THE LANCET
Respiratory Medicine

Supplementary appendix 2

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

Supplement to: 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.

This supplement contains the following items:

1. Original protocol
2. Final protocol
3. Summary of protocol changes
4. Original statistical analysis plan
5. Final statistical analysis plan
6. Summary of statistical analysis plan changes

Effect of early treatment with polyvalent immunoglobulin on acute respiratory distress syndrome associated with SARS-CoV-2 infections

ICAR (IgIV in Covid-related ARds)

BIOMEDICAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

Version V1.0 - 04/04/2020
N° EudraCT: 2020-001570-30 Project code: D20 – P013

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SIGNATURE page for a biomedical research PROTOCOL

Research Research Code: D20-P013
Title: Effect of early treatment with polyvalent immunoglobulin on acute respiratory distress syndrome associated with SARS-CoV-2 infections
ICAR (IgIV in Covid-related ARds)
Version N° 1.0 of: 04/ 04/2020

The research will be carried out in accordance with the protocol, with current good practices and with the legislative and regulatory provisions in force.

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The research received a favourable opinion from the CPP Ile de France X on 10th April 2020 and authorisation from the ANSM on 09th April 2020

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SUMMARY

Full title	Effect of early treatment with polyvalent immunoglobulin on acute respiratory distress syndrome associated with SARS-CoV-2 infections
Acronym	ICAR (IgIV in Covid-related ARds)
Coordinating Investigator	Dr Aurélien MAZERAUD, Service d'anesthésie-réanimation neurologique 1, rue Cabanis 75014 Paris
Sponsor	GHU Paris Psychiatrie et Neurosciences
Scientific justification	Mid-March 2020, 715 600 people were infected with Coronavirus Disease 2019 (COVID-19) worldwide, and 35500 people died, mainly from acute respiratory distress syndrome (ARDS). No specific pharmacological treatment of COVID-19 related ARDS is currently available. Pulmonary lesions are related to both the viral infection and an inflammatory reaction. Patients admitted to resuscitation have a cytokinetic inflammatory response and higher plasma concentrations of interleukin (IL) 2, IL 7, IL 10, Granulocyte Colony Stimulating Factor, interferon-inducible protein 10, Monocyte chemoattractant protein-1, macrophage inflammatory protein 1α, and tumor necrosis factor-alpha. The number of peripheral CD4 and CD8 T cells appears to be significantly reduced in the blood, while their status is hyperactivated. This redaction is evidenced by immunoreactive cytometric profiles for HLA-DR (CD4 3-47%) and CD38 (CD8 39-4%) or by an increase in the proportion of highly pro-inflammatory Th 17 CCR6+ lymphocytes. Besides, CD8 T cells would exhibit a highly cytotoxic profile characterized by high concentrations of cytotoxic granules (perforin+, granulysin+, or double-positive). Because of their immunomodulatory effect that may both attenuate the inflammatory response and enhance antiviral defense, we propose to evaluate the efficacy and safety of intravenous immunoglobulin (IVIG) administration in patients developing COVID-19 related ARDS. IVIG modifies T cells functions but also dendritic cell function and ultimately cytokine and chemokine networks. IVIG stimulates regulatory T cells proliferation that regulates CD4 and CD8 T cell activity. Also, IVIG restores regulatory T cells functions and modulate lymphocyte populations specifically altered during COVID-19. Besides, IVIG can modulate humoral acquired immunity through its effect on the idiotypic network and antibody

	production. IGIV also acts on innate immunity by antigen neutralization and modulation of phagocytic cells. These effects lead to a decrease in the production of pro-inflammatory cytokines and complement activation, key factors in COVID-19 related ARDS. It should be noted that IVIG is used as a treatment for a variety of autoimmune and inflammatory diseases. Both standard and polyclonal IVIG have significantly reduced mortality in patients with Kawasaki disease and improve outcomes in patients with polyneuropathy. More recently, it has been shown that IVIG may have a beneficial effect in diffuse interstitial lymphocytic pneumonitis and post-influenza ARDS. Few low-level of evidence data support the effect of IGIV during COVID-19. This treatment has been described as favorable in 3 cases of COVID-19 related ARDS and one with COVID-19-related myocarditis who received a high dose of intravenous immunoglobulin IVIG at the time of onset of distress, with a favorable clinical course. More recently, a retrospective study showed a decrease in mortality and ventilation time in patients with ARDS receiving mechanical ventilation treated early with a high dose of IGIV. Notably, there were no adverse events reported, including no renal impairment or allergic reactions. IVIG is a treatment option if it is well-tolerated, particularly concerning renal function. In adults, adverse events reported as possibly related to polyclonal IVIG during septic shock were allergic reactions; skin reactions such as erythema and exanthema; pruritus; nausea and vomiting; dyspnea; congestion; shock; and fever. Two trials reported no adverse events attributable to IVIG, and one trial reported adverse events, but none were ascribed to IVIG. The favorable benefits-risks balance encourages us to rapidly carry out a multicentre, placebo-controlled therapeutic trial testing the benefit of IVIG in COVID-19 related ARDS.
Primary objective and assessment criterion	The main objective is to determine whether the administration of IVIG at a dose of 2g/kg up to 72 hours after the start of invasive mechanical ventilation (IMV), in a patient with COVID-19 related ARDS, increases the number of days without IMV (ventilator-free days) up to day 28 (D28) after IMV initiation.

	The primary endpoint is the number of ventilator-free days at D28, which is, by definition, the number of days the participant was alive and free from IMV from the day of randomization to 28D. The outcome value is calculated as the sum of the days without VM; in case of death before D28, the score is zero. This parameter is a robust primary endpoint frequently used during ARDS. Only the last extubation will be considered as recently suggested in case of multiple invasive mechanical ventilation periods.
Secondary objectives and assessment criteria	Secondary objectives are to assess the impact of IVIG on the following outcomes, overall mortality rate, organ failure according to the SOFA score at 14 and 28 days, lung injury score at 14 and 28 days, the occurrence of grade 3 or 4 adverse events of IGIV, length of ICU stay, length of hospital stay, functional outcomes at D90 defined by the activities of daily living and instrumental activities of the daily living scales, and 90 days survival. The exploratory objectives are to evaluate the impact of IVIG on: • the incidence of occurrence of pulmonary embolism • the number of delirium free days according to the CAM-ICU (Annexe 1) at day 28 • the occurrence of ICU-acquired weakness defined by a MRC sum score < 48 at ICU discharge (Annexe 2) • the occurrence of ventilator associated pneumonia defined by a positive culture of pulmonary specimen • biological efficiency study through in-depth study of IGIV impact on cytokines, immune cells transcriptome and lymphocytes activation in an ancillary study
Experimental design	This is a Phase III double-blind, randomized, multicenter, parallel-group, concurrent, placebo-controlled study in hospitalized participants with COVID-19 requiring mechanical ventilation.
Population involved	Adult population hospitalized in ICU for SARS-CoV-2 ARDS

Inclusion criteria	Any patient in intensive care who meet all of the following: 1) Receiving invasive mechanical ventilation for less than 36 hours 2) Develops moderate to severe ARDS according to Berlin classification 3) Has a proven SARS-CoV-2 infection (by polymerase chain reaction) 4) Given consent by patient, family or deferred consent (emergency clause) 5) Is affiliated to a social security scheme (or exemption from affiliation)
Non-inclusion criteria	Any of the following: - Allergy to polyvalent immunoglobulins - Pregnancy or minor patient - Known Immunoglobulin A deficiency - Patient with acute renal failure on admission defined by a creatinine 3 times higher than baseline or creatinine >354 micromol/L or a diuresis of less than 0.3 mL/Kg for 24 hours or anuria for 12 hours - Participation in another interventional trial
Treatment being tested	Polyvalent human immunoglobulin at a dose of 2g/kg over 4 consecutive days started (i.e. 0.5g/Kg/d) during the first 24-72 hours of invasive mechanical ventilation (IMV)
Benchmark treatment	No reference treatment is currently proposed for COVID-19
Other procedures added by the research	Assessment at D28 and D90 of survival and functional status by telephone interview
Risks added by the research	Risks associated with the administration of immunoglobulins with a known safety profile in critically ill patients hospitalized for septic shock or ARDS. This therapeutic trial is classified as risk D according to the grid of GHU Paris – Psychiatrie & Neurosciences
Practical procedure	After verification of the inclusion and exclusion criteria, the consent of the patient or a relative or the emergency clause will be collected. Then the patient will be randomized to either the IVIG treatment group or the placebo group, through an online website.

	Patients in the treatment group will receive polyvalent immunoglobulin infusions to be started between 24 and 36 hours after the onset of IMV for 4 consecutive days. Patients in the placebo group will receive an equivalent volume of saline (NACL 0.9%) for the same duration. The principal investigator at each center will be collected trial data. In patients discharged before D28 or D90, a telephone interview will be conducted by a research technician from the experimental center. Adverse events will be reported in the trial's CRF. .
Number of subjects chosen	138
Number of centres	Patients will be enrolled in 36 participating ICUs, from 35 participating centers (35 different hospitals) nationwide in France.
Research period	- duration of inclusion: 1 month - duration of participation (treatment + follow-up): 3 months - total duration: 4 months
Number of inclusions expected per center and per month	3.8
Statistical analysis	Assuming that the number of days without IMV is 10 days in the placebo group and 15 days in the treatment group with a standard deviation of 6 days, adjusted for mortality and, given the uncertainty regarding the normality distributions assumption, the non-parametric Wilcoxon-Mann-Whitney test (U-test) was used for sample size estimation. Considering a 5% bilateral alpha risk, 90% power, and 0.6 effect size level, the number of subjects to be included is 138 patients, 69 in each arm. The statistical analysis plan will be developed and finalized before the database is locked and will describe the participating populations to be included in the analyses and the procedures for accounting for missing, unused and spurious data. The choice of statistical tests and multivariate models (parametric or non-parametric) will be done ex-post for each variable on the basis of the characteristics observed (normality of distributions and residuals, collinearity, etc.). All univariate or multivariate statistical analyses related to the primary and secondary objectives will be performed with the intention-to-treat (ITT) population. Per protocol population analyses may also be carried out. All tests will be bilateral with a significance level of 5%.

	The software used will be SPSS v26.
Interim Analysis	No interim analysis is planned
Funding source	-GHU Paris - Psychiatry and Neurosciences -Drugs (CLAIRYG 50MG/ML polyvalent immunoglobulins) supplied free of charge by the LFB laboratory
Data Safety Monitoring Board anticipated	Yes
Critical Events Validation Committee	It will meet twice in the trial. Its mission is to validate the evaluation of the main judgement criterion and secondary criteria subject to subjective interpretation: pneumopathy acquired under mechanical ventilation.

1. SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

1.1 Hypothesis for the research

Mid-March 2020, 715 600 people were infected with Coronavirus Disease 2019 (COVID-19) worldwide, and 35 500 people died, mainly from acute respiratory distress syndrome (ARDS). No specific pharmacological treatment of COVID-19 related ARDS is currently available (1).

Few low-level of evidence data support the effect of IGIV during COVID-19. This treatment has been described as favorable in 3 cases of COVID-19 related ARDS and one with COVID-19-related myocarditis who received a high dose of intravenous immunoglobulin IVIG at the time of onset of distress, with a favorable clinical course (2, 3). More recently, a retrospective study showed a decrease in mortality and ventilation time in patients with ARDS receiving mechanical ventilation treated early with a high dose of IVIG (4). Notably, there were no adverse events reported, including no renal impairment or allergic reactions. IVIG is a treatment option if it is well-tolerated, particularly concerning renal function (5). In adults, adverse events reported as possibly related to polyclonal IVIG during septic shock were allergic reactions (6, 7); skin reactions such as erythema and exanthema; pruritus; nausea and vomiting; dyspnea; congestion; shock; and fever (6–10). Two trials reported no adverse events attributable to IVIG, and one trial reported adverse events, but none were ascribed to IVIG (8, 9, 11).

The favorable benefits-risks balance encourages us to rapidly carry out a multicentre, placebo-controlled therapeutic trial testing the benefit of IVIG in COVID-19 related ARDS.

Description of knowledge relating to the pathology in question

To date there is very little pathophysiological knowledge to explain the manifestations of SARS-CoV-2 responsible for COVID-19. Based on existing observational data, it would appear that there are 3 phases during COVID-19: an invasion phase, covering the acquisition of the virus and the subsequent symptomatic viremia phase; in many, but not all, patients, an acceleration phase, when secondary virus-induced damage to target organs and tissues occurs, including the lungs, heart, gastrointestinal tract, and even a generalized cytokine storm. The third phase is the final phase of recovery.

First phase

A virological and animal study identified that SARS-CoV-2 uses the same cell entry receptor - Angiotensin II Converting Enzyme (ACE2) - as SARS-CoV. It is responsible for the virus's body penetration and is one of the determinants of the virulence of COVID-19. The expression of ACE2 is increased in hypertensive patients explaining the severity of the picture in this population.

Second acceleration phase

Clinical and autopsy data, multiplex cytokine assays, and cytometric profiles of circulating lymphocytes provide a better understanding of this runaway phase of COVID-19. Lymphopenia, delay in onset of respiratory distress, and extensive and

prolonged virus replication are common features in patients with severe forms of COVID-19 and are a risk factor for mortality (2).
When mechanical ventilation is required for ARDS, mortality associated with COVID-19 is 50%. The still morbidity is probably high given the significantly prolonged mechanical ventilation durations of the order of 21 days.
Therefore, treatment strategies for COVID-19 must be tailored to each phase. The best timing of antivirals, if any, may be in the pre-acceleration phase. Once clinical deterioration has begun, the first few days of deterioration may present a critical point where modulation of the inflammatory response may be helpful. The use of corticosteroids or polyvalent immunoglobulins was then proposed for the treatment of patients with severe COVID-19.
Pulmonary lesions are related to both the viral infection and an inflammatory reaction. Patients admitted to ICU present an intense cytokinic inflammatory response characterized by higher plasma concentrations of interleukin (IL) 2, IL 7, IL 10, Granulocyte Colony Stimulating Factor, interferon-inducible protein 10, Monocyte chemoattractant protein-1, macrophage inflammatory protein 1α, and tumor necrosis factor-alpha (12). In the blood, the number of peripheral CD4 and CD8 T cells appears to be significantly reduced, while their status is hyperactivated. This is evidenced by immunoreactive cytometric profiles for HLA-DR (CD4 3-47%) and CD38 (CD8 39-4%) or by an increase in the proportion of highly pro-inflammatory Th 17 CCR6+ lymphocytes. Besides, CD8, T cells exhibit a highly cytotoxic profile characterized by high concentrations of cytotoxic granules (perforin+, granulysin+ or double-positive, (13).

Summary of relevant pre-clinical experiments and clinical trials

Because of their immunomodulatory effect that may both attenuate the inflammatory response and enhance antiviral activity, we propose to evaluate the efficacy and safety of IVIG administration in patients developing COVID-19 related ARDS. IVIG modifies T cells functions but also dendritic cell function and ultimately cytokine and chemokine networks. IVIG stimulates regulatory T cells proliferation that regulate CD4 and CD8 T cell activity (13–15). Also, IVIG restores regulatory T cells functions and modulate lymphocyte populations specifically altered during COVID-19 (13).

In addition, IVIG can modulate humoral acquired immunity through its effect on the idiotypic network and antibody production. IGIV act also on innate immunity by antigen neutralization and modulation of phagocytic cells. These effects lead to a decrease in the production of pro-inflammatory cytokines and complement activation, key factors in COVID-19 related ARDS (14–17). It should be noted that IVIG is used as a treatment for a variety of autoimmune and inflammatory diseases. Both standard and polyclonal IVIG have significantly reduced mortality in patients with Kawasaki disease (18, 19) and improve outcomes in patients with polyneuropathy (20). More recently, it has been shown that IVIG may have a beneficial effect in diffuse interstitial lymphocytic pneumonitis (16), and in post-influenza ARDS (21).

Immunoglobulins have been tested during critical conditions such as sepsis and septic shock. A meta-analysis conducted by the Cochrane Database found that 10 trials of polyclonal IGIV in adults (n = 1430) and seven trials of polyclonal IVIG supplemented

with IgM (n = 528) showed significant reductions in mortality compared to placebo or no intervention (relative risks of 0.81 and 0.66 respectively) (5).
In adults, adverse events reported as possibly related to polyclonal IVIG during septic shock were allergic reactions (6, 7); skin reactions such as erythema and exanthema; pruritus; nausea and vomiting; dyspnea; congestion; shock; and fever and chills (6–10). Two trials reported no adverse events attributable to IVIG, and one trial reported adverse events, but none were evaluated as being related to IVIG (8, 9, 11).
To date, four clinical cases of patients with COVID-19 treated with IVIG have been reported in the literature. Of this three patients with ARDS and one with COVID-19-related myocarditis received a high dose of intravenous immunoglobulin at the onset of distress, with a favorable clinical course(2, 3). More recently, one multicentric retrospective study including 325 patients has been submitted to the MedRxiv repository suggesting that a high dose (>15g/day) initiated in the first 7 days of mechanical ventilation could reduce COVID-19 mortality from 53% to 27% (p=0.009, 13). Notably, there were no adverse reactions reported, including no renal failure or allergic reactions.

2. Description of the population to be studied and justification for the choice of participants

We propose to study patients with COVID-19 related ARDS. The IGIV could present beneficial effects on the late phase of SARS-CoV-2 when the immune response is overwhelming to lower the intensity of the cytokinic storm. Based on the availability and cost of IgIV, such treatment could not be evaluated in the entire population of patients presenting COVID-19. We thus chose to focus on a subpopulation of patients with a severe COVID-19. Therefore, we determined that the effectiveness of IVIG should be evaluated when mechanical ventilation for moderate to severe ARDS is introduced. We will use a PCR technique to diagnose a SARS-CoV-2 infection and the conventional Berlin definition of adult respiratory distress syndrome(22).
The proposed new "Berlin" definition of acute respiratory distress syndrome (ARDS) distinguishes, according to the PaO_2/FiO_2 ratio measured in the presence of a positive external expiratory pressure (PEEP) of at least 5 cmH2O, three levels of severity of ARDS: minimal (200 < PaO2/FiO2 ≤ 300 mmHg), moderate (100 < PaO2/FiO2 ≤ 200 mmHg) and severe (PaO2/FiO2 ≤ 100 mmHg). See Annexe 1.

2.1 Identification and description of the experimental medication or medications

Polyvalent human immunoglobulins, manufactured by the pharmaceutical group LFB biotherapies CLAYRIG® 10mg/mL

2.2 Description and justification of the dosage, administration method, administration design, and treatment period.

IVIG will be administered as an 8-hour infusion at a dose of 2g/kg over 4 consecutive days started (i.e., 0.5g/Kg/day). The dose of 2g/kg body weight is used in clinical cases reported in case reports of COVID-19 or in therapeutic trials for septic shock, influenza

pneumopathy, or interstitial lung disease (6, 9, 13). Also, based on the multicentric retrospective study, including 325 patients with COVID-19-related ARDS, a high dose (>15g/day) initiated in the first 7 days of mechanical ventilation could reduce COVID-19 mortality from 53% to 27% (p=0.009, 13). Therefore we chose to administer the IVIG early during the ARDS course, meaning between the 24th and the 72 hours after mechanical ventilation initiation.
The intravenous route allows controlled administration over an extended period of time. The administration is usually fractioned into 4 administrations in this indication. After administration, immunoglobulins have a prolonged half-life and action of approximately 35 days, according to the summary of product characteristics. The plasma peak of immunoglobulins is immediate after administration, and they diffuse into the different compartments within 3 to 5 days. Their prolonged action justifies initial administration without a maintenance dose in this therapeutic trial and will cover the period of the resuscitation stay. The administration of the drug is detailed in Chapter 7.

