THE LANCET
Respiratory Medicine

Supplementary appendix 1

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

Supplement to: Mazeraud A, Jamme M, Mancusi RL, et al. Intravenous immunoglobulins in patients with COVID-19-associated moderate-to-severe acute respiratory distress syndrome (ICAR): multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2021; published online Nov 11. http://dx.doi.org/10.1016/S2213-2600(21)00440-9.

SUPPLEMENTARY MATERIAL

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Appendix 1 : List of Hospitals and Investigators

1. **Groupe Hospitalier Universitaire Paris – Psychiatrie & Neurosciences (GHU Paris) 1, rue Cabanis 75674 Paris Cedex 14 :** Docteur Aurélien MAZERAUD Investigateur Principal Neuroanesthésie Neuroréanimation
2. **Hôpital Raymond Poincaré 104, boulevard Raymond Poincaré 92380 Garches** : Docteur Djillali ANNANE Investigateur Principal Réanimation médico chirurgicale
3. **Hôpital Pitié Salpêtrière 47 83 Boulevard de l'Hôpital, 75013 Paris :** Docteur Benjamin ROHAUT Investigateur Principal Neurologie
4. **Groupement Hospitalier Edouar Herriot 5, Place d'Arsonval 69437 Lyon Cedex 03 :** Docteur Laurent Argaud Investigateur Principal Réanimation médicale
5. **CHU Saint Antoine 184 Rue du Faubourg Saint Antoine, 75012 Paris : Docteur Marc** Garnier Investigateur Principal Anesthésie et Réanimation
6. **CHU Lariboisiere 2 Rue Ambroise Paré, 75010 Paris :** Docteur Megarbane Bruno Investigateur Principal Réanimation Médicale et Toxicologique
7. **CH Aulnay Boulevard Robert Ballanger, 93600 Aulnay sous Bois :** Docteur François Santoli Investigateur Principal Médecine intensive et Réanimation
8. **CH Chalons en Champagne, 51 Rue du Maréchal Gallieni, 78100 Saint Germain en Laye :** Docteur Hervé Outin Investigateur Principal Réanimation Polyvalente
9. **CH Poissy 30 Rue du Maréchal Gallieni, 78100 Saint Germain en Laye** : Docteur Hervé OUTIN Investigateur Principal Service de Médecine Intensive Réanimation
10. **CH Etampes, 26 Avenue Charles De Gaulle, 91150 Etampes :** Docteur Shidasp Siami Investigateur Principal Réanimation Polyvalente/Surveillance Continue
11. **Institut Mutualiste Montsouris, 42 Boulevard Jourdan, 75014 Paris :** Docteur Christian lamer Investigateur Principal Réanimation Polyvalente
12. **Institut Gustave Roussy, 114 Rue Edouard Vaillant, 94800 Villejuif :** Docteur Annabelle Stoclin Investigateur Principal Réanimation USC
13. **CHU Robert Débré, Rue du Général Koenig, 51100 Reims :** Docteur Bruno Mourvillier Investigateur Principal Médecin Polyvalente Intensive Réanimation
14. **Centre Hospitalier de Dieppe, Avenue Pasteur BP 219, 76200 Dieppe :** Docteur Pierre Louis Declerque Investigateur Principal Médecine Intensive Réanimation

15. **Hôpital de Hautepierre, 1 Avenue Molére, 67098 Strasbourg :** Docteur Julien Pottecher –Investigateur Principal Service d'Anesthésie Réanimation Chirurgicale
16. **CHU de Grenoble, CS 10217 38043 Grenoble Cedex 9 :** Professeur Carole Scwebel Investigateur Principal Réanimation Médicale
17. **CHU Nancy –Brabois, Institut Lorrain du cœur et des vaisseaux Louis Mathieu, rue du Morvan, 54511 Vandoeuvre les Nancy Cedex :** Professeur Marie Reine Losser – Investigateur principal Service d'Anesthésie Réanimation Chirurgicale
18. **Grand Hôpital de l'est francilien – site de ,Jossigny, 2 4 Cours de la Gondoire 77600 Jossigny :** Docteur Jonathan Zarka Investigateur Principal Réanimation Médicale
19. **CHU Amiens, Sud Amiens 80054 Cedex 1 :** Professeur Michel Slama Investigateur Principal Réanimation Médicale
20. **Hôpital ,Jaques Cartier, 6 Avenue du Noyer Lambert, 91300 Massy :** Docteur Cyril Goulenok Investigateur principal Service d'Anesthésie Réanimation Chirurgicale
21. **Fondation Ophtalmologique Rothschild, 29 rue Manin 75040 Paris Cedex 19 :**Docteur Pierre Trouiller Investigateur Principal Service d'Anesthesie Réanimation Chirurgicale
22. **Hôpital Avicenne, 125 rue de Stalingrad, 93000 Bobigny :** Professeur Stéphane Gaudry Investigateur Principal Réanimation Médicale
23. **Anesthésie ORL Pr. Aubrun, Hôpital de la Croix Rousse Novembre 2019 2 Rue Marius Audin 69003 Lyon** : Docteur Mazard Tessa Investigatrice Principale Anesthésie réanimation
24. **Service de réanimation médicale Hôpital de Tarbes Boulevard DE LATTRE DE TASSIGNY BP 1330 65013 Tarbes** : Docteur Madeux Benjamin Investigateur Principal Réanimation médicale
25. **Service de réanimation à l'Hôpital Nord Franche Comté 100 Route de Moval, 90400 Trévenans** : Docteur Moneger Guy Investigateur Principal Réanimation médicale
26. **Service de Médecine Intensive Réanimation, CHU, 30 Bd. Jean Monnet, 44 093 NANTES cedex 1** : Professeur Reignier Jean Investigateur Principal Réanimation médicale
27. **Service de réanimation polyvalente, rond point de Girac CS 55015 St Michel Angouleme** : Docteur Schnell David Investigateur Principal Anesthésie réanimation
28. **Hôpital d'instruction des armées Percy 2 Rue du Lieutenant Raoul Batany, 92140 Clamart :** Docteur Rudnicki Stéphane Investigateur Principal Anesthésie réanimation

29. **Service de Réanimation Médicale. CHR Orléans, 14 avenue de l'Hôpital CS 86709 – 45067 Orléans CEDEX 2 – France :** Docteur Muller Grégoir Investigateur Principal
30. **Service d'anesthésie réanimation, Pôle de Médecine intensive/réanimation Hôpital Salengro Rue Emile Laine CHRU de Lille 59037 Lille Cedex** : Professeur Poissy Julien Investigateur Principal Service d'anesthésie réanimation
31. **Hopital de Vannes Réanimation polyvalente 56000 CHBA Vannes** : Docteur Agathe Delbove Investigatrice Principal Service d'anesthésie réanimation
32. **CHU Pitié Salpétriere Service de réanimation chirurgicale (Pr Constantin) 91 Boulevard de l'hopital 75012** : Professeur Jean Michel Constantin Investigateur Principal Service d'anesthésie Réanimation
33. **CH Valenciennes Avene desandrouin 59300 Valenciennes** : Docteur Fabien Lambiotte Investigateur Principal Service de réanimation
34. **Hôpital Robert Boulin 112 rue de la marne 33500 Libourne** : Docteur Aurélie Martin Investigatrice Principale Service de réanimation
35. **Groupe Hospitalier Saint Vincent, Strasbourg** : Docteur Thierry Braun Investigateur Principal Service de réanimation
36. **Centre hospitalier de Béthune 27 Rue Delbecque, 62660 Beuvry** : Docteur Christophe Vinsonneau Investigateur Principal Service de réanimation
37. **CHU Angers Service de réanimation médicale 4 rue Larray 49933 Angers CEDEX** : Professeur Pierre ASFAR Investigateur Principal Service de Réanimation
38. **CH Nord Ardennes Service de Réanimation Charleville Mézieres 45 avenue de Manchester 08000 Charleville Mezieres** : Docteur Philippe MATEU Investigateur Principal Service de Réanimation
39. **Hopîtal Jacques Monod Service de Réanimation 29 Avenue Pierre Mendès France, 76290 Montivilliers (Havre)** : Docteur Caroline LEMAITRE Investigateur Principal Service de Réanimation
40. **Hôpital Paris Saint Joseph 185 Rue Raymond Losserand, 75014 Paris :** Docteur Cédric Bruel Investigateur Principal Service de réanimation
41. **Hôpital Européen Georges Pompidou 25 rue Leblanc, 75015 PARIS** : Professeur DIEHL Jean Luc Investigateur Principal Service de réanimation
42. **CH Victor Dupouy 69 rue du Lieutenant Colonel Prudhon 95100 Argenteuil** : Docteur PLANTEFEVE Gaétan Jean Investigateur Principal Réanimation Polyvalente USC
43. **CHU de Poitiers, 2 rue de la milétrie CS 90577, 86021 Poitiers Cx** : Professeur Arnaud THILLE Investigateur Principal Service de médecine intensive réanimation

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Appendix 2. Supplementary Methods

Berlin criteria for Acute Respiratory Distress Syndrom

- Acute, meaning onset over 1 week or less
- Bilateral opacities consistent with pulmonary edema must be present and may be detected on CT or chest radiograph
- PF ratio <300mmHg with a minimum of 5 cmH20 PEEP (or CPAP)
- "must not be fully explained by cardiac failure or fluid overload," in the physician's best estimation using available information — an "objective assessment" (e.g. echocardiogram) should be performed in most cases if there is no clear cause such as trauma or sepsis.

