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Use of covid-19 convalescent plasma to treat patients admitted to hospital for covid-19 with or without underlying immunodeficiency: open label, randomised clinical trial

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ABSTRACT

OBJECTIVE To evaluate the efficacy of covid-19 convalescent plasma to treat patients admitted to hospital for moderate covid-19 disease with or without underlying immunodeficiency (CORIPLASM trial).

DESIGN Open label, randomised clinical trial.

SETTING CORIMUNO-19 cohort (publicly supported platform of open label, randomised controlled trials of immune modulatory drugs in patients admitted to hospital with moderate or severe covid-19 disease) based on 19 university and general hospitals across France, from 16 April 2020 to 21 April 2021.

PARTICIPANTS 120 adults (n=60 in the covid-19 convalescent plasma group, n=60 in the usual care group) admitted to hospital with a positive SARS-CoV2 test result, duration of symptoms ‹9 days, and World Health Organization score of 4 or 5. 49 patients (n=22, n=27) had underlying immunosuppression.

INTERVENTIONS Open label randomisation to usual care or four units (200-220 mL/unit, 2 units/day over two consecutive days) of covid-19 convalescent plasma with a seroneutralisation titre ›40.

MAIN OUTCOME MEASURES Primary outcomes were proportion of patients with a WHO Clinical Progression Scale score of ≥6 on the 10 point scale on day 4 (higher values indicate a worse outcome), and survival without assisted ventilation or additional immunomodulatory treatment by day 14. Secondary outcomes were changes in WHO Clinical Progression Scale scores, overall survival, time to discharge, and time to end of dependence on oxygen supply. Predefined subgroups analyses included immunosuppression status, duration of symptoms before randomisation, and use of steroids.

RESULTS 120 patients were recruited and assigned to covid-19 convalescent plasma (n=60) or usual care (n=60), including 22 (covid-19 convalescent plasma) and 27 (usual care) patients who were immunocompromised. 13 (22%) patients who received convalescent plasma had a WHO Clinical Progression Scale score of ≥6 at day 4 versus eight (13%) patients who received usual care (adjusted odds ratio 1.88, 95% credible interval 0.71 to 5.24). By day 14, 19 (31.6%) patients in the convalescent plasma group and 20 (33.3%) patients in the usual care group needed ventilation, additional immunomodulatory treatment, or had died. For cumulative incidence of death, three (5%) patients in the convalescent plasma group and eight (13%) in the usual care group died by day 14 (adjusted hazard ratio 0.40, 95% confidence interval 0.10 to

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Treatment with convalescent plasma (ie, passive polyclonal antibody administration to provide immediate immunity) has been used to improve the survival rate of patients with severe acute respiratory syndromes of viral causes in emergency settings and when no specific antiviral treatment is available

⇒ At the early stages of the covid-19 pandemic, using high titre covid-19 convalescent plasma seemed to be an immediate therapeutic option, but many randomised clinical trials and observational studies have reported conflicting results on the efficacy of convalescent plasma

⇒ Evaluation of the efficacy of covid-19 convalescent plasma in patients with underlying immunosuppression has been limited and the emergence of variants resistant to other passive immunotherapies (ie, monoclonal antibodies) has restricted the treatment options for these patients

WHAT THIS STUDY ADDS

⇒ This multicentre, randomised clinical trial indicates that transfusion of high titre covid-19 convalescent plasma to patients admitted to hospital with mild-to-moderate covid-19 within nine days of the onset of symptoms might not improve early outcomes

⇒ In the subgroup of patients with immunosuppression, the evidence indicated a lower odds of death at 14 and 28 days after transfusion of covid-19 convalescent plasma, but this finding was not significant

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ This study, and other trials and cohort studies, support further evaluation of transfusion of covid-19 convalescent plasma in patients with underlying immunosuppression

⇒ Treatment options for patients who are immunocompromised are scarce if non-existent because of the changing genetic variability of the SARS-CoV2 virus

1.53), and seven (12%) patients in the convalescent plasma group and 12 (20%) in the usual care group by day 28 (adjusted hazard ratio 0.51, 0.20 to 1.32). In a subgroup analysis performed in patients who were immunocompromised, transfusion of covid-19 convalescent plasma was associated with mortality (hazard ratio 0.39, 95% confidence interval 0.14 to 1.10).

CONCLUSIONS In this study, covid-19 convalescent plasma did not improve early outcomes in patients with moderate covid-19 disease. The efficacy of convalescent plasma in patients who are immunocompromised should be investigated further.

TRIAL REGISTRATION ClinicalTrials.gov NCT04345991.

Introduction

Early in the covid-19 pandemic, transfusion of covid-19 convalescent plasma was identified as a potential treatment that needed evaluation.[1] The overall efficacy of covid-19 convalescent plasma in patients admitted to hospital for covid-19 has not been established.[2] High titre convalescent plasma might be beneficial, however, particularly if used early before seroconversion[3 4] or in patients who lack an effective humoral response.[5 6] Treatment with monoclonal antibodies has been shown to be effective as an early intervention[7] or later in seronegative patients admitted to hospital.[8] Major limitations exist for monoclonal antibodies, however, including accessibility and cost,[9] as well as loss of efficacy, as recently shown with the emergence of the immune evading omicron subvariants of the SARS-CoV-2 virus.[10]

By contrast with monoclonal antibodies, covid-19 convalescent plasma, from convalescent donors who have been vaccinated, is cheaper, readily available, and adaptable to a changing viral landscape, and potentially less prone to immune resistance. Although the recent omicron variant dominant periods have been associated with a decrease in the efficacy of almost all available monoclonal antibodies,[11] high titre convalescent plasma (before the omicron dominant period) from convalescent donors who were vaccinated might retain anti-omicron neutralisation activity.[12] This anti-omicron neutralisation capacity is further increased in plasma from donors convalescing after the omicron variant of the virus who were vaccinated.[13]

As well as immunomodulating drugs that specifically target the inflammatory phase of the disease, oral direct antiviral agents, such as molnupiravir[14] or nirmatrelvir with ritonavir,[15] are another therapeutic option. These drugs have drawbacks, however, such as the need to start treatment within five days of the onset of symptoms and drug interactions for nirmatrelvir-ritonavir, particularly in patients who are immunosuppressed. The intravenous antiviral agent, remdesivir, has shown only limited efficacy against the SARS-CoV-2 virus in patients admitted to hospital with covid-19.[16] Careful assessment of the efficacy and safety of covid-19 convalescent plasma therefore is an important aspect of public health, particularly in patients who are immunosuppressed and do not have a vaccine mediated immune response. These patients are at risk of severe disease and have limited treatment options. We report the results of a randomised controlled trial that assessed the efficacy of covid-19 convalescent plasma (four units, about 840 mL) in patients with and without immunosuppression, who were admitted to hospital with moderate SARS-CoV-2 infection associated with pneumonia but who did not require assisted ventilation at the time of inclusion.

Methods

Trial design

CORIMUNO-19 is a publicly supported platform, established by Assistance Publique-Hôpitaux de Paris, France, at the beginning of the covid-19 pandemic, dedicated to performing cohort, open label, randomised controlled trials of immune modulatory drugs in patients admitted to hospital with moderate or severe covid-19 disease.[17] CORIPLASM (Efficacy of Convalescent Plasma to Treat Covid-19 Patients, a Nested Trial in the CORIMUNO-19 Cohort) was an embedded multicentre, open label, randomised controlled trial in patients with moderate covid-19 pneumonia conducted in French hospitals. Online supplemental appendix II and III have the full trial protocol and statistical analysis plan.

Study population and randomisation

At hospital admission, patients were evaluated for eligibility criteria: adults aged ≥18 years admitted to hospital, positive test result for the SARS-CoV-2 virus by nasopharyngeal polymerase chain reaction or computed tomography scan, or both, before randomisation, onset of symptoms <9 days, illness of mild or moderate severity according to the WHO Clinical Progression Scale (admitted to hospital, mild disease, no oxygen needed; admitted to hospital, moderate disease, oxygen <3 litres needed, online supplemental appendix I), not pregnant, no previous severe grade 3 allergic reaction to plasma transfusion, and no current bacterial infection reported.

ABO compatibility with available covid-19 convalescent plasma was verified before inclusion of patients. Written informed consent was obtained from all patients or their legal representatives at inclusion in CORIMUNO-19. Specific written informed consent was sought from eligible patients before inclusion in the CORIPLASM trial. The independent clinical research organisation compiled the computerised

randomisation list, and the patient's randomisation number was accessed through a secure site by a site study team member. Randomisation was performed within two hours of enrolment. Eligible patients were randomised 1:1 to receive convalescent plasma or usual care. Usual care could include the use of dexamethasone, tocilizumab, supportive care, including supplemental oxygen, antiviral agents, and antibiotics. A data and safety monitoring board provided guidance on the trial after inclusion of every 60 patients.

Study product

Convalescent donors were eligible for plasma donation 15 days after the end of symptoms related to covid-19 disease. Apheresis plasma was collected by Etablissement Français du Sang and underwent pathogen reduction (Intercept Blood System, Cerus, Concord, CA) and standard testing according to current regulations in France. Anti-SARS-CoV-2 potency was assessed in each donation, with a requirement for a SARS-CoV-2 seroneutralisation titre ≥40, as described by Gallian et al.[18] Antibody content was determined by immunoglobulin G enzyme linked immunosorbent assay (Euroimmun, Bussy-Saint-Martin, France). Covid-19 convalescent plasma with a seroneutralisation titre ≥40, made available for the trial and collected between April and June 2020, gave a mean enzyme linked immunosorbent assay ratio of 6.1 (standard deviation 2.9, range 0.4-13.0). After the first three patients received two units of ABO compatible covid-19 convalescent plasma according to the protocol, all subsequent patients randomised to the convalescent plasma group received four units of convalescent plasma (200-220 mL/unit, 2 units/day over two consecutive days) provided by different donors.

Study endpoints

As in all of the CORIMUNO-19 nested trials, an early primary endpoint was defined as a WHO Clinical Progression Scale score of ≥6 (online supplemental appendix I) on day 4 of randomisation. Higher values on the WHO Clinical Progression Scale indicate a worse outcome. The primary endpoint specific to the CORIPLASM trial was survival without the need for assisted ventilation (including non-invasive ventilation or high flow oxygen) at day 14 of randomisation (WHO Clinical Progression Scale score <6) or additional immunomodulatory treatment, with the exception of corticosteroids included within the standard of care (changes to the protocol, online supplemental file 1). Secondary endpoints were WHO Clinical Progression Scale score on days 4, 7, and 14 after randomisation, overall survival on days 14 and 28 after randomisation (ie, for the periods days 1-14 and days 1-28, respectively), time to discharge, time to end of dependence on oxygen supply, and changes to a series of biological parameters at days 4, 7, and 14 after randomisation.

Predefined subgroup analyses included immunosuppression status (underlying immunodeficiency: yes/no), duration of symptoms before randomisation (≤5 days, >5 days), and use of steroids. Safety data included all clinical and biological adverse events observed during the study follow-up. Immunodeficiency was defined as the presence of at least one of these medical conditions: active malignant neoplasm, lymphoid or myeloid neoplasms, haematopoietic stem cell or solid organ transplantation, or HIV/AIDS and not receiving highly active antiretroviral treatment.

Statistical analysis

The sample size was set at 120 participants (60 per group), with a bayesian interim analysis after 60 participants were randomised. We computed that the trial would have a frequentist power of 97.2% to detect a decrease in event proportions from 0.50 to 0.20, and 73.9% to detect a decrease in event proportions from 0.50 to 0.30. The study statisticians, who were masked to the group assignments, oversaw the interim and final analyses. Interim analysis reports were shared only with members of the data and safety monitoring board and not with the trial investigators. The trial investigators were blinded to all results during the trial.

The treatment effect was mainly expressed as an absolute risk difference for the early primary endpoint, and a hazard ratio for the longer term primary endpoint. Both were analysed in a bayesian framework. A posterior probability of absolute risk difference <0 or hazard ratio <1 but >0.99 at the interim analysis or >0.95 at the final analysis, indicated efficacy. We also computed posterior probabilities of absolute risk difference <−5.5% and hazard ratio <0.85, denoting a moderate or greater effect. At the interim analysis, a posterior probability of moderate or greater impact <0.20 defined a futility boundary. The treatment effect was summarised by the posterior median and equal tail credible intervals.

Because decision rules are one sided, consistent credible intervals would theoretically be one sided 95% credible intervals, but we chose to report two sided 90% credible intervals with the same upper boundary. For the early primary endpoint, the posterior distribution of absolute risk difference was computed analytically, with a beta prior distribution, with parameters one and one for the proportion in each group. An odds ratio adjusted for age and centre (centre being treated as a random effect) was also estimated with a bayesian logistic regression model. For the longer term primary endpoint, the posterior hazard ratio distribution adjusted for age and centre was computed with Markov chain Monte Carlo with normal prior distributions, with mean 0 and variance

10^6 for the log hazard ratio. Different prior distributions were used as sensitivity analyses.

Secondary outcomes were analysed in a frequentist framework, except for WHO Clinical Progression Scale scores, analysed as an ordinal variable with a bayesian proportional odds model. Analyses of secondary outcomes were also adjusted for age and centre. For time to discharge and time to end of dependence on oxygen supply, we estimated adjusted subdistribution hazard ratios with Fine-Grey models, death being the competing event. Estimating subdistribution hazard ratios was preferred over cause specific hazard ratios because subdistribution hazard ratios have a one-to-one relation with the cumulative incidence (ie, the proportion) of events, and we considered that subdistribution hazard ratios would therefore be more relevant than the ratio of rates at which these events occur in time. We used interaction tests between the treatment group and subgroups to test for treatment effect heterogeneity between the subgroups, with similar regression models as the main adjusted analyses. The statistical analysis plan has full details of the statistical analyses (online supplemental appendix III).

Analyses were done on an intention-to-treat basis. The original protocol specified a modified intention-to-treat analysis excluding patients declining the intervention and those who could not receive the planned plasma treatment because ABO compatible covid-19 convalescent plasma was not available. Because those situations did not occur, no modified intention-to-treat analysis was performed. No correction for multiplicity was done for secondary outcomes, and corresponding results should be regarded as exploratory. Two interim analyses were conducted (online supplemental table S1). Statistical analyses were done with SAS (version 9.4, SAS Institute) and R (version 4.0.5, R Foundation) statistical software.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research, because the trial has been designed in an emergency setting. However, according to the French law, the results have been sent to all participants or to their families.