2.3 Summary of the known and foreseeable benefits and risks for the research participants

The risks associated with the administration of immunoglobulin are the occurrence of an episode of arterial hypotension of anaphylactic origin or circulatory failure. These events have become rarer with the use of newer immunoglobulin preparation techniques. There is a risk of renal failure, which is not reported in recent studies of sepsis and septic shock or other patient populations with interstitial lung disease or neuropathy (6, 9, 13). Nevertheless, not all recent studies have reported adverse events related to IVIG. It should be noted that these adverse events were not reported in the 4 cases of COVID-19 treated with IVIG (12, 20).

Also, there is an increased risk of thromboembolic events due to product-induced hyperviscosity. This risk is not reported in ICU studies, and prolonged administration minimizes this risk. The risk of deep vein thrombosis in a population of immobilized patients without thrombotic prophylactic therapy would be approximately 1.6%, and the risk of pulmonary embolism would be lower. This was not reported in a cohort of 117 patients, the authors of which concluded that their use is safe (13).

COVID-19 related ARDS is associated with a very high mortality rate of around 50% (27). The individual benefits expected from a new therapy in this context are an increase in the chances of survival at the individual level and a reduction in the duration of mechanical ventilation, which is associated with significant morbidity. On a collective scale, reducing the duration of mechanical ventilation will increase the availability of ventilators and resuscitation beds in a context of high tension throughout the SARS-CoV-2 pandemic. This study will also providehigh-quality evidence for the effects of IGIV in the context of COVID-19 relate ARDS.

3. OBJECTIVES

3.1 Primary objective

The main objective is to verify if the administration of IVIG at a dose of 2g/kg over four consecutive days up 24-72 hours after the start of IMV, in patients with COVID-19 related ARDS, increases the number of days alive without IMV (ventilator-free days) up to day 28 (D28) after IMV initiation.

3.2 Secondary objectives

The secondary objectives are to assess the impact of IVIG on mortality, organ failure, resuscitation complications, and functional and psychological sequelae at D28 and D90 and their side effects.

3.3 Objective of complementary study

All patients included in the trial will be offered the opportunity to participate in the complementary study on the biological effects of IVIG. This study will aim to evaluate the biological parameters of responses to IVIG by performing cytokine assays and lymphocyte profiles in flow cytometry based on the evolution of COVID-19 in resuscitation. One 5ml blood sample will be taken at D1, D7, D14, D21, and D28 in this study.

4. EXPERIMENTAL PLAN

4.1 Description of the primary and secondary assessment criteria

4.1.1 Primary assessment criterion

The primary endpoint is the number of ventilator-free days at D28, which is, by definition, the number of days the participant was alive and free from IMV from the day of randomization, which is 0D, to D28. The score is calculated by the sum of the number of days the patient did not receive IMV; the score is zero in case of death before day 28. This outcome is a validated and commonly used primary endpoint in trials on ARDS (24).

In case of multiple invasive mechanical ventilation periods, only the last extubation will be considered free of IMV (25)..

4.1.2 Secondary assessment criteria

Secondary objectives are to assess the impact of IVIG on the following outcomes:

- Overall Mortality Rate at J28 and J90
- Total duration of mechanical ventilation, ventilatory withdrawal, curarization, use of non-invasive ventilation (NIV), high flow oxygen therapy (HFO) WHO ordinal severity scale
- WHO ordinal scale of severity of COVID impairment
- Organ failures according to the SOFA score achieved at D1, D7, D14, D21, and D28, according to Annex 9
- Clinical Efficacy Criteria: Radiological score according to the quadrant method, the chest x-ray is divided into 4 quadrants. The existence of alveoli-interstitial opacities in one quadrant adds 1 point to the score. P/F ratio value, lung compliance at D1, D7, D14, D21, and D28
- Biological efficacy endpoints: inflammatory syndrome at D1, D3, and D7, D14, D21, and D28 by measuring serum C-reactive protein, procalcitonin, white blood cell count, and d-dimer levels.
- Occurrence of ventilator-associated pneumonia defined by a positive microbiological sample after 48 hours of IMV, at 28D and 90D.
- Occurrence of an adverse event related to immunoglobulins (D1, D2, D3, D4, D5, D6 and D7, D14, D21, and D28: KDIGO 3 stage renal failure, hypersensitivity manifestations with cutaneous or hemodynamic manifestations, aseptic meningitis defined by a clinically objectified meningeal syndrome upon awakening, hemolytic anemia (defined by hemoglobin less than 8 g/dL, an indosable haptoglobin, and a positive direct Coombs test), leukoneutropenia (according to the WHO classification in Appendix X), Transfusion-Related Respiratory Distress Syndrome (TRALI) due to immunoglobulin
- KDIGO score (D1, D7, D14, D21, and D28) and the need for extrarenal purification.
- Occurrence of clinically detected deep vein thrombosis proven by Doppler ultrasound.
- Occurrence of a pulmonary embolism detected by a pulmonary angioscan.

Biological efficiency study through the in-depth study of IGIV impact on cytokines, immune cells transcriptome, and lymphocytes activation in an ancillary study

4.2 Description of research methodology

4.2.1 Experimental plan

The ICAR trial is a Phase III double-blind, randomized, multicenter, parallel-group, concurrent, controlled study in hospitalized participants with COVID-19 requiring mechanical ventilation. The participants will be randomized 1:1 to the Investigational arm or the Control arm. Participants randomized to the Investigational arm will receive Ig 2g/Kg administered IV for up to 4 days in addition to the standard of care (SOC), while participants in the Control arm will receive SOC alone.

4.2.2 Number of centers participating

Patients will be enrolled in 36 participating ICUs, from 35 participating centers (35 different hospitals) nationwide in France.

1. GHU Paris
2. Hôpital Raymond Poincaré
3. CHU Pitié Salpêtrière (2 ICU)
4. Hôpitaux civils de Lyon
5. CHU Saint Antoine
6. CHU Lariboisière
7. CH Aulnay
8. CH Chalons en champagne
9. CH Poissy
10. CH Etampes
11. Institut. Mutualiste Montsouris
12. Institut Gustave Roussy
13. CHU Robert Débré à Reims
14. Centre Hospitalier de Dieppe
15. Hôpital de Hautepierre (Strasbourg)
16. CHU de Grenoble
17. CHU Nancy
18. Grand Hôpital de l'Est Francilien (site de Jossigny)
19. CHU Sud Amiens
20. Hôpital Jacques Cartier (Massy)
21. Fondation ophtalmologique Rotschild
22. Hôpital Avicenne
23. Hôpital de la Croix Rousse
24. Hôpital de Tarbes
25. Hôpital Nord Franche-Comté
26. CHU Nantes
27. CH d'Angoulême
28. Hôpital d'instruction des armées Percy
29. CHR Orléans
30. Hôpital Salengro (Lille)
31. Hôpital de Vannes
32. CH Valenciennes
33. Hôpital Robert Boulin (Libourne)
34. Groupe Hospitalier Saint Vincent (Strasbourg)
35. Centre Hospitalier de Béthune

4.2.3 Identification of the subjects

In this research, the subjects will be identified as follows:
Centre no. (3 numeric positions) - no. order of selection of the person in the center (4 numeric positions) - initial last name - initial first name
This reference is unique and will be kept for the duration of the search.
After inclusion, the patient will be randomized to either the treatment or placebo group. The randomization result will be communicated to the hospital pharmacist so that the treatment corresponding to the patient's group is prepared.

4.2.4 Randomization

After screening for inclusion and exclusion criteria and obtaining consent, patients will be randomized (1:1 ratio) to IVIG or placebo groups. Randomization will be performed by an online web-based central using a pre-prepared randomization list, stratified by center and by the time of IMV on randomization: less than 12 hours, between 12 and 24 hours, and between 24 and 36 hours, balanced by randomly variable block size (2 and 4). The group treatment is disclosed to the investigator only after all information regarding patient enrolment is recorded in the online system. Patients are screened for enrolment by the principal investigator and the research team at each study center.

4.2.5 Blinding methods and provisions put in place to maintain blindness

Both trial participants, care providers, and outcome assessors will be blinded after the patients' assignment to one of the trial groups. The double blinding will be provided by the hospital pharmacy of each establishment using opaque sleeves to hide the product packaging, and opaque tubing will be used. Nurses won't be blind to the study as they receive and prepare the product before administration.

4.2.6 Procedures for breaking the blind, if applicable

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting

- the clinical research department outside an emergency during working days, and to the opening hours 9 am - 5 pm, by fax at 01 45 65 76 09
- the GHU –Paris hospital pharmacy, telephone number: 07 84 05 03 40 or 06.78.4129.62 (24h/24).

5. PROCEDURE FOR THE RESEARCH

5.1 Inclusion visit

The inclusion visit will be carried out by a physician who is part of the research team, in each participating center. The purpose will be to verify the inclusion and non-inclusion criteria.

Screening and eligibility data (Day 0)

- Patient's initials, gender, date of birth
- Verification of inclusion and exclusion criteria
    - Mechanical ventilation initiation time
    - PaO_2/FiO_2 value < 200
    - PEEP Value

- Chest X-ray or lungs CT-scan
- Specimen positive for SARS-CoV-2 in PCR
- Informed consent or emergency clause

Baseline Data (Day 0)

Demographic characteristics: age, gender, known pregnancy and number of weeks of amenorrhea, height, weight

Previous history: Chronic alcoholism, Active smoking, No. of pack-years, IV drug addiction Respiratory history, Suspected COPD, Documented COPD GOLD stage (Cf Appendix 4), Asthma, Cystic fibrosis, Diffuse interstitial lung disease, Sleep apnea syndrome, with or without equipment, Other respiratory disease, Previous history and cardiovascular risk factors, Heart failure, NYHA stage (Appendix 5), Treated hypertension Treatment (especially ACE inhibitors), Converting enzyme inhibitors, Angiotensin II receptor antagonists, Ischemic heart disease, Diabetes under treatment Insulin-dependent, Hematological history, Hemoglobinopathy, Heterozygous sickle cell disease Homozygous sickle cell disease Thalassemia, Other Hemoglobinopathy, Hematological cancer History of immunodepression, HIV, Active solid cancer, Autoimmune disease, Type (Systemic connective tissue disease, Systemic vasculitis, Systemic joint disease, Organ-specific autoimmune diseases), Chronic renal failure (chronic dialysis), Liver failure, CHILD-PUGH score (see Appendix 6), Neuromuscular disorder, Dementia.

They will be used to calculate the Charlson comorbidity score (Appendix 7), the performance status (Appendix X), the current medications, as well as the inclusion and non-inclusion criteria.

Pathology criteria: Precursor symptom(s), date of onset of symptoms, Types of symptoms Fever, Cough, Sore throat, Chest pain, Arthro-Myalgias, Fatigue, Feeling unwell, Dyspnea, Headache, confusion, altered consciousness, Abdominal pain, Vomiting, Nausea, Diarrhea

Biological data: blood gas analysis, ionogram, urea, bilirubinemia, platelet count. A beta-HCG assay will be performed for all non-menopausal women.

Radiological and scannographic data will be collected; in particular the existence of a pulmonary embolism and the type and percentage of pulmonary involvement).

The following other parameters will be collected: positive COVID-19 sample, initial respiratory or systemic co-infection, treatment with hydroxychloroquine or corticoids or macrolides, IGS 2 score on admission (Help for calculation: https://www.srlf.org/scores-utiles-resuscitation/score-igs-ii/, Appendix 8), SOFA score on admission (Appendix 9),date of Hospital admission, date of ICU admission.

5.2 Follow-up Visits

Visits will be done daily throughout the stay in intensive care until D28. If the patient has been discharged before D28, will still be warranted visits to D14, D21, and D28 to collect primary and secondary outcome data. An electronic case report file will be available to the research team of each institution on an online platform (Research Electronic Data Capture, REDCap, Vanderbilt University). Activities of Daily Living and Instrumental Activities of Daily Living will be collected on day 90 with a phone call. Study data will be collected and managed using REDCap electronic data capture tools hosted at Centre Hospitalier Sainte-Anne(26). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to standard statistical packages; 4) procedures for data integration and interoperability with external sources.

Daily Follow-Up D0-D28

- Vital status, extubation, re-intubation, tracheostomy, ICU discharge
- Supportive treatment administered: Continuous intravenous sedation, neuromuscular blocker, prone position initiated in the last 24 hours, nitric oxide, almitrine, extracorporeal life-sustaining support
- Respiratory variables: Tidal volume, Plateau pressure, compliance, PaO2/FiO2
- Weaning initiation defined as the first use of spontaneous breathing trial or T-tube trial, use of spontaneous breathing ventilator mode
- COVID-19 treatment: hydroxychloroquine, azithromycin, other ATB, corticosteroids, interleukin inhibitors, antiretroviral therapy
- Complementary tests: leukocytes and lymphocytes count, platelet count, fibrinogen, D-Dimer, procalcitonin, and C reactive protein.
- Radiological score (according to the lung injury score, Annexe 2)
- SOFA score (Annexe 6) and KDIGO score (Annexe 9)
- CAM-ICU (Annexe 1)
- IVIG adverse event occurrence:
- Manifestations of cutaneous hypersensitivity
- Occurrence of hypersensitivity manifestation with hypotension (defined as a mean blood pressure of less than 65 mmHg for 30 minutes, after correction for hypovolemia).
- Doppler ultrasound evidence of deep venous thrombosis
- Existence of a pulmonary embolism proven but CT-scan
- Possible transfusion-associated lung injury
- Aseptic meningitis defined by a clinically objectified meningeal syndrome upon awakening

- Hemolytic anemia (defined as hemoglobin less than 8 g/dL, undosable haptoglobin, and a positive direct Coombs test)

D28 follow-up

- Days on mechanical ventilation
- Vital status and date of death (for patients who died)
- Days on tracheostomy if realized.
- ICU complications: Catheter-related infection, Number of the episode of ventilator-associated pneumonia (VAP), Digestive hemorrhage, Pressure sores (>grade 2), Confusion according to the CAM-ICU (Annexe 1), Focal neurological deficit, Toxidermia
- Functional status: MRC Score at discharge (Annexe 2), ADL value, IADL value

5.3 End of research visit

D90 follow-up

- Days on mechanical ventilation
- Vital status and date of death (for patients who died)
- Days on tracheostomy if realized.
- ICU complications: Catheter-related infection, Number of the episode of ventilator-associated pneumonia, Digestive hemorrhage, Pressure sores (>grade 2), Confusion according to the CAM-ICU (Annexe 1), Focal neurological deficit, Toxidermia
- Functional status: MRC Score at discharge (Annexe 2), ADL value, IADL value

If the patient has been discharged before D90, information will be collected by telephone. The elements necessary for the evaluation of the secondary outcomes are part of routine care as well. Nevertheless, an assessment at D28 and D90 will be systematic.

5.4 Expected length of participation and description of the chronology and duration of the research.

Inclusion period	1 month
The included subjects' length of participation, of which:	
• Treatment period:	4 days
• Follow-up period:	3 months
Total research period:	4 months

5.5 Table or diagram summarising the chronology of the research

Timepoint	D0	D1	D2	D3	D4	D5	D6	D7	D14	D15 -20	D21	D22 -27	D28	D90
Consent collection	x													
Pursuit consent collection		x	x	x	x	x	x	x	x	x	x	x	x	
Demographics, medical history, disease characteristics	x													
Administration of IVIG or Placebo Therapy		x	x	x	x									
Main outcome measurement		x	x	x	x	x	x	x	x	x	x	x	x	
Collection of clinical data	x	x	x	x	x	x	x	x	x	x	x	x	x	
Complete blood count, blood gas, creatinine	x	x		x				x	x		x		x	
Leukocytosis, C-reactive protein, biobank collection	x			x				x			x			
SOFA score		x		x				x	x	x	x		x	
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Final assessment of the primary outcome													x	x
Final assessment of secondary outcomes													x	x

5.6 Usual care procedures and additional study procedures

Procedures	Usual care procedures	Additional procedures
Treatments	Treatment of ARDS in ICU related to SARS-CoV-2 (sedation, curare administration, mechanical ventilation, ventral flow, nitric oxide administration of antiretroviral treatments of antibiotic treatments)	Administration of IVIG/Placebo at D1, D2, D3, D4
Consultations	Daily ICU Consultations	Consultation at D28 and D90
Blood samples	ICU entry assessment including white blood count, ionogram, creatinine, coagulation assessment, D-dimer, PCR for SARS-CoV-2	The research added no additional examination. Realization of a biobank (ancillary study)
Imaging	Diagnostic inclusion scan and chest X-ray in case of suspected pneumopathy	No
Bacteriological samples	In case of suspicion of pneumopathy acquired	No

	under mechanical ventilation	

5.7 Biological Collection (ancillary study)

Blood samples at D1, D3, D5, D7, D14, and D21 from the research participants will be collected.
During the research, the samples will be kept in the GHU Paris Biological Resource Centre laboratory, under the responsibility of Doctor Macarena Cuenca-Maia for six months at - 80°C.
At the end of the study, authorization will be requested from the Ministry of Scientific Research to store the biological samples at the GHU Biological Resource Center.

Type of sample	**Quantity**	**Storage location**	**Collection supervisor**	**Purpose of the collection**	**Storage period**	**Outcome (destruction, etc.)**
Blood	5ml	GHU Paris	Dr Macarena Cuenca-Maia	Efficacy analysis	6 months	Analysis at the Pasteur Institute flow cytometry analysis and cytokine profile

5.8 Termination rules

5.8.1 Criteria and methods for treatment discontinuation

5.8.1.1 Different situations

- Temporary treatment discontinuation: the investigator should document the reason for the discontinuation and its resumption in the clinical report form (CRF).

- Premature termination of treatment, but the subject remains in the research until the end of participation; the investigator must document the reason.
- Premature discontinuation of treatment and termination of research participation.
The investigator must:

- Document the reason(s)
- Collect the evaluation criteria at the time of termination of research participation if the subject agrees.
- Provide for follow-up of the subject, especially in the event of a severe adverse event.

The primary reason for study treatment discontinuation should be documented on the appropriate CRF form. Patients who discontinue study treatment will not be replaced.

5.8.1.2 Criteria and methods for the premature termination of the research

Any subject may discontinue participation in the research at any time for any reason.
The investigator may temporarily or permanently discontinue a subject's participation in research for any reason that affects the subject's safety or is in the subject's best interests.
In the event of premature termination of a subject's research, or withdrawal of consent, data about the subject collected prior to the premature termination may be used.
The CRF should list the different reasons for stopping participation in the research:

- Ineffectiveness
- Adverse event
- Other medical problem
- Subject Personal Reason
- Explicit withdrawal of consent
- Loss of follow-up

5.8.2 Follow-up of the subjects after the premature termination of treatment

Stopping a subject's participation will in no way change his or her usual management of the disease.
If serious adverse events occur, the investigator should report to the sponsor and follow up for 28 days after premature discontinuation of treatment.
In the event of premature discontinuation of treatment following a severe adverse event, a severe adverse event report will be faxed (01 45 65 76 09) to the sponsor. The serious adverse event will be monitored until it is resolved.

5.8.3 Methods for replacing subjects, if applicable

The living or non-living status will be collected by telephone if necessary. However, due to the average ventilation time of 20 days and convalescence time in the hospital, it is not expected that there will be any lost subjects and, therefore, no replacement subjects.