ARDS is categorized as being mild, moderate, or severe according to PaO2/FiO2 on PEEP 5+; Mild 200 – 300; Moderate 100 – 200; Severe < 100

Ventilator-free days (VFD) definition

According to recommendations in Yehya et al.(1), the parameters for the primary objective calculation are defined as follows:

- Day 0 (day of randomization)
- Time frame (28 days)
- Successful extubation (extubation 48 h without reintubation in a 28 days survivor)
- Interval reintubations (count from last successful extubation)
- Death before D28 (VFD = 0)
- Death after D28 (censor after D28; use D28 ventilation and survival status for calculating VFDs)
- Non-invasive support (do not count)
- Tracheostomy (treat as all invasive ventilation)

Therefore, the primary endpoint VFD is defined as follows:

- VFD = 0 if the patient dies within 28 days after randomization
- VFD = x if ventilation (including NIV, IMV and ECMO) time = 28 – x.
- VFD = 0 if ventilation (including NIV, IMV and ECMO) time ≥ 28.

Randomization method

The randomization list was generated by an independent statistician, using R (package blockrand: "Randomization for Block Random Clinical Trial" - Version 1.5, 2020-04-01[2]).

The random block list of sizes two and four and stratified at the center level and time in IMV (<=12hours, >12 hours- < = 24 hours, >24 - <=72 hours) was uploaded by the study data manager into the online REDCap eCRF system.

Missing data management

For the primary endpoint (VFD)

The patients discharged from the Hospital before day 28 after randomization were contacted by telephone interview regarding their current and past ventilation status on day 28 to complete information on ventilation status.

Given the type of patient and pathology, only two patients were lost to follow-up before day 28. One patient was transferred on the day of randomization to another hospital, and one patient was discharged on day eight and could not be re-contacted. For both patients, VFDs were assumed to be equal to zero.

For the patient who withdrew consent on day three, VFDs were assumed to be equal to zero as specified in the SAP.

For mortality analysis at 28 and 90 days, patients lost at follow-up or withdrawing was be censored at the last known alive date.

For missing data for the individual SOFA components, the value zero (normal) was assumed for that component(3).

For missing data for one of the four components of the lung injury score, it was considered 0, and the mean was realized(4).

No imputation was carried out for missing data. For each parameter assessed both at baseline and subsequent visits, the missing data by the experimental group are reported in Table S1 and Table S2.

Efficacy Analysis

In the SAP, the COX model was planned to verify the differential risk of death at 28 and 90 days between the two experimental arms; verification by log-log plot revealed that the requirements were not met. Therefore, the unadjusted Odds Ratios was used to assess the risk of in-hospital death.

In addition, the adjusted ORs for the following risk factors at baseline were estimated: age <=65 years >-65 years, sex, and BMI >=30 and <30 using the logistic model.

Secondary Outcomes

Prespecified secondary outcomes such as ccomplement system study, bronchoalveolar lavage study, medical research council sum score y or serial biological markers or day 3 outcometimepoints that were prespecified couldare not be presentedshown due to missingness.

Sensitivity analysis

In order to confirm the obtained results in the ITT analysis, both the main objective and the competing risks (mortality at 28 days and days on mechanical ventilation) were verified on the per-protocol population.

The population per-protocol was identified according to the following criteria:

- administered dose intensity =100% ±5%.
- start of experimental treatment no later than the second day after randomization.

No other protocol deviations were found. For the main objective and competing risks, we had no missing data.

Subgroup Analysis

For HRs in the subgroup analysis, the significance of the interaction was tested with the method proposed by Altman & Bland 2003 (5).

Statistical Analysis

All statistical analyses were performed on the intention-to-treat population.

All descriptive analyses, statistical tests on means, medians, and frequencies, as well as analyses of survival data and Cox models, were performed with SPSS (IBM, Version 26.0. Armonk, NY).
The following RStudio(Version 1.3.1093) packages have been used for the graphs:

- ggplot2
- survival
- survminer

For the primary objective (Ventilator Free days), the Clustered Wilcoxon rank-sum test (Rosner-Glynn-Lee method) stratified by center and IMV duration was estimated with the RStudio (Version 1.3.1093) "clusrank" package, the script used is reported below.

```
## Clustered signed rank test using RGL method.

Library(clusrank)

clusWilcox.test(VFDays ~ Treatment + cluster(center) + stratum(strate_rando), data = icar_wilcox, method = "rgl")
```

Supplementary material and methods for the immunological study

Fluorescence staining and flow cytometry

The following monoclonal antibodies were used in this study: CD3-allophycocyanin-H7 (clone SK7, dilution factor: 1/20); CD4-Pacific Blue (clone RPA-T4, 1/40); CD8-Brilliant Violet 650 (clone SK1, 1/50); CD25-PE-Cyanine7 (clone M-A251, 1/10); CD45RA-Brilliant Violet 711 (clone HI 100, 1/40), and γδ TCR-PerCP-Cyanine5.5 (clone B1, 1/10) from BD Biosciences; CD127-allophycocyanin (clone REA614, 1/20) from Miltenyi Biotec. In all experiments, the Live/Dead blue Dye (Invitrogen) was used to exclude dead cells. Frozen PBMCs were incubated during 10 min in RPMI 1640 Glutamax (Gibco) supplemented with 5% FCS (Biochrom) warmed up to 37 °C then washed in PBS. Cell suspensions were collected and dispensed into 96-well round-bottom microtiter plates (Greiner Bioscience; 2×10^6cells/well). PBMCs were washed and incubated for 30 min at +4 °C with Live/Dead blue dye in PBS. Five percent (vol/vol) heat-inactivated human AB serum (Abcys) was added for an extra 15 min at +4 °C. Next, cells were labeled for 30 min at +4 °C with antibodies diluted in PBS with 5% FCS (Biochrom) and 0.1% NaN3 (Sigma-Aldrich) PBS. Cells were then washed, fixed with 2% paraformaldehyde, and events acquired using BD Fortessa flow cytometer (BD Biosciences). List-mode data files were analyzed using Diva software (BD Biosciences). Data acquisition was performed on the Cochin Cytometry and Immunobiology (CYBIO) facility

Analysis of cytokine and chemokine plasma concentrations

A multiplex cytokine immunoassay panel was used to quantify plasma concentrations of interleukin 6, interleukin 13 and of tumor necrosis factor a (MesoScale Discovery, Rockville, Maryland, USA). A standard curve was generated for each set of reagents. The minimum and maximum detection limits depend on the cytokines and chemokines and all of them were in the detection range. Quantification was performed using Workbench4.0 (MesoScale Discovery).

Appendix 3. Supplementary Tables

Table S1. Baseline characteristics (additional data)

	Intravenous Immunoglobulins (No. 69)	Placebo (No. 77)	Missing Value	
	mean (SD) median [IQR]	mean (SD) median [IQR]	IVIG	Placebo
Demographic and comorbidities				
Body Mass Index (kg/m^2)			-	-
Underweight (below 18.5) No. (%)	0 (0)	0 (0)		
Healthy weight (18.5 to 24.9) No. (%)	9 (13)	12 (16)		
Overweight (25.0 to29.9) No. (%)	22 (32)	33 (43)		
Obesity (30 or higher) No. (%)	34 (49)	26 (34)		
Class 3 Obesity (40 or higher) No. (%)	4 (6)	6 (8)		
Charlson Comorbidity Index (CCI) median [IQR]	3 [1-4]	3 [2-4]	-	-
No comorbidity (CCI = 0) No. (%)	8 (12)	2 (3)		
Moderate comorbidity (CCI = 1–5) No. (%)	56 (81)	70 (91)		
Severe comorbidity (CCI >5) No. (%)	5 (7)	5 (7)		
Treated for hypertension No. (%)	36 (52)	35 (46)	-	-
Smoking No. (%)	2 (3)	4 (5)	-	-
WHO Performance status No. (%)			8	8
Fully active, able to carry on all pre-disease performance without restriction No. (%)	45 (74)	60 (87)		
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work No. (%)	11 (18)	4 (6)		
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours No. (%)	3 (5)	4 (6)		
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours No. (%)	1 (2)	-		
Completely disabled; cannot carry on any self-care; totally confined to bed or chair No. (%)	1 (2)	1 (2)		
Covid-19 course				
Time from symptom onset to ICU admission (days)	9.4 (6.84) 8.0 [6.0-11.0]	9.3 (6.70) 8.0 [6.0-12.5]	-	3
Time from symptom onset to endotracheal intubation (days)	2.3 (2.4) 1.0 [1.0-3.0	1.7 (1.5) 1.0 [1.0-2.0]	-	-

	Intravenous Immunoglobulins (No. 69)	Placebo (No. 77)	Missing Value	
	mean (SD) median [IQR]	mean (SD) median [IQR]	IVIG	Placebo
Time between initiation of invasive mechanical ventilation and randomization –no. (%)			-	-
≤12 hours	23 (33)	31 (40)		
>12 ≤24 hours	23 (33)	23 (30)		
>24 ≤72 hours	23 (33)	23 (30)		
Simplified Acute Physiology Score II ø	41.2 (12.3) 41.0 [32.0-50.0]	40.4 (11.6) 39.0 [31.5-50.0]	-	-
Critical illness and acute respiratory distress syndrome severity at randomization				
Sequential organ Failure Assessment score at randomization †† median [IQR]	6.0 [4.0-8.0]	6.0 [3.0-8.0]	1	-
2-3	12 (18)	20 (26)		
4-5	20 (29)	16 (21)		
6-7	17 (25)	13 (17)		
8-9	13 (19)	17 (22)		
10-11	1 (2)	3 (4)		
12-14	5 (7)	8 (10)		
Kidney disease improving global outcome score median (IQR)	0 [0-0]	0 [0-0]	-	-
Vasopressor support No. (%)	36 (52)	35 (46)	-	-
Lung injury score†	3.0 (0.54) 3.0 [2.7-3.3]	3.1 (0.52) 3.0 [3.0-3.5]	1	-
$PaO_2:FiO_2$	128.7 (45.48) 124.0 [96.0-154.8]	119.0 (49.18) 110.0 [80.0-152.0]	1	2
Lung compliance (mL/cm H_2O)	31.8 (10.84) 32 [25-39]	27.9 (11.0] 28 [23-36]	14	14
Radiological Score: Number of quadrant(s) with alveoli-interstitial opacities No. (%)			32	37
Median [IQR]	4 [2-4]	4 [3-4]		
1 no. (%)	2 (5)	-		
2 no. (%)	9 (22)	6 (12)		
3 no. (%)	5 (12)	9 (18)		