Results

Between 16 April 2020 and 21 April 2021, 120 patients (60 in the covid-19 convalescent plasma group and 60 in the usual care group) were enrolled (online supplemental figure S1). Table 1 shows the characteristics of the study participants, which were well balanced between the two groups.

Median time from onset of symptoms to randomisation (transfusion of covid-19 convalescent plasma or usual care) was seven days in both groups. We saw a positive anti-S and anti-N SARS-CoV-2 serology in 10/23 (44%) evaluable patients receiving convalescent plasma and in 9/27 (33%) evaluable patients receiving usual care. Underlying immunodeficiency was present in 22/60 (37%) and 27/60 (45%) patients in the convalescent plasma and usual care groups, respectively. One patient was thought to have covid-19 disease based on a typical chest computed tomography scan at inclusion, but was later reclassified as non-indicative of SARS-CoV-2 infection, and pulmonary oedema from cardiac origin was diagnosed. Online supplemental table S2 reports other treatments received before and after randomisation until day 14.

An intention-to-treat analysis was performed on 120 patients; two patients in each group were lost to follow-up at the day 28 evaluation but discharged alive before day 28 (figure 1). One patient did not receive a plasma infusion because of sudden worsening after randomisation and transfer to the intensive care unit. Nine patients received two units of convalescent plasma (three based on the protocol and six because of worsening of clinical status leading to admission to the intensive care unit), and 50 received four units of convalescent plasma. Same day transfusion was performed in 78% of patients, whereas 12 (20%) and one (2%) patient received a transfusion one and three days after randomisation, respectively.

Primary outcomes

Thirteen (22%) patients in the covid-19 convalescent plasma group versus eight (13%) patients in the usual care group had a WHO Clinical Progression Scale score of ≥6 at day 4 (median posterior absolute risk difference 8.0%, 90% credible interval −3.2% to 19.4%; adjusted odds ratio 1.88, 95% credible interval 0.71 to 5.24; table 2, online supplemental table S3, and online supplemental figure S2). The WHO Clinical Progression Scale score on day 4 was analysed as an ordinal outcome in a proportional odds model, giving a median posterior adjusted odds ratio of 1.42 (95% credible interval 0.70 to 2.91), hence showing higher scores in the covid-19 convalescent plasma group, although the difference was not significant. By day 14, patients in the convalescent plasma and usual care groups needed non-invasive or high flow ventilation (n=15 in the convalescent plasma group and n=13 in the usual care group) or additional immunomodulatory treatment in the form of anti-interleukin 6 receptor monoclonal antibody (n=0 in the convalescent plasma group and n=5 in the usual care group), or had died (n=2 in each group). Also, one and five patients died after reaching the primary outcome in the convalescent plasma and usual care groups, respectively. Figure 2 shows the cumulative incidence of assisted ventilation or death. The median posterior adjusted hazard ratio was 1.04 (95% credible interval 0.55 to 1.97), and the posterior probability of a moderate or

Table 1 | Characteristics of participants at baseline in the two groups. Total group numbers that are not n=60 are indicated

	Covid-19 convalescent plasma group (n=60)	Usual care group (n=60)
Age (years)	64.5 (55.7-76.6)	67.0 (58.3-78.9)
Men	37/60 (62)	39/60 (65)
Weight (kg)	80.0 (68.5-93.5)	78.5 (67.0-89.5) (n=56)
Body mass index	27.8 (24.2-32.3) (n=55)	27.7 (22.9-32.3) (n=52)
Obesity (body mass index ≥30)	21/60 (35)	15/58 (26)
WHO Clinical Progression Scale score (0-10)*:	5.0 (5.0-5.0)	5.0 (4.5-5.0)
Score 4	9/60 (15)	15/60 (25)
Score 5	51/60 (85)	44/60 (73)
Score 6	0/60	1/60 (2)
Temperature (°C)	37.2 (36.7-38.1)	37.4 (36.7-38.7)
Respiratory rate (breaths/min)	22.0 (20.0-28.0) (n=43)	24.0 (18.0-28.0) (n=39)
Oxygen flow (L/min)	2.0 (2.0-5.0) (n=50)	3.0 (2.0-4.0) (n=45)
SpO_2 (%)	95.0 (94.0-96.0)	95.0 (93.0-96.0)
Time from onset of symptoms to randomisation (days)	7.0 (5.0-9.0)	7.0 (4.0-8.5)
Diagnosis of SARS-CoV-2 infection:		
Positive rRT-PCR test result	58/60 (97)	58/60 (97)
Typical chest CT scan only	2/60 (3)	1/60 (2)
None of the above†	0/60	1/60 (2)
Positive SARS-Cov-2 serology	10/23 (44)	9/27 (33)
Chronic cardiac disease	17/60 (28)	15/60 (25)
Diabetes	18/60 (30)	14/60 (23)
Chronic kidney disease (stages 1-3)	5/60 (8)	10/60 (17)
Asthma	4/60 (7)	7/60 (12)
Chronic pulmonary disease (except asthma)	4/60 (7)	7/60 (12)
Active malignant neoplasm	15/60 (25)	16/60 (27)
Lymphoid neoplasm	8/60 (13)	10/60 (17)
Myeloid neoplasm	4/60 (7)	7/60 (12)
Haematopoietic stem cell transplantation	2/60 (3)	1/60 (2)
Solid organ transplantation	1/60 (2)	1/60 (2)
AIDS/HIV not on HAART	0/60	1/60 (2)
Immunodeficiency‡	22/60 (37)	27/60 (45)
Current or former smoker	11/56 (20)	17/60 (25)
Laboratory values:		
C reactive protein (mg/L)	74.1 (27.7-108.7) (n=58)	84.4 (40.3-166.0) (n=58)
D-Dimer (µg/L)	580 (380-1070) (n=41)	921 (580-1650) (n=44)
Neutrophil count (10^9/L)	4.5 (2.5-6.3) (n=47)	3.8 (2.7-5.4) (n=55)
Lymphocyte count (10^9/L)	0.7 (0.6-1.1) (n=48)	0.8 (0.5-1.1) (n=54)
Lymphocytes to neutrophils ratio	0.2 (0.1-0.3) (n=47)	0.2 (0.1-0.4) (n=54)
Haemoglobin (g/dL)	12.4 (10.8-13.4) (n=57)	12.2 (10.1-13.7) (n=59)
Platelet count (g/L)	192 (145-263)(n=57)	153 (117-213) (n=59)
Alanine aminotransferase (IU/L)	40.0 (23.0-74.0) (n=54)	32.5 (22.0-47.5) (n=48)
Aspartate aminotransferase (IU/L)	44.0 (30.0-68.0) (n=54)	37.5 (28.0-52.0) (n=48)
Albumin (g/L)	34.2 (29.7-37.9) (n=32)	33.8 (30.2-39.0) (n=31)
Creatinine (µmol/L)	67.5 (55.0-84.0) (n=58)	77.0 (55.0-100.0) (n=59)
Ferritin (mg/L)	1137 (461-1472) (n=33)	945 (416-2160) (n=31)
Lactate dehydrogenase (g/L)	432 (344-535) (n=38)	366 (295-475) (n=36)
Creatine phosphokinase (IU/L)	78 (47-355) (n=24)	62 (41-141) (n=27)

Values are number/total number (%) or median (interquartile range).

CT=computed tomography; HAART=highly active antiretroviral therapy; rRT-PCR=real time reverse transcription polymerase chain reaction; SpO_2=oxygen saturation measured by pulse oximeter.

*Score 4: admitted to hospital, no oxygen treatment; score 5: admitted to hospital, oxygen by mask or nasal prongs; score 6: admitted to hospital, oxygen by non-invasive ventilation or high flow.

†Patient was included based on typical covid-19 chest CT scan at inclusion, but then reclassified as non-indicative of SARS-CoV-2 infection.

‡Active malignant neoplasm, lymphoid neoplasm, myeloid neoplasm, haematopoietic stem cell or solid organ transplantation, AIDS/HIV not on antiretroviral treatment (patients might have more than one of these conditions).

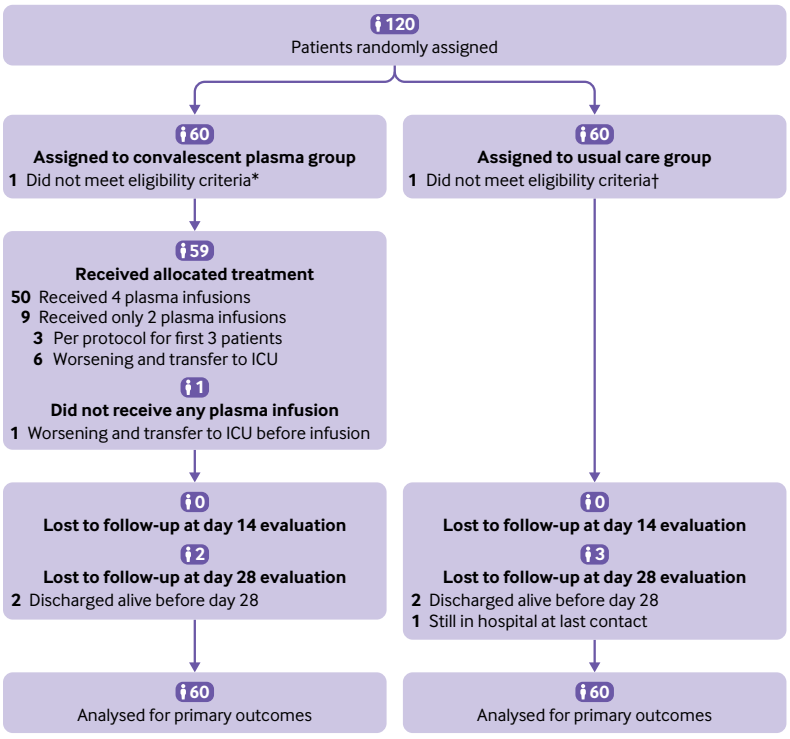

Figure 1 | Flowchart of CORIPLASM (Efficacy of Convalescent Plasma to Treat COVID-19 Patients, a Nested Trial in the CORIMUNO-19 Cohort) clinical trial. *No SARS-CoV-2 infection. †Received non-invasive ventilation. ICU=intensive care unit

greater benefit was 0.269 (table 2 and online supplemental table S4). The results were consistent across the range of prior distributions used in the sensitivity analyses (online supplemental figure S3).

Secondary outcomes

At day 14, three (5%) and eight (13%) patients had died in the covid-19 convalescent plasma and usual care groups, respectively (adjusted hazard ratio 0.40, 95% confidence interval 0.10 to 1.53) (figure 3 and online supplemental table S5). At day 28, nine (12%) and 12 (20%) patients had died in the convalescent plasma and usual care groups, respectively (0.51, 0.20 to 1.32). The distribution of WHO Clinical Progression Scale scores from day 1 to day 14 did not differ significantly within groups, with a posterior odds ratio of 1.04 (95% credible interval 0.37 to 2.86) for the convalescent plasma group compared with the usual care group in a longitudinal ordinal model. The WHO Clinical Progression Scale scores tended to be higher in the convalescent plasma group between days 3 and 5, and then lower at day 14, with lower mortality (figure 4 and online supplemental table S6), although these findings were not significant. At day 14 and day 28, 38 and 48 patients in the convalescent plasma group and 36 and 45 in the usual care group, respectively, were discharged, with an adjusted day 28 subdistribution hazard ratio of 0.99 (95% confidence interval 0.65 to 1.49) adjusted for age and centre (online supplemental table S7). The incidence of not needing oxygen by day 28 was not different between the groups: 76% and 62% by day 14 and 82% and 71% by day 28 in the convalescent plasma and usual care groups, respectively (subdistribution hazard ratio 1.18, 95% confidence interval 0.73 to 1.91) (online supplemental table S7).

Subgroup analyses

Figure 5 shows the primary outcome at day 14 (need for non-invasive or mechanical ventilation, use of additional immunomodulatory drugs, or death), with no difference in the subgroups. In the 47 patients who had an underlying immunodeficiency, the rate of a WHO Clinical Progression Scale score of ≥6 at day 4 was not significantly different in the covid-19 convalescent plasma group compared with the usual care group (24% *v* 15%, adjusted odds ratio 1.97, 95% confidence interval 0.53 to 7.39). At day 28, four of 21 patients had died in the convalescent plasma group versus nine of 26 patients in the usual care group (hazard ratio 0.39, 95% confidence interval 0.14 to 1.10) (figure 6). Despite these findings favouring convalescent plasma, we found no evidence of an interaction between immunodeficiency status and treatment (P=0.34): 4/21 patients died in the covid-19 convalescent plasma group versus 9/26 in the usual care group (hazard ratio 0.39, 95% confidence interval 0.14 to 1.10) (figure 6). We found limited mortality in the absence of underlying immunodeficiency (figure 7). Duration of symptoms or use of dexamethasone had no effect on day 28 survival (figure 5). Post hoc analysis of

Table 2 | Primary and secondary efficacy outcomes

	Convalescent plasma group (n=60)	Usual care group (n=60)	Treatment effect
Primary outcomes			
No (%) of patients with WHO Clinical Progression Scale score ≥6 at day 4:	13 (22)	8 (13)	8.0% (90% CrI −3.2% to 19.4%)*
Posterior probability of any benefit (%)			11.9
Posterior probability of moderate or greater benefit (%)†			2.4
No (%) of patients needing ventilation, additional immunomodulators, or death up to day 14:	19 (32)	20 (33)	1.04 (90% CrI 0.61 to 1.78)‡
Posterior probability of any benefit (%)			45.2
Posterior probability of moderate or greater benefit†			26.9
Secondary outcomes			
Overall survival:			
No (%) of patients who died days 0-14	3 (5)	8 (13)	0.40 (95% CI 0.10 to 1.53)§
No (%) of patients who died days 0-28	7 (12)	12 (20)	0.51 (95% CI 0.20 to 1.32)§
Median (IQR) WHO Clinical Progression Scale score:			
Day 4	5 (5-5)	5 (4-5)	1.42 (95% CrI 0.70 to 2.91)¶
Day 7	5 (4-5)**	5 (4-5)††	1.20 (95% CrI 0.61 to 2.37)¶
Day 14	3 (2-4)††	3 (2-5)††	0.59 (95% CrI 0.30 to 1.13)¶
Days 2-14 (longitudinal analysis)	—	—	1.04 (95% CrI 0.37 to 2.86)¶
Time to discharge:			
No (%) of patients discharged at day 28	48 (80)	45 (75)	0.99 (95% CI 0.65 to 1.49)‡‡
Time to end of dependence on oxygen supply:†			
No/total No (%) of patients not needing oxygen at day 28	42/51 (82)	32/45 (71)	1.18 (95% CI 0.73 to 1.91)‡‡

CI=confidence interval (frequentist analysis); CrI=credible interval (bayesian analysis); IQR=interquartile range.
Moderate or greater benefit was defined as an absolute risk difference <−5.5% for day 4 outcome and hazard ratio <0.85 for day 14 outcome.
*Median posterior absolute risk difference; median posterior odds ratio adjusted for age and centre was 1.88 (90% credible interval 0.83 to 4.44).
†For participants needing oxygen at randomisation (WHO Clinical Progression Scale score ≥5).
‡Median posterior hazard ratio adjusted for age and centre.
§Hazard ratio adjusted for age and centre.
¶Median posterior odds ratio in a proportional odds model adjusted for age and centre.
**n=58 with available data.
††n=59 with available data.
‡‡Subdistribution hazard ratio adjusted for age and centre.

antibody potency in transfused covid-19 convalescent plasma in relation to outcome did not show a significant dose effect (online supplemental table S8).

