(HR < 0.2) = P(HR > 5) = 0.05 (SD 0.975) or P(HR < 0.2) = P(HR > 5) = 0.025 (SD 0.82), and two enthusiastic informative priors centred on half the log HR and the log HR reported for for death or mechanical ventilation in an observational

study (Huet et al. Lancet Rheumatol 2020; 2: e393–400 https://doi.org/10.1016/S2665-9913(20)30164-8, which reported a hazard ratio of 0.22 in a similar population), and the same variance as for the sceptic prior with SD 0.975.

### 4.4 Calculation of the outcome

The short term primary outcome will simply use the values of WHO scores reported on day 4 (and day 1 in the group 2). Missing data will be considered as failure but an analysis of observed data and imputation by the last observation carried forward (LOCF) will be added.
For longer-term outcomes, discrepancies between the reported WHO scores and reported data for oxygen or ventilation status, for instance, which includes missing data, will be handled by considering the most severe scenario (for instance a patients with WHO score 5 but noted as under mechanical ventilation will be considered as ventilated, and a patient noted as under nasal canula but with a WHO score of 7 or more as under mechanical ventilation). Monitoring of such discrepancies will be carried out to limit at best their occurrence.
Moreover, since non-invasive ventilation or high flow may be more prone to centre-specific practice or device ability, a sensitivity analysis only considering mechanical ventilation (i.e. survival without need for mechanical ventilation) will be considered in the group 1.
For the day 14 primary outcome, patients discharged alive before day 14 without information on respiratory status at day 14 will be considered as being alive without need for ventilation at day 14 (or maximum theoretical follow-up if shorter than 14 days). A close data monitoring will be carried out to limit this situation as much as possible.
The definition of the outcomes in the protocol states that "New Do-Not-Resuscitate (DNR) orders" in group 1 and "DNR orders" in group 2 will be considered as events. The precise definition of "new DNR order" is set as DNR orders posterior to the date of randomization and that have been noted as having been effectively used to limit care.

### 4.5 Subgroup analyses

The protocol specified that, at the end of the study, subgroup analyses would be performed according to antiviral therapies at baseline. Moreover interactions between experimental treatments and antiviral therapies will be explored and tested.
These analyses will be performed using frequentist methods.

## 5 Secondary efficacy outcomes analysis

### 5.1 Definitions

#### *5.1.1 Group 1: patients not requiring ICU*

- WHO progression scale at 4, 7 and 14 days
- Overall survival at 14, 28 and 90 days
- Time to discharge
- Time to oxygen supply independency
- ~~Time to negative viral excretion~~

Biological parameters improvement: Estimated GFR, CRP, myoglobin, CPK, cardiac hs troponin, ferritin, lactate, cell blood count, liver enzymes, LDH, D-Dimer, albumin, fibrinogen, triglycerides, coagulation tests, urine electrolyte, creatinuria, proteinuria, uricemia, IL-6, procalcitonin, immunophenotype, and exploratory tests.

#### *5.1.2 Group 2: patients requiring ICU*

- WHO progression scale at 4, 7 and 14 days
- Overall survival at 14, 28 and 90 days

- 28-day ventilator free-days
- ~~Respiratory acidosis at day 4 (arterial blood pH of <7.25 with a partial pressure of arterial carbon dioxide [$PaCO_2$] of ≥60 mm Hg for >6 hours)~~
- Evolution of $PaO_2/FiO_2$ ratio
- Time to oxygen supply independency
- Duration of hospitalization
- ~~Time to negative viral excretion~~
- Time to ICU and hospital discharge.