	Intravenous Immunoglobulins (No. 69)	Placebo (No. 77)	Missing Value	
	mean (SD) median [IQR]	mean (SD) median [IQR]	IVIG	Placebo
4 no. (%)	25 (61)	35 (69)		
None no. (%)	-	1 (2)		
Pulmonary embolia no. (%)	5 (8)	7 (11)	3	11
% of pulmonary impairment	57.7 (19.89) 63.0 [40.0-75.0]	52.7 (21.38) 50.0 [31.5-75.0]	56	60
Acute respiratory distress syndrome management				
Tidal volume, ml/kg of predicted body weight	6.2 (0.87) 6.2 [5.6-6.7]	6.2 (0.84) 6.2 [5.8-6.6]	7	4
Positive end expiratory pressure – cm H_2O	12.0 (3.5) 12.0 [9.8-14.0]	11.8 (2.7) 12.0 [10.0-14.0]	11	11
Inspiratory plateau pressure – cm H_2O	24.5 (4.7) 24 [22-28]	24.9 (4.32] 25 [22-28]	11	13
Covid-19 treatment before and two days after syndrome management*			2	1
Corticosteroids No. (%)	49 (71)	55 (71)		
Hydroxychloroquine (HCQ) No. (%)	8 (12)	4 (5)		
Antiretroviral therapy No. (%)	12 (17)	9 (12)		
Tocilizumab (anti IL6) No. (%)	5 (7)	7 (9)		
Antibiotics therapy No. (%)	56 (81)	65 (84)		
Non-invasive ventilation No. (%)	46 (67)	36 (47)		
High Flow Nasal Oxygen Therapy No. (%)	4 (6)	10 (13)		
Awake prone positioning No. (%)	20 (29)	13(17)		
Laboratory value				
Leucocytes (G/L)	9.7 (6.05) 9.1 [6.3-11.8]	9.8 (4.74) 9.6 [7.1-11.9]	5	8
Lymphocytes count ($x10^9$/L)	1.1 (1.7) 0.8 [0.5-1.1]	0.9 (1.2) 0.6 [0.4-0.9]	16	16
Creatinine (micromol/L)	104.4 (138.5) 77 [58-100]	92.3 (60.9) 72 [60-103	4	5
d-dimers (microgrammes/L)	2545 (3374) 1290 [899-2290]	2928 (3405) 1883 [954-3317]	32	33

	Intravenous Immunoglobulins (No. 69)	Placebo (No. 77)	Missing Value	
	mean (SD) median [IQR]	mean (SD) median [IQR]	IVIG	Placebo
C-Reactive Protein (mg/L)	167.1 (82.6) 181.0 [95.5-219.8]	157.6 (91.8) 132.5 [85.0-216.5]	25	23
Platelet count ($x10^9$/L)	292 (135.8) 263 [197-348]	252 (108.7) 270 [217-335]	7	9

IVIG : Intravenous Immunoglobulins, CI : Confidence interval, IQR : Interquartile Range ; WHO : World Health Organisation, ICU : Intensive Care Unit.
†† In case of missing data for one SOFA components, the value of 0 (normal) was assumed;
† For missing data for one of the 4 component of the lung injury score, it was considered to be 0, and the mean was realized;
f FiO_2 denotes the fraction of inspired oxygen and PaO_2 the partial pressure of arterial oxygen in mmHg.
ø Scores on the Simplified Acute physiological Score II range from 0 to 163, with higher scores indicating greater severity of illness.
* multiple choice question;

Table S2 – Others secondary outcomes

Outcomes	Intravenous immunoglobulins (No. 69)	Placebo (No. 77)	Difference (95% CI)	Missing Value IVIG	Missing Value Placebo
Death at 28 days – no. (%)	24 (34.8)	20 (26.0)	**Adjusted OR (95% CI°)** 1.65 (0.78 to 3.49)		
Death at day 90 – no. (%)	28 (40.6)	31 (40.3)	**Adjusted OR (95% CI)** 1.08 (0.54 to 2.18)		
Sequential Organ Failure Assessment §					
24 hours Median [IQR]	7 [7 to 10]	7 [6 to 8]			
No. of patients	62	73		6	3
Day 7 Median [IQR]	5 [3 to 8]	5 [3 to 8]			
No. of patients	56	56		4	9
Day 14 Median [IQR]	7 [4 to 10]	7 [4 to 8]			
No. of patients	37	42		6	7
Day 21 Median [IQR]	6 [3 to 10]	6 [4 to 8]			
No of patients	21	31		7	8
Day 28 Median [IQR]	7 [3 to 10]	6 [4 to 10]			
No. of patients	16	23		-	7
Lung compliance					
24 hours Mean (95%CI) Median [IQR]	34.0 (30.2 to 37.8) 32.0 [22.0 to 46.0]	31.6 (28.3 to 34.9) 30.0 [22.8 to 39.3]	2.5 (-2.5 to 7.4)		
No. of patients	47	58		21	18
Day 7 Mean (95%CI) Median [IQR]	31.5 (27.1 to 35.9) 30.0 [21.3 to 38.0]	31.3 (27.3 to 35.3) 30.0 [24.0 to 38.0]	0.21 (-5.7 to 6.1)		
No. of patients	36	35		24	30
Day 14 Mean (95%CI) Median [IQR]	23.6 (19.1 to 28.1) 22.0 [16.0 to 30.0]	32.0 (25.5 to 38.5) 30.0 [22.0 to 35.5]	-8.5 (-6.3 to -0.7)		
No. of patients	23	25		20	24
Day 21 Mean (95%CI) Median [IQR]	20.8 (13.6 to 28.1) 19.0 [11.0 to 31.0]	24.2 (17.8 to 30.6) 21.0 [17.0 to 32.5]	-3.3 (-12.4 to 5.7)		
No of patients	11	13		17	26
Day 28 Mean (95%CI) Median [IQR]	22.8 (7.0 to 38.6) 19.5 [12.3 to 30.3]	27.8 (19.0 to 36.5) 24.0 [14.0 to 42.5]	-4.9 (-21.0 to 11.9)		
No. of patients	6	16		10	14
PaO_2/FiO_2 Ratio					
24 hours Mean (95%CI) Median [IQR]	151.8 (124.3 to 179.3) 135.0 [101.5 to 172.0]	143.0 (128.6 to 157.4) 135.0 [97.0 to 177.0]	8.8 (-20.7 to 38.3)		
No. of patients	61	71		7	5
Day 7					

Outcomes	Intravenous immunoglobulins (No. 69)	Placebo (No. 77)	Difference (95% CI)	Missing Value IVIG	Placebo
Mean (95%CI) Median [IQR]	170.0 (141.0 to 198.8) 154.0 [115.0 to 194.0]	175.4 (146.8 to 204.0) 153.0 [112.0 to 215.0]	-5.5 (-45.6 to 34.7)		
No. of patients	55	55		5	10
Day 14 Mean (95%CI) Median [IQR]	160.2 (136.2 to 184.3) [151.0 [98.0 to 222.0]	169.3 (142.5 to 196.1) 148.5 [103.3 to 205.5]	-9.1 (-45.2 to 27.0)		
No. of patients	35	42		8	7
Day 21 Mean (95%CI) Median [IQR]	172.4 (140.8 to 204.1) 177.0 [113.0 to 215.0]	183.2 (153.1 to 213.2) 182.0 [101.0 to 248.0]	-10.7 (-54.6 to 33.1)		
No of patients	21	31		7	8
Day 28 Mean (95%CI) Median [IQR]	150.7 (112.3 to 189.1) 142.0 [108.0 to 175.0]	152.1 (116.2 to 188.0) 145.0 [70.5 to 219.0]	-1.41(-54.4 to 51.6)		
No of patients	15	24		1	6
Lung injury score					
24 hours Median [IQR]	3.0 [2.5-3.2]	3.1 [3.0-3.5]			
No. of patients	68	76		1	1
Day 7 Median [IQR]	2.7 [2.0 -3.0]	2.8 [2.1 -3.3]			
No. of patients	58	57		2	8
Day 14 Median [IQR]	2.7 [2.0 – 3.3]	2.7 [2.3 - 3.3]			
No. of patients	38	42		5	7
Day 21 Median [IQR]	2.0 [2.0 – 3.0]	2.4 [1.5 -3.0]			
No. of patients	26	32		2	7
Day 28 Median [IQR]	2.5 [1.9 -3.1]	2.7 [2.0 – 3.3]			
No. of patients	18	28		-	2
Lung radiological score					
24 hours Median [IQR]	4 [2 to 4]	4 [3 to 4]			
No. of patients	24	34		44	42
Day 7 Median [IQR]	4 [2 to 4]	4 [2.5 to 4]			
No. of patients	17	25		43	40
Day 14 Median [IQR]	4 [3 to 4]	4 [4 to 4]			
No. of patients	10	17		33	32
Day 21 Median [IQR]	2.5 [2.0 to 3.3]	3 [1 to 4]			
No of patients	6	15		22	24
Day 28 Median [IQR]	2 [1 to 4]	4 [3 to 4]			
No. of patients	7	14		9	16
C-reactive protein (mg/L)					
24 hours Mean (95%CI) Median [IQR]	157.4 (122.0 to 192.8) 128.0 [59.0 to 246.0]	143.8 (114.3 to 173.9) 119.0 [60.5 to 223.0]	13.6 (-31.7 to 58.9)		
No. of patients	23	31		45	45
Day 7 Mean (95%CI) Median [IQR]	123.2 (86.7 to 159.8) 73 [26 to 193]	116.8 (79.5 to 154.1) 65 [30 to 222]	6.5 [-44.8 to 57.8]		