5.8.4 Terminating part or all of the research

The GHU Paris as a sponsor or the Competent Authority (ANSM) may prematurely interrupt temporarily or permanently all or part of the research, following the recommendations of an Independent Supervisory Committee in the following situations:
- In the event of unexpected serious adverse events in one treatment arm or an imbalance of serious adverse events between the two treatment arms, requiring a re-evaluation of the benefit/risk ratio of the research.
- If unforeseen events, or new information on the product, make it unlikely to achieve the research objectives, it may lead the sponsor or the Competent Authority (ANSM) to terminate the study prematurely.
- If it appears that the inclusion objectives are not being met, the promoter reserves the right to suspend inclusions permanently.
In case of premature study termination, the sponsor's decision and justification are transmitted to the Competent Authority (ANSM) and the CPP.

6. ELIGIBILITY CRITERIA

6.1 Inclusion criteria

Any patient in intensive care who meet all of the following criteria:

1) Receiving invasive mechanical ventilation for less than 36 hours
2) Develops moderate to severe ARDS meeting the Berlin criteria
3) Has a proven SARS-CoV-2 infection (by polymerase chain reaction)
4) Given signed informed consent by the patient, or by his/her legal/authorized representative, or deferred consent (emergency clause)
5) Is affiliated to a social security scheme (or exemption from affiliation)
6) Inclusion also of a protected patient (under guardianship and curation)

6.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Allergy to polyvalent immunoglobulins
- Pregnancy or minor patient
- Known Immunoglobulin A deficiency
- Patient with acute renal failure on admission defined by a creatinine 3 times higher than baseline or creatinine >354 micromol/L or a diuresis of less than 0.3 mL/Kg for 24 hours or anuria for 12 hours
- Participation in another interventional trial

6.3 Recruitment methods

We plan to include 3.8 patients per center over one inclusion month.

Number of patients to be included	138
Number of Centres	36
Inclusion period	1 month
Number of Subjects/Centre	4
Number of patients per month per center	3.8

7. TREATMENT ADMINISTERED TO RESEARCH PARTICIPANTS

7.1 Description of the experimental medication or medications

7.1.1 Experimental medication 1

Patients in the intervention group will receive an infusion of 2g/Kg IVIG to be started between 24 and 72 hours after initiation of IVM in 4 injections over 4 consecutive days of 0.5 g/Kg.
The IVIG that will be used will be those with the best tolerance profile, especially regarding renal function. The risks associated with the administration of IVIG will be minimized by infusing the product over long periods of time (>8h), by splitting doses, and by using sucrose, maltose, and glucose-free product such as CLAIRYG®. The use of loop diuretics should be kept to a minimum, and blood volume should be adjusted.
Although IVIG doses vary according to the pathologies, they are average 2 g/kg administered over 24 hours for Kawasaki syndrome or septic shock. In clinical cases reported to Wuhan of COVID-19, dosages ranged from 1.5 g/Kg to 2.5 g/Kg per day. This dosage ensures a satisfactory risk/efficacy balance. The infusion should be administered slowly over 8 hours. This flow can be slowed down to 24 hours if necessary. Patients in the placebo group will receive an equivalent volume of saline 20mL/Kg.
The double-blind will be provided by the hospital pharmacy of each establishment using opaque sleeves to hide the product packaging and must be returned to the pharmacy once empty.

7.2 Description of the non-experimental treatment or treatments (medications required for carrying out the research)

No ancillary treatment is planned in the trial.

7.3 Description of the traceability elements that accompany the experimental medication or medications

Experimental drugs will be tracked using dedicated blood-derived drug sheets for safety reasons. Placebo and experimental drug administration will be and collected through the CRF.

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

Other treatments will be left to the discretion of the teams taking care of the patients. On the other hand, participation in another intervention study is an exclusion criterion.

7.5 Methods for monitoring compliance with the treatment

The immunoglobulin and placebo vials will be returned empty to the pharmacy for inventory.

8. ASSESSMENT OF EFFICACY

8.1 Description of parameters for assessing the efficacy

The primary endpoint is the number of ventilator-free days at D28, which is, by definition, the number of days the participant was alive and free from IMV from the day of randomization, which is day 0, to day 28.
If the patient dies before D28, the score is 0. If the patient is not extubated at D28, the score is 0.
The score is calculated by the sum of the number of days the patient did not receive IMV. Multiple invasive mechanical ventilation periods, only the last extubation will be considered free.

Secondary objectives are to assess the impact of IVIG on the following outcomes:

- Overall Mortality Rate at J28 and J90
- Total duration of mechanical ventilation, ventilatory withdrawal, curarization, use of non-invasive ventilation (NIV), high flow oxygen therapy (HFO) WHO ordinal severity scale
- WHO ordinal scale of severity of COVID impairment
- Organ failures according to the SOFA score achieved at D1, D7, D14, D21 and D28, according to Annex 9
- Clinical Efficacy Criteria: Radiological score according to the quadrant method, the chest x-ray is divided into 4 quadrants. The existence of alveolo-interstitial opacities in one quadrant adds 1 point to the score. P/F ratio value, lung compliance at D1, D7, D14, D21, and D28
- Biological efficacy endpoints: inflammatory syndrome at D1, D3 and D7, D14, D21, and D28 by measuring serum C-reactive protein, procalcitonin, white blood cell count, and d-dimer levels.
- Occurrence of ventilator-acquired pneumonitis defined by an evocative radio-clinical setting associated with bacteriological sampling by culturing tracheal secretions, bronchiolo-alveolar lavage or protected distal sampling.
- Occurrence of an adverse event related to immunoglobulins (D1, D2, D3, D4, D5, D6 and D7, D14, D21, and D28: KDIGO 3 stage renal failure, hypersensitivity manifestations with cutaneous or hemodynamic manifestations, aseptic meningitis defined by a clinically objectified meningeal syndrome upon awakening, hemolytic anemia (defined by hemoglobin less than 8 g/dL, an indosable haptoglobin, and a positive direct Coombs test), leukoneutropenia (according to the WHO classification in Appendix X), Transfusion-Related Respiratory Distress Syndrome (TRALI) due to immunoglobulin
- KDIGO score (D1, D7, D14, D21, and D28) and the need for extrarenal purification, occurrence of clinically detected deep vein thrombosis proven by

Doppler ultrasound. Occurrence of a pulmonary embolism detected by a pulmonary angioscanner.

The main goals of the biological efficacy study is (1) to evaluate the effect of IVIG administration on the global immune response (2) to compare the immune response patterns in patients who will further deteriorate and die in ICU versus survivors. To do so, we propose to perform (i) a multiplex analysis of plasma cytokines and chemokines and (ii) transcriptome analysis to phenotype the effects of IVIG on the immune response with a particular focus on T cells. These results will help us identify molecular candidates involved in COVID-19 induced ARDS and identify immune cells mainly involved in its pathogeny to be further studied by (iii) flow cytometry.

Whether IVIG shows benefits or not, we propose to decipher mechanisms involved in the recovery or worsening of patients. Besides understanding at the cellular and molecular levels IgIV modulation of inflammatory mediators in COVID-19, this study will allow us to identify new targets to modulate the excessive immune reaction responsible for the pathogenicity of the SARS-CoV-2 virus.

This study will be led in collaboration with Dr. Bruno Lucas from Institut Cochin.

8.2 Anticipated methods and timetable for measuring, collecting, and analyzing the parameters for assessing the efficacy

Time point	D0	D1	D2	D3	D4	D5	D6	D7	D14	D15 -20	D21	D22 -27	D28	D90
Administration of IVIG or Placebo Therapy		**x**	**x**	**x**	**x**									
Leukocytosis, C-reactive protein, biobank collection	**x**							**x**	**x**		**x**		**x**	

The medication circuit will be the responsibility of the pharmacy for use inside each recruiting center.

Each pharmacy will receive the treatment under study: active drug (CLAIRYG® 50MG/ML polyvalent immunoglobulin) supplied for LFB laboratories as an injectable solution for infusion delivered in 100ml and 200ml vials. They will be stored between 2°C and 8°C in the original packaging, away from light.

The supply of therapeutic units:

- Initial Provisioning

Each pharmacy places an order at LFB according to the usual means of LFB controls, specifying the ICAR COVID study. The initial order planned in the trial is 200g.

Bottle of CLAIRYG® 50MG/ML Bottle of 100 ml = 10. Bottle of 200ml = 5 g

The placebo: NACL 0.9%, not provided by the laboratory, will be made available by the sponsor at each center's pharmacy.

- the pharmacy of each center orders at LFB as inclusions occur to replenish a 200g stock.

Each pharmacy keeps an accounting of the immunoglobulin stock according to its current system.

Methods of dispensing:

- The pharmacy of each center receives:

1- The result of patient randomization

2-The prescription from the investigator (each center is organized according to its internal system of prescription and traceability of drugs) knowing that the doctor is blind.

3-A nurse from the ICU comes to pick up the therapeutic units at the hospital pharmacist.

The pharmacist delivers the treatment for 24 hours in a pocket on which a sleeve will be placed to mask the treatment. Vials of experimental drug or placebo are destroyed on-site according to local procedure.

Biological samples will be sent to the laboratory according to the usual way of complementary examinations from each center, which will then be sent to the GHU Paris Biological Resource Centre.

The biological collections will be managed by the biological resource center (Dr Cuenca-Maia) of the GHU Paris and forwarded by the investigator of each center to the center of the coordinating investigator.

9. SPECIFIC RESEARCH COMMITTEES

9.1 Scientific committee

A scientific committee formed by the scientific manager Pr Tarek Sharshar and composed of Pr Michel Wolff and Dr Franck Verdonk.

9.2 Steering committee

No steering committee is foreseen in this trial.

9.3 Endpoint Adjudication Committee

- Committee Members: Dr. Mazeraud, Dr. Sharshar, Dr. Schimpf, Dr. Daniel, Dr. Legouy, Dr. Wolff
- Responsibilities: Validate the evaluation of the primary endpoint and secondary endpoints subject to subjective interpretation: ventilator-associated pneumonia.
- Operating methods: physical meeting or teleworking sessions twice during the trial.

The first meeting will be held at the end of the inclusions and the second meeting three months after the trial start.

10. SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE RESEARCH

10.1 Description of parameters for assessing safety

Adverse events will be systematically investigated at each visit during this study.
We will routinely collect adverse events from IVIG. According to the Summary of Product Characteristics for CLAIRYG® which will be used in this study, the main expected adverse reactions are:
- So-called allergic reactions, which are rare with new products and which generally improve with appropriate symptomatic treatment;
- An increased risk of thromboembolism, monitored by the occurrence of deep vein thrombosis or pulmonary embolism;
- The occurrence of acute renal failure; defined by a KDIGO 3 stage (Annexe)
- Other effects, including aseptic meningitis, hemolytic anemia, leuko-neutropenia, Transfusion-Related Respiratory Distress Syndrome (TRALI), etc., were also observed.

Other adverse events are usually rapidly regressive within a few days, such as leuko-neutropenia.

10.2 Anticipated methods and timetable for measuring, collecting, and analyzing the parameters for assessing safety

The clinical-biological parameters collected daily will allow identifying the occurrence of adverse events through daily visits collecting creatinine and diuresis.
Hypotension that does not respond to volume expansion defined by a mean blood pressure of less than 65 mmHg for more than 30 minutes despite filling.
Occurrence of a new clinically monitored thromboembolic event.
The occurrence of aseptic meningitis or TRALI cannot be demonstrated with certainty because of the high probability of the patient receiving sedation leading to coma and because of the high probability of altered haematosis related to the natural course of the disease.

10.3 Procedures in place for recording and reporting adverse events

10.3.1 Definitions

According to Article R1123-39 of the French Public Health Code and the guideline on good pharmacovigilance practices (EMA, 2012):

- **Adverse event**

Any untoward medical occurrence in a patient or clinical trial subject is administered a medicinal product and does not necessarily have a causal relationship with this treatment.

- **Adverse drug reaction**

Any response to a medicinal product which is noxious and unintended.

- **Serious adverse event**

Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/congenital disability.

- **Unexpected adverse reaction**

An adverse reaction, the nature, severity, or outcome of which is not consistent with the applicable product information: the summary of product characteristics for an authorized product or the investigator's brochure for an unauthorized investigational product.
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According to the notice to sponsors of clinical trials for medications (ANSM):

- **New safety issue**

Any new safety information:
- that could significantly alter the assessment of the benefit-risk ratio for the experimental medication or the trial
- or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the trial

Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction occurring
b) suspected unexpected serious adverse reactions occurring in patients who have finished the trial and about whom the sponsor is notified by the investigator, who also provides any follow-up reports
c) any new fact relating to the conduct of the clinical trial or the development of the experimental medication if the new fact is likely to affect participant safety
Examples:
- a serious adverse event likely to be related to the investigations and to the trial's diagnostic procedures and which could modify the conduct of this trial

- a significant risk for the trial participants such as ineffectiveness of the experimental medication used in the trial in treating a life-threatening illness
- significant safety results from a recently completed research carried out on animals (such as carcinogenicity research)
- the premature termination, or temporary interruption, of a trial conducted with the same experimental medication in another country, for safety reasons
- an unexpected serious adverse reaction associated with a non-experimental medication required for carrying out the trial (e.g., challenge agents, rescue treatment)
d) recommendations from the data safety monitoring board (DSMB), if applicable, if they are relevant to the safety of the participants
e) any unexpected serious adverse reaction reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication

10.3.2 The investigator's roles

10.3.2.1 Regulatory obligations of the investigator (Art R1123-54 of the French Public Health Code)

The investigator must notify the sponsor, **immediately on the day when the investigator becomes aware**, of all the serious adverse events, except those that are listed in the protocol (see. section 10.3.3.1) or in the investigator's brochure as not requiring immediate notification.

These serious adverse events are recorded in the "adverse event" section of the case report form, and the investigator must immediately notify the sponsor's Vigilance division (see 10.3.4).

10.3.2.2 The investigator's other roles

Any participant, from the signing of the informed consent, adverse events (AEs), whether severe or not (spontaneously reported by the participants or observed by the investigators or consisting of an abnormal laboratory or radiology result etc.) must be completed in the CRF or e-CRF.
If possible, symptoms and abnormal laboratory findings should be grouped into a single syndrome or diagnosis. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. Then, only the diagnosis will be documented as an AE and not the individual symptoms/signs.
The investigator should assess the severity of each adverse event and report all serious and non-serious adverse events in the electronic case report form (e-CRF).
The investigator should document serious adverse events to the best of his or her ability and give a definitive medical diagnosis whenever possible.
The investigator should assess the severity of the adverse events and the causal relationship of the serious adverse events to the investigational drug(s).
The method used by the investigator, based on the WHO (WHO Uppsala Monitoring Centre) method, is based on the following 4 causality terms:

- Certain,
- Probable/plausible,

- Possible,
- Unlikely (not excluded).

Their definition is presented in the following table (taken from WHO-UMC causality categories, version of 17/04/2012).

Certain

- Event or laboratory test abnormality, with plausible time relationship to drug intake **
- It cannot be explained by disease or other drugs
- Respons to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

Probable / Likely

- Event or laboratory test abnormality, with reasonable time relationship to drug intake**
- Unlikely to be attributed to disease or other drugs
- ·Response to withdrawal clinically reasonable
- Rechallenge not required

Possible

- Event or laboratory test abnormality, with reasonable time relationship to drug intake **
- Could also be explained by disease or other drugs
- information on drug withdrawal may be lacking or unclear

Unlikely

- Event or laboratory test abnormality, with a time to drug intake **
- that makes a relationship improbable (but not impossible)
- disease or other drugs provide plausible explanations

*All points should be reasonably complied with
** Or study procedures

10.3.3 Specific features of the protocol

All serious and non-serious adverse events must be reported in the CRF.

10.3.3.1 Serious adverse events that do not require the investigator to notify the sponsor immediately

- Death
- Grade Neutropenia ≥ 3 according to the CTCAE scale
- Renal insufficiency stage KDIGO 3 (see appendix 2)
- Suspicion of TRALI
- Radiologically proven venous thrombosis or pulmonary embolism

These serious adverse events are only collected in the case report form. Extraction of these serious adverse events from the case report will be made at the end of the study.

● Natural and habitual evolution of the pathology:

Patients admitted to ICU for COVID-19-related ARDS have hypoxic major respiratory failure in the foreground, often leading to the use of mechanical ventilation. After initiation of mechanical ventilation, patients may experience circulatory failure requiring vasopressor treatment in more than 75% of cases, renal failure in approximately 25% of cases, pulmonary embolism or other thromboembolic events in more than 50% of cases.
Patients may present in ICU a complication increasing morbi-mortality such as nosocomial infection (ventilator acquired pneumonia, catheter-related infection), complications related to invasive procedures (pneumothorax...). After sedation withdrawal, patients may develop delirium or ICU neuromyopathy, probably very frequently.

The mortality of ARDS related to COVID-19 in ICU is 50%. It is related to uncontrolled respiratory failure leading to hypoxia and cardiac arrest, uncontrolled circulatory failure, limitations, and cessation of therapy or complications of ICU.

The main objective of the research is to show an increase in the number of days living without mechanical ventilation. The mortality rate related to the pathology studied approaches 50% at one month.
Deaths are not to be notified immediately to the promoter but to be collected in the case report as they are linked to the natural and usual evolution of the pathology.
An extraction of deaths from the CRF will be performed after 3 weeks from the beginning of the study. The extraction of the deaths will be transmitted to the members of the Independent Supervisory Committee.
In the event of an imbalance between groups/mortality rate higher than the expected 20% frequency having an impact on the safety of the participants and requiring an urgent safety measure from the sponsor, a safety development will be transmitted to ANSM without delay.

● Adverse events that may be related to treatments prescribed as part of care during research follow-up

These adverse reactions should be reported by the investigator to the regional pharmacovigilance center to which the investigator belongs.
- So-called allergic reactions, which are rare with new products and which generally improve with appropriate symptomatic treatment;
- An increased risk of thromboembolism, monitored by the occurrence of deep vein thrombosis or pulmonary embolism;
- The occurrence of acute renal failure; defined by a KDIGO 3 stage
- Other effects include aseptic meningitis, hemolytic anemia, leuko-neutropenia, TRALI.

10.3.3.2 Serious adverse events that require the investigator to immediately notify the sponsor

The investigator must report all adverse events that meet one of the seriousness criteria below, except for events listed in section 10.3.3.1 as not requiring notification:
1- Death
2- Life-threatening situation
3- Requiring hospitalization or prolonging hospitalization
4- Persistent or significant disability or incapacity
5- Congenital abnormality or congenital disability
6- Or any other adverse event considered "medically significant."

10.3.3.3 Other events that require the investigator to immediately notify the sponsor

Adverse events considered "medically significant," i.e., events that could endanger the trial subject or require intervention to prevent one of the defining characteristics or consequences of a severe adverse event (SAE): none

These adverse events should be notified to the sponsor by the investigator without delay from the day on which they become known to the sponsor, in the same way, and within the same timeframe as serious adverse events.