Adverse events

Adverse events were reported in 44 (73%) and 36 (60%) patients in the covid-19 convalescent plasma (n=124 events) and usual care (n=103 events) groups, respectively (incidence rate ratio 1.06, 95% confidence interval 0.63 to 1.77; online supplemental table S9). We found serious adverse events in 30 (50%) and 26 (43%) patients in the convalescent plasma (n=46 events) and usual care (n=48 events) groups, respectively (incidence rate ratio 0.84, 95% confidence interval 0.46 to 1.54). We found 10 sepsis related events with usual care (six with convalescent plasma) and four incidences of acute pulmonary oedema with convalescent plasma (none with usual care).

Causes of death were covid-19 related acute respiratory distress syndrome (n=3 in the convalescent plasma group and n=10 in the usual care group), cardiac origin (n=2 convalescent plasma, n=0 usual care), sepsis (n=2 convalescent plasma, n=3 usual care), gastrointestinal (n=0 convalescent plasma, n=1 usual care), vascular (n=1 convalescent plasma, n=0 usual care), and one of unknown origin (convalescent plasma).

Discussion

Principal findings

In this CORIPLASM trial, we found no difference in early outcomes between the covid-19 convalescent plasma and usual care groups for patients admitted to hospital for covid-19 disease not requiring assisted ventilation. The survival rate at day 14 and day 28 was higher in the convalescent plasma group but this finding was not significant.

The lack of efficacy associated with covid-19 convalescent plasma agrees with the results of most prospective randomised clinical trials of patients admitted to hospital for covid-19 disease.[19] Only a small number of randomised studies have reported better survival after treatment with convalescent plasma,[20 21] whereas several other trials, notably the large RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial,[22] found no evidence of

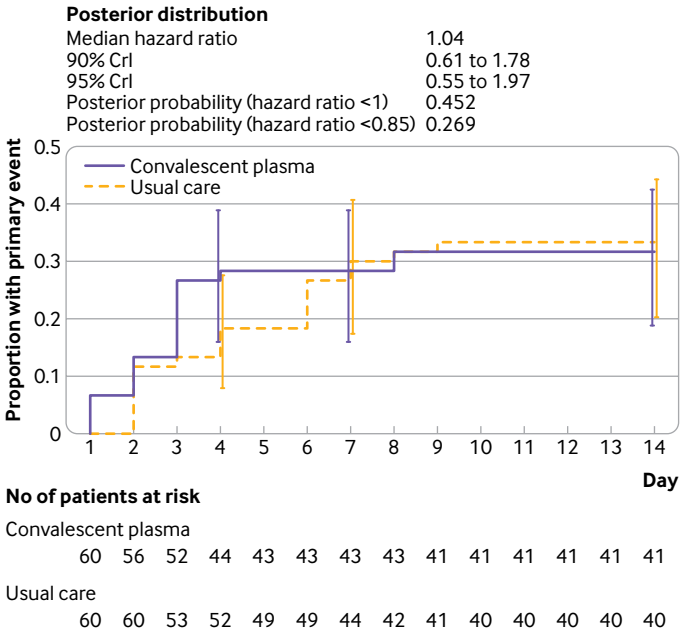

Figure 2 | Study outcomes in covid-19 convalescent plasma and usual care groups. Cumulative incidence of non-invasive or mechanical ventilation, use of additional immunomodulatory drugs, or death over 14 days (events on day 1 of randomisation occurred on the same day but after randomisation). CrI=credible interval

survival benefit with convalescent plasma. Large retrospective studies in the US reported evidence of reduced mortality associated with treatment with covid-19 convalescent plasma in patients admitted to hospital with covid-19.[23 24] The reasons for these discrepancies might be related to the characteristics of the convalescent plasma, time to treatment from first symptoms, treatment modalities, and patient characteristics.

Our study included a substantial proportion of patients with underlying immunosuppression. Similar to previous findings,[25] we found that these patients with covid-19 have a worse prognosis, as seen in the usual care group. Several studies have suggested that convalescent plasma might be particularly effective in patients who lack an immune response, particularly a humoral response. We reported previously that treatment with covid-19

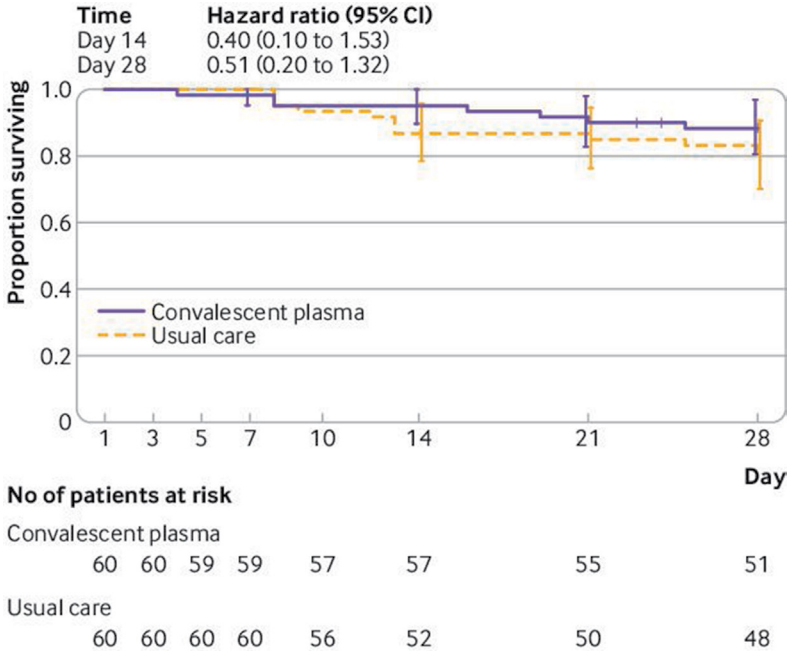

Figure 3 | Overall survival during follow-up in covid-19 convalescent plasma and usual care groups. CI=confidence interval

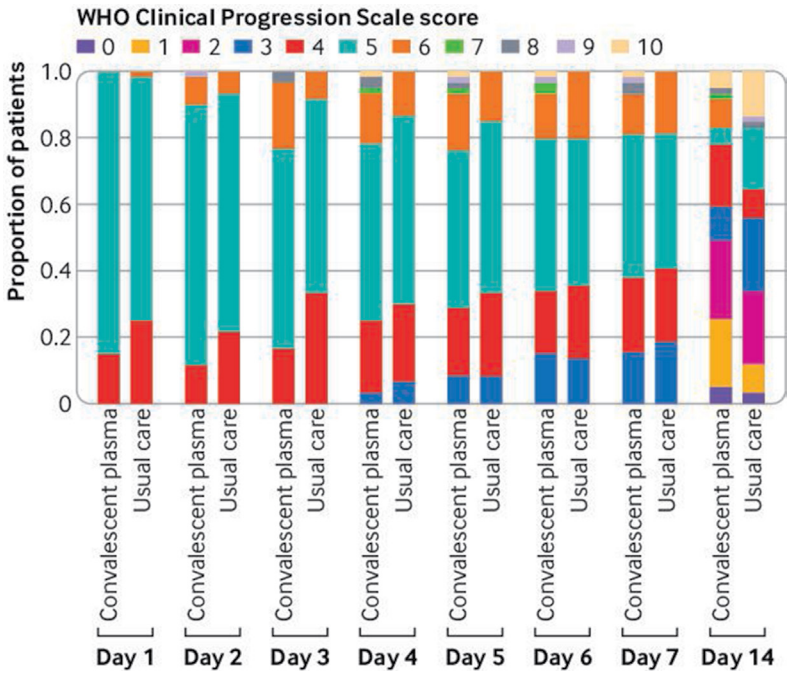

Figure 4 | Distribution of World Health Organization Clinical Progression Scale scores during follow-up in covid-19 convalescent plasma and usual care groups

convalescent plasma was associated with a favourable outcome in patients who were immunosuppressed (mainly B cell haematological malignancies treated with anti-CD-20 monoclonal antibodies).[6] Further evidence was provided by two independent exposed and non-exposed studies with propensity score in patients with underlying immunosuppression. Hazard ratios of 0.52 (95% confidence interval 0.29 to 0.92) and 0.50 (0.34 to 0.72) were reported in favour of convalescent plasma treatment, respectively.[6 7] This reduction in mortality was similar to patients with immunosuppression randomised to the convalescent plasma group in the CORIPLASM trial.

Comparison with other studies

Most other randomised trials published so far did not report subgroup analyses for patients with underlying immunosuppression. One exception is the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community Acquired Pneumonia) trial that investigated convalescent plasma in critically ill patients with covid-19.[22] Although the overall results of this study did not provide evidence of the efficacy of covid-19 convalescent plasma in these patients, a prespecified subgroup analysis showed a potential benefit of convalescent plasma in patients with immunodeficiency. Another

Subgroup	No of events/total: Convalescent plasma (n=60)	No of events/total: Usual care (n=60)	Adjusted hazard ratio (95% CI)	Interaction P
Immunodeficiency				
No	13/39	10/34	1.22 (0.61 to 2.44)	0.53
Yes	6/21	10/26	0.80 (0.34 to 1.87)	
Symptom duration				
≤5 days	7/20	8/20	0.90 (0.38 to 2.12)	0.79
>5 days	12/40	12/40	1.07 (0.54 to 2.13)	
Corticosteroids				
No	8/30	12/37	0.84 (0.40 to 1.78)	0.56
Yes	11/30	8/23	1.23 (0.57 to 2.66)	
Dexamethasone				
No	10/36	14/43	0.89 (0.45 to 1.77)	0.64
Yes	9/24	6/17	1.23 (0.51 to 2.93)	

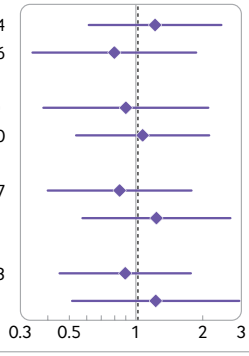

Figure 5 | Subgroup analyses. Day 14 primary outcomes (need for non-invasive or mechanical ventilation, use of additional immunomodulatory drugs, or death) in covid-19 convalescent plasma and usual care groups. Dashed line indicates overall estimate of treatment effect. Because only one patient was receiving antiviral agents at randomisation, no subgroup analysis according to antiviral agents was done. CI=confidence interval

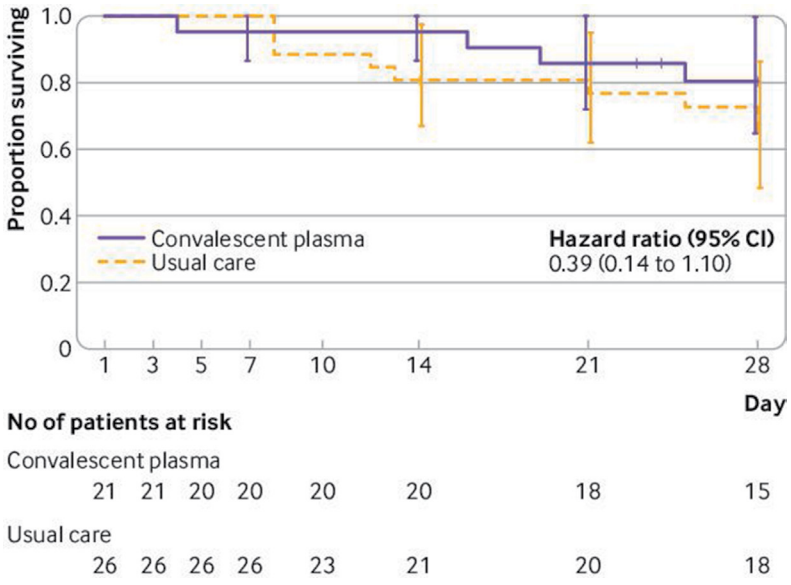

Figure 6 | Overall survival during follow-up in patients with immunosuppression in covid-19 convalescent plasma and usual care groups. CI=confidence interval

randomised trial performed in patients with a diverse range of clinical conditions reported a significant effect of covid-19 convalescent plasma on clinical improvement and survival in the subgroup of 56 individuals with cancer.[26] Finally, a meta-analysis incorporating the CORIPLASM trial has confirmed the potential benefit of covid-19 convalescent plasma in individuals with immunosuppression with mild-to-moderate covid-19 disease, based on greater statistical power because of the large number of individuals with immunosuppression included in the meta-analysis (1487 from randomised trials, 265 from case series, and 368 from cohorts).[27]