Outcomes	Intravenous immunoglobulins (No. 69)	Placebo (No. 77)	Difference (95% CI)	Missing Value IVIG	Placebo
No. of patients	37	35		23	30
Day 14 Mean (95%CI) Median [IQR]	163.1 (115.8 to 210.4) 169.0 [33 to 264]	161.2 (124.2 to 198.1) 139.5 [103 to 234]	1.9 (56.9 to 60.7)		
No. of patients	25	24		18	25
Day 21 Mean (95%CI) Median [IQR]	108.9 (64.7 to 153.2) 65.5 [37.8 to 193.8]	127.7 (71.1 to 184.3) 107 [53 to 153]	-18.8 (-89.2 to 51.7)		
No of patients	18	20		10	19
Day 28 Mean (95%CI) Median [IQR]	94.5 (11.3 to 177.7) 23 [8 to 94]	141.1 (93.3 to 188.8) 123 [81 to 201]	-46.1 (-136 to 44)		
No of patients	15	16		1	14
Procalcitonin PCT (ng/mL)					
24 hours Mean (95%CI) Median [IQR]	1.7 (0.5 to 2.9) 0.3 [0.2 to 0.7]	0.7 (0.4 to 1.1) 0.2 [0.1 to 0.9]	0.6 (0.3 to 2.3)		
No. of patients	37	36		31	45
Day 7 Mean (95%CI) Median [IQR]	4.6 (0 to 11.3) 0.2 [0.1 to 0.9]	0.7 (0 to 1.5) 0.2 [0.1 to 0.5]	3.9 (-2.8 to 10.6)		
No. of patients	28	29		23	30
Day 14 Mean (95%CI) Median [IQR]	8.4 (0 to22.7) 0.7 [0.3 to 3.1]	1.0 (0 to 2.0) 0.4 [0.2 to 0.9]	7.4 (-4.5 to 19.3)		
No. of patients	18	24		18	25
Day 21 Mean (95%CI) Median [IQR]	3.5 (0 to 9.4) 0.4 [0.1 to 1.6]	0.8 (0.1 to 1.5) 0.3 [0.2 to 0.9]	2.7 (-3.1 to 8.6)		
No of patients	14	17		10	19
Day 28 Mean (95%CI) Median [IQR]	7.7 (0 to 23.5) 0.3 [0.1 to 1.7]	2.7 (0.0 to 5.4) 0.5 [0.2 to 5.1]	5.0 [-9.9 to 19.9)		
No of patients	15	16		1	14
Functional Status					
WHO score at 28 days ¤ Median [IQR]	3 [1 to 5]	3 [1 to 7]		1	4
No of patients	43	52			
Discharge at home no. (%)	16 (37)	19 (37)			
Discharged home but on oxygen or with activity limitation no. (%)	-	1 (2)			
Hospitalized without oxygen no. (%)	6 (14)	7 (13)			
Hospitalized on oxygen with nasal canula or single mask no. (%)	9 (21)	6 (11)			
Non-invasive ventilation no. (%)	2 (5)	1 (2)			
High flow oxygen therapy (Optiflow) no. (%)	1 (2)	-			
Invasive mechanical ventilation no. (%)	7 (16)	13 (25)			
Invasive ventilation and vasopressor or dialysis or ECMO no. (%)	2 (5)	5 (10)			
WHO score at 90 days ¤ Median [IQR]	1 [1 to 2]	1 [1 to 1]		1	1

Outcomes	Intravenous immunoglobulins (No. 69)	Placebo (No. 77)	Difference (95% CI)	Missing Value IVIG	Placebo
No of patients	39	44			
Discharge at home no. (%)	28 (72)	35 (79)			
Discharged home but on oxygen or with activity limitation no. (%)	2 (5)	1 (2)			
Hospitalized without oxygen no. (%)	6 (15)	4 (9)			
Hospitalized on oxygen with goggles or single mask no. (%)	2 (5)	1 (2)			
Non-invasive ventilation no. (%)	-	2 (5)			
High flow oxygen therapy (Optiflow) no. (%)	-	-			
Invasive mechanical ventilation no. (%)	1 (3)	1 (2)			
Invasive ventilation and vasopressor or dialysis or ECMO no. (%)	-	-			
ICU length of stay ¤ (days) Mean (95%CI) Median [IQR]	 28.8 (21.8 to 35.9) 21.0 [12.3 to 44.5]	 30.0 (22.2 to 28.1) 21.0 [11.5 to 43.0]	 -1.2 (-11.7 to 9.3)	-	-
Length of hospital stay ¤ (days) Mean (95%CI) Median [IQR]	 52.2 (45.06) 34 [25-55]	 46.0 (32.12) 39 [23-56]		-	-
Curarisation (days) Median [IQR] Mean (95% CI)	 7 [4 to12] 9.5 (7.6 to 11.4)	 6 [3 to 14] 9.2 (7.2 to 11.1)	 0.3 (-2.4 to 3.1)	2	4
Time to first T-tube trial (days) Median [IQR]	 9 [3 to 14]	 9 [4-18]	 -1 [-5 to 2]	0	0

¤Only in survivors

WHO World Health Organisation; ECMO Extracorporeal Membrane Oxygenation, ICU Intensive Care Unit

337 **Table S3. Subgroups analysis**

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	IVIG	Placebo	Difference or Odds Ratio
Time to randomization			
Less than 12 hours	pts. 23	pts. 31	
Median Ventilation free days at 28 days (95% CI)	0.0 (0.0 to 13.0)	0.0 0.0 to 10.0)	0.0 (0.0 to 0.0)
Death at 28 days - n (%)	11 (48)	7 (23)	3.14 (0.97 to 10.17)
Death at 90 days - n (%)	12 (52)	15 (48)	1.16 (0.40 to 3.43)
>12 ≤24 hours	pts. 23	pts. 23	
Median Ventilation free days at 28 days (95% CI)	0.0 (0.0 to 10.0)	7.5 (0.0 to 20.0)	0.0 (-8.0 to 0.0)
Death at 28 days - n (%)	7 (30)	4 (17)	2.08 (0.51 to 8.40)
Death at 90 days - n (%)	7 (30)	4 (17)	2.08 (0.51 to 8.40)
>24 ≤ 72 hours	pts. 23	pts. 23	
Median Ventilation free days at 28 days (95% CI)	5.0 (0.0 to 16.0)	0.0 (0.0 to 6.0)	0.0 (0.0 to 5.0)
Death at 28 days - n (%)	6 (26)	9 (39)	0.55 (0.16 to 1.92)
Death at 90 days - n (%)	9 (39)	12 (52)	0.59 (0.18 to 1.90)
Age			
Age < 65 years	pts 31	pts 28	
Median Ventilation free days at 28 days (95% CI)	6.5 (0.0 to 10.0)	0.0 (0.0 to 11.0)	0.0 (0.0 to 6.0)
Death at 28 days - n (%)	6 (19)	4 (14)	1.38 (0.35 to 5.52)
Death at 90 days - n (%)	8 (26)	6 (21)	1.22 (0.36 to 4.09)
Age ≥ 65 years	pts. 38	pts. 49	
Median Ventilation free days at 28 days (95% CI)	0.0 (0.0 to 0.0)	0.0 (0.0 to 8.0)	0.0 (0.0 to 0.00)
Death at 28 days - n (%)	18 (47)	16 (33)	1.86 (0.78 to 4.44)
Death at 90 days - n (%)	20 (53)	25 (51)	1.07 (0.46 to 2.49)
Patients alive at day seven	pts. 61	pts. 69	
Median Ventilation free days at 28 days (95% CI)	2.5 (0.0 to 10.0)	0.0 (0.0 to 9.0)	0.0 (0.0 to 0.0)
Death at 28 days - n (%)	17 (28)	13 (19)	1.66 (0.73 to 3.77)
Death at 90 days - n (%)	21 (34)	24 (35)	0.98 (0.48 to 2.06)
BMI (kg/m 2)			
BMI (kg/m 2) >= 30	pts 38	pts 32	
Median Ventilation free days at 28 days (95% CI)	5.0 (0.0 to 13.0)	0.0 (0.0 to 8.0)	0.0 (0.0 to 5.0)
Death at 28 days - n (%)	12 (32)	11 (32)	0.84 (0.31 to 2.29)
Death at 90 days - n (%)	14 (37)	14 (44)	0.71 (0.27 to 1.86)
BMI (kg/m 2) <30	pts 31	pts 45	
Median Ventilation free days at 28 days (95% CI)	0.0 (0.0 to 7.0)	0.0 (0.0 to 9.0)	0.0 (-1.0 to 0.0)
Death at 28 days - n (%)	12 (39)	9 (20)	2.53 (0.90 to 7.06)
Death at 90 days - n (%)	14 (45)	17 (38)	1.36 (0.54 to 3.44)
Corticosteroids administration			
Patients who received corticosteroids	pts 49	pts 55	
Median Ventilation free days at 28 days (95% CI)	0.0 (0.0 to 8.0)	0.0 (0.0 to 8.0)	0.0 (0.0 to 0.0)
Death at 28 days - n (%)	14 (29)	11 (20)	1.60 (0.65 to 3.96)
Death at 90 days - n (%)	18 (37)	22 (40)	0.87 (0.39 to 1.92)
Patients who did not receive corticosteroids	pts. 18	pts. 21	
Median Ventilation free days at 28 days (95% CI)	0.0 (0.0 to 10.0)	0.0 (0.0 to 15.0)	0.0 (0.0 to 0.0)
Death at 28 days - n (%)	10 (56)	9 (43)	1.67 (0.47to 5.93)
Death at 90 days - n (%)	10 (56)	9 (43)	1.67 (0.47 to 5.93)

