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

Statistical Analysis Plan for CORIMUNO-19-CORIPLASM Trial

Version 1.2

October 10, 2021

Redacted by Raphaël Porcher and Gabriel Baron
Validated by Philippe Ravaud

Coordinating Investigator: Pr Karine Lacombe
SMIT
Saint-Antoine Hospital, Paris, France
Tel: +33 149283196
E-mail: karine.lacombe2@aphp.fr

Co-Investigators

Pr Pierre Tiberghien,
Etablissement Français du Sang (EFS)

Pr Xavier de Lamballerie,
IHU Méditerranée Infection (MI)
<table>
<thead>
<tr>
<th>Immune COVID 19 group</th>
</tr>
</thead>
</table>
| **Pr Olivier Hermine,**  
Service Hématologie Adulte  
Necker Hospital, Paris, France  
Tel: +33 144495282 +33603707920  
E-mail: olivier.hermine@aphp.fr |
| **Pr Xavier Mariette,**  
Service Rhumatologie  
Hôpital du Kremlin Bicêtre  
Tel: +33145213758 +33623268104  
E-mail: xavier.mariette@aphp.fr |
| **Dr Pierre Louis Tharaux**  
INSERM U970, PARCC  
HEGP  
Tel: +33689502948  
E-mail: pierre-louis.tharaux@inserm.fr |

<table>
<thead>
<tr>
<th>Methodologist and statisticians:</th>
</tr>
</thead>
</table>
| **Pr Philippe Ravaud**  
Centre d’Epidémiologie Clinique.  
Hôpital Hôtel Dieu  
1 Place du Parvis Notre Dame  
75004 Paris  
E-mail: philippe.ravaud@aphp.fr |
| **Statistician:**  
**Pr Raphael Porcher**  
Centre d’Epidémiologie Clinique.  
Hôpital Hôtel Dieu  
1 Place du Parvis Notre Dame  
75004 Paris  
E-mail: raphael.porcher@aphp.fr |
| **Pr Matthieu Resche-Rigon**  
Hôpital Saint-Louis  
1 av Claude vellefaux  
75010 Paris  
E-mail: matthieu.resche-rigon@u-paris.fr |
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<td>DRCD-Siège : Cécile Kedzia - E-mail: <a href="mailto:cecile.kedzia@aphp.fr">cecile.kedzia@aphp.fr</a></td>
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<td>Damien Vanhoye - E-mail: <a href="mailto:damien.vanhoye@aphp.fr">damien.vanhoye@aphp.fr</a></td>
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1 Summary

**CORIMUNO-CORIPLASM: EFFICACY OF CONVALESCENT PLASMA TO TREAT SARS-COV2 INFECTED PATIENTS, A NESTED TRIAL IN THE CORIMUNO-19 COHORT**

**Rationale**

The coronavirus disease 2019 (COVID-19) viral pneumonia is now a worldwide pandemic caused by the Severe acute respiratory virus coronavirus 2 (SARS-CoV-2).

Convalescent plasma treatment, i.e. passive polyclonal antibody (Ab) administration to provide immediate immunity, has been used to improve the survival rate of patients with severe acute respiratory syndromes of viral etiology. A systematic review and exploratory meta-analysis performed in 2014 identified 32 studies of SARS coronavirus infection and severe influenza. These studies involved 699 treated patients and 568 untreated “controls” (and 60 patients with unknown status). The review revealed evidence for a consistent reduction in mortality upon plasma therapy. Furthermore, exploratory post hoc meta-analysis showed a significant reduction in the pooled odds of mortality following treatment, compared with placebo or no therapy (odds ratio, 0.25; 95% CI:0.14–0.45; with limited heterogeneity: I² = 0%).

A review identified 8 observational studies at moderate to high risk of bias that reported improved mortality after SARS-CoV-2 infected patients received various amount of convalescent plasma. At time of study planning, and to the best of the knowledge of investigators, at least one study evaluating convalescent plasma to treat SARS-CoV-2 infected patients was underway in China. In an uncontrolled case series of 5 critically ill patients with COVID-19 and acute respiratory distress syndrome (all on mechanical ventilation), administration of convalescent plasma containing neutralizing antibody was followed by an improvement in clinical status in all 5 patients.