10.3.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE shall be the subject of a written report signed by the investigator using the SAE notification form specific to the research and provided for this purpose (in the observation notebook).
Each item in this document should be completed by the investigator to allow the sponsor to perform a relevant analysis, including the nature of the severity endpoint and the causal link between the reported event and the study product/research added procedures (this implies that follow-up by the investigator may continue after the participant's exit from the trial).
The initial notification of a severe adverse event to the sponsor should be followed promptly by a detailed written follow-up report(s) to monitor the case's progress vigilantly or supplement the information.
The investigator should provide the sponsor with any documents that may be useful to the sponsor (medical reports, biological results, results of additional tests, etc.), whenever possible. These documents should be made anonymous. Also, they must be completed with the following information: research acronym, participant number, and initials.
Any adverse event will be monitored until it is fully resolved (stabilized at a level acceptable to the investigator or returned to the previous state) even if the participant has left the research.
The initial notification, the SAE follow-up reports, and any other document will be sent to the promoter exclusively by fax to 01 445 65 76 09.
In the case of a search with e-CRF :

- the investigator completes the ISG notification form in the e-CRF, validates it, prints it, signs it, and sends it by fax ;
- if it is impossible to connect to the e-CRF, the investigator shall complete, sign and send the ISG notification form to the Vigilance Sector. As soon as the connection is re-established, he will regularize by completing the ISG notification form in the e-CRF.
The investigator should respond to any request for additional information from the sponsor.

10.3.5 Period for notifying the sponsor

The investigator should immediately notify the sponsor of serious adverse events as defined in the relevant section:
- from the date of the start of treatment with an investigational drug,
- for the duration of the participant's follow-up, as provided for by the research,
- up to 28 days after taking IVIG following the completion of treatment with the participant's investigational drug.

10.3.6 The sponsor's roles

The sponsor, represented by its DRCI, continuously assesses the safety of each experimental medication throughout the research.

10.3.6.1 Analysis and declaration of serious adverse events

The sponsor assesses:
- the seriousness of all adverse events reported
- the causal relationship of these events with each experimental medication and/or specific medical procedures/exams added by the research and with other possible treatments
- the expected or unexpected nature of these adverse reactions

All serious adverse events which the investigator and/or the sponsor believe could reasonably have a causal relationship with the experimental medication are considered as suspected adverse reactions.

All suspected unexpected serious adverse reactions are declared by the sponsor, within the legal time frame, to the Agence Nationale de Sureté du Médicament and to the relevant Comité de Protection des Personnes (CPP, ethical committee).

- The initial declaration must be made with no delay after the date on which the serious adverse event occurs in the case of death or of a life-threatening diagnosis.

- The initial declaration must be made with no delay after the date on which the serious adverse event occurs in the case of other serious situations.

- The follow-up declaration must be made with no delay.

Any suspected unexpected serious adverse reaction must also be declared electronically in the Eudravigilance European database for adverse events due to medications established by the European Medicines Agency (EMA).

The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the research subjects.

Specific cases of serious adverse events of special interest:
At the request of ANSM, the sponsor may be asked to declare serious adverse events of special interest, in accordance with the same procedures and deadlines as suspected unexpected serious adverse reactions.

Specific case of double-blind trials:
After unblinding by the sponsor, if the administered product is the investigational product: the related and unexpected case will therefore be reported immediately as a suspected unexpected serious adverse reaction within the regulatory timeframe mentioned above). If the product administered is the placebo, any unexpected events that may be related to it (allergy to excipients, etc.).

10.3.6.2 Analysis and declaration of other safety data

This relates to any safety data or the new fact that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the research, or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the research.

New facts must be declared to the competent authorities within 15 calendar days of the sponsor becoming aware. Additional relevant information must be sent within an additional 8 days after the 15 day deadline.

10.3.6.3 Annual safety report

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- an analysis of the safety of the research subjects
- a description of the patients included in the trial (demographic characteristics, etc.)
- a line listing of suspected serious adverse reactions that occurred during the period covered by the report
- a cumulative summary tabulation of serious adverse events that have occurred since the start of the research

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorized the trial.

10.3.7 Data Safety Monitoring Board

For this biomedical research, it has not been considered beneficial to convene a DSMB.

11. DATA MANAGEMENT

11.1 Data collection methods

Trial data will be collected in the trial's electronic CRF as inclusions, and patient follow-up visits by the investigator or collaborators occur.

11.2 Identification of data collected directly in the CRFs and that will be considered as source data

None.

11.3 Right to access source data and documents

11.3.1 Access to data

In accordance with GCPs (Good Clinical Practice) :
- the sponsor is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research will be carried out, to the source data, to the source documents and the reports, with the goal of quality control and audit by the sponsor
- the investigators will make available to those in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.3.2 Source documents

Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during the research. These documents will be kept for 15 years by the investigator or by the hospital in the case of a hospital medical file.

11.3.3 Data confidentiality

Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research subjects, and in particular, the identity of the participants and the results obtained.

These individuals, as well as the investigators themselves, are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).
During or after the biomedical research, the data collected about the research subjects and sent to the sponsor by the investigators (or any other specialized parties) will be made non-identifying.
Under no circumstances should the names and addresses of the subjects involved be shown.
The sponsor will ensure that each research subject has given permission in writing for access to personal information about him or her, which is strictly necessary for the quality control of the research.

11.4 Data processing and storage of documents and data

11.4.1 Identification of the manager and the location(s) for data processing

The GHU DRCI biostatistician will analyze the data collected in the trial.

11.4.2 Data entry

Data entry will be carried out by the investigator and his collaborators in the eCRF.

11.4.3 Data processing (CNIL, the French Data Protection Authority) in France

This research falls under the "Méthodologie de référence" (MR-001) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978 relating to information technology data files and privacy. This change was approved in a decision made on 5 January 2006. Le GHU Paris Psychiatrie et Neurosciences, the research sponsor, has signed a commitment to comply with this " Méthodologie de référence "

11.4.4 Data processing (CNIL) outside of France

The data collected in the trial will not be sent to the European Union or a "suitable" country.

11.4.5 Archival

Specific documents for biomedical research relating to medication for human use will be archived by the investigator and the sponsor for a period of 15 years after the end of the study.

This indexed archival includes, in particular:

- A sealed envelope containing the original copies of all information sheets and consent forms signed for all individuals at the center that participated in the research for the investigator
- A copy of all the information notes and consent forms signed for all subjects at the center that participated in the research for the sponsor
- "Research" binders for the Investigator and the sponsor, including:
  - the successive versions of the protocol (identified by the version no. and date), and the appendices
  - the ANSM authorizations and CPP favorable opinions
  - letters of correspondence
  - the inclusion list or register
  - the appendices specific to the research
  - the final research report
- The data collection documents

11.05 Ownership of the data

Le GHU Paris Psychiatrie et Neurosciences is the owner of the data, which cannot be used or disclosed to a third party without its prior approval.

12. STATISTICAL ASPECTS

12.1 Description of statistical methods to be used, including the timetable for the planned interim analyses

The statistical analysis plan will be developed and finalized before the database is locked and will describe the participating populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary objectives.

The primary and secondary analyses will be stratified by age categories, sex, and other clinically relevant factors (comorbidities). Demographic characteristics and parameters identified at enrolment will be summarized using descriptive statistical methods.

Demographic summaries will include gender, race/ethnicity, and age. For demographic and categorical background characteristics, a Cochran-Mantel-Haenszel test will be used to compare treatment groups. For continuous demographic and baseline characteristics, a Wilcoxon test will be used to compare treatment groups.

The number of days without mechanical ventilation will be presented as a mean with standard deviation and 95% confidence interval. The groups will be analyzed in terms of intention to treat. The difference between the two groups will be analyzed by a non-parametric test of comparison of means, stratified for the primary endpoint. The point

estimate of the difference between treatments and the associated 95% confidence interval will be provided.

A regression model for censored data (Cox model) will explore prognostic factors. The IGIV immunological and pathological related efficacy endpoints will also be compared according to their distribution and analyzed using Student, Mann-Whitney, and Fisher tests.

Other variables will be presented as means and standard deviations or medians and interquartile ranges according to their distribution and analyzed by Student, Mann-Whitney, and Fisher tests.

Parameters measured on a time scale from randomization or start of administration will be compared between treatment groups using the Log-Rank test.

The choice of statistical tests and multivariate models (parametric or non-parametric) will be made for each variable based on observed characteristics (normality of distributions and residuals, collinearity).

The statistical analyses relating to the main objective will be carried out as intention to treat. Secondary analyses on the population per-protocol may also be carried out.

For the main objective, both general and subgroups, the following evidence-based medicine statistics (effect size) will be provided: confidence intervals, numbers needed to treat, and absolute risk reduction.

All tests will be bilateral with a significance threshold of 5%.

The software used will be SPSS v26 (SPSS Inc., Chicago, IL, USA).

12.2 Calculation hypotheses for the number of subjects required and the result

We hypothesize that the number of days without IMV is 10 days in the placebo group and 15 days in the experimental group with a standard deviation of 6 days, considering mortality of 50% and 40% in the placebo and experimental groups, respectively (26, 27). The number of days without IMV in the placebo group is (50% x 10 D) + (50% x 0 D) or 5 D on average, and following the same calculation for the experimental group of (60% x 15 D) + (40% x 0 D) or 9 D.

Therefore, a mean value of 5 days without ventilation in the placebo group versus 9 in the experimental group is assumed, and the 6-day standard deviation is assumed to be stable. Given the uncertainty regarding the assumption of normality of distributions, the non-parametric Wilcoxon-Mann-Whitney test (U-test) was used for the estimation of the sample size. Considering a bilateral alpha risk of 5% and a power of 90% and an effect size of 0.6, the number of subjects to be included is 138 patients, 69 in each arm.

A 4-day reduction in IMV duration is a reasonable clinical objective. A total of 138 patients is achievable as each of the 36 participating units is able to accommodate more than 40 ARDS patients over one month.

12.3 Specify if subjects who leave the research prematurely will be replaced and in what proportion.

No subject replacement. No premature exit or predictable loss of sight.

12.4 Anticipated level of statistical significance

All tests will be bilateral with a significance threshold of 5%.

12.5 Statistical criteria for termination of the research.

None. No interim analysis planned.

12.6 Method for taking into account missing, unused or invalid data

Given the ICU setting, no missing data on the primary outcome are expected, even in the case of off-duty transfers, as these transfers are from ICU to ICU and are traced. Missing data on important confounding factors will be valued using a multiple chain equation imputation (MICE) method as part of robustness analysis.

12.7 Management of modifications made to the analysis plan for the initial strategy.

Any changes to the analysis plan in response to protocol amendments or changes in the study process will be defined prior to database freezing and documented in a protocol amendment. Any unplanned analysis will be considered a posthoc analysis in the scientific report.

12.8 Selection of populations

This population is representative of the general population, and positive results from the ARDS linked to COVID could be rapidly extrapolated to the general population. A positive result will be quickly disseminated.

13. QUALITY CONTROL AND ASSURANCE

Each biomedical research project managed by Le GHU Paris Psychiatrie et Neurosciences is ranked from A to D according to the projected risk incurred by research subjects using the classification of biomedical research sponsored by Le GHU Paris Psychiatrie et Neurosciences

13.1 General organization

The sponsor must be responsible for the safety and respect of those subjects who have agreed to participate in the research. The sponsor must implement a quality assurance system to best monitor the conduct of the study in the investigation centers.

For this purpose, the sponsor shall delegate Clinical Research Associates (CRA), whose primary role is to carry out regular follow-up visits at the research locations after having carried out initial visits.
The objectives of monitoring the research, as defined in the French Good Clinical Practices (BPC section 5.18.1), are to verify that:

- the rights, safety, and protection of the research subjects are met
- the data reported is exact, complete, and consistent with the source documents
- the research is carried out in accordance with the protocol in force, with the French GCPs, and with the legislative and regulatory provisions in force

13.1.1 Strategy for opening the centers

The strategy for opening the centers set up for this research is massive and urgent, as called for in response to the health crisis at COVID-19.

13.1.2 Level of center monitoring

In the case of this Phase III research, the choice of an appropriate level of monitoring was weighted according to the complexity, impact, and budget of the study. To this end, the promoter, in agreement with the coordinating investigator, determined the logistic and impact score that made it possible to obtain the high level of monitoring to be implemented on the research.

13.2 Quality control

A CRA appointed by the sponsor will be responsible for the proper conduct of the research, for collecting and documenting, recording and reporting the data generated in writing, in accordance with the Standard Operating Procedures applied within the DRCI and in accordance with the French Good Clinical Practices as well as with the legislative and regulatory provisions in force.

The investigator and the members of the investigator's team agree to make themselves available during Quality Control visits carried out at regular intervals by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the research protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

13.3 Case Report Form

Electronic CRF:

All information required according to the protocol must be entered in the case report forms. The data must be collected as and when they are obtained and clearly recorded in these case report forms. Each missing data item must be coded.
This digital case report form will be implemented in each center's thanks to a web-based data collection medium. Investigators will be given a document offering guidance in using this tool.
When the investigators complete the case report via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality, and relevance of all the data entered. Also, the data are immediately verified as they are entered, thanks to consistency checks. Thus, the investigator must validate any changes to the values in the case report form. These modifications will be subject to an audit trail. A justification can be added when applicable as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the research. The investigator must archive a copy of the certified document that was delivered to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance by the investigator or any other individual involved in conducting the research, with the protocol, with the standard operating procedures, with the good clinical practices, or with the legislative and regulatory provisions in force must be noted in a declaration of non-compliance addressed to the sponsor. As a first step, major or critical non-compliances will be reviewed and processed by the DRCI's medical coordinator in order to implement the necessary corrective or preventive actions. Next, the non-compliances will be sent to the Quality - Risk Management Division of the DRCI for verification and analysis. These verifications could result in the investigator in charge of the research location in question being asked for information or could lead to compliance or audit visits.

13.5 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents, and reports may be subject to regulatory audits and inspections. Medical secrecy cannot be invoked in opposition to these audits and inspections.

An audit can be carried out at any time by individuals appointed by the sponsor and who are not associated with the research directors. The objective of the audit is to ensure the quality of the research, the validity of the results, and compliance with the legislation and regulations in force.

The individuals who lead and monitor the research agree to comply with the sponsor's requirements and with the competent authority regarding research audits or inspections.

The audit may be applicable to all stages of the research, from the development of the protocol to the publication of the results and the organization of the data used or produced as part of the research.

13.6 Primary investigator's commitment to assume responsibility

Before starting the research, each investigator will give the sponsor’s representative a copy of his/her personal curriculum vitæ, signed and dated, with his/her number in the RPPS (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will undertake to comply with the legislation and to carry out the research according to French GCP, adhering to the Declaration of Helsinki terms in force.

The primary investigator at each participating center will sign a responsibility commitment (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their employees will sign a delegation of duties form specifying each person's role.

13.7 Pharmacist's commitment to assume responsibility

Pharmacists from the various recruiting centers will each sign a commitment of responsibility for the trial. They will be responsible for all their collaborators who will be involved in the preparation of the UTs and their dispensing.

14. ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for obtaining information and consent from research participants

In accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research can be carried out on a person without free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.

An initial consent for the patient may be requested in the event that the patient is able to provide informed consent, which is unlikely given the seriousness of COVID-19 and the emergency situation.
The second permits, in the event that it is impossible for the person sought to consent in writing, the collection of the consent in order of priority by the trusted person, a family member, or, failing that, by a close relative. These should be completely independent of the investigator and sponsor.

The third permits the patient's consent, as soon as his or her condition permits, for the continuation of the research.
However, if no consent could be obtained for the inclusion of the patient, in this particular context of a medical emergency, the law allows the inclusion of the patient without his or her consent or that of a trusted person or family member (in the absence of the latter). Patients with ARDS related to COVID-19 are unable to receive information and give written consent in the initial phase. They are sometimes urgently ventilated invasively and sedated to treat life-threatening distress. It is likely that most subjects will not be in a position to give consent at the time of inclusion. The possibility of emergency consent is therefore provided for. The patient is informed as soon as possible, and his consent is requested for the continuation of the research and the use of the data (Law 2004-806 of 09 August 2004, Art L1122-1-2 and Art L 1111-6).
The briefing note and a copy of the consent form, dated and signed by the individual who participates in the research and by the investigator or the physician representing him or her, shall be given to the individual before participation in the study.
Also, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his or her consent, or the consent of any other person in the cases provided for in Articles L. 1122-1-1 to L. 1122-2 of the CSP and the procedures for providing the information to collect it. He or she shall retain the original copy of the dated and signed consent form.
A copy of this document is given to the research participant. The investigator should keep the original copy in his/her archives for a minimum of 15 years. The third copy is archived by the promoter.

14.2 Subject prohibited from participating in another research or an exclusion period anticipated after the study, if applicable

At the end of the subject's participation, a period of exclusion of 28 days is defined within the framework of this research.
During participation, the subject may not participate in any other intervention research protocol involving the human subject without first discussing the matter with the physician who is following him or her in the research.

14.3 Compensation for subjects

There is no anticipated compensation for subjects.

14.4 Registration on the national register of subjects participating in biomedical research relating to the products listed in Article L. 5311-1 of the French Public Health Code

Patients included in the trial will not be included in the national register of subjects participating in biomedical research.

14.5 Legal obligations

14.5.1 The sponsor's role

Assistance Publique - Hôpitaux de Paris (Le GHU Paris Psychiatrie et Neurosciences) is the sponsor of this research, and by delegation, the Clinical Research and Innovation Office (DRCI) carries out the research's missions in accordance with Article L.1121-1 of the French Public Health Code. Assistance Publique - Hôpitaux de Paris reserves the right to halt the research at any time for medical or administrative reasons. In this case, notification will be sent to the investigator

14.6 Request for an opinion from the Comité de Protection des Personnes (CPP, ethical review board)

Le GHU Paris Psychiatrie et Neurosciences, as sponsor, obtains for this biomedical research relating to medication for human use and prior to starting the study, the favorable opinion of the appropriate CPP, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

14.7 Request for authorization to ANSM

Le GHU Paris Psychiatrie et Neurosciences, as sponsor, obtains for this biomedical research relating to medication for human use and, prior to starting the study, authorization from the ANSM, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

14.8 Commitment to compliance with the MR 001 "Méthodologie de Reference"

Le GHU Paris Psychiatrie et Neurosciences, the research sponsor, has signed a commitment to comply with this "Méthodologie de reference".

14.9 Request for the opinion of the CCTIRS (advisory committee on the processing of research information in the area of health) and request for authorization from CNIL (French data protection authorities)

Not applicable.

14.10 Standard declaration to the CNIL [add if applicable]

Not applicable.

14.11 Modifications to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain a favorable opinion from the CPP and authorization from the ANSM within the scope of their respective authorities prior to starting the research.
The information sheet and the consent form can be revised if necessary, in particular, if there is a substantial modification to the research or if adverse reactions occur.

14.12 Final research report

The final biomedical research report referred to in Article R1123-60 of the French Public Health Code is drawn up and signed by the sponsor and the investigator. A summary of the report written according to the competent authority's reference plan will need to be sent to the competent authority and ethical review board within one year after the end of the research, meaning the end of the participation of the last research subject.

15. FUNDING AND INSURANCE

15.1 Funding source

GHU Paris Psychiatrie et Neurosciences.

15.2 Insurance

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide total compensation for all harmful consequences of the research for the research subjects and their beneficiaries unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against said compensation.

The GHU Paris - Psychiatry and Neurosciences has taken out an insurance policy with the SHAM company, guaranteeing its civil liability as well as that of any participant (doctor or staff involved in carrying out the research), in accordance with the article L.1121-10 of the CSP.

16. PUBLICATION RULES

The GHU Paris must obligatorily be mentioned in the affiliations of the author(s) of the publications resulting from this research and cite the promoter GHU Paris (DRCI).

16.1 Mention of the affiliation of Le GHU Paris Psychiatrie et Neurosciences for projects sponsored or managed by Le GHU Paris Psychiatrie et Neurosciences

The institution GHU Paris must appear under the acronym "GHU Paris" first in the address.