339

340 95% CI. 95% Confidence Interval ; BMI : Body Mass Index; pts : patients

Table S4. Unplanned subgroups analysis

	IVIG	Placebo	Difference	p
Per-protocol population*	pts 40	pts 46		
Ventilation free days at 28 days Median (95% CI)	0.0 (0.0 to 13.0)	0.0 (0.0 to 15.0)	0.0 (0.0 to 0.0)	0.939
Death at 28 days - n (%)	15 (37.5)	13 (28.3)	Odds Ratio (95% CI) 1.46 (0.59 to 3.61)	0.408
Death at 90 days - n (%)	19 (47.5)	17 (37.0)	Odds Ratio (95% CI) 1.47 (0.62 to 347)	0.376

* Per-protocol population was identified according to the following criteria:

- administered dose intensity =100% ±5%.
- start of experimental treatment no later than the second day after randomization.

Table S5: Treatment exposure

	Intravenous Immunoglobulins (No. 66)*	Placebo (No. 73)**
Duration of treatment days*** Mean (95% CI) Median [IQR]	 3.9 (3.8 to 4.0) 4.0 [4.0-4.0]	 4.0 (3.9 to 4.0) 4.0 [4.0-4.0]
Day from randomization to first administration - no. (%)****		
First day Second Day Third Day Fourth Day Fifth Day Missing data	58 (95) - 2 (3) - 1 (2) 5	62 (94) 4 (6) - - - 7
Cumulative dose ml Mean (95%IC) Median [IQR]	 3327 (3127-3527) 3400 [2800-4000]	 3304 (3172-3436) 3400 [2950-3630]
Dose intensity† (%) Mean (95%IC) Median [IQR]	 96.3 (92.1-1100.0) 100.0 [96.0-.100.0]	 98.4 (95.0-100.0) 100.0 (97.0-100.0)
Patients with dose intensity below the dose defined as per protocol – no. (%) Mean dose intensity (95%IC) Median dose intensity [IQR]	 26 (39.4) 84.3 (76.0-92.6) 93.2 [80.0-97.2]	 16 (21.9) 85.1 (79.2-91.1) 89.2 [77.0-96.7]
Patients with dose intensity more than as per protocol – no. (%) Mean dose intensity (95%IC) Median dose intensity [IQR]	16 (24.2) 110.2 (105.1-115.4) 106.0 [102.1-116.2]	22 (30.1) 110.09 (105.6-116.2) 104.6 [101.2-121.2]

95% CI : 95% Confidence Interval; IQR : Interquartile Range

* datas were missing for two patients; one additional patient withdrew its consent at day 3,

** datas were. missing for three patients; one additional patient was lost to follow-up at day 0 (transferred at other hospital)

† Dose intensity =Total dose administered / Total dose defined per protocol (2g/Kg)

*** 8 pts. declare three days of treatment, for all the administered dose, is according to protocol, one patient was treated for three days dose administered 70% of that expected no adverse events reported

**** 4 pts start treatment at the second days after randomization, all of them in placebo group, for all the dose administered according to protocol; one patient was treated for three days dose administered 70% of that expected no adverse events reported; for five patients in IVIG group and, seven patients in the placebo group the treatment starting day was non available

One patient in IVIG group was not treated at day three, the total dose administered was 75% of that expected, no adverse events reported

One patient in placebo group stop treatment at day four for toxicity (serious adverse event reported: hypertension plus hyperkalemia treatment stopped)

Table S6. Intensive Care-related adverse events

	Intravenous Immunoglobulins (No. 68)*	Placebo (No. 76)**
Ventilator-acquired pneumonia¥	32	43
Catheter-associated infections	10	8
Delirium	11	10
Gastro-intestinal hemorrhage	1	3
Decubitus pressure sore(> grade 2)	1	4
Focal neurological deficit	2	2
Toxidermia	-	1

* One patient in intravenous immunoglobulins group withdrawal at three day

** One patient in placebo was lost at follow-up (transferred to another hospital at the randomization day)

¥ Four patients in the intravenous immunoglobulins group and four patients in the placebo group had two episodes of ventilator acquired pneumonia; five patients in the placebo group had three episodes of ventilator acquired pneumonia

Delirium was defined according to the Confusion Assessment Method for Intensive Care Unit, Ventilator acquired pneumonia was declared by investigators and had to be bacteriologically proven.

375

376 **Table S7. All serious adverse events**
377

	IVIG	Placebo
Septic shock	8	4
Pneumonia	5	5
Multiple organ dysfunction syndrome	5	3
Acute kidney injury	5	2
Pneumonia bacterial	5	1
Pulmonary embolism	4	1
Renal failure	2	2
Anaemia	2	1
Atrial fibrillation	2	1
Deep vein thrombosis	0	2
Hypertension	1	1
Pseudomonal sepsis	2	0
Pulmonary fibrosis	1	1
Sepsis	1	1
Shock haemorrhagic	1	1
Venous thrombosis limb	2	0
Acute pulmonary oedema	1	0
Aplastic anaemia	1	0
Aspergillus infection	1	0
Atrioventricular block complete	1	0
Autoimmune haemolytic anaemia	1	0
Blood loss anaemia	0	1
Bronchopulmonary aspergillosis	1	0
Candida sepsis	1	0
Cardiac arrest	1	0
Cardio-respiratory arrest	1	0
Cerebral infarction	1	0
Cholangitis infective	1	0
Coombs positive haemolytic anaemia	1	0
Decubitus ulcer	0	1
Disturbance in attention	1	0
Drug reaction with eosinophilia and systemic symptoms	1	0
Duodenal ulcer haemorrhage	1	0
Encephalopathy	1	0
Endotracheal intubation complication	0	1
Enterobacter pneumonia	0	1
Fluid overload	0	1
Gastric ulcer	0	1
Haematoma muscle	0	1
Haemodilution	1	0
Haemorrhagic stroke	0	1
Haemothorax	1	0
Herpes zoster	0	1
Hyperkalaemia	0	1
Hypokalaemia	1	0
Hypoxia	0	1
Intestinal ischaemia	1	0
Ischaemic hepatitis	0	1
Metabolic acidosis	1	0
Metabolic encephalopathy	1	0
Myoclonus	1	0
Nervous system disorder	0	1
Neuromyopathy	1	0
Pneumomediastinum	1	0
Pneumonia staphylococcal	0	1
Procedural pneumothorax	1	0
Pseudomonas bronchitis	0	1
Pulmonary haemorrhage	1	0

	IVIG	Placebo
Pulmonary oedema	0	1
Renal impairment	0	1
Renal tubular necrosis	0	1
Respiratory tract infection	1	0
Right ventricular failure	0	1
Supraventricular tachycardia	1	0
Systemic inflammatory response syndrome	2	0
Thrombocytopenia	0	1
Thrombosis	1	0
Urinary tract infection	0	1
Urosepsis	1	0
Total	78	47

Table S8 Cytokines concentrations over time

	Inclusion		Day 7		Day 14		Day 28	
	IVIG	Placebo	IVIG	Placebo	IVIG	Placebo	IVIG	Placebo
N° patients	21	14	26	19	19	19	13	16
Interleukin 6 (pg/mL) *f*	9,3 (5,1-23,2)	7,4 (3,3-31,7)	23,3(10,5 -49,2)	16,3(3,6-50,4)	11,2(3,5-23,8)	21,9(7,0-49,8)	9,0(1,5-28,0)	5,3(2,8-13,4)
N° patients	11	6	18	12	14	10	12	8
Interleukin 13 (pg/mL) †	3,2(1,1 - 6,3)	2,8(2,4-4,6)	7,0 (5,7-8,4)	2,7(1,7-3,7)***	4,0(3,6-5,2)	3,2(1,8-4,1)	2,5(2,0-3,3)	3.0(2,2-4,0)
N° patients	21	15	27	20	20	16	13	17
Tumor necrosis factor-alpha (pg/mL) *f*	1,4 (1,1-2,4)	1,4(1,0-2,0)	1,4(1,0-2,0)	1,7(1,1-2,3)	1,8(1,2-3,1)	1,5(1,3-2,2)	1,5(1,1-2,8)	2,0(1,4-3,8)

IVIG: Intravenous Immunoglobulins

f Analysis of variance for an effect of IVIG, p=Non Significant

†Two way analysis of variance p for treatment 0.0002, difference at day 7 p<0,0001