An antibody dose effect has been reported in several randomised studies[3 28] as well as in the early access programme in the US.[23] In the CORIPLASM trial, 800-880 mL of covid-19 convalescent plasma were transfused to patients randomised to the convalescent plasma group. In most studies so far, patients most often received 250-500 mL of convalescent plasma, except in the CAPSID (A Clinical Trial of Convalescent Plasma Compared to Best Supportive Care for Treatment of Patients With Severe Covid-19) trial where patients received 700-750 mL of convalescent plasma.[24 28] The CAPSID trial reported a significant antibody dose effect for several outcomes, including survival at day 28. By contrast, the CORIPLASM protocol recommended four covid-19 convalescent plasma units provided by different donors for each patient, which resulted in less variation in mean

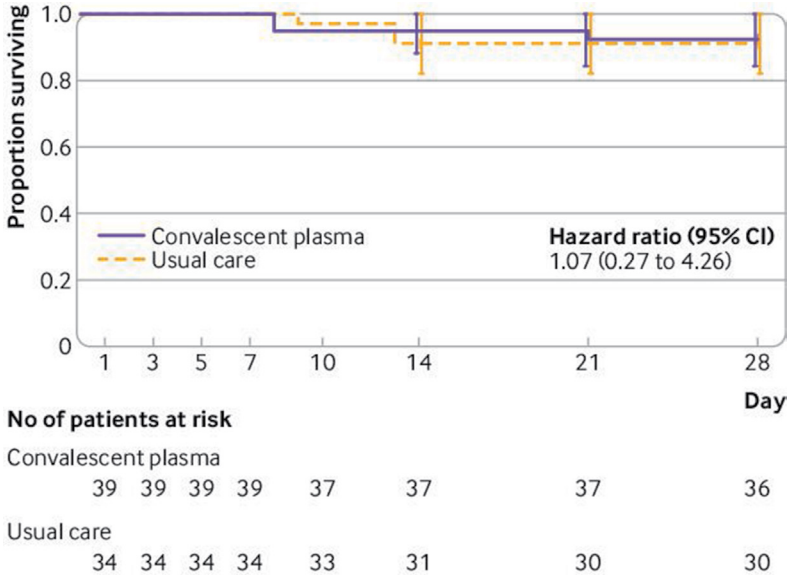

Figure 7 | Overall survival during follow-up in patients with no underlying immunodeficiency in covid-19 convalescent plasma and usual care groups. CI=confidence interval

antibody content in transfused convalescent plasma from patient to patient. This difference in transfusion practice might explain why we did not see an antibody dose effect in our study. Furthermore, convalescent plasma for the CORIPLASM study was collected early in the covid-19 crisis when vaccination was not available and before the occurrence of relevant SARS-CoV-2 variants.

Several studies have shown that plasma provided by convalescent donors who were vaccinated strongly increased anti-SARS-CoV-2 antibody titres and seroneutralisation ratios and also increased cross reactivity with a broader spectrum for variants to which the donor had not been exposed.[12 29] High titre plasma from these convalescent donors who were vaccinated might have increased clinical efficacy. Early intervention with covid-19 convalescent plasma has been associated with improved outcome.[3 4] Patients in our study had a median duration of symptoms of seven days at the time of inclusion, a short time period compared with most trials of patients admitted to hospital. Prespecified subgroup analyses, however, did not favour increased efficacy of convalescent plasma associated with a shorter time since onset of symptoms. The high number of patients with underlying immunosuppression, for whom seroconversion is not expected early on, might have contributed to this finding. Also, and as found in other covid-19 trials, early admission to hospital might be associated with more severe disease.[8 22]

Patients in the covid-19 convalescent plasma group tended to have worsening pulmonary clinical conditions than patients in the usual care group early after transfusion. The occurrence of early transient pulmonary worsening after transfusion of convalescent plasma has also been reported elsewhere,[30] and might be related to antibody dependent enhancement involving immune complex mediated inflammatory immunopathology in infected tissues.[31] Also, an antibody dependent Fc receptor mediated infection of tissues macrophages (and circulating monocytes) might result in a massive inflammatory response, as recently reported,[32] which could also contribute to pulmonary worsening after transfusion of convalescent plasma.

These early outcomes are seldom reported in clinical studies, and distinguishing early pulmonary worsening from transfusion associated circulatory overload, transfusion related acute lung injury, or overall disease worsening, possibly started before transfusion, can be challenging. The transfusion of four units of plasma might have contributed to circulatory overload in some patients. Further spacing of administration of convalescent plasma (ie, 1 unit/day over four days) could reduce this risk. Early worsening did not prevent subsequent improvement and increased survival as early as day 14 after randomisation, although this effect was not significant. Antibody mediated SARS-CoV-2 uptake by monocytes and macrophages triggering inflammatory cell death and inhibition of viral replication might be a mechanism for subsequent improvement in disease.[33]

Limitations of this study

Our study had some limitations. The relatively small size of the trial limited the ability to appropriately assess outcomes, such as patient mortality, but we did access treatment with covid-19 convalescent plasma in immunosuppressed patients. Also, information on patient serostatus at inclusion was often not available. Although the mean antibody ratio in transfused convalescent plasma in our study was well above the US Food and Drug Administration threshold for high titre convalescent plasma (Euroimmun anti-SARS-CoV-2 immunoglobin G ratio >3.5),[34] transfusion of higher titre plasma from convalescent donors who were vaccinated might improve efficacy.[3 12 23 26]

The emergence of the omicron variant of the SARS-CoV-2 virus with its BA.1-BA.5 subvariants has highlighted the risks associated with immune resistant SARS-CoV-2 and loss of efficacy of available monoclonal antibodies.[11] Whereas several months are necessary to produce one or more new monoclonal antibodies more suited to changes in circulating viral strains, convalescent plasma, particularly from donors who are vaccinated, has shown increased resilience to immune resistant SARS-CoV-2 variants,[12 30] increased scalability because of the existing collection infrastructure, as well as increased adaptability. The time between the onset of a covid-19 variant and the availability of convalescent plasma from donors infected with the variant disease is about four weeks.

Conclusions

The results of the CORIPLASM trial, along with recent data from other trials and cohort studies, support further evaluation and consequent use of convalescent plasma in patients who are immunocompromised for whom treatment options are limited. Recent guidelines from the Association for the Advancement of Blood and Biotherapies suggest transfusion of covid-19 convalescent plasma in addition to standard of care for patients admitted to hospital with covid-19 and pre-existing immunosuppression.[34]

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Contributors KL and PT were involved in the protocol and study design, including conceptualisation, methodology, funding acquisition, and resources. NS and TS did the data curation, investigation, project administration, supervision, and validation. RP and GB did the data analysis. TH, AM, TC, SG-L, FA, JS, GM-B, FB, CC, OH, VP, MM, XL, PB, FP, PS, SR, LP, and J-MM included the patients. OH, XM, P-LT, MR-R, and PR designed the CORIMUNO-19 platform trial and conceptualised the embedded trials. The manuscript was drafted by KL and PT, and read and edited by all authors who approved the final manuscript. RP and GB had direct access to the data. KL is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Ethics approval This study involves human participants and was approved by CPP Ile de France VI on 10 April 2020 (No 26-20 Med.1°). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. The data for this article will be made available after publication on request from any qualified researchers or academics. The data include: analysed deidentified participant data, data dictionary, study protocol, statistical analysis plan, and informed consent form, among other data. The data will be shared for two years after publication on receipt of a request sent to raphael.porcher@aphp.fr.

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Supplementary Appendix I

Early treatment of hospitalized COVID-19 not requiring assisted ventilation convalescent plasma: an option for immunosuppressed patients

Table of Contents

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Methodology and statistics
Methodology: Philippe Ravaud
Statistics: Raphaël Porcher (statistics lead), Gabriel Baron, Elodie Perrodeau (internal independent statistician)

Data Monitoring Committee-1
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.

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

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Chair: Yazdan Yazdanpanah
Claire Madelaine, Eric D'Ortenzio, Oriane Puéchal, Caroline Semaille

Local clinical centres of CORIMUNO-CORIPLASM
To be completed

Lacombe K, *et al. BMJMED* 2023; 2:e000427. doi: 10.1136/bmjmed-2022-000427

Supplementary Methods

Ten-points WHO ordinal clinical progression scale

Score	Descriptor
0	Uninfected; non viral RNA detected
1	Asymptomatic; viral RNA detected
2	Symptomatic; Independent
3	Symptomatic; Assistance needed
4	Hospitalized; No oxygen therapy
5	Hospitalized; oxygen by mask or nasal prongs
6	Hospitalized; oxygen by NIV or High flow
7	Intubation and Mechanical ventilation, pO2/FIO2 ≥ 150 OR SpO2/FIO2 ≥ 200
8	Mechanical ventilation, (pO2/FIO2 < 150 OR pO2/FIO2 < 200), OR vasopressors (norepinephrine > 0.3 µg/kg/min)
9	Mechanical ventilation, pO2/FIO2 < 150 AND vasopressors (norepinephrine > 0.3 µg/kg/min), OR Dialysis, OR ECMO
10	Dead

Changes 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 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.

Statistical Methods

CORIMUNO-19 trials were planned to provide rapid information on the clinical efficacy of sarilumab 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 after inclusion of 60, 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 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 co-primary outcome and hazard ratio (HR) for the day 14 co-primary 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. The original protocol specified a modified

ITT analysis excluding patients declining the intervention and those unable to receive planned plasma therapy due to unavailability of ABO compatible blood products. Since those situations did not occur, no modified ITT analysis was performed.

The posterior distributions of the difference in day 4 co-primary 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 co-primary outcome, 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. In addition, to account for individuals included while 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.

Survival without ventilation or additional immunomodulatory treatment was portrayed by Kaplan–Meier plots. The posterior distribution of the hazard ratio was calculated by a Bayesian Cox proportional-hazards model estimated using MCMC, adjusted for age at inclusion and centre (as a random effect).

Posterior distributions were summarised 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 or additional immunomodulatory treatment. An unadjusted analysis was also added as a sensitivity analysis. Another sensitivity analysis was carried out, without considering immunomodulators. Events considered were then the need of ventilator use (invasive mechanical ventilation, non-invasive ventilation, or high flow device) and death.

Pre-planned subgroup analyses according to antivirals at baseline and post-hoc subgroup analyses according to corticosteroid therapies, specifically receiving dexamethasone, immunodeficiency, and symptoms duration (up to 5 days, vs more than 5 days) 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 4.0.5 and JAGS version 4-10.

Supplementary Results

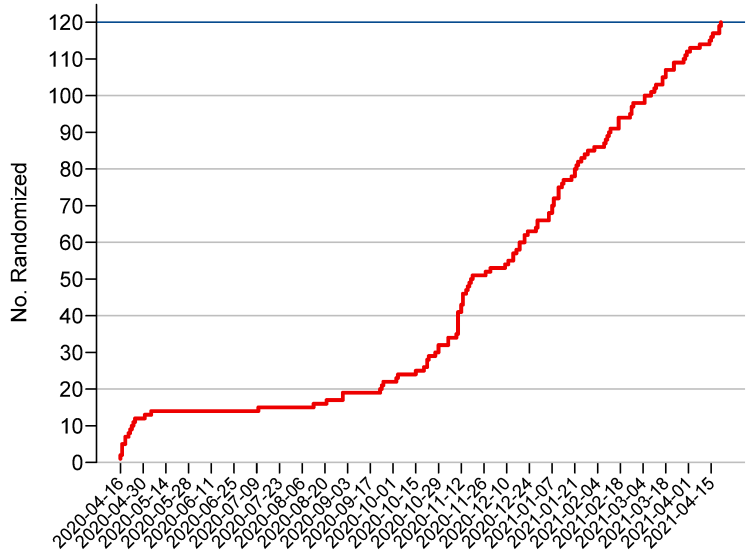

Figure S1. Accrual curve in the trial.

Table S1. Results of interim analyses.
The protocol specified that one interim analysis would be carried out after inclusion of a total of 60 patients. Given a slowdown in accrual rate, a first interim analysis was performed on data from patients included up to 30 November 2020 (N=53). A second interim analysis was then rescheduled when 60 patients would have been included, and by the time the DSMB was convened, 66 patients had been included (up to the 29 December 2020).

	First interim analysis	Second interim analysis
Date of randomisation of last patient analysed	30 November 2020	29 December 2020
No. randomised (convalescent plasma / usual care)	53 (26/27)	66 (33/33)
Day 4 co-primary outcome		
Median posterior RD of WHO-CPS ≥ 6 (90% CrI)	8.7% (–10.3 to 27.9)	8.6% (–10.3 to 27.5)
Posterior P(RD < 0)	0.224	0.184
Posterior P(RD < –5.5%)	0.109	0.071
Day 14 co-primary outcome		
Median posterior HR for primary event (90% CrI)	0.76 (0.36 to 1.59)	0.78 (0.42 to 1.43)
Posterior P(HR < 1)	0.725	0.744
Posterior P(HR < 0.85)	0.540	0.526

RD, risk difference; HR, hazard ratio.

Table S2. Treatments received before and after randomisation, until day 14.
Values are n (%).

	Convalescent plasma (N=60)			Usual care (N=60)		
Time from randomization	**Before**	**After**	**Any**	**Before**	**After**	**Any**
Anticoagulants	44 (73)	37 (62)	57 (95)	35 (58)	43 (72)	58 (97)
Antibiotics	19 (32)	31 (52)	40 (67)	24 (40)	36 (60)	44 (73)
Hydroxychloroquine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Antiviral drugs*	0 (0)	1 (2)	1 (2)	1 (2)	3 (5)	3 (5)
Immuno-modulators	0 (0)	3 (5)	3 (5)	0 (0)	6 (10)	6 (10)
Corticosteroids	30 (50)	33 (55)	49 (82)	23 (38)	41 (68)	47 (78)
Dexamethasone	24 (40)	24 (40)	41 (68)	17 (28)	27 (45)	38 (63)

* All received remdesivir (none received lopinavir/ritonavir). Antivirals such as valacyclovir were not considered.

Table S3. Detailed analysis of the day 4 co-primary outcome.
The early primary endpoint was a WHO-CPS score ≥ 6 at day 4 of randomization. According to the protocol, patients with a new do-not-resuscitate order at day 4 were be considered as with a score ≥ 6. Odds ratios (OR) are adjusted on age and centre. A risk difference (RD) < 0 or OR < 1 are in favour of convalescent plasma.