### 5.2 Methods for analysis

Time-to-event outcomes will be analysed using Cox or Fine-Gray regression models adjusted for the same variables as the day 14 primary outcome; results will be expressed as hazard ratios with 95% confidence interval. Competing risks analyses (Fine-Gray model) will be used for time to discharge, time and time to oxygen supply independency, for which death will be considered as a competing event. When several timepoints are mentioned, separate models will be estimated at 14, 28 and 90 days. Point estimates of survival in each arm will be presented together with Kaplan-Meier survival curves. For the WHO ordinal scale, Bayesian proportional odds models will be used to compare the distribution of ordinal scores at day 4, 7 and 14, adjusted for age and centre, and a longitudinal version of the model with a time effect and a random subject effect will be used to analyse all scores up to day 14. The distribution of scores will be described at 4 (primary outcome), 7, and 14 days. For 14 days scores, a tolerance of plus/minus two days will be used, the value closest to 4 days being used, values before days 14 having precedence over values after day 14.
For biological outcomes, only descriptive analyses will be performed.
Time to negative viral excretion and respiratory acidosis at day 4 (in group 2) had been mentioned in the original protocol but are not recorded in the CRF, so they cannot be analysed.

## 6 Safety analysis

### 6.1 Definitions

Adverse events are spontaneously declared on the CRF. For each adverse event, the following information is collected:

- Classification of the adverse event (AE) as a serious adverse event (SAE);
- Seriousness criteria for SAEs;
- Intensity (severity): mild, moderate or severe;
- Start/end dates;
- Investigator judgement on relationship with the study treatment, concomitant treatment, pre-existing disease and COVID-19;
- Modification of study treatment;
- Symptomatic treatment;
- Outcome.

Moreover, major safety endpoints are monitored: blood cells and platelets counts and liver transaminases, are monitored frequently, every three days systematically:

- Neutrophil count;
- Platelet count;
- Liver enzymes: ALT and AST;
- Occurrence of skin rashes;
- Systolic and diastolic blood pressure;

- Ventilator asynchronization.

### 6.2 Analysis

Adverse events and their characteristics will be described using numbers and percentages per treatment arm. The proportion of participants with each of the reported events, as well as the proportions of participants with at least one SAE will be compared using Fisher's exact tests. The total number of AE/SAEs and SAEs will also be described for each arm, and compared using Poisson models (with a robust error variance if necessary).

## 7 Summary of changes since previous versions

The numbering of SAP versions follows the. one of the core SAP for all CORIMUNO-19 trials, but for a specific trial (i.e., CORIMUNO-19-ANA here), all versions do not necessarily exist.

### 7.1 Version 1.4 compared to previous working versions and version 1.0

- A new paragraph 5.4 has been introduced to better separate the final analysis and data presentation of the primary outcomes from the analyses carried interim analyses aiming at trial monitoring (paragraph 5.3). Subsequent paragraph numbering have been adapted accordingly.
- Adjustment of analyses on age has been made explicit instead of "for major prognostic factors". The choice of age as only adjustment factor (in addition to centre, the randomization stratification variable) has been determined by the DSMB.
- Practical settings for the Bayesian analyses have been detailed.
- The use of a Fine-Gray model to estimate the hazard ratio of the longer-term outcome in group 2 has been made explicit. This choice is natural given the primary outcome is expressed as a cumulative incidence in a competing risks framework.
- For secondary outcomes, the analysis of the WHO score over time has been changed from the planned ranked ANCOVA approach to a longitudinal proportional odds model. This choice was determined because the latter has been advocated for analysing the WHO ordinal scale in the context of COVID-19 trials, and because the large number of ties on this scale may limit the advantage of ranked ANCOVA. Of note, the proportional odds model is close to Wilcoxon rank-sum tests, but (1) provides an interpretable measure of treatment effect and (2) allows for adjustment.
- Analysis of biological outcomes over time has been specified.

### 7.2 Version 2.0 compared to 1.4

- The handling of patients discharged alive before day 14 for the day 14 primary outcome (as alive without the need for ventilation) has been clarified. This was decided early for allowing interim analyses when day 14 outcome was not recorded for a majority of patients, while (1) ensuring the assumption of uninformative censoring would hold and (2) avoiding later event being unduly influential if those observations were censored.
- The mention of the JAGS software (and version) for Bayesian analyses has been added.
- A tolerance of plus/minus two days for defining day 14 WHO scores has been added.

### 7.3 Version 2.1 compared to 2.0

- The parameterization of enthusiastic informative priors in the sensitivity analysis to the priors used in the Bayesian analysis of the survival co-primary outcome, based on a recently published study, has been defined.

- Added a table with frequentist operational characteristics of the design for the time-to-event outcome.