386 **Table S9 Proportion of circulating lymphocytes over time**

	Inclusion		Day 7		Day 14		Day 28	
	IVIG	Placebo	IVIG	Placebo	IVIG	Placebo	IVIG	Placebo
N° patients	16	8	21	13	14	12	9	6
Percent of CD4 T cells among $CD3^+$ TCRγδ - cells median±IQR Δ	79 (64-87)	78 (66-85)	77 (68-86)	81 (68-91)	76(66-85)	75(67-92)	59(45-74)	79(73-84)*
Regulatory CD4 T cells median±IQR †	6(4-77)	6(4-7)	6(4-7)	4(4-6)	6(4-10)	5(4-7)	6(5-7)	4(3-5)*
Memory CD4 T cells median±IQR *f*	50(44-56)	47(42-68)	60(44-64)	44(35-54)	56(47-6-8)	45(37-67)	62(60-78)	41(33-53)**
Naive CD4 T cells median±IQR ¥	44(35-59)	46(27-54)	38(26-52)	51(39-62)	36(26-47)	49(29-60)	30(16-38)	55(44-62)**
Percent of CD8 T cells among $CD3^+$ TCRγδ- cells median±IQR Δ	16(8-30)	17(12-31)	15(11-25)	17(7-26)	17(13-25)	18(7-26)	35(22-39)	18(14-23)*
Memory CD8 T cells median±IQR *ff*	50(37-68)	34(26-59)	50(35-62)	34(23-48)	56(44-67)	36(28-55)*	65(46-71)	49(44-59)
Naive CD8 T cells median±IQR ¥¥	54(43-68)	67(42-76)	50(41-67)	67(54-78)	46(36-58)	65(47-74)	36(28-55)	52(43-57)

387 IVIG : Intravenous Immunoglobulins ; CD Cluster of differenciation ;

388 *p<0.05, **p<0.01

389 Δ Analysis of variance for an effect of IVIG p=NS

390 † Two way analysis of variance p for treatment 0.015

391 *f* Two way analysis of variance p for treatment 0.006

¥ Two way analysis of variance p for treatment 0.0016

¥¥ Two way analysis of variance p for treatment 0.0096

ff Two way analysis of variance p for treatment 0.006

Table S10 CONSORT Checklist

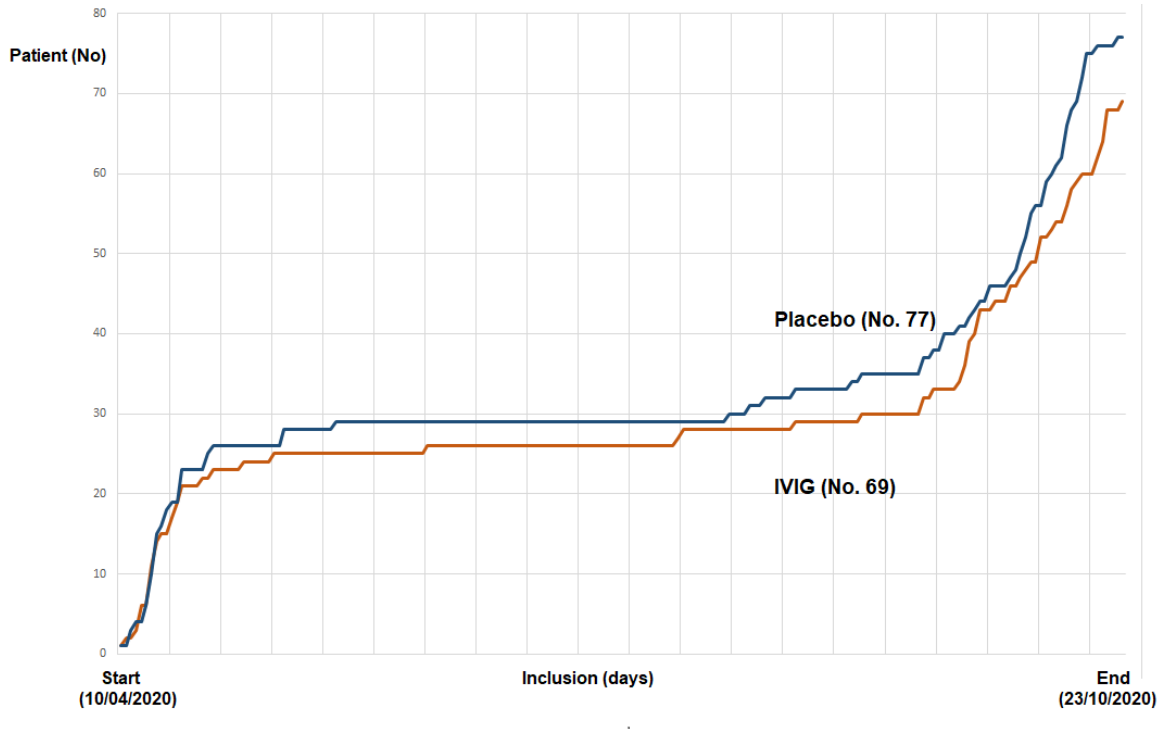
CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	12
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	18 Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	20 Table 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	20 Table 2 and sup Table S2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	20 Table 2
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	25 Figure 2 and Table S2
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	22 Table 3 and Table S6
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15-16
Other information			
Registration	23	Registration number and name of trial registry	11
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	11

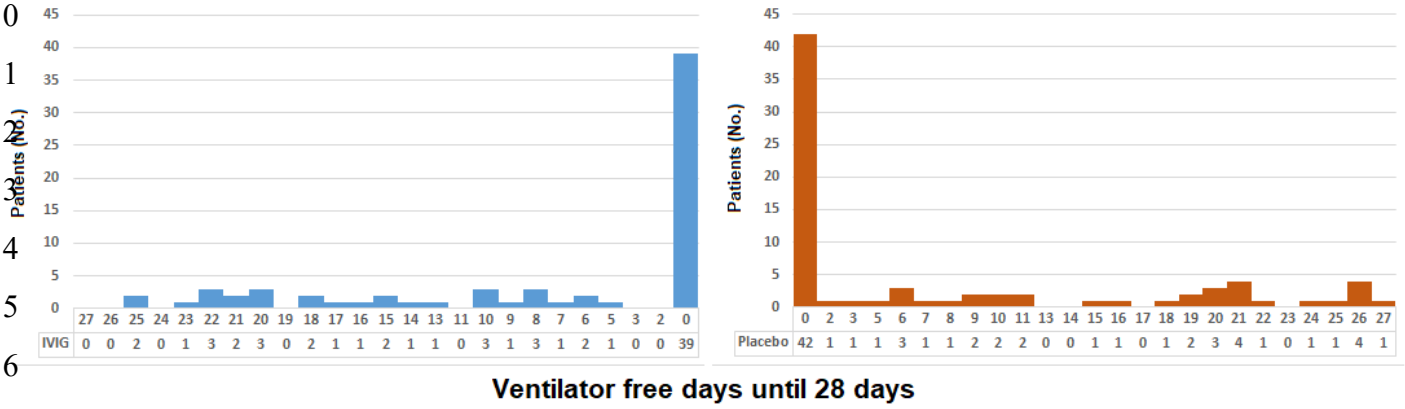
Appendix 4. Supplementary Figures

Figure S1. Cumulative inclusions by treatment group



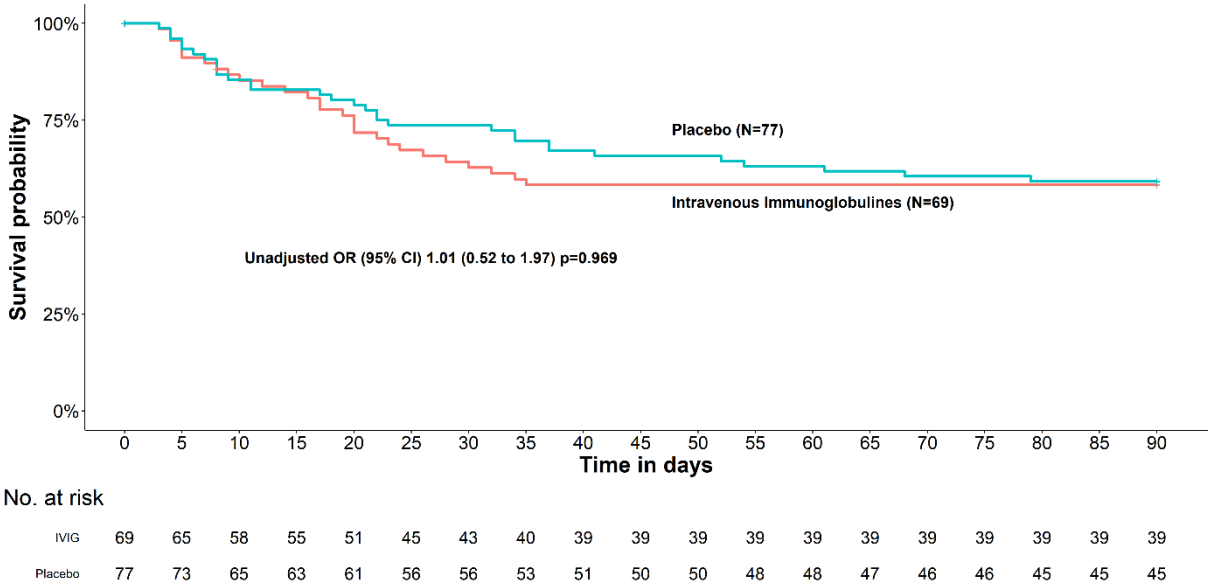
IVIG : Intravenous immunoglobulins. The two periods of inclusion are related to the "first wave" and "second wave" that occurred in France during the epidemics course.