	Convalescent plasma (N=60)	Usual care (N=60)	Risk Difference	Adjusted Odds Ratio
N (%) WHO ≥ 6	13 (22%)	8 (13%)		
Posterior Median	22.3%	14.1%	+8.0%	1.88
90% CrI			-3.2 to +19.4	0.83 to 4.44
95% CrI	13.2 to 33.7	7.0 to 24.2	-5.4 to +21.7	0.71 to 5.24
Posterior probabilities*				
P(any benefit)			0.119	0.104
P(moderate or greater benefit)			0.024	0.055

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)

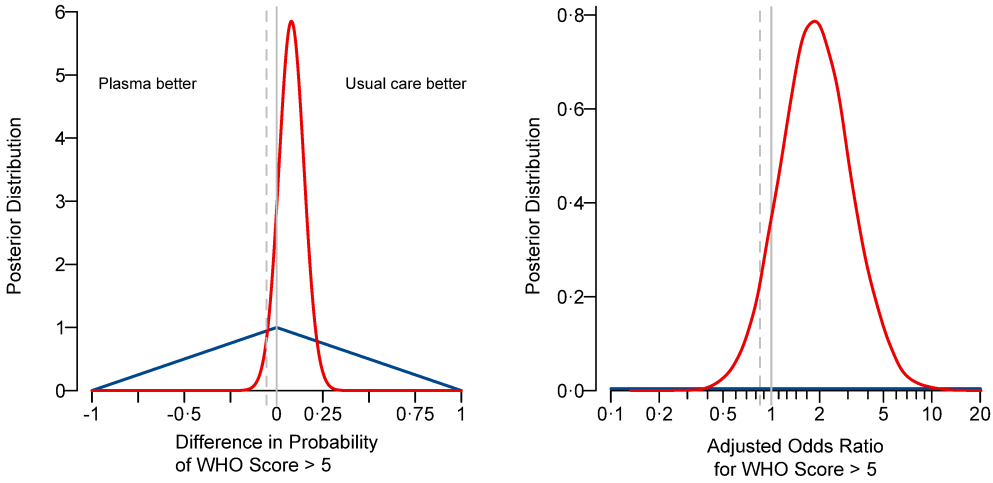

Figure S2. Posterior density of the risk difference and adjusted odds ratio for the day 4 outcome.
The red line represents the posterior density, and the dark blue line represents the minimally informative priors. The solid grey lines indicates an RD of 0 or an OR of 1, representing no treatment effect, and the dashed grey lines indicate a moderate benefit (RD = 5.5%, OR=0.85).

Table S4. Sensitivity analyses 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 convalescent plasma.

Parameter	Bayesian adjusted analysis (primary analysis)	Bayesian unadjusted analysis	Frequentist analysis*	Bayesian adjusted analysis without immunomodulators†
Median posterior HR	1.04	1.04	1.35	1.00
90% CrI	0.61 to 1.78	0.61 to 1.76	0.77 to 2.41	0.59 to 1.72
95% CrI	0.55 to 1.97	0.55 to 1.94	0.69 to 2.69	0.53 to 1.91
Posterior probabilities				
P(HR < 1)	0.452	—	0.189	0.496
P(HR < 0.95)	0.391		0.151	0.434
P(HR < 0.85)	0.269		0.087	0.301
P(HR < 0.8)	0.212	—	0.063	0.239
P-value	—	0.54	—	—

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.
† Events considered were thus the need of ventilator use (invasive mechanical ventilation, non-invasive ventilation, or high flow device) and death.

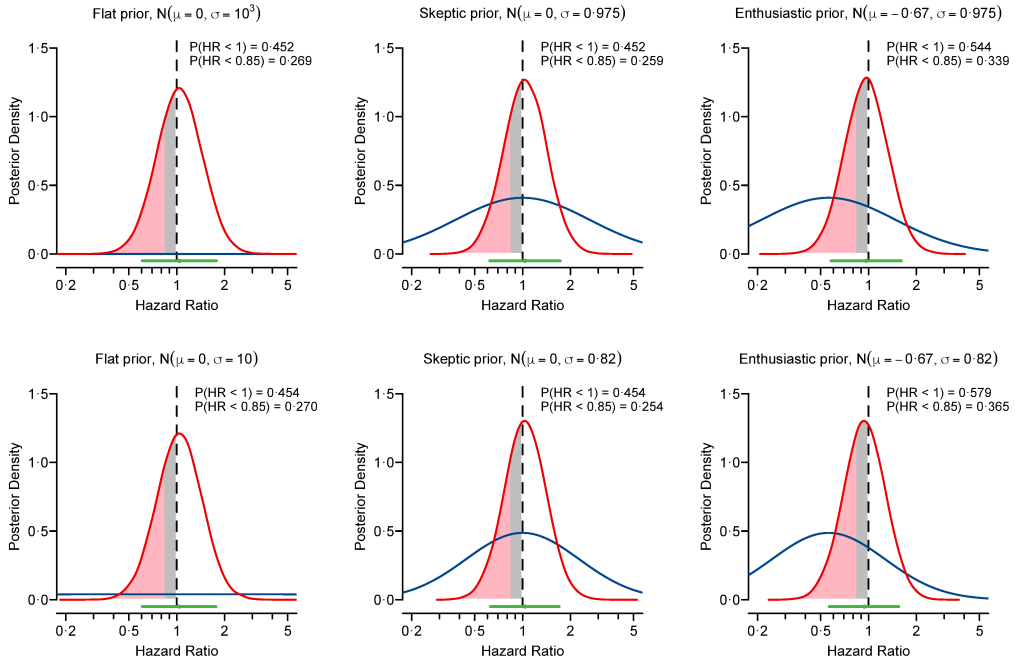

Figure S3. Sensitivity analysis to the choice of priors in the Bayesian analysis of the day 14 co-primary outcome.
The posterior densities (red lines) are plotted for different priors represented in dark blue. The grey line indicates a HR of 1 representing no treatment effect. Posterior probabilities of HR < 0.85 (red shaded region) and of HR < 1 (grey shaded plus red shaded regions) are also presented. The green 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 ($\sigma = 0.975$) and (HR < 0.2) = P(HR > 5) = 0.025 ($\sigma = 0.82$). Enthusiastic priors are 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 $\sigma = 0.82$. In all cases, the posterior median HR was close to one, and the posterior probability of at least a moderate benefit (HR < 0.85) was less than 0.37.

Table S5. Overall survival at pre-specified timepoints.
Hazard ratios (HRs) are adjusted on age and centre.

	Convalescent plasma (N=60)		Usual care (N=60)		Adjusted
	N deaths	Survival (95% CI)	N deaths	Survival (95% CI)	HR (95%CI)
Day 14	3	95% (90 to 100)	8	87% (78 to 96)	0.40 (0.10 to 1.53)
Day 28	7	88% (80 to 97)	12	80% (70 to 91)	0.51 (0.20 to 1.32)

OS: overall survival; HR: hazard ratio; CI: confidence interval

Table S6. WHO-CPS scores during follow-up.
Odds ratios (ORs) were obtained from Bayesian proportional odds models adjusted for age and centre. For longitudinal data, time was used as a main effect in the model, and the model was also adjusted on the baseline WHO-CPS score. Missing values for patients discharged were imputed at a score 3, and a window of plus/minus 2 days was used for day 14 scores. For longitudinal analyses, only missing values on the day after discharge were imputed at a score 3; subsequent missing values were not imputed. An OR < 1 indicates efficacy of convalescent plasma compared to usual care. CrI: credible interval. The timepoints predefined in the protocol were day 4, day 7 and day 14. To provide more information, results have been added at the other available timepoints following the request of one reviewer.

	Convalescent plasma (N=60)		Usual care (N=60)		
	N	Median (IQR)	N	Median (IQR)	Adjusted OR (95% CrI)
Day 2	60	5 (5 to 5)	60	5 (5 to 5)	1.86 (0.71 to 5.22)
Day 3	60	5 (5 to 5)	60	5 (4 to 5)	2.99 (1.40 to 6.80)
Day 4*	60	5 (5 to 5)	60	5 (4 to 5)	1.42 (0.70 to 2.91)
Day 5	59	5 (4 to 5)	60	5 (4 to 5)	1.32 (0.67 to 2.63)
Day 6	59	5 (4 to 5)	59	5 (4 to 5)	1.08 (0.54 to 2.14)
Day 7*	58	5 (4 to 5)	59	5 (4 to 5)	1.20 (0.61 to 2.37)
Day 14*	59	3 (2 to 4)	59	3 (2 to 5)	0.59 (0.30 to 1.13)
Longitudinal analysis*	60	—	60	—	1.04 (0.37 to 2.86)

IQR: inter-quartile range; OR: odds ratio; CrI: credible interval. * Predefined analysis in the protocol.

Table S7. Time to discharge and oxygen supply independency at multiple timepoints.
Subdistribution hazard ratios (SHRs) are obtained from Fine-Gray models adjusted on age and centre.

	Convalescent plasma (N=60)		Usual care (N=60)		Adjusted
	N events	Proportion (95% CI)	N events	Proportion (95% CI)	SHR (95%CI)
Time to discharge					
Day 14	38	63% (50 to 74)	36	60% (46 to 71)	—
Day 28	48	80% (67 to 88)	45	75% (62 to 84)	0.99 (0.65 to 1.49)
Time to oxygen supply independency*					
Day 14	39/51	76% (62 to 86)	28/45	62% (46 to 75)	—
Day 28	42/51	82% (68 to 91)	32/45	71% (55 to 82)	1.18 (0.73 to 1.91)

CI: confidence interval; SHR: subdistribution hazard ratio.
* Time to oxygen supply independency was analysed for participants needing oxygen at randomisation (i.e., with WHO-CPS score 5 or more).

Table S8. Assessment of a neutralizing Ab dose effect.

The amount of neutralising SARS-CoV-2 antibodies received was transformed in "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 (adapted from Körper S, Weiss M, Zickler D, et al. Results of the CAPSID randomized trial for high-dose convalescent plasma in patients with severe COVID-19. J Clin Invest 2021; 131: e152264). 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, volume 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 was related to the neutralising units, only outcomes for patients who received four plasma infusions were analysed, by dichotomising the units of neutralising antibodies at the median value (which was 9). Data on neutralising antibodies were missing for 6 individuals. In the convalescent plasma group, the median units of neutralising antibodies was 8 (minimum 0 [patient who did not receive plasma], maximum 16, first quartile 5, third quartile 10).

	Two plasma infusions (N=8*)	**Four plasma infusion (N=45*)**
Median units of neutralising antibodies (range)	5 (2 to 8)	9 (1.25 to 16)
Received < 9 U, n (%)	—	21 (47%)
Day 4 co-primary outcome (WHO-CPS ≥ 6)		
Among those who received < 9 U, n/N (%)	—	3/21 (14%)
Among those who received ≥ 9 U, n/N (%)	—	4/24 (17%)
Adjusted odds ratio (95% CI)	—	1.14 (0.21 to 6.27)
Day 14 co-primary outcome		
Among those who received < 9 U, n/N (%)	—	7/21 (33%)
Among those who received ≥ 9 U, n/N (%)	—	6/24 (25%)
Adjusted hazard ratio (95% CI)	—	0.66 (0.22 to 1.96)
Day 28 death		
Among those who received < 9 U, n/N (%)	—	3/21 (14%)
Among those who received ≥ 9 U, n/N (%)	—	3/24 (12%)
HR (95% CI)	—	0.97 (0.19 to 4.88)

* Volume and neutralising antibodies titres missing for 1 individual who received 2 infusions and 5 individuals who received 4 infusions.

Arbitrary units (U) of neutralising antibodies were determined so that the infusion of 200 mL of plasma with titre 1:40 corresponded to 1 U.

Table S9. Adverse events, serious adverse events and causes of deaths.

	Convalescent plasma (N=60)	Usual care (N=60)	*P* value
Adverse events (AE)			
Patients with at least one AE	44 (73%)	36 (60%)	0.17*
Patients with multiple AE	30 (50%)	25 (42%)	
Number of events	124	103	
Incidence rate per 1000 patient-day (95%CI)	30.4 (21.5 to 43.0)	28.8 (19.7 to 42.0)	
Incidence rate ratio (95%CI)	1.06 (0.63-1.77)	ref	0.83†
Serious adverse events (SAE)			
Patients with at least one SAE	30 (50%)	26 (43%)	0.58*
Patients with multiple SAE	8 (13%)	11 (18%)	
Incidence rate per 1000 patient-day (95%CI)	11.3 (7.6 to 16.7)	13.4 (8.5 to 21.1)	
Incidence rate ratio (95%CI)	0.84 (0.46 to 1.54)	ref	0.57†
Number of events (imputability according to investigator)	46 (10)	48 (0)	
Type of SAE (imputability according to investigator)			
Blood and lymphatic system disorders	*3*	*0*	
Leukopenia	1	0	
Neutropenia	1	0	
Thrombocytopenia	1	0	
Cardiac disorders	*4 (2)*	*0*	
Arrhythmia supraventricular	1	0	
Cardiac failure	1	0	
Cardiogenic shock	1 (1)	0	
Myocardial ischaemia	1 (1)	0	
Gastrointestinal disorders	*3*	*1*	
Abdominal pain	1	0	
Gastrointestinal haemorrhage	0	1	
Intestinal ischaemia	1	0	
Vomiting	1	0	
General disorders and administration site conditions	*7 (1)*	*9*	
Asthenia	0	1	
Disease complication	5 (1)	5	
General physical health deterioration	0	1	
Illness	1	0	
Malaise	0	1	
Pyrexia	1	1	
Hepatobiliary disorders	*3 (1)*	*0*	
Hepatic cytolysis	3 (1)	0	
Infections and infestations	*6*	*10*	
Bacterial sepsis	0	1	
Citrobacter infection	0	1	
Clostridium difficile colitis	0	1	
Escherichia pyelonephritis	0	1	
Pneumonia	1	1	
Pneumonia parainfluenzae viral	0	1	
Pseudomonas infection	0	1	
Respiratory tract infection viral	1	0	
Sepsis	0	1	
Septic shock	1	1	
Staphylococcal infection	1	0	
Staphylococcal sepsis	1	0	
Stenotrophomonas infection	1	0	
Urosepsis	0	1	
Investigations	3	*1*	
Alanine aminotransferase increased	1	0	
Gamma-glutamyltransferase increased	1	0	
Oxygen consumption increased	0	1	
Oxygen saturation decreased	1	0	
Metabolism and nutrition disorders	*2(1)*	*2*	
Fluid overload	1 (1)	0	
Hyperglycaemia	1	0	
Hypokalaemia	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*0*	*2*	
Adenocarcinoma of colon	0	1	
Plasma cell myeloma recurrent	0	1	
Bone and joints	*0*	*1*	
Hip prosthesis dislocation	0	1¶	
Psychiatric disorders	*0*	*1*	
Psychiatric decompensation	0	1	
Renal and urinary disorders	*0*	*1*	
Renal failure	0	1	

