Supplementary Appendix I

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

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

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* The first meeting of Data Monitoring Committee 2 was held on May 9, 2020

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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

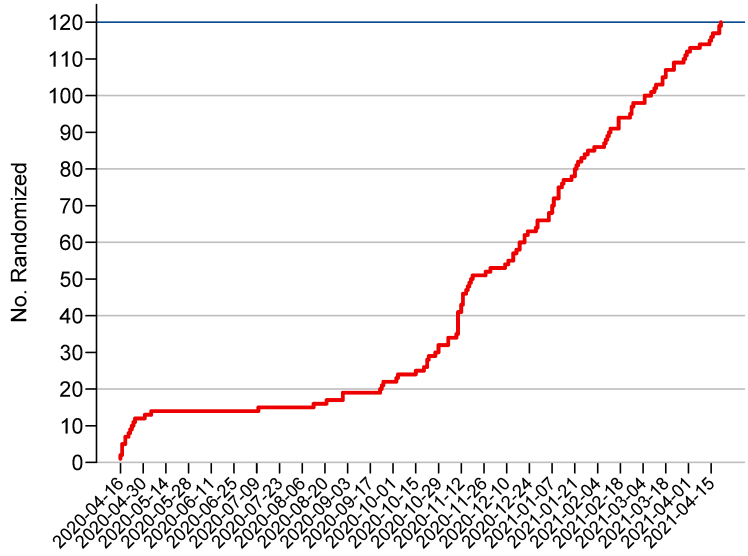

Figure S1. Accrual curve in the trial.

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)

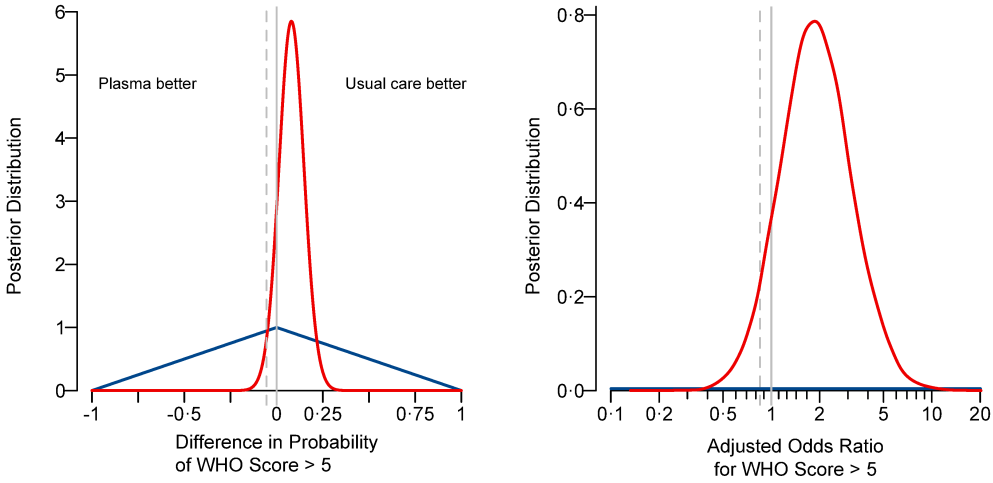

Figure S2. Posterior density of the risk difference and adjusted odds ratio for the day 4 outcome.
The red line represents the posterior density, and the dark blue line represents the minimally informative priors. The solid grey lines indicates an RD of 0 or an OR of 1, representing no treatment effect, 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.

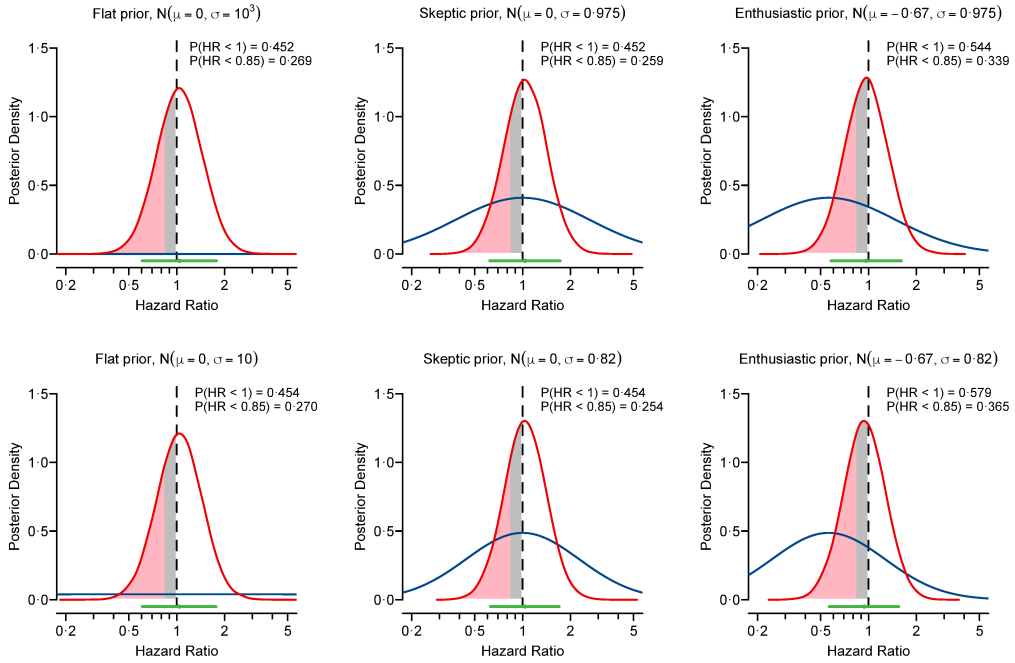

Figure S3. Sensitivity analysis to the choice of priors in the Bayesian analysis of the day 14 co-primary outcome.
The posterior densities (red lines) are plotted for different priors represented in dark blue. The grey line indicates a HR of 1 representing no treatment effect. Posterior probabilities 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)