Figure S2. Ventilator-free days frequency distribution



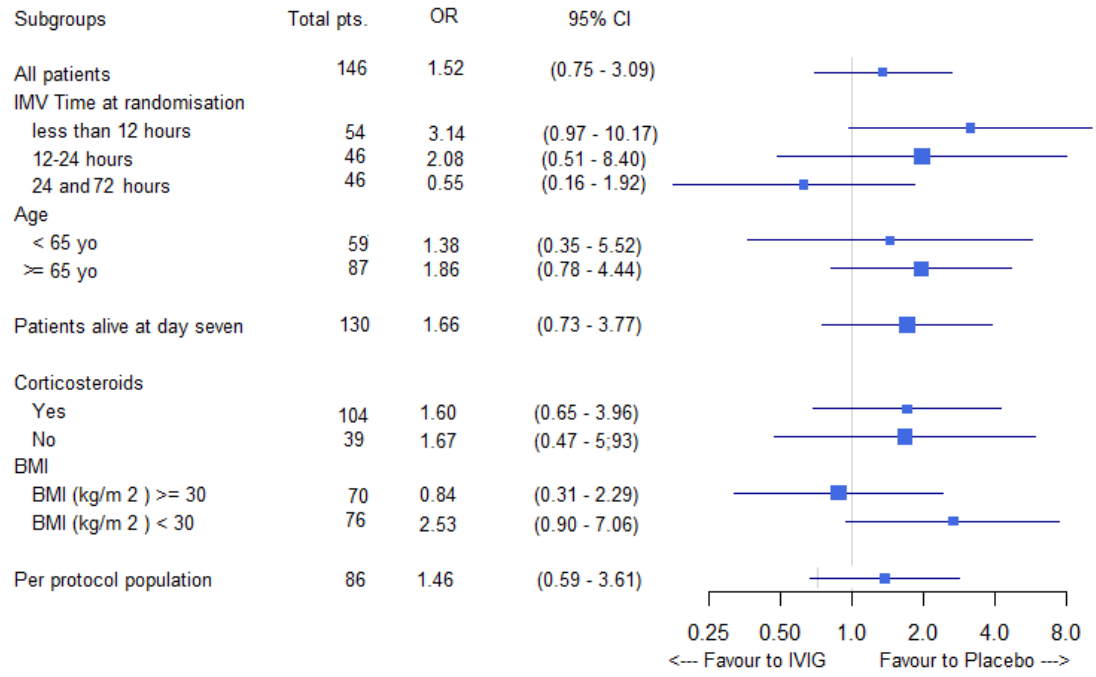
IVIG : Intravenous Immunoglobulins. Patients with prolonged mechanical ventilation during 28 days or more represent 15/39 in the intravenous immunoglobulins group and 22/42 in the placebo group.

Figure S3. Survival at days 90*



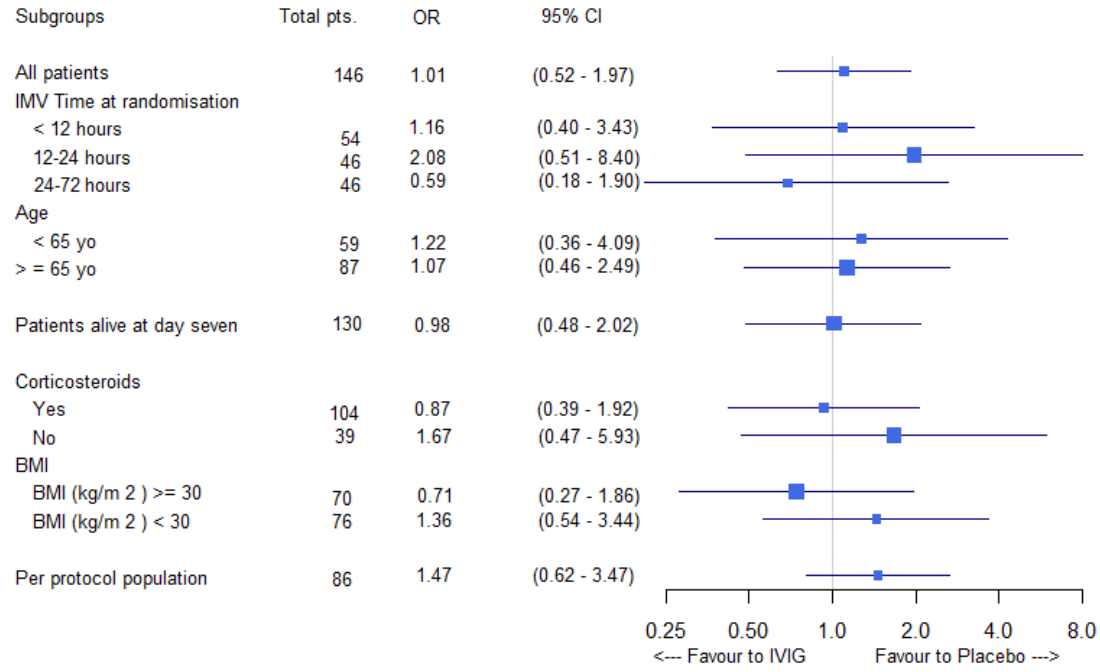
IVIG: Intravenous immunoglobulins; OR : Odds Ratio

Figure S3. Unadjusted 28 days Odds Ratio: subgroup analysis



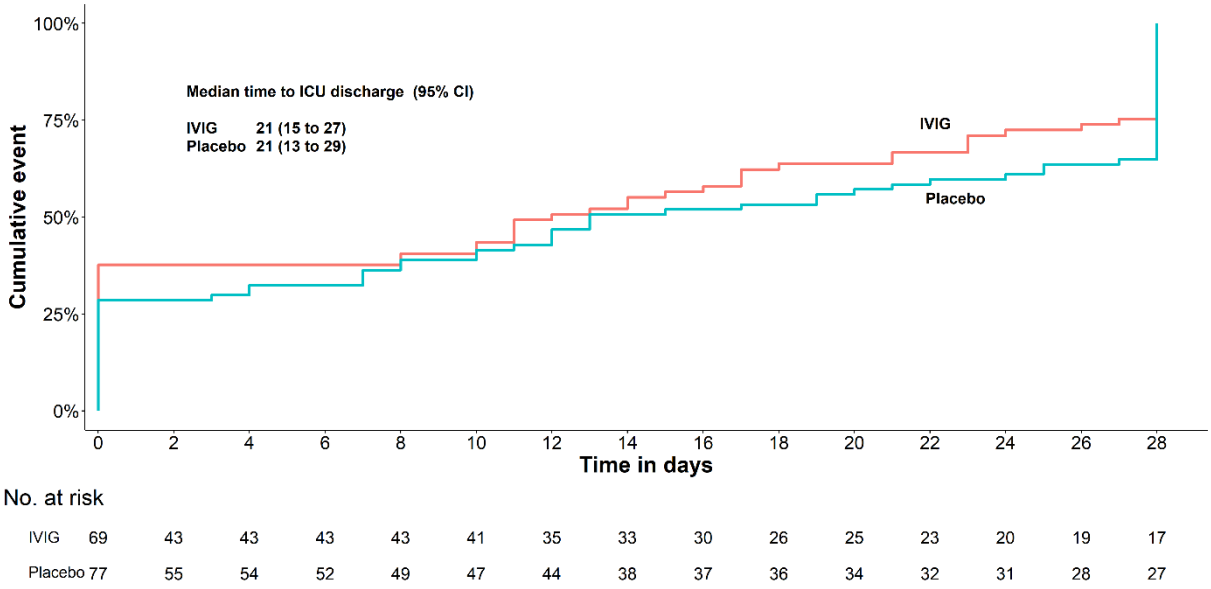
IMV: Invasive mechanical ventilation, BMI: Body Mass Index; yo : years old; pts: patients; OR : Odds Ratio ; 95% CI : % Confidence Interval; IVIG : Intravenous Immunoglobulins. For ORs, the interaction tested with the method proposed by Altman & Bland (5) did not show statistical significance

Figure S4. Unadjusted 90 days Odds Ratio: subgroup analysis



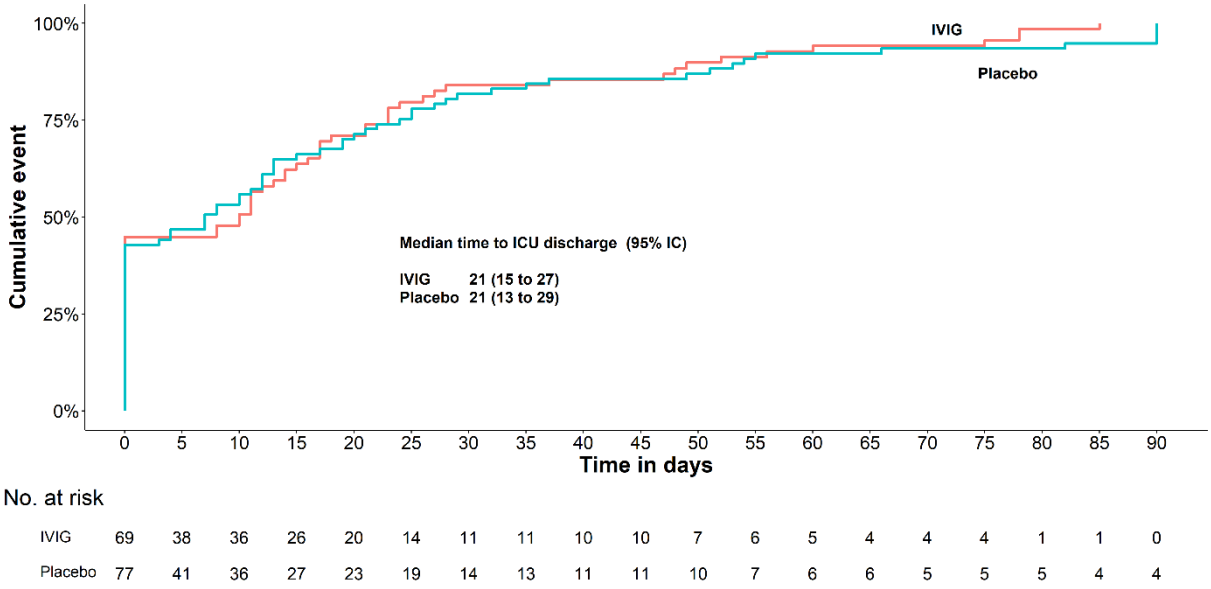
IMV: Invasive mechanical ventilation, BMI: Body Mass Index; yo : years old; pts: patients; OR : Odds Ratio; 95% CI : % Confidence Interval; IVIG : Intravenous Immunoglobulins. For ORs, the interaction tested with the method proposed by Altman & Bland (5) did not show statistical significance