	Convalescent plasma (N=60)	Usual care (N=60)	*P* value
Respiratory, thoracic and mediastinal disorders	*11 (4)*	*18*	
Acute pulmonary oedema	4 (4)		
Acute respiratory distress syndrome	1	1	
Acute respiratory failure	1	1	
Dyspnoea	0	3	
Hypoxia	0	1	
Pneumonia aspiration	0	1	
Respiratory disorder	2	4	
Respiratory distress	2	4	
Respiratory failure	1	3	
Social circumstances	*2*	*1*	
Dependence on oxygen therapy	2	1	
Vascular disorders	*2 (1)*	*1*	
Haemodynamic instability	0	1	
Hypertension	1	0	
Hypertensive crisis	1	0	
Deaths	**9**	**14**	
Causes of death			
Covid-related	3	10	
Cardiologic	2	0	
Sepsis	2	3	
Gastrointestinal	0	1	
Vascular	1	0	
Other	1‡	0	

* Fisher's exact test
† Poisson model with offset and robust error variance
‡ Intercurrent disease occurring in a 88 year-old patient while in a nursing home
¶ Imputability was not reported for this SAE

Trial Protocol (Appendix II)

CORIMUNO-19-CORIPLASM Protocol, Version 4.0 (17 November 2020)

Statistical Analysis Plan (Appendix III)

CORIMUNO-19-CORIPLASM Statistical Analysis Plan, Version 1.2 (10 October 2021)

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

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

CORIMUNO-19

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

Project code number: APHP200375

Addendum 4: Protocol CORIMUNO19-CORIPLASM

V4.0 du 17/11/2020

TABLE OF CONTENTS

1 SYNOPSIS

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

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For the Immune COVID-19 – CORIPLASM group

2 RATIONALE

2.1 COVID 19 disease

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)[1]. The number of cases, and associated mortality has increased dramatically since the first cases in Wuhan, China in December 2019[2]. To date, no specific treatment has been proven to be effective for COVID-19[3]. Treatment is currently mainly supportive, with in particular mechanical ventilation for the critically ill patients (6.1% in a series of 1099 cases in China[ii]). Novel therapeutic approaches are in acute need. In this context, the therapeutic potential associated with convalescent plasma needs to be explored[4,5].

2.2 Convalescent plasma to treat viral diseases

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[6]. Indeed, a number of studies, unfortunately all inadequately controlled for bias, have reported positive outcomes, including decreased mortality in the so-called Spanish Influenza A (H1N1) infections in 1915-1917[7], the more recent Influenza A (H1N1) infections in 2009/2010[8], and more importantly here, SARS-CoV infections in 2003[9]. A systematic review and exploratory meta-analysis

performed in 2014 identified 32 studies of SARS coronavirus infection and severe influenza[7i]. 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: $I^2 = 0\%$)[7,10].

2.3 Convalescent plasma to treat SARS-CoV infected patients

In addition to being both highly pathogenic coronavirus with lung tropism, SARS-CoV-2 and SARS-CoV have been recently found to bind to the same entry receptor (ACE2) with similar affinity[11]. Furthermore, SARS-CoV polyclonal Ab inhibit SARS-CoV-2 spike glycoprotein (S) - mediated entry into cells.

SARS-CoV convalescent plasma has been shown to contain neutralizing Ab against the involved virus[12].Furthermore, neutralizing Ab elicited by primary infection of SARS-CoV can protect mice from re-infection[13]. Very recently, similar findings have been reported in monkeys regarding SARS-CoV-2[14]. Importantly, passive intra-peritoneal transfer of such SARS-CoV(1) Ab to naïve mice can prevent SARS-CoV replication in the respiratory tract[14].

The above mentioned review identified 8 observational studies at moderate to high risk of bias that reported improved mortality after SARS-CoV – infected patients received various amount of convalescent plasma[7]. Notably, a small retrospective case-comparison study (19 vs 21 patients) showed a case fatality rate reduction after convalescent plasma treatment of 23% (95% CI: 6%-42%, p=0,049)[15]. Each patient received 200 to 400 ml of plasma. Also, a case series including 80 treated patients reported an overall mortality rate of 12,5% in severe deteriorating SARS-CoV (1) - infected patients while the overall SARS-related mortality rate in Hong-Kong was 17% during the SARS epidemic in 2003[10]. The mean volume of plasma infused was 279 + 127 ml (range 160-640 ml). Interestingly, a subgroup analysis found that those treated with a PCR positive but seronegative for SARS-CoV-1 has a significantly better outcome (i.e. discharge by day 22 vs after day 22 or death) than those who were seropositive at the time of plasma infusion (61% vs 21%, p<0.001). Similarly, those receiving convalescent plasma before (versus after) 14 days after onset of symptoms

were found to have a better outcome. In multivariate analysis, the time of convalescent plasma was reported to stay significant.

Overall, these findings favor an early administration during the infectious course, at a time where pathology may be driven mainly by viral replication. Lastly, and to the best of our knowledge, at least one study evaluating convalescent plasma to treat SARS-CoV-2 infected patients is underway in China[16]. In a recently reported 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 [17].

In all cases, a close monitoring of treated patients with convalescent plasma to verify for any unintended side effects, in particular evidence of inflammatory flare-up, will be necessary.

2.4 Convalescent plasma mechanism of action

2.4.1 Ab-mediated immunopathology in CoV diseases

Although these last observations of TRALI appear isolated, the issue of potential toxicity associated with convalescent plasma needs to be addressed carefully. SARS-CoV-2 infected patients, as well as SARS-CoV (1) and MERS-CoV patients exhibit acute lung injury (ALI), that may evolve into acute respiratory disease syndrome (ARDS) and death. Such ALI is driven by acute inflammation through mechanisms that remain elusive.

Experimental studies as well as observations in humans suggest that at least initially in the course of SARS-CoV(1) - associated disease, the immune response, notably Ab-mediated, may aggravate ALI by skewing inflammation-resolving responses[18]. Such an Ab-dependent enhancement (ADE) has been suspected in a large variety of diseases[19]. However, with the notable exception of secondary dengue as well as dengue and respiratory syncytial virus (RSV) vaccinations, observations were made in the majority of cases *in vitro* or in animal models and limited evidence from epidemiological series or pathophysiology studies in humans have been reported so far. Heterotopic and/or non (i.e. insufficiently) - neutralizing Ab have been suggested to be contributive. The potential role of such Ab in elderly patients, previously exposed to a variety of coronavirus, is unknown but may contribute to the severity of COVID-19 in this population. Experimental MERS-CoV data in rabbits suggest that

failing to develop neutralizing Ab (or waning titers at distance of infection) may be a risk factor for severe lung disease upon re-exposure to MERS-CoV[20]. From a mechanistic perspective, non-neutralizing Ab may favor a more efficient viral uptake into the target cell in Fc-gamma or complement-mediated binding leading to enhanced replication and pathogenicity[21]. Furthermore, and as reported with inactivated RSV vaccination, a Th2-type immunopathologic responses upon rechallenge has been described in a mouse model following vaccination with an inactivated SARS-CoV(1) vaccine[22].

2.4.2 Early vs late Ab responses in CoV diseases

Peak in viral load in SARS patients has been reported to coincide with the first appearance of an Ab response[23]. *In vitro*, higher concentration of Ab collected from SARS-CoV(1) -infected patients (i.e. non-convalescent) facilitated SARS-CoV(1) infection and induced higher levels of virus-induced apoptosis[24]. Importantly, this phenomenon occurred via anti-spike (S) Ab that mediated ADE, but not via anti-nucleocapsid (N) Ab[xxi,25]. A possibly relevant observation is that temporal changes in S-specific and N-specific neutralizing Ab responses may differ significantly in patients who have either recovered from or succumbed to SARS-CoV(1) infection[26]. In comparison to patients who subsequently died, recovered patients had a delayed but sustained increase in (serum) neutralizing Ab titers with an increasing contribution of anti N Ab (not observed in patients that subsequently died). Increasing Ab affinity is most probably occurring as well. Long-term persistence of robust Ab (and cytotoxic T cell responses) has been reported in patients infected with SARS CoV-1 (1)[27]. Interestingly, very recent data in COVID-19 patients indicates seroconversion occurring after 6-12 days, but not followed by rapid decline in viral load[28]. This later finding is compatible with a suboptimal endogenous early Ab-response with regard to SARS-CoV-2 replication.

Taken together, these findings suggest that the absence of reported serious adverse effects associated with convalescent plasma may be, at least in partly, in relation with a different quality of Ab in convalescent patients versus earlier during the acute phase of the disease. An appropriate assessment of the Ab response in convalescent patients with a requirement for the presence of an anti-SARS-Cov-2 neutralizing Ab titer at an adequate level in the collected plasma will be an important prerequisite.

We therefore hypothesize that early administration of convalescent plasma containing polyclonal neutralizing Abs may inhibit viral entry and replication (as recently suggested in vitro[xii]) and consequently blunt an early pro-inflammatory pathogenic endogenous Ab response.

3 INVESTIGATIONAL MEDICINAL PRODUCT: CONVALESCENT PLASMA

3.1 Convalescent plasma collection

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 (per at date regulation regarding blood donation) 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[29] 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) studies[xiii], a titer of ≥ 1/40 as assessed by cytopathic effect - based virus neutralizing tests (described in[30]) 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. A mean of approximately 660 ml of plasma may undergo pathogen reduction treatment. At least two pathogen reduction technologies have has been found to adequately inactivate MERS-CoV in blood products[31,32]. Although formally untested as of now, one can reasonably assume approaching efficacy regarding SARS-CoV-2 in plasma. After an earlier report reporting a slight reduction in Ebola virus IgG and neutralizing activity in a convalescent plasma after Intercept pathogen reduction[33], a recently published larger study found that Intercept treatment did not significantly reduce Ebola virus IgG titers or neutralizing activity[34].

Presence of infectious viremia in convalescent patients is not expected, despite a recent report of positive RT-PCR recurrence on repeat throat swabs in in 4 asymptomatic patients 5 to 13 days after hospital discharge[35]. In addition to being an isolated observation as of now, establishing whether viral RNA detected by PCR in such a setting is associated with infectious virus remains to be established. Furthermore, current knowledge regarding viremia kinetics is not in favor of viremia occurring in convalescent, i.e. asymptomatic, patients. Lastly, previous studies with coronavirus or influenza infection convalescent plasma do not report adverse events suggestive of discernable "re"infection in patients acutely infected at time of transfusion. To verify these findings, the absence of SARS-CoV-2 RNA in the collected plasma will be checked before infusion (as per regulatory requirements for all infectious agents).

As mentioned earlier, convalescent donor's candidate for plasma donation should undergo eligibility screening just like any other donor, including eligibility criteria pertaining to prior COVID-19 disease. Such donors will therefore be eligible for standard blood donation. This consideration may result in questioning additional safety measures such as verifying the absence of viral RNA and/or pathogen reduction if not performed usually on blood products in the given jurisdiction. In France, plasma for transfusion currently undergoes pathogen reduction or quarantine for at least 2 months until a renewed microbiological assessment at time of subsequent plasma donation.

Current regulation authorizes a plasma donation up to every 2 weeks. Convalescent donors will be invited to undergo 3 donations at 2 week intervals. The protocol for convalescent plasma collection has received ANSM approval (18/3/20) and ethics approval (Comité de protection des personnes, Ile de France, 26/3/20). Once treated and qualified, plasma will be cryopreserved (in 200 to 220 ml units) and made available for clinical use.

3.2 Safety of convalescent Plasma infusion

Convalescent plasma adverse events

None of the studies analyzed in the 2015 systematic review reported serious adverse events, although reporting of such events was most certainly not comprehensive. In a

convalescent plasma trial for Ebola disease to which contributed the Etablissement Français du Sang (EFS) in 2015, no serious adverse events were evidenced in 99 patients (minor adverse events were observed 8% of patients, mostly an increase in temperature (5%) and/or itching or skin rash (4%))[36]. Notably, 2 case reports of possible transfusion-related acute lung injury (TRALI) following convalescent plasma have been reported in a patient with Ebola disease[37] and patient with MERS-CoV[38]. In both cases, transfused plasmas were found free of anti-HLA or anti-HNA Ab. In recent case series mentioned above, and although administered late in the course of the disease (10 to 22 days after onset), transfusion of 400 ml of ABO-compatible convalescent plasma was not associated with adverse events, including clinical or biological evidence for transfusion-associated inflammatory flare-up[16].

3.3 Justification of the schedule proposed for this nested trial

Two convalescent plasma units of 200 to 220 ml each will be transfused i.v. as early as possibleand no later than 10 days after onset 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. Transfusion monitoring, treatment and reporting of adverse events will be performed per ANSM hemovigilance regulation regarding transfusion of labile blood products as well as through the specific clinical trial vigilance.

3.4 Transfusion surveillance and reporting of adverse events through Hemovigilance system

3.4.1 Definition

An adverse event is defined as any untoward occurrence associated with the collecting, testing, processing, storage and distribution of blood and blood components that might lead to an adverse reaction in blood recipients or blood donors.

Adverse reactions in recipients include:

- hemolytic transfusion reactions, e.g. acute or delayed;
- delayed serological reactions as a result of allo-immunisation against red cell antigens;
- non-hemolytic transfusion reactions, e.g. transfusion related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), graft versus host disease (GvHD), febrile transfusion reactions and allergic reactions;

• other transfusion reactions, e.g. haemosiderosis and hyperkalemia;
• bacterial, viral, parasitical, fungal or transmissible spongiform encephalopathy (TSE) transmission.