**Eligibility criteria**

**Inclusion Criteria for the trial:**
1. Patients included in the CORIMUNO-19 cohort
2. Mild severity (grade 4 or 5 as described on the 10 pt WHO-CPS scale, see later) occurring up to day 10 after initiation of clinical symptoms

**Exclusion Criteria for the trial:**
1. Patients with exclusion criteria to the CORIMUNO-19 cohort.
2. Pregnancy
3. Current documented bacterial infection
4. Prior severe (≥ grade 3) allergic reactions to plasma transfusion

**Randomisation and Trial Monitoring**

All consecutive patients meeting the inclusion criteria will be randomised 1:1 either in the experimental arm (investigational medicinal product) or control arm (usual care), until a total of 120 patients in randomized (60 in each arm). An interim analysis is performed at mid-trial, but the inclusions will not be stopped in waiting for the interim analysis. At the interim and final analyses, efficacy and safety data will be reviewed by the DSMB. At the final analysis, there is a provision to extend the trial with additional inclusion of 60 patients (30 per arm), if results are promising, yet not conclusive.
Investigational medicinal product

The investigational medicinal product is a plasma unit provided by a COVID-19 convalescent pathogen-reduced (IA) plasma, fully compliant with ANSM regulation (ANSM authorisation, 11 May 2007) as detailed in the investigator’s brochure. This plasma unit will packaged and labelled per ANSM regulation regarding labile blood product. Upon receipt of a standard written prescription by the attending clinician, the EFS issuing department (service de délivrance de l’EFS), EFS personnel will select 2 ABO compatible plasma units in the “convalescent plasma” inventory. These 2 plasma will follow standard ANSM approved procedures regarding thawing, issuing to the clinical ward and traceability.

Thawed plasma will be delivered to the clinical ward per standard ANSM approved procedures. Similarly, plasma transfusion (i.v. infusion 200 mL/h, 3.5 mL/mn), per- and post transfusion surveillance as well as traceability and hemovigilance will be fully compliant with current regulations.

Plasma administration: Two convalescent plasma units of 200 to 220 mL each will be transfused i.v. in hospitalized patients with mild disease (WHO grade 4 or 5, annexe 1) as soon as possible, and up to day 10 after initiation of clinical symptoms. In the absence of acute unforeseen adverse events in the first 3 patients, an additional 2 plasma units of 200/220 mL each will be transfused 24 hours after first 2 units, i.e a total of 4 units / patient.

Convalescent plasma collection and manufacturing: Potential donors of convalescent plasma will be identified through various means, including hospitals taking care of such patient, practitioners treating outpatients or specific social messaging. Convalescent patients at least 14 days after the symptoms resolution will be invited to undergo plasma apheresis, pending general eligibility such as an age between 18 and 65 years old and weight not less than 50 kg. The convalescent donors will undergo standard pre-donation assessment to insure compliance with current regulations regarding plasma donation in France including standard microbiological assessment, as well as anti-HLA Ab detection in women with children. Furthermore, and importantly, an appropriate anti-SARS-CoV-2 neutralizing Ab activity titer should be verified. Based on prior SARS-CoV (1) studies13, a titer of >= 1/40 as assessed by cytopathic effect - based virus neutralizing tests (described in ) will be required. If found to be inadequate, the collected plasma may be oriented towards standard transfusion use, for example in trauma patients. The apheresis procedure will to be performed per standard procedures.

Duration of follow-up

28 days

Criteria for efficacy

Co Primary Endpoints

1. Survival without needs of ventilator utilization (including non-invasive ventilation, NIV or high flow [optiflow]) at day 14 of randomization (WHO score < 6) or additional immunomodulatory treatment (such as IL-6R Ab). Thus, events considered are the need of ventilator use (including non-invasive ventilation or optiflow), death, or use of an additional immunomodulatory treatment. 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 end point: WHO progression scale ≥ 6 at day 4, on the following scale:

<table>
<thead>
<tr>
<th>WHO-CPS scale</th>
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<th>Score</th>
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<tr>
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<th>2</th>
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A patient with new DNR order at day 4 will be considered as with a score > 5

**Secondary end-points** will be WHO progression scale at 4, 7 and 14 days, overall survival at 14, and 28 days, time to discharge, time to oxygen supply independency.

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, and exploratory tests.

### Criteria for safety
- Number of serious adverse events
- Cumulative incidence of serious adverse events (SAEs)
- Cumulative incidence of Grade 3 and 4 AEs.

Occurrence of severe adverse events known to be associated with plasma transfusion such as transfusion associated circulatory overload (TACO), transfusion related acute lung injury (TRALI), and severe allergy will be reported without delay to the sponsor.

Occurrence of systemic and/or local (lungs) inflammation associated with convalescent plasma transfusion will also be reported without delay to the sponsor.