16.2 Mention of the Le GHU Paris Psychiatrie et Neurosciences manager (DRCI) in the acknowledgments of the text

- ”The sponsor was GHU Paris – Psychiatrie et Neurosciences.

16.3 Mention of the financier in the acknowledgments of the text

”The research was funded by a grant from le GHU Paris Psychiatrie et Neurosciences.”

This research has been registered on the website http://clinicaltrials.gov/ under number *registration number*. NCT04350580

List of abreviations

COVID-19 Coronavirus Disease due to SARS-CoV-2
ARDS Acute respiratory distress syndrom
IVIG Intravenous Immunoglobulin
SARS-CoV-2 severe acute respiratory syndrome virus number. 2
ACE2 AngiotensinII converting enzyme
IL Interleukin
PaO2 partial pressure of oxygen in arterial blood
FiO2 fraction of oxygen in inhaled. Gaz
PEEP positive end expiratory pressure
IMV invasive mechanical ventilation
SOFA Sequential Organ Failure Assessment (SOFA
CTCAE Common Terminology Criteria for Adverse Events
ADL Activities of daily living
IADL Instrumental activities of daily living
CT computed tomography
CAM-ICU Confusion assessment method for the intensive care unit
ICU Intensive Care Unit
VAP ventilator acquired pneumonia
D Day
PCR Polymerase Chain Reaction
CRF Clinical report Form
ANSM Agence nationale de sureté du médicament
CPP Comité de protection des personnes
TRALI Transfusion associated Lung Injury
DSMB Data safety monitoring board
SAE Severe Adverse. Event
CNIL Commission national de l'informatique et des libertés
CRA Clinical Research Associates
BPC Bonnes pratiques cliniques

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LIST OF ADDENDA

Each addendum and the addendum version record are attached, independent of the protocol. Each addendum can be modified (change of addendum version) without changing the protocol version.

Annexe 1 Score des défaillances viscérales SOFA[34]

SOFA SCORE	**1**	**2**	**3**	**4**
Respiration *PaO2 :FiO2*	<400	<300	<200*	<100*
Coagulation *Plaquettes x10³/mm³*	<150	<100	<50	<20
Foie *Bilirubine, mg/dl (µmol/l)*	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (>204)
Cardiovasculaire *Hypotension*	MAP<70 mm Hg	Dopamine ≤5 γ/kg/min ou Dobutamine	Dopamine >5 γ/kg/min ou adrénaline ou noradrénaline ≤0.1 γ/kg/min	Dopamine >15 γ/kg/min ou adrénaline ou noradrénaline >0.1 γ/kg/min
Neurologique *Glasgow*	13-14	10-12	6-9	>6
Rénal *Créatinine, mg/dl (µmol/l) ou diurèse*	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or < 500 ml/jour	>5.0 (>440) or <200 ml/jour

*** avec assistance respiratoire**

Annexe 2 Lung injury score

	Score
Chest radiograph	
No alveolar consolidation	0
Alveolar consolidation confined to 1 quadrant	1
Alveolar consolidation confined to 2 quadrants	2
Alveolar consolidation confined to 3 quadrants	3
Alveolar consolidation confined to 4 quadrants	4
Hypoxaemia score	
PaO_2/FiO_2 ⩾300	0
PaO_2/FiO_2 225–299	1
PaO_2/FiO_2 175–224	2
PaO_2/FiO_2 100–174	3
PaO_2/FiO_2 <100	4
PEEP score (when mechanically ventilated)	
⩽5 cm H_2O	0
6–8 cm H_2O	1
9–11 cm H_2O	2
12–14 cm H_2O	3
⩾15 cm H_2O	4
Respiratory system compliance score (when available)	
⩾80 ml/cm H_2O	0
60–79 ml/cm H_2O	1
40–59 ml/cm H_2O	2
20–39 ml/cm H_2O	3
⩽19 ml/cm H_2O	4
The score is calculated by adding the sum of each component and dividing by the number of components used.	
No lung injury	0
Mild to moderate lung injury	0.1–2.5
Severe lung injury (ARDS)	>2.5

Annexe 3

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

_____

† CTCAE v4.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

Annexe 4 Activities of a daily living scale

ECHELLE A.D.L **(Aide-soignante Infirmière)**	**1ère évaluation** **Date :** **Score:**	**2ème évaluation** **Date :** **Score:**	**3ème évaluation** **Date :** **Score:**
HYGIENE CORPORELLE			
. autonomie	**1**	**1**	**1**
. aide	**½**	**½**	**½**
. dépendant(e)	**0**	**0**	**0**
HABILLAGE			
. autonomie pour le choix des vêtements et l'habillage	**1**	**1**	**1**
. autonomie pour le choix des vêtements, l'habillage mais a besoin d'aide pour se chausser	**½**	**½**	**½**
. dépendant(e)	**0**	**0**	**0**
ALLER AUX TOILETTES			
. autonomie pour aller aux toilettes, se déshabiller et se rhabiller ensuite	**1**	**1**	**1**
. doit être accompagné(e) ou a besoin d'aide pour se déshabiller ou se rhabiller	**½**	**½**	**½**
. ne peut aller aux toilettes seul(e)	**0**	**0**	**0**
LOCOMOTION			
. autonomie	**1**	**1**	**1**
. a besoin d'aide	**½**	**½**	**½**
. grabataire	**0**	**0**	**0**
CONTINENCE			
. continent(e)	**1**	**1**	**1**
. incontinence occasionnelle	**½**	**½**	**½**
. incontinent(e)	**0**	**0**	**0**
REPAS			
. mange seul(e)	**1**	**1**	**1**
. aide pour couper la viande ou peler les fruits	**½**	**½**	**½**
. dépendant(e)	**0**	**0**	**0**
TOTAL			

Annexe 5 - IADL-4

Echelle d'activités instrumentales de la vie quotidienne : version courte à 4 items (d'après Lawton & Brody)

MODE D'EMPLOI

Cette échelle doit être remplie par un membre du personnel médico-social en utilisant une ou plusieurs des sources d'informations suivantes : le malade, sa famille, ses amis. Choisir la réponse qui correspond le mieux aux capacités du sujet. On peut s'aider du questionnaire situé au verso.
Les 4 activités font l'objet d'une cotation en 3, 4 ou 5 points selon les items. Dans un deuxième temps, la cotation de chacun des items est transformée en codage binaire 0 ou 1.
Codez 0 tout item pour lequel le sujet est autonome (la cotation ne dépasse pas 1).
Codez 1 tout item pour lequel le sujet est dépendant (la cotation est supérieure ou égale à 2)
Nom : Prénom :
Date :

CAPACITÉ À UTILISER LE TÉLÉPHONE

1. Utilise le téléphone de sa propre initiative, cherche et compose les numéros, etc.
2. Compose un petit nombre de numéros bien connus.
3. Répond au téléphone, mais n'appelle pas.
4. Incapable d'utiliser le téléphone.

MOYEN DE TRANSPORT

1. Peut voyager seul(e) et de façon indépendante (par les transports en commun ou avec sa propre voiture).
2. Peut se déplacer seul(e) en taxi, pas en autobus.
3. Peut prendre les transports en commun si accompagné(e).
4. Transport limité au taxi ou à la voiture, en étant accompagné(e).
5. Ne se déplace pas du tout.

RESPONSABILITÉ POUR LA PRISE DES MÉDICAMENTS

1. S'occupe lui (elle)-même de la prise : dosage et horaire.
2. Peut les prendre lui (elle)-même, s'ils sont préparés et dosés à l'avance.
3. Incapable de les prendre lui (elle)-même.

CAPACITÉ À GÉRER SON BUDGET

1. Totalement autonome (gérer le budget, faire des chèques, payer des factures, ...).
2. Se débrouille pour les dépenses au jour le jour, mais a besoin d'aide pour gérer son budget à long terme (pour planifier les grosses dépenses).
3. Incapable de gérer l'argent nécessaire à payer ses dépenses au jour le jour

Guide d'utilisation pratique des 4 IADL

1) Répondez-vous au téléphone sans difficulté ? ☐ OUI ☐ NON

2) Appelez-vous seul au téléphone quelques numéros connus ? ☐ OUI ☐ NON

3) Cherchez-vous vous–même des numéros dans l'annuaire (ou 118 ou Internet) ? ☐ OUI ☐ NON

4) Conduisez-vous votre voiture ? ☐ OUI ☐ NON

5) Utilisez-vous seul les transports en commun ? (bus, train, avion)? ☐ OUI ☐ NON

6) Allez-vous sans problème dans des endroits inconnus ? ☐ OUI ☐ NON

7) Comment vous organisez-vous pour la prise de vos médicaments ?
Je les prépare et les prends moi-même (dosage et horaire corrects)
On me les prépare d'avance
On doit me faire penser à les prendre

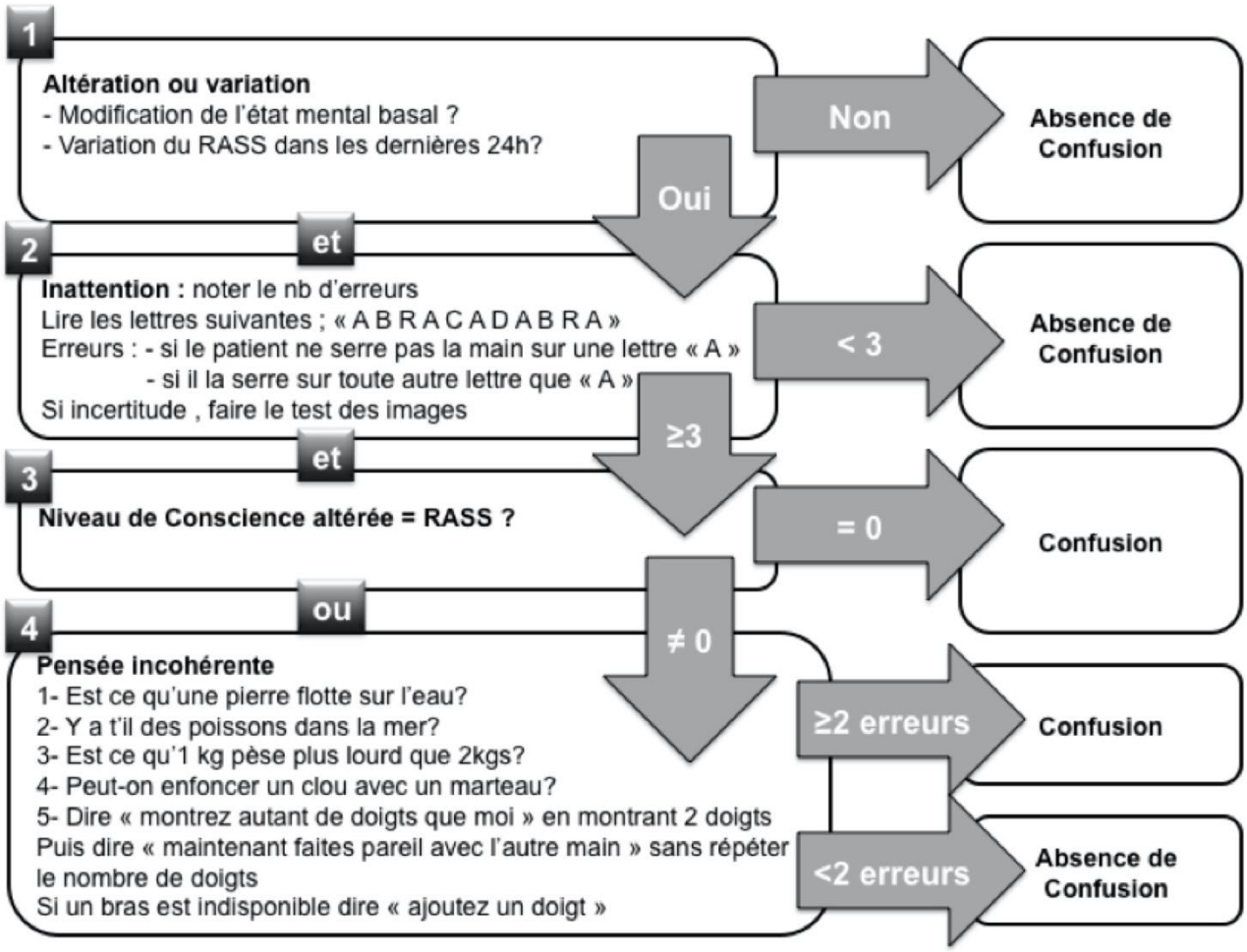
8) Les oubliez-vous souvent ? ☐ OUI ☐ NON

9) Comment réglez-vous vos achats ?
J'utilise des chèques, ma carte bancaire ou l'argent liquide sans problème
Je ne règle jamais moi-même aucun achat

10) Est-ce que vous payez vous-même vos factures ? ☐ OUI ☐ NON

11) Est-ce que vous avez besoin d'aide pour gérer votre budget ? ☐ OUI ☐ NON
OUI (gère seulement les dépenses au jour le jour) NON

Annexe 6 Score *Confusion Assessment Method for Intensive Care Unit* CAM-ICU



Le score de CAM-ICU[2] permet un diagnostic rapide de syndrome confusionnel en réanimation à l'aide de 4 critères: 1) Rapidité d'installation ou fluctuation 2) Inattention 3) La désorganisation de la pensée 4) Altération du niveau de conscience. La présence des critères 1 et 2 puis 3 ou 4 est nécessaire au diagnostic de syndrome confusionnel. C'est un outil diagnostique consensuel de syndrome confusionnel présentant une sensibilité et spécificité élevés, une faible variabilité inter-observateur et une valeur clinique majeure. Dans une étude réalisée par Ely *et al.* la présence d'une confusion attestée par ce score montrait une mortalité à 6 mois après sortie de réanimation plus élevée dans le groupe de patient présentant une confusion (hazard ratio, 3.2; 95% intervalle de confiance a 95%, 1.4 à 7.7; p = .008)[2].

Annexe 7 Medical Research Council score

Muscle group evaluated

- Wrist extension
- Elbow flexion
- Shoulder abduction
- Dorsiflexion foot
- Knee extension
- Hip flexion

Appointed score

- 0, no visible/palpable contraction
- 1, visible/palpable contraction without movement of the limb
- 2, movement of the limb, but not against gravity
- 3, movement against gravity
- 4, movement against gravity and some resistance
- 5, normal

Each muscular group from each side is evaluated. The quotations are added to each other. The MRC sum score ranges from 0 to 6, 48 being the threshold for ICU acquired weakness.

<u>Annexe 8</u> : tableau de calcul du score de IGS II *(indice de gravité simplifié)*

Entrée	Chir urgente :8 pts		Médecine : 6 pts		Chir programmée	
Age (ans)	<40 :0 pt	40 – 59 : 7 pts	60 – 69 : 12 pts	70 – 74 : 15	75 – 79 : 16 pts	>80 :18
Température (°c)	<39 :0 pt				>39 : 3 pts	
Urée (mmol/L)	<10 :0 pt	10 – 29,9 :6pts	>30 : 10 pts			
Na (mEqL)	125 _ 144 : 0 pt	>145 : 1 pt	<125 :5 pts			
Maladie chronique	Aucune :0 pt	Cancer métastasé :9	Mal hémato :10	SIDA : 17 pts		
PAs (mmHg)	<70 : 13 pts	70 – 99 : 5 pts	100 – 199 : 0 pt	>200 : 2 pts		
GB / mm^3	<1000 :12 pts	1000 – 19000 :0 pt	>20000 : 3 pts			
Bicar (mEq/L)	>20 :0 pt	15 – 19 :3 pts	<15 :6 pts			
Glasgow	<6 :26 pts	6 – 8 :13 pts	9 – 10 : 7 pts	11 – 13 : 5 pts	14 – 15 : 0 pt	
FC / mn	<40 : 11 pts	40 – 69 :2 pts	70 – 119 :0	120 – 159 : 4 pts	>160 : 7 pts	
Diurèse (L/24h)	<0,5 :11 pts	0,5 – 0,99 : 4 pts	>1 :0 pt			
K+ (mEq/l)	<3 :3 pts	3 – 4,9 :0 pt	>5 :3 pts			
Bilirubine (µom/L)	<68,4 : 0 pts	68,4 – 102,6 : 4 pts	>102,6 : 9 pts			

Annexe 9 Kidney Disease: Improving Global Outcomes – Grading of Acute Kidney Injury

Stage	Serum creatinine	Urine output
1	1.5-1.9×baseline or ≥0.3 mg/dl (≥26.5 mmol/l) increase	<0.5 ml/kg/h for 6-12 h
2	2.0-2.9×baseline	<0.5 ml/kg/h for >12 h
3	3.0×baseline, or increase in serum creatinine ≥4.0 mg/dl (≥353.6 mmol/l), or initiation of RRT, or decrease in eGFR <35 ml/min/1.73 m^2 for patients <18 years	<0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

KDIGO: Kidney disease: Improving global outcomes; RRT: Renal replacement therapy; eGFR: Estimated glomerular filtration rate

Annexe 10 Response to reviewers

We thank the reviewers for their evaluation of the project. The reviewers suggested us to link our study to other existing trials such as CORIMMUNO or DISCOVERY. We would have been delighted to participate to these trials. Unfortunately, our solicitations did not allow us to participate to the trial.

Concerning the inclusion criteria, the reviewer number 2 suggested that the ARDS criteria should be homogenized. We propose to study patients with COVID-19 related ARDS. The IGIV could present beneficial effects on the late phase of SARS-CoV-2 when the immune response is overwhelming to lower the intensity of the cytokinic storm. Based on the availability and cost of IgIV, such treatment could not be evaluated in the entire population of patients presenting COVID-19. We thus chose to focus on a subpopulation of patients with a severe COVID-19.
The 2012 "Berlin" definition of acute respiratory distress syndrome (ARDS) distinguishes, according to the PaO_2/FiO_2 ratio measured in the presence of a positive external expiratory pressure (PEEP) of at least 5 cmH2O, three levels of severity of ARDS: minimal (200 < PaO2/FiO2 ≤ 300 mmHg), moderate (100 < PaO2/FiO2 ≤ 200 mmHg) and severe (PaO2/FiO2 ≤ 100 mmHg).
We therefore determined that the effectiveness of IVIG should be evaluated when mechanical ventilation for moderate to severe ARDS is introduced. We will use a PCR technique to diagnose an SARS-CoV-2 infection and the conventional Berlin definition of adult respiratory distress syndrome.

The benefits of a new therapy in COVID-19 are to increase the survival rate and to reduce the duration of mechanical ventilation, which is associated with is also significant morbidity. On a collective scale, reducing the duration of mechanical ventilation will increase the availability of ventilators and ICU beds to limit the shortage observed during the SARS-CoV-2 pandemic. We chose the ventilation free days at day 28 as a main outcome for two main reasons. (1) This outcome has been used in the evaluation of treatment of the ARDS by corticosteroids. (2) This outcome is composite integrating both mortality and the duration of mechanical ventilation. This outcome is then important both on an individual but also collective point of view. The risk of evaluation bias concerning the number of ventilation free days at day 28 is low as both its components are objectively collected, i.e. the duration of mechanical ventilation and survival. As a secondary analysis, each component will be evaluated independently. The duration of mechanical ventilation could depend on clinical judgement as the moment of mechanical weaning and extubation may show inter-operator variability. To prevent this, the attending physicians will be blind to the arm allocation. Also, to prevent imbalance across centers with slightly different standards for mechanical ventilation weaning, the randomization will be stratified on centers.

Reviewer number 4 did not raise any question

We thank the reviewer number 7 for his suggestions and questions. Reviewer 7 raised the question of the size of the expected effect IVIG, the fact to include de novo 126 patients and raised the issue of the use of corticosteroids.