3.4.2 Notification system

Reporting and analysis of adverse events and reactions associated with transfusion requires close cooperation between the clinical department where transfusion took place, the hospital blood bank that issued the transfused blood component and the blood establishment that collected and distributed the blood unit (if different from the hospital blood bank).

Any adverse event related to plasma transfusion will be notified to the competent authority according to usual procedures in compliance with the on-going regulation (article R. 1221-51 CSP).

The clinical department where transfusion took place must report any adverse event observed in patient following plasma transfusion to the person in charge of Hemovigilance in the "Hospital" without delay, the regulation underlines a report within 8 hours after observation. The reporting can be done easily by all available means (see Annex 3)
and take into account in real time. If the haemovigilance correspondent cannot be join or is not available, the adverse event must be directly notified by phone (or any usual way) to the EFS to the service that delivered the plasma unit. The Biologist of the EFS will take into account the information forthwith and inform the person in charge of Haemovigilance in the "Hospital" as soon as possible.
Once notified, the "hospital hemovigilance officer" carries out with the investigations and informs the blood establishment (EFS) hemovigilance officer. Together, they submit an official declaration to the authorities (ANSM) through e-fit database:

- without delay in case of serious adverse events (defined as adverse events that might have led to death or life-threatening, disabling or incapacitating conditions for recipients or donors, or which might have resulted in prolonged hospitalisation or morbidity) or death, at latest within the 48 hours after observation.

- Within the 15 days following the observation for the non-serious adverse events.

In summary, any investigator or any other healthcare professional who finds or has knowledge of:

- **a serious incident**, must report it without delay to the hemovigilance correspondent of the establishment where the incident took place or in which the incident was discovered (article R .1221-49)

- **an adverse reaction occurring in a recipient of the experimental LBP**, will have to report it without delay to the hemovigilance correspondent of the establishment in which the product was administered (article R.1221-49.2)

And consequently, the hemovigilance correspondent of the health establishment or the transfusion establishment (EFS) will have to declare to the ANSM particularly serious incidents and adverse reactions reported by the health professional (investigators especially).

If necessary, a completed standard questionnaire (additional sheet available on the ANSM website or on E FIT) or any other useful document (copy of reports, diagrams, results of internal investigations ...) are provided in documents related to the declaration.

For safety assessment by the sponsor and reporting adverse events to the competent authorities within the framework of the regulations on clinical trials:

see chapter 9. RECORDING AND REPORTING ADVERSE EVENTS

3.5 Traceability of transfused plasma:

The three 200 - 220 mL plasma units treated by the Intercept pathogen attenuation process are identified by the product codes 20312, 20313 and 20314 and the national single number of the apheresis plasma donation.

Plasma units are obtained, prepared and delivered in a strict observance of the existing rules. A VI-49 code is registered on the donation file at time of donation in order to trigger the additional analyzes (notably the nucleic acid detection of the SARS-CoV-2) and allow the reservation of these plasmas for the clinical trial. A mention (PlasmACoV2) is added on a temporary label to help the operators to track them in the stock. The final label respect all the existing specification (without any modification).

These plasma units are delivered according to the existing procedures and accompanied by usual documents which allow to perform the traceability and guarantee the formal link between donor – plasma - patient. The transfusion feedback will be carried out in accordance with the procedure existing in the site of their transfusion. All information about transfusion and transfused patients will be recorded in the transfusion management software (CTSserveur INLOG).

4 THE CORIMUNO-CORIPLASM PROTOCOL:

4.1 Description of the 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[39] 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) studies[13], a titer of >= 1/40 as

assessed by cytopathic effect - based virus neutralizing tests (described in[40]) 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. A mean of approximately 660 ml of plasma may undergo pathogen reduction treatment. At least two pathogen reduction technologies have has been found to adequately inactivate MERS-CoV in blood products[41,42]. Although formally untested as of now, one can reasonably assume approaching efficacy regarding SARS-CoV-2 in plasma. After an earlier report reporting a slight reduction in Ebola virus IgG and neutralizing activity in a convalescent plasma after Intercept pathogen reduction[43], a recently published larger study found that Intercept treatment did not significantly reduce Ebola virus IgG titers or neutralizing activity[44].

Presence of infectious viremia in convalescent patients is not expected, despite a recent report of positive RT-PCR recurrence on repeat throat swabs in in 4 asymptomatic patients 5 to 13 days after hospital discharge[45]. In addition to being an isolated observation as of now, establishing whether viral RNA detected by PCR in such a setting is associated with infectious virus remains to be established. Furthermore, current knowledge regarding viremia kinetics is not in favor of viremia occurring in convalescent, i.e. asymptomatic, patients. Lastly, previous studies with coronavirus or influenza infection convalescent plasma do not report adverse events suggestive of discernable “re”infection in patients acutely infected at time of transfusion. To verify these findings, the absence of SARS-CoV-2 RNA in the collected plasma will be checked before infusion.

As mentioned earlier, convalescent donor’s candidate for plasma donation should undergo eligibility screening just like any other donor, including eligibility criteria pertaining to prior COVID-19 disease. Such donors will therefore be eligible for standard blood donation. This consideration may result in questioning additional safety measures such as verifying the absence of viral RNA and/or pathogen reduction if not performed usually on blood products in the given jurisdiction. In France, plasma for transfusion currently undergoes pathogen reduction or quarantine for at least 2 months until a renewed microbiological assessment at time of subsequent plasma donation.

Current regulation authorizes a plasma donation up to every 2 weeks. Convalescent donors will be invited to undergo 3 donations at 2 week intervals. The protocol for convalescent plasma collection has received ANSM approval (18/3/20) and ethics approval (Comité de protection des personnes, Ile de France, 26/3/20). Once treated and qualified, plasma will be cryopreserved (in 200 to 220 ml units) and made available for clinical use.

4.2 Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including rescue medications

The medical staff is expected to monitor patients and administer any drug required for the treatment and/or prevention of all the usual complications that can develop in this setting.

As mentioned earlier, transfusion surveillance, treatment and reporting of adverse events will be performed per ANSM hemovigilance regulation regarding transfusion of labile blood products.

Furthermore, safety assessment by the sponsor and reporting adverse events to the competent authorities will be performed within the framework of the regulations on clinical trials.

Transfusion will be at a slow rate and under close monitoring, notably to identify and treat circulatory overload occurrence or other transfusion-related immediate side effects. Close monitoring will obviously be maintained after transfusion to detect any further unintended side effects, in particular evidence of increased inflammatory in the lungs or systemically.

4.3 PLASMA supply of the investigational centers

Convalescent plasma will be issued by the local EFS blood issuing center as all other blood products issued for patients in the given hospital, and in compliance with ANSM hemovigilance regulation.

4.4 Traceability in investigational centers

In accordance with the rules of Good Practices and to track the treatment given to each patient, all the information related to the treatment will be collected on a traceability sheet

(Issuing, date of administration, time of administration, blood product identification number, and expiry date, and dose administered). Furthermore, transfusion traceability as per ANSM hemovigilance regulation will be undertaken as well.

4.5 Methods for monitoring compliance with the treatment

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

4.6 Control

Control patients will receive the best standard of care.

5 DESIGN AND DATA COLLECTION

5.1 Design

This is a nested randomized trial within the CORIMUNO-19 platform trial (see protocol synopsis of CORIMUNO-19 in annex 2).

An average of 120 participants will be expected (60 participants in each arm) (see statistical section);

Availability of ABO compatible plasma will be checked by investigator when a CORIMUNO-19 patients is eligible. If so, randomization will be undertaken and patient will be offered to participate in this nested trial if he is allocated to the experimental arm.

Information and written consent collection will be done by the investigator

5.2 Specificity of the convalescent plasma treatment arm and associated controls

Eligible randomized patients may not be able to receive the intended plasma treatment because of ABO-compatible blood product unavailability. This may occur especially early-on, at a time when eligible (i.e. more than 14 days after disease resolution) convalescent plasma donors will be in limited numbers. As mentioned above, and to ensure proper

randomization, availability of ABO compatible plasma will be verified with EFS for all eligible patients subjected to subsequent randomisation. This may be important, considering a potential association between recipient blood group and COVID-19 occurrence[46] or severity (not reported as of 28/3/20).

5.3 Inclusion Criteria:

- Patients included in the CORIMUNO-19 cohort
- Mild severity (grade 4 or 5 as described in the WHO scale, see annexe 1) occurring up to day 10 after initiation of clinical symptoms.

5.4 Exclusion Criteria:

- Pregnancy
- Current documented and uncontrolled bacterial infection.
- Prior severe (≥ grade 3) allergic reactions to plasma transfusion

6 ENPOINTS FOR THE CORIPLASM TRIAL

6.1 Efficacy endpoints

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 (other than steroids). 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.

   Early end point: WHO progression scale ≥ 6 (see annex 1) at day 4 of randomization. A patient with new DNR order at day 4 will be considered as with a score > 5

Secondary end-points:

1. WHO progression scale (annex 1) at 4, 7 and 14 days after randomization, overall survival at 14 and 28 after randomization, time to discharge, time to oxygen supply independency.
2. Biological parameters (as per the CORIMUNO-19 biological follow-up) improvement at day 4, 7 and 14 after randomization.

6.2 Safety endpoints

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.

6.3 Specific data to be collected for this trial

Standard surveillance of plasma transfusion and reporting of adverse events per ANSM hemovigilance

7 EXPECTED BENEFITS AND RISKS

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

Other benefits are to:

- blunt not only the pneumopathy-induced damage but also other COVID-19-associated injuries such as acute kidney injury (AKI), myocarditis, secondary bacterial infections.
- shorten the duration of hospital stay with minimization of physical (hospital acquired pressure ulcers, increased morbidity and mortality associated with nosocomial infections), psychological and economic complications related with prolonged stay.
- Shortening the hospital stay fosters not only individual clinical benefit but also collective clinical benefit through facilitation of collective access to caregivers.

The expected risk are:

In France all transfusion-related adverse events are reported to the ANSM through the hemovigilance system. In 2018, with 280 000 plasma transfused, incidence of TACO, TRALI and allergy (all imputability) were 2.1, 1.0 and 103.7 / 100 000 plasma transfused, respectively. Among allergies with a reasonable imputability (imputability grade 2 and 3), incidence of severe allergy (severity grade 3) was 29/ 100 000 plasma transfusion[47].

Special attention should be paid to clinical signs suggesting circulatory overload in patients with cardiac insufficiency during plasma transfusion as well as immediately after due to the risk of TACO "Transfusion-Associated Circulatory Overload ".
A slow infusion rate (< 3 ml / mn) as well as prophylactic diuretics especially furosemide with a dosage of 20 to 40mg depending on the patient's profile, may be considered in patients with cardiac insufficiency.

8 STATISTICAL METHODS

8.1 Principles of cohort multiple randomized controlled trials

The key features of the cohort multiple Randomized Controlled Trials (cmRCT) design are:
(I) Recruitment of a large observational cohort of patients with the condition of interest
(II) Regular measurement of outcomes for the whole cohort
(III) Capacity for multiple randomised controlled trials over time
Patients enrolled in the cohort agree to allow their longitudinal data to be used in the aggregate. They also allow their data to be used to identify them to be invited to participate in research interventions or for comparison purposes for intervention trials that may be conducted with other patients while they are participating in the cohort.
In the cmRCT design, as described to patients when they consent to participate in the cohort, only eligible patients randomly selected to be offered an intervention, but not eligible non-selected patients, are contacted and offered treatment. Eligible patients not selected are not notified about the trial. Consent for specific trials will be obtained from those eligible patients who are invited and accept the offer to participate. Post-intervention outcomes among eligible patients who accept the offer to receive the intervention will be compared with outcomes among patients from the cohort who were identified as eligible

for the intervention, but were not randomly selected to be offered the intervention and not contacted about the intervention.

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

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

For the CORIMUNO-19-CORIPLASM trial, individuals in the cohort eligible in the participating centers are randomized 1:1 until a predefined sample size is reached. **An interim analysis is performed at mid-trial, but inclusions are not frozen to wait for the interim analysis.**

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

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

In a Bayesian analysis, the specification of the prior distribution is crucial. For the CORIMUNO-19- CORIPLASM trial, we want the conclusions to depend primarily on data from the trial, not on prior opinion. An uninformative prior for the hazard ratio will therefore be used. More precisely, the prior distribution for the log hazard ratio will be a Gaussian distribution with mean 0 and variance 106. For binary outcomes, let p denote the probability of outcome in a given arm; the prior distribution of p is set as a beta prior distribution with parameters 1 and 1, equivalent to a uniform distribution on the interval

(0,1). This corresponds to a hypothetical situation where we would have data on two individuals treated with the corresponding arm strategy, and observing that exactly 1 of the 2 experiencing the outcome. These prior distributions ensure very little influence of our prior opinion on conclusions.

For now, the calculations in this protocol have been performed for a sample size of 60 individuals per arm, with interim analyses after 30. However, this may be adapted to allow continuing the trial if results are promising, though not formally achieving the predefined efficacy boundary. Additional calculations have therefore been performed with the additional recruitment of 30 individuals per arm after the total sample size of 120 has been reached (see below). This may also be modified in future protocols.

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

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

8.3 Statistical criteria for termination of the study

This section describes the Bayesian monitoring of the trial. We defined two co-primary outcomes, one time-to-event outcome evaluated up to day 14, and an early success outcome evaluated on day 4. Methods for trial monitoring have been developed for the early outcome because (1) short-term outcomes are obtained more quickly so are easier for early interim decision and (2) calculations of all possible outcomes are more tractable for binary outcomes. For analyses based on the hazard ratio, which allow to account for all information gathered in the trial (even for patients who do not have the entire follow-up necessary to evaluate a binary outcome), the same decision boundaries will be used. It is not expected that the properties of the boundaries would be significantly different when using the posterior distribution of the hazard ratio (similarly to the use of O'Brien Fleming boundaries in frequentist trials for continuous, binary or survival outcomes). 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 < 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/).