### 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 **total sample size will be 60 (30 in each arm) at the interim analysis, and 120 (60 per arm) at the second analysis.**

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 re-adapted 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.

The interim 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. The final analysis will be performed in the modified Intention to treat (mITT) basis. All randomized participants will be included in the mITT population except those who have not accepted the intervention and those who are unable to receive planned plasma therapy due to the unavailability of ABO compatible blood products.
2 Major amendments to the protocol
The original definition of the longer-term co-primary outcome was:
“Survival without needs of ventilator utilization (including non-invasive ventilation, NIV or high flow [optiflow]) at day 14 of randomization (WHO score < 6) or additional immunomodulatory treatment (such as steroids or IL-6R Ab).”
Owing to the fact that dexamethasone became part of standard of care, an amendment submitted on the 19-01-2021 (authorised on the 11-03-2021) modified the outcome as:
“Survival without needs of ventilator utilization (including non-invasive ventilation, NIV or high flow [optiflow]) at day 14 of randomization (WHO score < 6) or additional immunomodulatory treatment (such as IL-6R Ab).”
Thus administration of steroids was never considered as an event for analysis.

3 Analysis population
3.1 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.

3.2 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. At the final stage, a modified ITT analysis will be carried out as primary analysis, where patients who have not accepted the intervention or who were unable to receive planned plasma therapy due to unavailability of ABO compatible blood products would be excluded. Given those situations did not occur, only the ITT analysis will be carried out.
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.

3.3 Sample size
The total sample size has been fixed for the whole 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 arm) depending of the recommendations of the DSMB (see below).
4 Analysis principles

4.1 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 age and centre as a random effect (randomisation stratification). At the final analysis stage, secondary analyses will be carried out adjusting for age and 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 two-sided 90% 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.

4.2 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.

4.3 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.

4.4 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.

5 Co-primary outcome analysis
5.1 Definitions

Two co-primary outcomes are used, 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.

1) Longer-term outcome: Survival without needs of ventilator utilization (including non-invasive ventilation, NIV or high flow [optiflow]) at day 14 of randomization (WHO score < 6) or additional immunomodulatory treatment (such as IL-6R Ab). Thus, events considered are the need of ventilator use (including non-invasive ventilation or optiflow), death, or use of an additional immunomodulatory treatment. 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 outcome: OMS progression scale ≥6 at day 4, defined as follow:

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5.2 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 (current 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. More comprehensive simulation studies will be performed to describe the properties of the design in an appendix to the protocol. Also, in all what follows, we assume the “event” corresponding to the outcome being detrimental to patients, so that an effective treatment would lower the event rate, or achieve a hazard ratio \( q < 1 \). When the clinical definition of the outcome is opposite, then analysis will be performed on the inverse (e.g. failure instead or success, or inverse of the hazard ratio \( 1/q \)).

5.2.1 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 the first trials conducted in the cmRCT, we want the conclusions to depend primarily on data from the trial, not on prior opinion. An uninformative prior for the hazard ratio will therefore be used. More precisely, the prior distribution 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.

5.2.2 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.

5.2.3 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. |
|--------------------------------------------------|------------------|------------------|------------------|------------------|
| Scenario                                         | No effect        | Very large effect| Large effect     | Mild effect      |
| Parameterizations                                | \(p_c=0.5,\)     | \(p_c=0.5,\)     | \(p_c=0.5,\)     | \(p_c=0.5,\)     |
|                                                   | \(p_b=0.5\)      | \(p_b=0.2\)      | \(p_b=0.3\)      | \(p_b=0.35\)     |
| 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.
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. Golden 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).

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Failure rate p in each group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No effect</td>
</tr>
<tr>
<td>Parameterizations</td>
<td>p_C=0.5, p_E=0.5</td>
</tr>
<tr>
<td>Corresponding hazard ratio</td>
<td>1</td>
</tr>
<tr>
<td>Probability of early stopping for efficacy</td>
<td>0.011</td>
</tr>
<tr>
<td>Probability of efficacy at 2nd stage</td>
<td>0.043</td>
</tr>
<tr>
<td>Overall probability of rejection</td>
<td>0.054</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Failure rate p in each group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No effect</td>
</tr>
<tr>
<td>Parameterizations</td>
<td>p_C=0.5, p_E=0.5</td>
</tr>
<tr>
<td>Probability of occurrence</td>
<td>0.307</td>
</tr>
<tr>
<td>Probability of efficacy at 3rd stage</td>
<td>0.018</td>
</tr>
<tr>
<td>Overall probability of rejection</td>
<td>0.050</td>
</tr>
</tbody>
</table>

5.2.4 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 two-sided 90% credibility intervals. Similarly, for longer-term outcomes, the posterior distribution of the hazard ratio will be displayed, and summarized by its median and two-sided 90% credibility intervals. 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.
5.3 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 and two-sided 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, and two-sided 90% and 95% credible intervals. 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.