The reviewer 7 suggested us to link our study to other existing trials such as CORIMMUNO or DISCOVERY so as not to include de novo 126 patients. We would have been delighted to participate to these trials. Unfortunately, our solicitations did not allow us to participate to these trials.
Concerning the number of patients to be included according to the size effect, we hypothesize that the number of days without IMV is 10 days in the placebo group and 15 days in the experimental group with a standard deviation of 6 days, considering a mortality of 50% and

40% in the placebo and experimental groups respectively (26, 27). The number of days without IMV in the placebo group is (50% x 10 D) + (50% x 0 D) or 5 D on average, and following the same calculation for the experimental group of (60% x 15 D) + (40% x 0 D) or 9 D.

Therefore, a mean value of 5 days without ventilation in the placebo group versus 9 in the experimental group is assumed, and the 6-day standard deviation is assumed to be stable. Given the uncertainty regarding the assumption of normality of distributions, the non-parametric Wilcoxon-Mann-Whitney test (U-test) was used for the estimation of the sample size. Considering a bilateral alpha risk of 5% and a power of 90% and an effect size of 0.6, the number of subjects to be included is 138 patients, 69 in each arm.

In our opinion, a 4-day reduction in IMV duration is a reasonable clinical objective. Showing a more modest effect on the number of ventilation free days at day 28 could raise the question clinical relevancy of such effect. More recently, one multicentric retrospective study including 325 patients has been submitted to the MedRxiv repository suggesting that a high dose (>15g/day) initiated in the first 7 days of mechanical ventilation could reduce COVID-19 mortality from 53% to 27% (p=0.009, 13). Besides the fact that such publication has not been peer-reviewed, these results support the size of the effect of IVIG we hypothesized in the ICAR Trial.

Finally, a recent trial suggests that corticosteroids could present a survival benefit of ARDS before the COVID-19 crisis. We therefore considered that corticosteroids could represent a standard of care of ARDS. Thus, the administration of corticosteroids will be allowed concomitantly with the use of IGIV and will be collected through the study. Recently, it has been mentioned in a news release that corticosteroids could present a survival benefit on COVID-19 related ARDS. If this would be verified, we would include steroids as a standard of care and evaluate the use of IVIG as an adjunctive treatment to corticosteroids. A post-hoc analysis will be conducted evaluating the interaction between the effects of corticosteroids and the effects of IVIG.

Effect of early treatment with polyvalent immunoglobulin on acute respiratory distress syndrome associated with SARS-CoV-2 infections

ICAR (IgIV in Covid-related ARds)

BIOMEDICAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

Version V 3.02 - 08/08/2020
N° EudraCT : 2020-001570-30 Project code: D20 – P013

Coordinating Investigator	Dr. Aurélien Mazeraud Service de Neuroanesthésie Neuroréanimation GHU Paris a.mazeraud@ghu-paris.fr
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SIGNATURE page for a biomedical research PROTOCOL

Research Research Code: D20-P013
Title: Effect of early treatment with polyvalent immunoglobulin on acute respiratory distress syndrome associated with SARS-CoV-2 infections
ICAR (IgIV in Covid-related ARds)
Version N° 1.0 of: 04/ 04/2020

The research will be carried out in accordance with the protocol, with current good practices and with the legislative and regulatory provisions in force.

Coordinating Investigator:
Dr Aurélien MAZERAUD — Date: ……/……/……..
Service de Neuroanesthésie et de Neuroréanimation — Signature:
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The research received a favourable opinion from the CPP Ile de France X on 10th April 2020 and authorisation from the ANSM on 09th April 2020

TABLE OF CONTENTS

SUMMARY

Full title	Effect of early treatment with polyvalent immunoglobulin on acute respiratory distress syndrome associated with SARS-CoV-2 infections
Acronym	ICAR (IgIV in Covid-related ARds)
Coordinating Investigator	Dr Aurélien MAZERAUD, Service d'anesthésie-réanimation neurologique 1, rue Cabanis 75014 Paris
Sponsor	GHU Paris Psychiatrie et Neurosciences
Scientific justification	Mid-March 2020, 715 600 people were infected with Coronavirus Disease 2019 (COVID-19) worldwide, and 35500 people died, mainly from acute respiratory distress syndrome (ARDS). No specific pharmacological treatment of COVID-19 related ARDS is currently available. Pulmonary lesions are related to both the viral infection and an inflammatory reaction. Patients admitted to resuscitation have a cytokinetic inflammatory response and higher plasma concentrations of interleukin (IL) 2, IL 7, IL 10, Granulocyte Colony Stimulating Factor, interferon-inducible protein 10, Monocyte chemoattractant protein-1, macrophage inflammatory protein 1α, and tumor necrosis factor-alpha. The number of peripheral CD4 and CD8 T cells appears to be significantly reduced in the blood, while their status is hyperactivated. This redaction is evidenced by immunoreactive cytometric profiles for HLA-DR (CD4 3-47%) and CD38 (CD8 39-4%) or by an increase in the proportion of highly pro-inflammatory Th 17 CCR6+ lymphocytes. Besides, CD8 T cells would exhibit a highly cytotoxic profile characterized by high concentrations of cytotoxic granules (perforin+, granulysin+, or double-positive). Because of their immunomodulatory effect that may both attenuate the inflammatory response and enhance antiviral defense, we propose to evaluate the efficacy and safety of intravenous immunoglobulin (IVIG) administration in patients developing COVID-19 related ARDS. IVIG modifies T cells functions but also dendritic cell function and ultimately cytokine and chemokine networks. IVIG stimulates regulatory T cells proliferation that regulates CD4 and CD8 T cell activity. Also, IVIG restores regulatory T cells functions and modulate lymphocyte populations specifically altered during COVID-19. Besides, IVIG can modulate humoral acquired immunity through its effect on the idiotypic network and antibody

	production. IGIV also acts on innate immunity by antigen neutralization and modulation of phagocytic cells. These effects lead to a decrease in the production of pro-inflammatory cytokines and complement activation, key factors in COVID-19 related ARDS. It should be noted that IVIG is used as a treatment for a variety of autoimmune and inflammatory diseases. Both standard and polyclonal IVIG have significantly reduced mortality in patients with Kawasaki disease and improve outcomes in patients with polyneuropathy. More recently, it has been shown that IVIG may have a beneficial effect in diffuse interstitial lymphocytic pneumonitis and post-influenza ARDS. Few low-level of evidence data support the effect of IGIV during COVID-19. This treatment has been described as favorable in 3 cases of COVID-19 related ARDS and one with COVID-19-related myocarditis who received a high dose of intravenous immunoglobulin IVIG at the time of onset of distress, with a favorable clinical course. More recently, a retrospective study showed a decrease in mortality and ventilation time in patients with ARDS receiving mechanical ventilation treated early with a high dose of IGIV. Notably, there were no adverse events reported, including no renal impairment or allergic reactions. IVIG is a treatment option if it is well-tolerated, particularly concerning renal function. In adults, adverse events reported as possibly related to polyclonal IVIG during septic shock were allergic reactions; skin reactions such as erythema and exanthema; pruritus; nausea and vomiting; dyspnea; congestion; shock; and fever. Two trials reported no adverse events attributable to IVIG, and one trial reported adverse events, but none were ascribed to IVIG. The favorable benefits-risks balance encourages us to rapidly carry out a multicentre, placebo-controlled therapeutic trial testing the benefit of IVIG in COVID-19 related ARDS.
Primary objective and assessment criterion	The main objective is to determine whether the administration of IVIG at a dose of 2g/kg up to *96* hours after the start of invasive mechanical ventilation (IMV), in a patient with COVID-19 related ARDS, increases the number of days without IMV (ventilator-free days) up to day 28 (D28) after IMV initiation.

	The primary endpoint is the number of ventilator-free days at D28, which is, by definition, the number of days the participant was alive and free from IMV from the day of randomization to 28D. The outcome value is calculated as the sum of the days without VM; in case of death before D28, the score is zero. This parameter is a robust primary endpoint frequently used during ARDS. Only the last extubation will be considered as recently suggested in case of multiple invasive mechanical ventilation periods.
Secondary objectives and assessment criteria	Secondary objectives are to assess the impact of IVIG on the following outcomes, overall mortality rate, organ failure according to the SOFA score at 14 and 28 days, lung injury score at 14 and 28 days, the occurrence of grade 3 or 4 adverse events of IGIV, length of ICU stay, length of hospital stay, functional outcomes at D90 defined by the activities of daily living and instrumental activities of the daily living scales, and 90 days survival. The exploratory objectives are to evaluate the impact of IVIG on: • the incidence of occurrence of pulmonary embolism • the number of delirium free days according to the CAM-ICU (Annexe 1) at day 28 • the occurrence of ICU-acquired weakness defined by a MRC sum score < 48 at ICU discharge (Annexe 2) • the occurrence of ventilator associated pneumonia defined by a positive culture of pulmonary specimen • biological efficiency study through in-depth study of IGIV impact on cytokines, immune cells transcriptome and lymphocytes activation in an ancillary study
Experimental design	This is a Phase III double-blind, randomized, multicenter, parallel-group, concurrent, placebo-controlled study in hospitalized participants with COVID-19 requiring mechanical ventilation *using a sequential design*.
Population involved	Adult population hospitalized in ICU for SARS-CoV-2 ARDS

Inclusion criteria	Any patient in intensive care who meet all of the following: 1) Receiving invasive mechanical ventilation for less than *72* hours 2) Develops moderate to severe ARDS according to Berlin classification 3) Has a proven SARS-CoV-2 infection (by polymerase chain reaction) 4) Given consent by patient, family or deferred consent (emergency clause) 5) Is affiliated to a social security scheme (or exemption from affiliation) *6) Inclusion also of the protected patient (under guardianship and curation)*
Non-inclusion criteria	Any of the following: - Allergy to polyvalent immunoglobulins - Pregnancy or minor patient - Known Immunoglobulin A deficiency - Patient with acute renal failure on admission defined by a creatinine 3 times higher than baseline or creatinine >354 micromol/L or a diuresis of less than 0.3 mL/Kg for 24 hours or anuria for 12 hours - Participation in another interventional trial *It should be noted that chronic renal failure dialysis is not a criterion for non-inclusion*
Treatment being tested	Polyvalent human immunoglobulin at a dose of 2g/kg over 4 consecutive days started (i.e. 0.5g/Kg/d) during the first 24-*96* hours of invasive mechanical ventilation (IMV)
Benchmark treatment	No reference treatment is currently proposed for COVID-19
Other procedures added by the research	Assessment at D28 and D90 of survival and functional status by telephone interview
Risks added by the research	Risks associated with the administration of immunoglobulins with a known safety profile in critically ill patients hospitalized for septic shock or ARDS. This therapeutic trial is classified as risk D according to the grid of GHU Paris – Psychiatrie & Neurosciences

Practical procedure	After verification of the inclusion and exclusion criteria, the consent of the patient or a relative or the emergency clause will be collected. Then the patient will be randomized to either the IVIG treatment group or the placebo group, through an online website. Patients in the treatment group will receive polyvalent immunoglobulin infusions to be started between 24 and *72* hours after the onset of IMV for 4 consecutive days. Patients in the placebo group will receive an equivalent volume of saline (NACL 0.9%) for the same duration. The principal investigator at each center will be collected trial data. In patients discharged before D28 or D90, a telephone interview will be conducted by a research technician from the experimental center. Adverse events will be reported in the trial's CRF. .
Number of subjects chosen	138
Number of centres	Patients will be enrolled in *39* participating ICUs, from *38* participating centers (*38* different hospitals) nationwide in France.
Research period	- duration of inclusion: *9* month - duration of participation (treatment + follow-up): 3 months - total duration: *12* months
Number of inclusions expected per center and per month	0.4
Statistical analysis	Assuming that the number of days without IMV is 10 days in the placebo group and 15 days in the treatment group with a standard deviation of 6 days, adjusted for mortality and, given the uncertainty regarding the normality distributions assumption, the non-parametric Wilcoxon-Mann-Whitney test (U-test) was used for sample size estimation. Considering a 5% bilateral alpha risk, 90% power, and 0.6 effect size level, the number of subjects to be included is 138 patients, 69 in each arm. The statistical analysis plan will be developed and finalized before the database is locked and will describe the participating populations to be included in the analyses and the procedures for accounting for missing, unused and spurious data. The choice of statistical tests and multivariate models (parametric or non-parametric) will be done ex-post for each variable on the basis of the characteristics observed (normality of distributions and residuals, collinearity, etc.).

	All univariate or multivariate statistical analyses related to the primary and secondary objectives will be performed with the intention-to-treat (ITT) population. Per protocol population analyses may also be carried out. All tests will be bilateral with a significance level of 5%. The software used will be SPSS v26.
Interim Analysis	*One interim analysis will be performed.* *The interim an analysis will be conducted when about 50 participants (25 participants in the IgIV arm and 25 participants in the SOC arm) have completed the Day 28 assessment. The purpose of this analysis is to evaluate efficacy of IgIV with the application of a futility criterion based on the results on VFDs change from baseline on Day 28. The following futility criterion will be used for this first interim analysis:* *If the difference in the VFDs is less than 3 days improvement between both treatment arms, benefit of IgIV treatment is not expected. For a final decision to stop the study for futility, the results on other endpoints will be considered as well.* *For the primary objective (VFDs) to account for multiple testing due to the interim analysis, an adjustment for type I error alpha will be applied using the O'Brien-Fleming spending function, which would expend two-sided alpha = 0.003 at the interim analysis (critical value = ±3.6128) and leave nominal two-sided alpha of 0.0497 for the final analysis (critical value = ±1.9601).*
Funding source	-GHU Paris - Psychiatry and Neurosciences -Drugs (CLAIRYG 50MG/ML polyvalent immunoglobulins) supplied free of charge by the LFB laboratory
Data Monitoring Committee	*An Independent Data Monitoring Committee (IDMC) will be responsible for closely reviewing the safety and efficacy data from the interim analysis and for providing their recommendations on continuation of the study. The IDMC will meet after 50 participants have completed the study.*
Data Safety Monitoring Board anticipated	Yes
Critical Events Validation Committee	It will meet twice in the trial. Its mission is to validate the evaluation of the main judgement criterion and secondary criteria subject to subjective interpretation: pneumopathy acquired under mechanical ventilation.

1. SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

1.1 Hypothesis for the research

Mid-March 2020, 715 600 people were infected with Coronavirus Disease 2019 (COVID-19) worldwide, and 35 500 people died, mainly from acute respiratory distress syndrome (ARDS). No specific pharmacological treatment of COVID-19 related ARDS is currently available (1).

Few low-level of evidence data support the effect of IGIV during COVID-19. This treatment has been described as favorable in 3 cases of COVID-19 related ARDS and one with COVID-19-related myocarditis who received a high dose of intravenous immunoglobulin IVIG at the time of onset of distress, with a favorable clinical course (2, 3). More recently, a retrospective study showed a decrease in mortality and ventilation time in patients with ARDS receiving mechanical ventilation treated early with a high dose of IVIG (4). Notably, there were no adverse events reported, including no renal impairment or allergic reactions. IVIG is a treatment option if it is well-tolerated, particularly concerning renal function (5). In adults, adverse events reported as possibly related to polyclonal IVIG during septic shock were allergic reactions (6, 7); skin reactions such as erythema and exanthema; pruritus; nausea and vomiting; dyspnea; congestion; shock; and fever (6–10). Two trials reported no adverse events attributable to IVIG, and one trial reported adverse events, but none were ascribed to IVIG (8, 9, 11).

The favorable benefits-risks balance encourages us to rapidly carry out a multicentre, placebo-controlled therapeutic trial testing the benefit of IVIG in COVID-19 related ARDS.

Description of knowledge relating to the pathology in question

To date there is very little pathophysiological knowledge to explain the manifestations of SARS-CoV-2 responsible for COVID-19. Based on existing observational data, it would appear that there are 3 phases during COVID-19: an invasion phase, covering the acquisition of the virus and the subsequent symptomatic viremia phase; in many, but not all, patients, an acceleration phase, when secondary virus-induced damage to target organs and tissues occurs, including the lungs, heart, gastrointestinal tract, and even a generalized cytokine storm. The third phase is the final phase of recovery.

First phase

A virological and animal study identified that SARS-CoV-2 uses the same cell entry receptor - Angiotensin II Converting Enzyme (ACE2) - as SARS-CoV. It is responsible for the virus's body penetration and is one of the determinants of the virulence of COVID-19. The expression of ACE2 is increased in hypertensive patients explaining the severity of the picture in this population.

Second acceleration phase

Clinical and autopsy data, multiplex cytokine assays, and cytometric profiles of circulating lymphocytes provide a better understanding of this runaway phase of COVID-19. Lymphopenia, delay in onset of respiratory distress, and extensive and

prolonged virus replication are common features in patients with severe forms of COVID-19 and are a risk factor for mortality (2).
When mechanical ventilation is required for ARDS, mortality associated with COVID-19 is 50%. The still morbidity is probably high given the significantly prolonged mechanical ventilation durations of the order of 21 days.
Therefore, treatment strategies for COVID-19 must be tailored to each phase. The best timing of antivirals, if any, may be in the pre-acceleration phase. Once clinical deterioration has begun, the first few days of deterioration may present a critical point where modulation of the inflammatory response may be helpful. The use of corticosteroids or polyvalent immunoglobulins was then proposed for the treatment of patients with severe COVID-19.
Pulmonary lesions are related to both the viral infection and an inflammatory reaction. Patients admitted to ICU present an intense cytokinic inflammatory response characterized by higher plasma concentrations of interleukin (IL) 2, IL 7, IL 10, Granulocyte Colony Stimulating Factor, interferon-inducible protein 10, Monocyte chemoattractant protein-1, macrophage inflammatory protein 1α, and tumor necrosis factor-alpha (12). In the blood, the number of peripheral CD4 and CD8 T cells appears to be significantly reduced, while their status is hyperactivated. This is evidenced by immunoreactive cytometric profiles for HLA-DR (CD4 3-47%) and CD38 (CD8 39-4%) or by an increase in the proportion of highly pro-inflammatory Th 17 CCR6+ lymphocytes. Besides, CD8, T cells exhibit a highly cytotoxic profile characterized by high concentrations of cytotoxic granules (perforin+, granulysin+ or double-positive, (13).

Summary of relevant pre-clinical experiments and clinical trials

Because of their immunomodulatory effect that may both attenuate the inflammatory response and enhance antiviral activity, we propose to evaluate the efficacy and safety of IVIG administration in patients developing COVID-19 related ARDS. IVIG modifies T cells functions but also dendritic cell function and ultimately cytokine and chemokine networks. IVIG stimulates regulatory T cells proliferation that regulate CD4 and CD8 T cell activity (13–15). Also, IVIG restores regulatory T cells functions and modulate lymphocyte populations specifically altered during COVID-19 (13).
In addition, IVIG can modulate humoral acquired immunity through its effect on the idiotypic network and antibody production. IGIV act also on innate immunity by antigen neutralization and modulation of phagocytic cells. These effects lead to a decrease in the production of pro-inflammatory cytokines and complement activation, key factors in COVID-19 related ARDS (14–17). It should be noted that IVIG is used as a treatment for a variety of autoimmune and inflammatory diseases. Both standard and polyclonal IVIG have significantly reduced mortality in patients with Kawasaki disease (18, 19) and improve outcomes in patients with polyneuropathy (20). More recently, it has been shown that IVIG may have a beneficial effect in diffuse interstitial lymphocytic pneumonitis (16), and in post-influenza ARDS (21).