Let us denote p_E and p_C the event rates in the experimental and control arms, respectively. At the interim analysis, the posterior probability of a lower event rate in the experimental than in the control arm is calculated, i.e. P ($p_E < p_C$ | data), which we term the posterior probability of efficacy. The posterior probability P ($p_E < p_C$ - | data) is also computed, corresponding to the probability to achieve at least a treatment effect, termed the posterior probability of sufficient efficacy. At each interim analysis, if the posterior probability of sufficient efficacy is less than 0.20, the trial may be stopped for futility upon decision of the DSMB (indicative and not binding futility boundary). If the posterior probability of efficacy is higher than 0.99, then the trial may be stopped for efficacy (again this boundary is not binding and the DSMB may propose to continue the accrual based on other information, such as secondary outcomes or safety). The choice of interim monitoring for futility based on the posterior probability of sufficient efficacy and not the posterior probability of efficacy is justified by the need to increase the chance of early stopping for futility when information increases, if the experimental treatment is no better than the control. Conversely, keeping a constant futility boundary on the posterior probability of efficacy would decrease the chances of early stopping if additional analyses are performed, because under the null, as information increases, the posterior distribution of efficacy would converge to 0.5. This boundary is stricter than using a boundary on the posterior probability of efficacy (grey line on the figure 1, left panel), but this choice is justified by the need to quickly identify treatments with a large effect. The futility threshold (0.20) may be revised in future trials, if expected effects are lower.

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

occur after final recruitment, and a posterior probability of efficacy higher than 0.95 will be considered as indicating efficacy.

To compute the probability of sufficient efficacy, we assumed that the hazard ratio for time-to-event outcomes should be at least 0.85, which translates to an event rate of 45.5% in the experimental arm when it is 50% in the control arm. Accordingly, □ was set to 0.055 for calculations with binary outcomes. The table 1 presents the properties of the design under different scenarios, with first stage sample size 60 (30 patients per arm) and second-stage sample size 60 (30 additional per arm).

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

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

In terms of trial monitoring, it is also planned that more interim analyses would be performed, primary safety reviews, but the posterior distribution of key efficacy parameters should then also be presented to the DSMB, without formal stopping rules. This may be performed on a weekly basis according to the CORIMUNO cohort protocol, and adapted according to actual accrual in the trial.

8.4 Number of participants and justification

The total sample size is fixed at 120 (60 per arm) for the final analysis, with interim analysis after 60 (30 per arm). Overall, the CORIMUNO-19-CORIPLASM trial **may therefore accrue between 60 patients and 120 patients in total**.

- The calculations shown in the table 1 show that the type I error rate of the design would be 4.7% if the event rate is 0.50 in each arm, and the power to detect a decrease from 0.50 to 0.20 would be 97.2% (e.g. a difference in expected survival rate without needs of ventilator utilization of 50% in the control group and 80% in the experimental group). This trial would also have power 73.9% to detect a decrease from 0.50 to 0.30.

8.5 Anticipated level of statistical significance

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

8.6 Subject replacement strategy

No subject replacement is planned.

8.7 Method for taking into account missing, unused or invalid

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

8.8 Management of modifications made to the analysis plan for the initial strategy

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

The original SAP as well as the modified SAP will be kept in the study files, with the justification for any modification.

8.9 Choice of individuals to be included in the analyses

For interim monitoring, the analysis will be carried out according to the intention to treat (ITT) principle, i.e. each randomized participant will be analyzed in the group assigned to him/her by randomization, regardless of the actual treatment received or other protocol deviations. A modified ITT may be added (see threrafter).

The primary endpoints analyses 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.

9 RECORDING AND REPORTING ADVERSE EVENTS: SPECIFICITIES FOR THIS RESEARCH ON A LABILE BLOOD PRODUCT

9.1 Definitions applicable to labile blood products in the context of an interventional research

- **Adverse event :**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

An adverse event occurring in donors and related or likely to be related to blood samples or occurring in recipients and related or likely to be related to the administration of a labile blood product.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the participant enrolled in the study, requires hospitalization or prolongs existing hospitalization, or any other morbid condition.

- **Incident**

Incident related to blood samples, biological qualification of donation, preparation, conservation, distribution, delivery or use of labile blood products, due to an accident or error, likely to affect the safety or quality of this product and cause adverse reactions.

- **Serious incident**

Incident likely to cause serious adverse reactions.

9.2 Obligations of the investigator

The investigator notifies the sponsor **without delay** on the day the investigator becomes aware :

- For the experimental group with transfusion: **any adverse event (serious or not serious) linkely related to plasma transfusion, which** occurs during the study
- For the control group: only serious adverse event and adverse event deemed "medically significant" except those which are listed in the protocol as not requiring a notification without delay.

Serious adverse events that require the investigator to notify the sponsor without delay :

- Serious adverse event:

A serious adverse event is any untoward medical occurrence that:

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

- Adverse event deemed "medically significant" that require the investigator to notify without delay the sponsor :

Any other grade III or higher severe or toxic clinical complication (defined accordingly to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE).

The sponsor will particularly monitor hematological abnormalities (grade > 3), serious liver damage (DILI, hepatic insufficiency and isolated increased of hepatic enzymes > grade 4), serious infections (Bacterial, Fungal) and hypersensitivity reactions.

Isolated biological disturbance without clinical complication or organ damage must notify to the sponsor if the grade CTCAE is > to grade 3

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

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

- Normal and natural course of the condition
- Scheduled inpatient hospitalization for monitoring the condition under investigation (with no deterioration in the subject's medical condition compared to baseline)
- Inpatient hospitalization for routine treatment or monitoring the condition under investigation, not associated with a deterioration in the subject's medical condition
- Any routine complications occurring in patients infected by COVID 19 (except death)

- Special circumstances
- Hospitalization for a pre-existing illness or condition
- Hospitalization for a medical or surgical treatment scheduled prior to the study
- Admission for social or administrative reasons
- Emergency care (< 12 hours)

- Adverse events potentially related to treatments prescribed as part of the care provided during the study follow-up

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

Period during which the investigator must send notification of AE and SAEs to the sponsor without delay

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

collect all SAEs possibly related to the IMP, but must transmit all possible SAEs related to the IMP of which he has knowledge.

9.3 Obligations of the sponsor

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

The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below.

❖ For serious adverse events likely to be related to the convalescent plasma:
- refer to the Investigator's Brochure

❖ For serious adverse events that may be related to the medicinal product necessary for the conduct of the research (diuretic in case of cardiac insufficiency):
Refer to the SmPC in force of the specialty used (furosemide)

The sponsor declares **without delay** to the competent authority (to the following addresses: **declarationsusars@ansm.sante.fr**, and in copy **econcoh@ansm.sante.fr** and **lotfi.boudali@ansm.sante.fr**) **any suspected serious adverse reaction in the recipient, any suspected adverse reaction, and any serious incident.**

The sponsor declares **without delay** to the competent authority **all relevant additional information at the same addresses**.

The sponsor will inform the competent authority and the Research Ethics Committee **without delay** upon knowledge of **any emerging safety issue** and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities (to the following addresses: **vig-essaiscliniques@ansm.sante.fr**, and in copy **econcoh@ansm.sante.fr** and **lotfi.boudali@ansm.sante.fr**) **any additional relevant information** about the emerging safety issue in the form of a follow-up report, which must be sent **without delay** after learning of the information at the same addresses .

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1 ANNEX

Annex 1: WHO progression scale

OMS Progression scale	Descriptor	Score
Uninfected	Uninfected; non viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
Ambulatory	Symptomatic; Independent	2
Ambulatory	Symptomatic; Assistance needed	3
Hospitalized : mild disease	Hospitalized; No oxygen therapy	4
Hospitalized : mild disease	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized : severe disease	Hospitalized; oxygen by NIV or High flow	6
Hospitalized : severe disease	Intubation and Mechanical ventilation, pO2/FIO2>=150 OR SpO2/FIO2>=200	7
Hospitalized : severe disease	Mechanical ventilation, (pO2/FIO2<150 OR pO2/FIO2<200) OR vasopressors (norepinephrine >0.3 microg/kg/min)	8
Hospitalized : severe disease	Mechanical ventilation, pO2/FIO2<150 AND vasopressors (norepinephrine >0.3 microg/kg/min), OR Dialysis OR ECMO	9
Death	Dead	10

ANNEX 2 : BRIEF SYNOPSIS OF THE COVIMMUNO-19 PLATFORM TRIAL AND STATISTICAL CONSIDERATIONS

Summary :

The CORRIMUNO-19 cohort is specifically designed to conduct trials within cohorts.

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

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

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

1.1 Adding new trials in the cohort:

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

1.2 Clinical trial process

- Trials with no overlap of the targeted population i.e. with inclusion and exclusion criteria leading to distinct groups will be driven in parallel. Thus, patients of the cohort will be randomized in the trial corresponding to their characteristics.
- Trials with overlap of the targeted population will be driven sequentially. A first set of patients will be included in the first trial (A). After inclusion of the predefined number of patients in the i^{th} set, the set $(i+1)^{th}$ set of patients will be included in one (B) of the other trials with the overlapped targeted population. This allows to run the interim analyses of trial A on the *i*-th set and to continue to include patients in trials B. After the results of the interim analysis it will be decided to continue or not the trial A and potentially to come back to trial A or not for the $(i+2)^{th}$ set of patients
  The sample of the sets will depend of each trial.
- Inclusions of new sets will stop when statistical analyses conclude on futility or efficacy or by DSMB decision.

1.3 Methodological elements of trials nested in the cohort:

- Trials nested in the cohorts may involve:
  - All patients of the cohort
  - OR a subpopulation of patients with specific eligibility criteria (e.g., patients in ICU, patients with a specific biomarker, etc.)
- Endpoints of the trials may involve:
  - The endpoints regularly collected in the cohort (see section 4.4)
  - OR specific endpoints collected for the given trial
- Interventions may be of any type (e.g., medications, non-pharmacological treatments, organisation of care…). According to the cmRCT design, a random sample of patients is selected among all patients eligible for the trial and is proposed the intervention. Their outcome is compared to patients who did not receive the intervention.
- All elements of trials will be defined in specific dedicated protocols.
- Patients who will be proposed for the intervention will provide a new consent, specific for the trial. Patients who serve as controls will not provide a new consent, according to the cmRCT design.

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
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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 influenza7i. 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 – 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.

<table>
<tr><td>Investigational medicinal product</td><td>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.</td></tr>
<tr><td>Duration of follow-up</td><td>28 days</td></tr>
<tr><td>Criteria for efficacy</td><td>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>
<tr><td>WHO-CPS scale</td><td>Descriptor</td><td>Score</td></tr>
<tr><td>Uninfected</td><td>Uninfected; non viral RNA detected</td><td>0</td></tr>
<tr><td>Ambulatory</td><td>Asymptomatic; viral RNA detected</td><td>1</td></tr>
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</td></tr>
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	<table><tr><td>Ambulatory</td><td>Symptomatic; Independent</td><td>2</td></tr><tr><td>Ambulatory</td><td>Symptomatic; Assistance needed</td><td>3</td></tr><tr><td>Hospitalized : mild disease</td><td>Hospitalized; No oxygen therapy</td><td>4</td></tr><tr><td>Hospitalized : mild disease</td><td>Hospitalized; oxygen by mask or nasal prongs</td><td>5</td></tr><tr><td>Hospitalized : severe disease</td><td>Hospitalized; oxygen by NIV or High flow</td><td>6</td></tr><tr><td>Hospitalized : severe disease</td><td>Intubation and Mechanical ventilation, pO2/FIO2>=150 OR SpO2/FIO2>=200</td><td>7</td></tr><tr><td>Hospitalized : severe disease</td><td>Mechanical ventilation, (pO2/FIO2<150 OR SpO2/FIO2<200) OR vasopressor (norepinephrine >0.3 microg/kg/min)</td><td>8</td></tr><tr><td>Hospitalized : severe disease</td><td>Mechanical ventilation, pO2/FIO2<150 AND vasopressors (norepinephrine >0.3 microg/kg/min), OR Dialysis OR ECMO</td><td>9</td></tr><tr><td>Death</td><td>Dead</td><td>10</td></tr></table> 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 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. 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 am) 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:

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

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 $\theta < 1$. 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 $1/\theta$).

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 δ 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, δ 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 θ will be used to define posterior probability of efficacy as $P(\theta < 1)$ and the posterior probability of sufficient efficacy $P(\theta < \eta)$, with η 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.

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

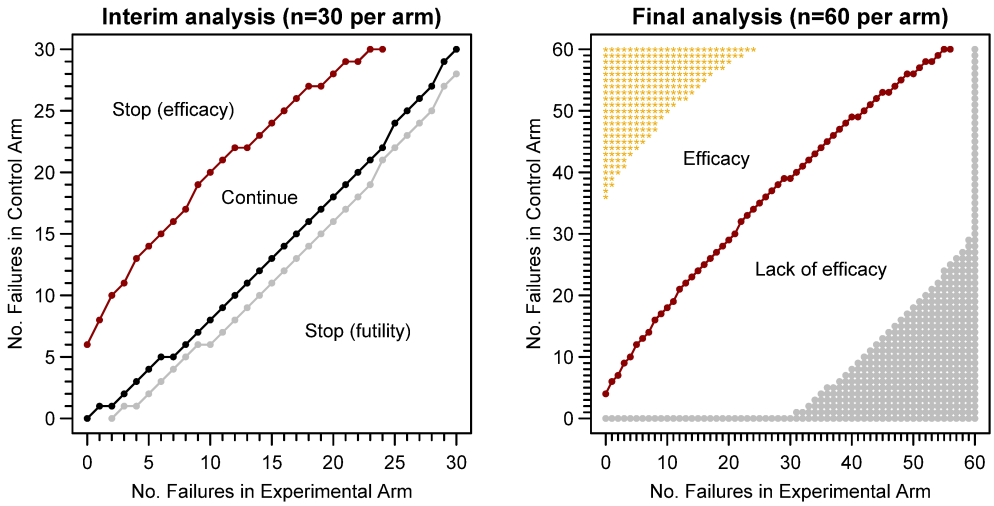

Figure 1. Decision boundaries for the interim and final analysis. Red lines indicate efficacy boundaries, and black lines futility boundaries. On the left plot, the interim analysis is performed after inclusion of 30 patients per

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

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

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

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

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 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 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 transformed in "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, volume 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 asynchronization.

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 mITT 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).

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