Figure S5. Time to ICU discharge at 28 days (Cumulative incidence plots)



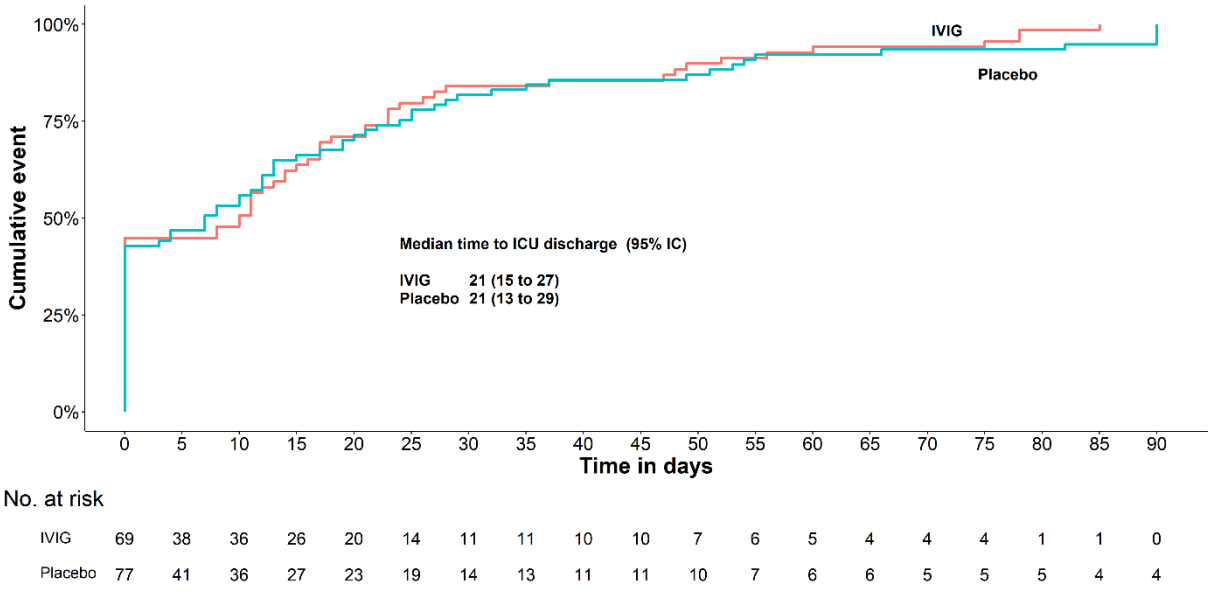
IVIG: Intravenous Immunoglobulins; ICU : Intensive Care Unit.

Figure S6. Time to ICU discharge at 90 days (Cumulative incidence plots)



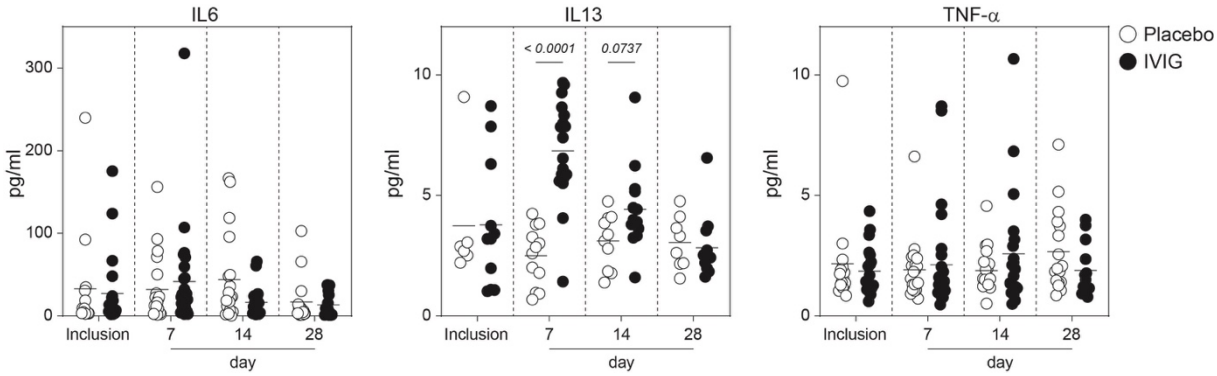
IVIG: Intravenous Immunoglobulins; ICU : Intensive Care Unit.

Figure S7. Time to Hospital discharge at 90 days (Cumulative incidence plots)



IVIG: Intravenous Immunoglobulins; ICU : Intensive Care Unit.

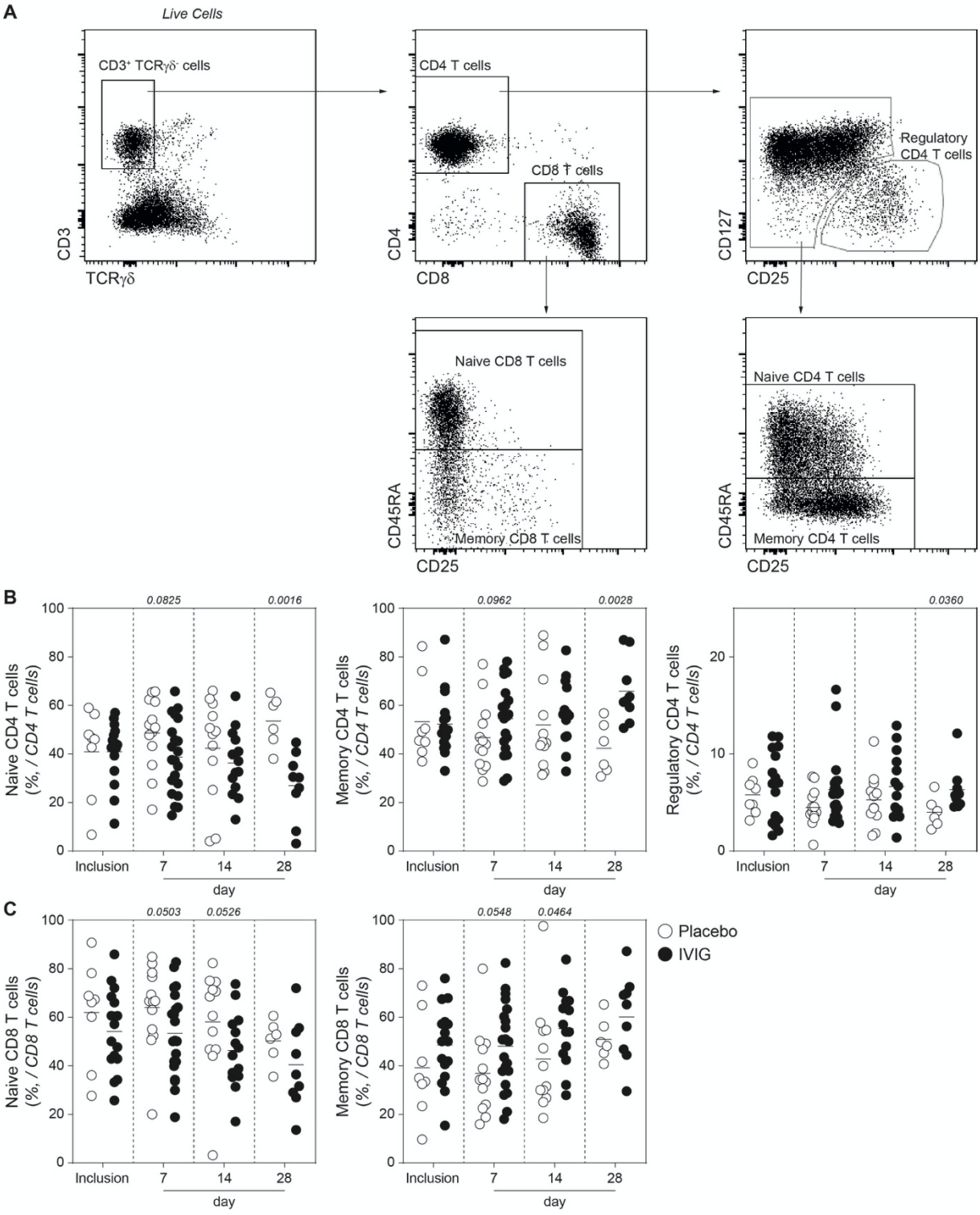
Figure S8 : Plasma concentrations of inflammatory cytokines in a subset of patients.



IL-6: Interleukin 6; IL13 : Interleukine 13; TNF- α. Tumor necrosis Factor alpha ; IVIG Intravenous immunoglobulins. P values were calculated with a Mann-Whitney test

Patients' plasma was collected at the time of inclusion and 7, 14, and 28 days later. Plasma concentrations of interleukin-6, interleukin-13, and tumor necrosis factor were then quantified using multiplex cytokine immunoassay.

Figure S9: Characterization of blood T cells in a subset of patients.



Peripheral blood from patients was collected at the time of inclusion and 7, 14, and 28 days later. Peripheral blood mononuclear cells were freshly purified on a Ficoll density gradient and then frozen in 10% dimethylsulfoxide / 90% fetal calf serum. A) Gating strategy used to define naive, memory and regulatory CD4 and CD8 T cells. B) Percentages of naive, memory and regulatory T cells among CD4 T cells. C) Percentages of naive and memory T cells among CD8 T cells.

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