Immunoglobulins have been tested during critical conditions such as sepsis and septic shock. A meta-analysis conducted by the Cochrane Database found that 10 trials of polyclonal IGIV in adults (n = 1430) and seven trials of polyclonal IVIG supplemented

with IgM (n = 528) showed significant reductions in mortality compared to placebo or no intervention (relative risks of 0.81 and 0.66 respectively) (5).
In adults, adverse events reported as possibly related to polyclonal IVIG during septic shock were allergic reactions (6, 7); skin reactions such as erythema and exanthema; pruritus; nausea and vomiting; dyspnea; congestion; shock; and fever and chills (6–10). Two trials reported no adverse events attributable to IVIG, and one trial reported adverse events, but none were evaluated as being related to IVIG (8, 9, 11).
To date, four clinical cases of patients with COVID-19 treated with IVIG have been reported in the literature. Of this three patients with ARDS and one with COVID-19-related myocarditis received a high dose of intravenous immunoglobulin at the onset of distress, with a favorable clinical course(2, 3). More recently, one multicentric retrospective study including 325 patients has been submitted to the MedRxiv repository suggesting that a high dose (>15g/day) initiated in the first 7 days of mechanical ventilation could reduce COVID-19 mortality from 53% to 27% (p=0.009, 13). Notably, there were no adverse reactions reported, including no renal failure or allergic reactions.

2. Description of the population to be studied and justification for the choice of participants

We propose to study patients with COVID-19 related ARDS. The IGIV could present beneficial effects on the late phase of SARS-CoV-2 when the immune response is overwhelming to lower the intensity of the cytokinic storm. Based on the availability and cost of IgIV, such treatment could not be evaluated in the entire population of patients presenting COVID-19. We thus chose to focus on a subpopulation of patients with a severe COVID-19. Therefore, we determined that the effectiveness of IVIG should be evaluated when mechanical ventilation for moderate to severe ARDS is introduced. We will use a PCR technique to diagnose a SARS-CoV-2 infection and the conventional Berlin definition of adult respiratory distress syndrome(22).
The proposed new "Berlin" definition of acute respiratory distress syndrome (ARDS) distinguishes, according to the PaO_2/FiO_2 ratio measured in the presence of a positive external expiratory pressure (PEEP) of at least 5 cmH2O, three levels of severity of ARDS: minimal (200 < PaO2/FiO2 ≤ 300 mmHg), moderate (100 < PaO2/FiO2 ≤ 200 mmHg) and severe (PaO2/FiO2 ≤ 100 mmHg). See Annexe 1.

2.1 Identification and description of the experimental medication or medications

Polyvalent human immunoglobulins, manufactured by the pharmaceutical group LFB biotherapies CLAYRIG® 10mg/mL

2.2 Description and justification of the dosage, administration method, administration design, and treatment period.

IVIG will be administered as an 8-hour infusion at a dose of 2g/kg over 4 consecutive days started (i.e., 0.5g/Kg/day). The dose of 2g/kg body weight is used in clinical cases reported in case reports of COVID-19 or in therapeutic trials for septic shock, influenza

pneumopathy, or interstitial lung disease (6, 9, 13). Also, based on the multicentric retrospective study, including 325 patients with COVID-19-related ARDS, a high dose (>15g/day) initiated in the first 7 days of mechanical ventilation could reduce COVID-19 mortality from 53% to 27% (p=0.009, 13). Therefore we chose to administer the IVIG early during the ARDS course, meaning between the 24th and the *96* hours after mechanical ventilation initiation.
The intravenous route allows controlled administration over an extended period of time. The administration is usually fractioned into 4 administrations in this indication. After administration, immunoglobulins have a prolonged half-life and action of approximately 35 days, according to the summary of product characteristics. The plasma peak of immunoglobulins is immediate after administration, and they diffuse into the different compartments within 3 to 5 days. Their prolonged action justifies initial administration without a maintenance dose in this therapeutic trial and will cover the period of the resuscitation stay. The administration of the drug is detailed in Chapter 7.

2.3 Summary of the known and foreseeable benefits and risks for the research participants

The risks associated with the administration of immunoglobulin are the occurrence of an episode of arterial hypotension of anaphylactic origin or circulatory failure. These events have become rarer with the use of newer immunoglobulin preparation techniques. There is a risk of renal failure, which is not reported in recent studies of sepsis and septic shock or other patient populations with interstitial lung disease or neuropathy (6, 9, 13). Nevertheless, not all recent studies have reported adverse events related to IVIG. It should be noted that these adverse events were not reported in the 4 cases of COVID-19 treated with IVIG (12, 20).

Also, there is an increased risk of thromboembolic events due to product-induced hyperviscosity. This risk is not reported in ICU studies, and prolonged administration minimizes this risk. The risk of deep vein thrombosis in a population of immobilized patients without thrombotic prophylactic therapy would be approximately 1.6%, and the risk of pulmonary embolism would be lower. This was not reported in a cohort of 117 patients, the authors of which concluded that their use is safe (13).

COVID-19 related ARDS is associated with a very high mortality rate of around 50% (27). The individual benefits expected from a new therapy in this context are an increase in the chances of survival at the individual level and a reduction in the duration of mechanical ventilation, which is associated with significant morbidity. On a collective scale, reducing the duration of mechanical ventilation will increase the availability of ventilators and resuscitation beds in a context of high tension throughout the SARS-CoV-2 pandemic. This study will also providehigh-quality evidence for the effects of IGIV in the context of COVID-19 relate ARDS.

3. OBJECTIVES

3.1 Primary objective

The main objective is to determine whether the administration of IVIG at a dose of 2g/kg over four consecutive days (i.e., 0.5g/kg/day) up during 24-*96* hours after the start of invasive mechanical ventilation (IMV), in a patient with COVID-19 related ARDS, increases the number of days without IMV (ventilator-free days) up to day 28 (D28) after IMV initiation.

3.2 Secondary objectives

The secondary objectives are to assess the impact of IVIG on mortality, organ failure, resuscitation complications, and functional and psychological sequelae at D28 and D90 and their side effects.

3.3 Objective of complementary study

All patients included in the trial will be offered the opportunity to participate in the complementary study on the biological effects of IVIG. This study will aim to evaluate the biological parameters of responses to IVIG by performing cytokine assays and lymphocyte profiles in flow cytometry based on the evolution of COVID-19 in resuscitation. One 5ml blood sample will be taken at D1, D7, D14, D21, and D28 in this study.

4. EXPERIMENTAL PLAN

4.1 Description of the primary and secondary assessment criteria

4.1.1 Primary assessment criterion

The primary endpoint is the number of ventilator-free days at D28, which is, by definition, the number of days the participant was alive and free from IMV from the day of randomization, which is 0D, to D28. The score is calculated by the sum of the number of days the patient did not receive IMV, but the score is zero in case of death before day 28. This is a validated and commonly used primary endpoint in trials on ARDS (24).

In case of multiple invasive mechanical ventilation periods, only the last extubation will be considered free of IMV (25).

4.1.2 Secondary assessment criteria

Secondary objectives are to assess the impact of IVIG on the following outcomes:

- Overall Mortality Rate at J28 and J90
- Total duration of mechanical ventilation, ventilatory withdrawal, curarization, use of non-invasive ventilation (NIV), high flow oxygen therapy (HFO) WHO ordinal severity scale
- WHO ordinal scale of severity of COVID impairment
- Organ failures according to the SOFA score achieved at D1, D7, D14, D21, and D28, according to Annex 9
- Clinical Efficacy Criteria: Radiological score according to the quadrant method, the chest x-ray is divided into 4 quadrants. The existence of alveolo-interstitial opacities in one quadrant adds 1 point to the score. P/F ratio value, lung compliance at D1, D7, D14, D21, and D28
- Biological efficacy endpoints: inflammatory syndrome at D1, D3, and D7, D14, D21, and D28 by measuring serum C-reactive protein, procalcitonin, white blood cell count, and d-dimer levels.
- Occurrence of ventilator-associated pneumonia, defined by a positive microbiological sample after hours of IMV.
- Occurrence of an adverse event related to immunoglobulins (D1, D2, D3, D4, D5, D6 and D7, D14, D21, and D28 : KDIGO 3 stage renal failure, hypersensitivity manifestations with cutaneous or hemodynamic manifestations, aseptic meningitis defined by a clinically objectified meningeal syndrome upon awakening, hemolytic anemia (defined by hemoglobin less than 8 g/dL, an indosable haptoglobin, and a positive direct Coombs test), leukoneutropenia (according to the WHO classification in Appendix X), Transfusion-Related Respiratory Distress Syndrome (TRALI) due to immunoglobulin
- KDIGO score (D1, D7, D14, D21, and D28) and the need for extrarenal purification.
- Occurrence of clinically detected deep vein thrombosis proven by Doppler ultrasound.
- Occurrence of a pulmonary embolism detected by a pulmonary angioscanner.

Biological efficiency study through in-depth study of IGIV impact on cytokines, immune cells transcriptome and lymphocytes activation in an ancillary study

4.2 Description of research methodology

4.2.1 Experimental plan

The ICAR trial is a Phase III double-blind, randomized, multicenter, parallel-group, concurrent, controlled study in hospitalized participants with COVID-19 requiring mechanical ventilation *using a sequential design*. The participants will be randomized 1:1 to the Investigational arm or the Control arm. Participants randomized to the Investigational arm will receive Ig 2g/Kg administered IV for up to 4 days in addition to the standard of care (SOC), while participants in the Control arm will receive SOC alone. *One interim analysis is planned.*

An Independent Data Monitoring Committee (IDMC) will be responsible for closely reviewing the safety and efficacy data from the interim analysis and for providing their recommendations on continuation of the study. The IDMC will meet after 50 participants have completed the study

4.2.2 Number of centers participating

Patients will be enrolled in *43* participating ICUs, from *42* participating centers (*42* different hospitals) nationwide in France.

1. GHU Paris
2. Hôpital Raymond Poincaré
3. CHU Pitié Salpêtrière (2 ICU)
4. Hôpitaux civils de Lyon
5. CHU Saint Antoine
6. CHU Lariboisière
7. CH Aulnay
8. CH Chalons en champagne
9. CH Poissy
10. CH Etampes
11. Institut. Mutualiste Montsouris
12. Institut Gustave Roussy
13. CHU Robert Débré à Reims
14. Centre Hospitalier de Dieppe
15. Hôpital de Hautepierre (Strasbourg)
16. CHU de Grenoble
17. CHU Nancy
18. Grand Hôpital de l'Est Francilien (site de Jossigny)
19. CHU Sud Amiens
20. Hôpital Jacques Cartier (Massy)
21. Fondation ophtalmologique Rotschild
22. Hôpital Avicenne
23. Hôpital de la Croix Rousse
24. Hôpital de Tarbes
25. Hôpital Nord Franche-Comté
26. CHU Nantes
27. CH d'Angoulême
28. Hôpital d'instruction des armées Percy
29. CHR Orléans
30. Hôpital Salengro (Lille)
31. Hôpital de Vannes
32. CH Valenciennes
33. Hôpital Robert Boulin (Libourne)
34. Groupe Hospitalier Saint Vincent (Strasbourg)
35. Centre Hospitalier de Béthune
36. *CHU Angers*
37. *CH-Nord-Ardennes*
38. *Hôpital Jacques Monod (Montivilliers)*
39. *Groupe Hospitalier Paris Saint Joseph*

40. *Hôpital Européen Georges Pompidou (HEGP)*
41. *CH Victor Dupouy (Argenteuil)*
42. *CHU de Poitiers*

4.2.3 Identification of the subjects

In this research, the subjects will be identified as follows:
Centre no. (3 numeric positions) - no. order of selection of the person in the center (4 numeric positions) - initial last name - initial first name
This reference is unique and will be kept for the duration of the search.
After inclusion, the patient will be randomized to either the treatment or placebo group. The randomization result will be communicated to the hospital pharmacist so that the treatment corresponding to the patient's group is prepared.

4.2.4 Randomization

After screening for inclusion and exclusion criteria and obtaining consent, patients will be randomized (1:1 ratio) to IVIG or placebo groups. Randomization will be performed by an online web-based central using a pre-prepared randomization list, stratified by center and by the time of IMV on randomization: less than 12 hours, between 12 and 24 hours, and between 24 and *72* hours, balanced by randomly variable block size (2 and 4). The group treatment is disclosed to the investigator only after all information regarding patient enrolment is recorded in the online system. Patients are screened for enrolment by the principal investigator and the research team at each study center.

4.2.5 Blinding methods and provisions put in place to maintain blindness

Both trial participants, care providers, and outcome assessors will be blinded after the patients' assignment to one of the trial groups. The double blinding will be provided by the hospital pharmacy of each establishment using opaque sleeves to hide the product packaging, and opaque tubing will be used. Nurses won't be blind to the study as they receive and prepare the product before administration.

4.2.6 Procedures for breaking the blind, if applicable

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting

- the clinical research department outside an emergency during working days, and to the opening hours 9 am - 5 pm, by fax at 01 45 65 76 09
- the GHU –Paris hospital pharmacy, telephone number: 07 84 05 03 40 or 06.78.4129.62 (24h/24).

5. PROCEDURE FOR THE RESEARCH

5.1 Inclusion visit

The inclusion visit will be carried out by a physician who is part of the research team, in each participating center. The purpose will be to verify the inclusion and non-inclusion criteria.

Screening and eligibility data (Day 0)

- Patient's initials, gender, date of birth
- Verification of inclusion and exclusion criteria
    - Mechanical ventilation initiation time
    - PaO_2/FiO_2 value < 200
    - PEEP Value
    - Chest X-ray or lungs CT-scan
    - Specimen positive for SARS-CoV-2 in PCR
    - Informed consent or emergency clause

Baseline Data (Day 0)

Demographic characteristics: age, gender, known pregnancy and number of weeks of amenorrhea, height, weight

Previous history: Chronic alcoholism, Active smoking, No. of pack-years, IV drug addiction Respiratory history, Suspected COPD, Documented COPD GOLD stage (Cf Appendix 4), Asthma, Cystic fibrosis, Diffuse interstitial lung disease, Sleep apnea syndrome, with or without equipment, Other respiratory disease, Previous history and cardiovascular risk factors, Heart failure, NYHA stage (Appendix 5), Treated hypertension Treatment (especially ACE inhibitors), Converting enzyme inhibitors, Angiotensin II receptor antagonists, Ischemic heart disease, Diabetes under treatment Insulin-dependent, Hematological history, Hemoglobinopathy, Heterozygous sickle cell disease Homozygous sickle cell disease Thalassemia, Other Hemoglobinopathy, Hematological cancer History of immunodepression, HIV, Active solid cancer, Autoimmune disease, Type (Systemic connective tissue disease, Systemic vasculitis, Systemic joint disease, Organ-specific autoimmune diseases), Chronic renal failure (chronic dialysis), Liver failure, CHILD-PUGH score (see Appendix 6), Neuromuscular disorder, Dementia.

They will be used to calculate the Charlson comorbidity score (Appendix 7), the performance status (Appendix X), the current medications, as well as the inclusion and non-inclusion criteria.

Pathology criteria: Precursor symptom(s), date of onset of symptoms, Types of symptoms Fever, Cough, Sore throat, Chest pain, Arthro-Myalgias, Fatigue, Feeling unwell, Dyspnea, Headache, confusion, altered consciousness, Abdominal pain, Vomiting, Nausea, Diarrhea

Biological data: blood gas analysis, ionogram, urea, bilirubinemia, platelet count. A beta-HCG assay will be performed for all non-menopausal women.

Radiological and scannographic data will be collected; in particular the existence of a pulmonary embolism and the type and percentage of pulmonary involvement).

The following other parameters will be collected: positive COVID-19 sample, initial respiratory or systemic co-infection, treatment with hydroxychloroquine or corticoids or macrolides, IGS 2 score on admission (Help for calculation: https://www.srlf. org/scores-utiles-resuscitation/score-igs-ii/, Appendix 8), SOFA score on admission (Appendix 9),date of Hospital admission, date of ICU admission.

5.2 Follow-up Visits

Visits will be done daily throughout the stay in intensive care until D28. If the patient has been discharged before D28, will still be warranted visits to D14, D21, and D28 to collect primary and secondary outcome data. An electronic case report file will be available to the research team of each institution on an online platform (Research Electronic Data Capture, REDCap, Vanderbilt University). Activities of Daily Living and Instrumental Activities of Daily Living will be collected on day 90 with a phone call. Study data will be collected and managed using REDCap electronic data capture tools hosted at Centre Hospitalier Sainte-Anne(26). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to standard statistical packages; 4) procedures for data integration and interoperability with external sources.

Daily Follow-Up D0-D28

- Vital status, extubation, re-intubation, tracheostomy, ICU discharge
- Supportive treatment administered: Continuous intravenous sedation, neuromuscular blocker, prone position initiated in the last 24 hours, nitric oxide, almitrine, extracorporeal life-sustaining support
- Respiratory variables: Tidal volume, Plateau pressure, compliance, PaO2/FiO2
- Weaning initiation defined as the first use of spontaneous breathing trial or T-tube trial, use of spontaneous breathing ventilator mode
- COVID-19 treatment: hydroxychloroquine, azithromycin, other ATB, corticosteroids, interleukin inhibitors, antiretroviral therapy
- Complementary tests: leukocytes and lymphocytes count, platelet count, fibrinogen, D-Dimer, procalcitonin, and C reactive protein.

- Radiological score (according to the lung injury score, Annexe 2)
- SOFA score (Annexe 6) and KDIGO score (Annexe 9)
- CAM-ICU (Annexe 1)
- IVIG adverse event occurrence:
- Manifestations of cutaneous hypersensitivity
- Occurrence of hypersensitivity manifestation with hypotension (defined as a mean blood pressure of less than 65 mmHg for 30 minutes, after correction for hypovolemia).
- Doppler ultrasound evidence of deep venous thrombosis
- Existence of a pulmonary embolism proven but CT-scan
- Possible transfusion-associated lung injury
- Aseptic meningitis defined by a clinically objectified meningeal syndrome upon awakening
- Hemolytic anemia (defined as hemoglobin less than 8 g/dL, undosable haptoglobin, and a positive direct Coombs test)

D28 follow-up

- Days on mechanical ventilation
- Vital status and date of death (for patients who died)
- Days on tracheostomy if realized.
- ICU complications: Catheter-related infection, Number of the episode of ventilator-associated pneumonia (VAP), Digestive hemorrhage, Pressure sores (>grade 2), Confusion according to the CAM-ICU (Annexe 1), Focal neurological deficit, Toxidermia
- Functional status: MRC Score at discharge (Annexe 2), ADL value, IADL value

5.3 End of research visit

D90 follow-up

- Days on mechanical ventilation
- Vital status and date of death (for patients who died)
- Days on tracheostomy if realized.
- ICU complications: Catheter-related infection, Number of the episode of ventilator-associated pneumonia, Digestive hemorrhage, Pressure sores (>grade 2), Confusion according to the CAM-ICU (Annexe 1), Focal neurological deficit, Toxidermia
- Functional status: MRC Score at discharge (Annexe 2), ADL value, IADL value

If the patient has been discharged before D90, information will be collected by telephone. The elements necessary for the evaluation of the secondary outcomes are part of routine care as well. Nevertheless, an assessment at D28 and D90 will be systematic.