5.3.1 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 will investigate different prior distributions, 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 $P(\text{HR} < 0.2) = P(\text{HR} > 5) = 0.05$ (SD 0.975) or $P(\text{HR} < 0.2) = P(\text{HR} > 5) = 0.025$ (SD 0.82), and two enthusiastic informative priors centred on a HR of 0.51 (mean log HR $\mu = -0.67$), which was considered as denoting a large effect in the trial planning, and are informative with $\sigma = 0.975$ or $\sigma = 0.82$.

5.4 Calculation of the outcome

The short term primary outcome will simply use the values of WHO scores reported on day 4. 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.

As a sensitivity analysis, an analysis of the outcome without considering immunomodulators will be carried out. Events considered were thus the need of ventilator use (invasive mechanical ventilation, non-invasive ventilation, or high flow device) and death. For the day 14 co-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.

For patients already receiving high-flow oxygen or non-invasive ventilation at randomization (this being a violation of inclusion criteria), the day 14 co-primary outcome will not consider high-flow oxygen or non-invasive ventilation as an event.
The definition of the outcomes in the protocol states that “New Do-Not-Resuscitate (DNR) orders 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.

5.5 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.

Additional post-hoc subgroup analyses will be carried according to the receipt of corticosteroids (in general), or specifically dexamethasone at baseline, as well as immunodeficiency at baseline and symptoms duration (up to 5 days, vs more than 5 days).

When the number of events in one subgroup is less than five, no treatment effect will be computed for that subgroup.

6 Secondary efficacy outcomes analysis
6.1 Definitions
- Overall survival at 14 and 28 days
- WHO progression scale at 4, 7 and 14 days
- Time to discharge
- Time to oxygen supply independency

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.

6.2 Methods for analysis
6.2.1 Time-to-event outcomes
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 and 28 days. When no timepoints were mentioned in the protocol (e.g., time to oxygen supply independency, time to discharge), the outcome will be analysed at day 28 only, but described at earlier timepoints. Point estimates of survival in each arm will be presented together with Kaplan-Meier survival curves.

6.2.2 WHO ordinal scale
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.

6.2.3 Biological and physiological outcomes
For biological outcomes, only descriptive analyses will be performed.
6.2.4 Assessment of a neutralizing antibody dose effect

An analysis of the co-primary outcomes will be performed according to the amount of neutralising SARS-CoV-2 antibodies received by the participants. The amount of neutralising antibodies received will be transformed into “neutralising units”, arbitrary defined as the volume of plasma received divided by the titre, and standardized so that one unit (U) corresponded to the infusion of 200 mL of plasma (which was the standard in the trial) with a titre of 1:40. Accordingly, the infusion of 200 mL of plasma with a titre of 1:80 would correspond to 2 U, as well as the infusion of 400 mL of plasma with a titre of 1:20. To account for the fact that titres result of dilutions by 2, volumes of plasma infused were rounded to either 200 mL or 400 mL, so that a similar precision was used for volume and titre (thus infusion of 202 mL or 213 mL, for instance, both corresponded to 200 mL).

Since the number of plasma infusions could be influenced by the outcome analysed (e.g. patients receiving 2 infusions only because of worsening), and be related to the neutralising units as well, only outcomes for patients who have received four plasma infusions will be analysed, by dichotomising the units of neutralising antibodies at the observed median value.

7 Safety analysis

7.1 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 asynchronisation.

7.2 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).
8 Summary of changes since previous versions

This version was based on the generic Statistical Analysis Plan version 2.1 of CORIMUNO-19 trials.
Subsequent changes to the SAP will be summarised here whenever relevant.

8.1 Version 1.1 compared to version 1.0

• The modified ITT analysis was cancelled, since no patient met criteria for inclusion in the ITT analysis but not the miITT analysis (§3.2).
• Added how to handle the calculation of the day 14 co-primary outcome for individuals receiving high-flow oxygen or non-invasive ventilation at randomisation (§5.4).
• Added subgroup analyses according to immunodeficiency at baseline and symptoms duration (up to 5 days, vs more than 5 days) (§5.5).

8.2 Version 1.2 compared to version 1.1

• Added analyses for assessing a neutralizing antibody dose effect (§6.2.4).