5.4 Expected length of participation and description of the chronology and duration of the research.

Inclusion period	*9* month
The included subjects' length of participation, of which:	
• Treatment period:	4 days
• Follow-up period:	3 months
Total research period:	*12* months

5.5 Table or diagram summarising the chronology of the research

Timepoint	D0	D1	D2	D3	D4	D5	D6	D7	D14	D15 -20	D21	D22 -27	D28	D90
Consent collection	x													
Pursuit consent collection		x	x	x	x	x	x	x	x	x	x	x	x	
Demographics, medical history, disease characteristics	x													
Administration of IVIG or Placebo Therapy		x	x	x	x									
Main outcome measurement		x	x	x	x	x	x	x	x	x	x	x	x	
Collection of clinical data	x	x	x	x	x	x	x	x	x	x	x	x	x	
Complete blood count, blood gas, creatinine	x	x		x				x	x		x		x	
Leukocytosis, C-reactive protein, biobank collection	x			x				x			x			
SOFA score		x		x				x	x	x	x		x	
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Final assessment of the primary outcome													x	x
Final assessment of secondary outcomes													x	x

5.6 Usual care procedures and additional study procedures

Procedures	**Usual care procedures**	**Additional procedures**
Treatments	Treatment of ARDS in ICU related to SARS-CoV-2 (sedation, curare administration, mechanical ventilation, ventral flow, nitric oxide administration of antiretroviral treatments of antibiotic treatments)	Administration of IVIG/Placebo at D1, D2, D3, D4
Consultations	Daily ICU Consultations	Consultation at D28 and D90

Blood samples	ICU entry assessment including white blood count, ionogram, creatinine, coagulation assessment, D-dimer, PCR for SARS-CoV-2	The research added no additional examination. Realization of a biobank (ancillary study)
Imaging	Diagnostic inclusion scan and chest X-ray in case of suspected pneumopathy	No
Bacteriological samples	In case of suspicion of pneumopathy acquired under mechanical ventilation	No

5.7 Biological Collection (ancillary study)

Blood samples at D1, D3, D5, D7, D14, D21 *and D28* from the research participants will be collected.
During the research, the samples will be kept in the GHU Paris Biological Resource Centre laboratory, under the responsibility of Doctor Macarena Cuenca-Maia for six months at - 80°C.
At the end of the study, authorization will be requested from the Ministry of Scientific Research to store the biological samples at the GHU Biological Resource Center.

Type of sample	**Quantity**	**Storage location**	**Collection supervisor**	**Purpose of the collection**	**Storage period**	**Outcome (destruction, etc.)**
Blood	5ml	GHU Paris	Dr Macarena Cuenca-Maia	Efficacy analysis	6 months	Analysis at the *Cohin Hospital* flow cytometry analysis and cytokine profile

5.8 Termination rules

5.8.1 Criteria and methods for treatment discontinuation

5.8.1.1 Different situations

- Temporary treatment discontinuation: the investigator should document the reason for the discontinuation and its resumption in the clinical report form (CRF).

- Premature termination of treatment, but the subject remains in the research until the end of participation; the investigator must document the reason.

- Premature discontinuation of treatment and termination of research participation.
The investigator must:

- Document the reason(s)
- Collect the evaluation criteria at the time of termination of research participation if the subject agrees.
- Provide for follow-up of the subject, especially in the event of a severe adverse event.

The primary reason for study treatment discontinuation should be documented on the appropriate CRF form. Patients who discontinue study treatment will not be replaced.

5.8.1.2 Criteria and methods for the premature termination of the research

Any subject may discontinue participation in the research at any time for any reason.
The investigator may temporarily or permanently discontinue a subject's participation in research for any reason that affects the subject's safety or is in the subject's best interests.
In the event of premature termination of a subject's research, or withdrawal of consent, data about the subject collected prior to the premature termination may be used.
The CRF should list the different reasons for stopping participation in the research:

- Ineffectiveness
- Adverse event
- Other medical problem
- Subject Personal Reason
- Explicit withdrawal of consent
- Loss of follow-up

5.8.2 Follow-up of the subjects after the premature termination of treatment

Stopping a subject's participation will in no way change his or her usual management of the disease.
If serious adverse events occur, the investigator should report to the sponsor and follow up for 28 days after premature discontinuation of treatment.
In the event of premature discontinuation of treatment following a severe adverse event, a severe adverse event report will be faxed (01 45 65 76 09) to the sponsor. The serious adverse event will be monitored until it is resolved.

5.8.3 Methods for replacing subjects, if applicable

The living or non-living status will be collected by telephone if necessary. However, due to the average ventilation time of 20 days and convalescence time in the hospital, it is not expected that there will be any lost subjects and, therefore, no replacement subjects.

5.8.4 Terminating part or all of the research

The GHU Paris as a sponsor or the Competent Authority (ANSM) may prematurely interrupt temporarily or permanently all or part of the research, following the

recommendations of an Independent Supervisory Committee in the following situations:
- In the event of unexpected serious adverse events in one treatment arm or an imbalance of serious adverse events between the two treatment arms, requiring a re-evaluation of the benefit/risk ratio of the research.
- If unforeseen events, or new information on the product, make it unlikely to achieve the research objectives, it may lead the sponsor or the Competent Authority (ANSM) to terminate the study prematurely.
- If it appears that the inclusion objectives are not being met, the promoter reserves the right to suspend inclusions permanently.
In case of premature study termination, the sponsor's decision and justification are transmitted to the Competent Authority (ANSM) and the CPP.

6. ELIGIBILITY CRITERIA

6.1 Inclusion criteria

Any patient in intensive care who meet all of the following criteria:

1) Receiving invasive mechanical ventilation for less than *72* hours
2) Develops moderate to severe ARDS meeting the Berlin criteria
3) Has a proven SARS-CoV-2 infection (by polymerase chain reaction)
4) Given signed informed consent by the patient, or by his/her legal/authorized representative, or deferred consent (emergency clause)
5) Is affiliated to a social security scheme (or exemption from affiliation)
6) *Inclusion also of a protected patient (under guardianship and curation)*

6.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Allergy to polyvalent immunoglobulins
- Pregnancy or minor patient
- Known Immunoglobulin A deficiency
- Patient with acute renal failure on admission defined by a creatinine 3 times higher than baseline or creatinine >354 micromol/L or a diuresis of less than 0.3 mL/Kg for 24 hours or anuria for 12 hours
- Participation in another interventional trial

It should be noted that chronic renal failure dialysis is not a criterion for non-inclusion

6.3 Recruitment methods

We plan to include 3.8 patients per center over one inclusion month.

Number of patients to be included	138
Number of Centres	43
Inclusion period	9 month
Number of Subjects/Centre	4
Number of patients per month per center	3.8

7. TREATMENT ADMINISTERED TO RESEARCH PARTICIPANTS

7.1 Description of the experimental medication or medications

7.1.1 Experimental medication 1

Patients in the intervention group will receive an infusion of 2g/Kg IVIG to be started between 24 and *96* hours after initiation of IVM in 4 injections over 4 consecutive days of 0.5 g/Kg.
The IVIG that will be used will be those with the best tolerance profile, especially regarding renal function. The risks associated with the administration of IVIG will be minimized by infusing the product over long periods of time (>8h), by splitting doses, and by using sucrose, maltose, and glucose-free product such as CLAIRYG®. The use of loop diuretics should be kept to a minimum, and blood volume should be adjusted.
Although IVIG doses vary according to the pathologies, they are average 2 g/kg administered over 24 hours for Kawasaki syndrome or septic shock. In clinical cases reported to Wuhan of COVID-19, dosages ranged from 1.5 g/Kg to 2.5 g/Kg per day. This dosage ensures a satisfactory risk/efficacy balance. The infusion should be administered slowly over 8 hours. This flow can be slowed down to 24 hours if necessary. Patients in the placebo group will receive an equivalent volume of saline 20mL/Kg.
The double-blind will be provided by the hospital pharmacy of each establishment using opaque sleeves to hide the product packaging and must be returned to the pharmacy once empty.

7.2 Description of the non-experimental treatment or treatments (medications required for carrying out the research)

No ancillary treatment is planned in the trial.

7.3 Description of the traceability elements that accompany the experimental medication or medications

Experimental drugs will be tracked using dedicated blood-derived drug sheets for safety reasons. Placebo and experimental drug administration will be and collected through the CRF.

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

Other treatments will be left to the discretion of the teams taking care of the patients. On the other hand, participation in another intervention study is an exclusion criterion.

7.5 Methods for monitoring compliance with the treatment

The immunoglobulin and placebo vials will be returned empty to the pharmacy for inventory.

8. ASSESSMENT OF EFFICACY

8.1 Description of parameters for assessing the efficacy

The primary endpoint is the number of ventilator-free days at D28, which is, by definition, the number of days the participant was alive and free from IMV from the day of randomization, which is day 0, to day 28.
If the patient dies before D28, the score is 0. If the patient is not extubated at D28, the score is 0.
The score is calculated by the sum of the number of days the patient did not receive IMV. Multiple invasive mechanical ventilation periods, only the last extubation will be considered free.

Secondary objectives are to assess the impact of IVIG on the following outcomes:

- Overall Mortality Rate at J28 and J90
- Total duration of mechanical ventilation, ventilatory withdrawal, curarization, use of non-invasive ventilation (NIV), high flow oxygen therapy (HFO) WHO ordinal severity scale
- WHO ordinal scale of severity of COVID impairment
- Organ failures according to the SOFA score achieved at D1, D7, D14, D21 and D28, according to Annex 9
- Clinical Efficacy Criteria: Radiological score according to the quadrant method, the chest x-ray is divided into 4 quadrants. The existence of alveolo-interstitial

opacities in one quadrant adds 1 point to the score. P/F ratio value, lung compliance at D1, D7, D14, D21, and D28

- Biological efficacy endpoints: inflammatory syndrome at D1, D3 and D7, D14, D21, and D28 by measuring serum C-reactive protein, procalcitonin, white blood cell count, and d-dimer levels.
- Occurrence of ventilator-acquired pneumonitis defined by an evocative radio-clinical setting associated with bacteriological sampling by culturing tracheal secretions, bronchiolo-alveolar lavage or protected distal sampling.
- Occurrence of an adverse event related to immunoglobulins (D1, D2, D3, D4, D5, D6 and D7, D14, D21, and D28: KDIGO 3 stage renal failure, hypersensitivity manifestations with cutaneous or hemodynamic manifestations, aseptic meningitis defined by a clinically objectified meningeal syndrome upon awakening, hemolytic anemia (defined by hemoglobin less than 8 g/dL, an indosable haptoglobin, and a positive direct Coombs test), leukoneutropenia (according to the WHO classification in Appendix X), Transfusion-Related Respiratory Distress Syndrome (TRALI) due to immunoglobulin
- KDIGO score (D1, D7, D14, D21, and D28) and the need for extrarenal purification, occurrence of clinically detected deep vein thrombosis proven by Doppler ultrasound. Occurrence of a pulmonary embolism detected by a pulmonary angioscanner.

The main goals of the biological efficacy study is (1) to evaluate the effect of IVIG administration on the global immune response (2) to compare the immune response patterns in patients who will further deteriorate and die in ICU versus survivors. To do so, we propose to perform (i) a multiplex analysis of plasma cytokines and chemokines and (ii) transcriptome analysis to phenotype the effects of IVIG on the immune response with a particular focus on T cells. These results will help us identify molecular candidates involved in COVID-19 induced ARDS and identify immune cells mainly involved in its pathogeny to be further studied by (iii) flow cytometry.

Whether IVIG shows benefits or not, we propose to decipher mechanisms involved in the recovery or worsening of patients. Besides understanding at the cellular and molecular levels IgIV modulation of inflammatory mediators in COVID-19, this study will allow us to identify new targets to modulate the excessive immune reaction responsible for the pathogenicity of the SARS-CoV-2 virus.

This study will be led in collaboration with Dr. Bruno Lucas from Institut Cochin.

8.2 Anticipated methods and timetable for measuring, collecting, and analyzing the parameters for assessing the efficacy

Time point	D0	D1	D2	D3	D4	D5	D6	D7	D14	D15 -20	D21	D22 -27	D28	D90
Administration of IVIG or Placebo Therapy		**x**	**x**	**x**	**x**									
Leukocytosis, C-reactive protein, biobank collection	**x**							**x**	**x**		**x**		**x**	

The medication circuit will be the responsibility of the pharmacy for use inside each recruiting center.

Each pharmacy will receive the treatment under study: active drug (CLAIRYG® 50MG/ML polyvalent immunoglobulin) supplied for LFB laboratories as an injectable solution for infusion delivered in 100ml and 200ml vials. They will be stored between 2°C and 8°C in the original packaging, away from light.

The supply of therapeutic units:

- Initial Provisioning

Each pharmacy places an order at LFB according to the usual means of LFB controls, specifying the ICAR COVID study. The initial order planned in the trial is 200g.

Bottle of CLAIRYG® 50MG/ML Bottle of 100 ml = 10. Bottle of 200ml = 5 g

The placebo: NACL 0.9%, not provided by the laboratory, will be made available by the sponsor at each center's pharmacy.

- the pharmacy of each center orders at LFB as inclusions occur to replenish a 200g stock.

Each pharmacy keeps an accounting of the immunoglobulin stock according to its current system.

Methods of dispensing:

- The pharmacy of each center receives:

1- The result of patient randomization

2-The prescription from the investigator (each center is organized according to its internal system of prescription and traceability of drugs) knowing that the doctor is blind.

3-A nurse from the ICU comes to pick up the therapeutic units at the hospital pharmacist.

The pharmacist delivers the treatment for 24 hours in a pocket on which a sleeve will be placed to mask the treatment. Vials of experimental drug or placebo are destroyed on-site according to local procedure.

Biological samples will be sent to the laboratory according to the usual way of complementary examinations from each center, which will then be sent to the GHU Paris Biological Resource Centre.

The biological collections will be managed by the biological resource center (Dr Cuenca-Maia) of the GHU Paris and forwarded by the investigator of each center to the center of the coordinating investigator.

9. SPECIFIC RESEARCH COMMITTEES

9.1 Scientific committee

A scientific committee formed by the scientific manager Pr Tarek Sharshar and composed of Pr Michel Wolff and Dr Franck Verdonk.

9.2 Steering committee

No steering committee is foreseen in this trial.

9.3 Endpoint Adjudication Committee

- Committee Members: Dr. Mazeraud, Dr. Sharshar, Dr. Schimpf, Dr. Daniel, Dr. Legouy, Dr. Wolff
- Responsibilities: Validate the evaluation of the primary endpoint and secondary endpoints subject to subjective interpretation: ventilator-associated pneumonia.
- Operating methods: physical meeting or teleworking sessions twice during the trial.

The first meeting will be held at the end of the inclusions and the second meeting three months after the trial start.

9.4 Indipendent Data Monitoring Committee (IDMC)

The Independent Data Monitoring Committee (IDMC) will be responsible for closely reviewing the safety and efficacy data from the interim analysis and providing recommendations on the continuation of the study. The IDMC will meet after 50 participants have completed the follow-up at 28D.

Committee members: Pr. Raphael Porcher (statistician), Pr. Antoine Roquilly (clinican), Dr Giulleme Turc (chair), Dr Franck Verdonk (secretary)

10. SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE RESEARCH

10.1 Description of parameters for assessing safety

Adverse events will be systematically investigated at each visit during this study.
We will routinely collect adverse events from IVIG. According to the Summary of Product Characteristics for CLAIRYG® which will be used in this study, the main expected adverse reactions are:
- So-called allergic reactions, which are rare with new products and which generally improve with appropriate symptomatic treatment;

- An increased risk of thromboembolism, monitored by the occurrence of deep vein thrombosis or pulmonary embolism;
- The occurrence of acute renal failure; defined by a KDIGO 3 stage (Annexe)
- Other effects, including aseptic meningitis, hemolytic anemia, leuko-neutropenia, Transfusion-Related Respiratory Distress Syndrome (TRALI), etc., were also observed.

Other adverse events are usually rapidly regressive within a few days, such as leuko-neutropenia.

10.2 Anticipated methods and timetable for measuring, collecting, and analyzing the parameters for assessing safety

The clinical-biological parameters collected daily will allow identifying the occurrence of adverse events through daily visits collecting creatinine and diuresis.

Hypotension that does not respond to volume expansion defined by a mean blood pressure of less than 65 mmHg for more than 30 minutes despite filling.

Occurrence of a new clinically monitored thromboembolic event.

The occurrence of aseptic meningitis or TRALI cannot be demonstrated with certainty because of the high probability of the patient receiving sedation leading to coma and because of the high probability of altered haematosis related to the natural course of the disease.

10.3 Procedures in place for recording and reporting adverse events

10.3.1 Definitions

<u>According to Article R1123-39 of the French Public Health Code and the guideline on good pharmacovigilance practices (EMA, 2012):</u>

- **Adverse event**

Any untoward medical occurrence in a patient or clinical trial subject is administered a medicinal product and does not necessarily have a causal relationship with this treatment.

- **Adverse drug reaction**

Any response to a medicinal product which is noxious and unintended.

- **Serious adverse event**

Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/congenital disability.

- **Unexpected adverse reaction**

An adverse reaction, the nature, severity, or outcome of which is not consistent with the applicable product information: the summary of product characteristics for an authorized product or the investigator's brochure for an unauthorized investigational product.
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According to the notice to sponsors of clinical trials for medications (ANSM):

- **New safety issue**

Any new safety information:
- that could significantly alter the assessment of the benefit-risk ratio for the experimental medication or the trial
- or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the trial

Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction occurring
b) suspected unexpected serious adverse reactions occurring in patients who have finished the trial and about whom the sponsor is notified by the investigator, who also provides any follow-up reports
c) any new fact relating to the conduct of the clinical trial or the development of the experimental medication if the new fact is likely to affect participant safety
Examples:
- a serious adverse event likely to be related to the investigations and to the trial's diagnostic procedures and which could modify the conduct of this trial
- a significant risk for the trial participants such as ineffectiveness of the experimental medication used in the trial in treating a life-threatening illness
- significant safety results from a recently completed research carried out on animals (such as carcinogenicity research)
- the premature termination, or temporary interruption, of a trial conducted with the same experimental medication in another country, for safety reasons
- an unexpected serious adverse reaction associated with a non-experimental medication required for carrying out the trial (e.g., challenge agents, rescue treatment)
d) recommendations from the data safety monitoring board (DSMB), if applicable, if they are relevant to the safety of the participants
e) any unexpected serious adverse reaction reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication

10.3.2 The investigator's roles

10.3.2.1 Regulatory obligations of the investigator (Art R1123-54 of the French Public Health Code)

The investigator must notify the sponsor, **immediately on the day when the investigator becomes aware**, of all the serious adverse events, except those that are listed in the protocol (see. section 10.3.3.1) or in the investigator's brochure as not requiring immediate notification.

These serious adverse events are recorded in the "adverse event" section of the case report form, and the investigator must immediately notify the sponsor's Vigilance division (see 10.3.4).

10.3.2.2 The investigator's other roles

Any participant, from the signing of the informed consent, adverse events (AEs), whether severe or not (spontaneously reported by the participants or observed by the investigators or consisting of an abnormal laboratory or radiology result etc.) must be completed in the CRF or e-CRF.
If possible, symptoms and abnormal laboratory findings should be grouped into a single syndrome or diagnosis. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. Then, only the diagnosis will be documented as an AE and not the individual symptoms/signs.
The investigator should assess the severity of each adverse event and report all serious and non-serious adverse events in the electronic case report form (e-CRF).
The investigator should document serious adverse events to the best of his or her ability and give a definitive medical diagnosis whenever possible.
The investigator should assess the severity of the adverse events and the causal relationship of the serious adverse events to the investigational drug(s).
The method used by the investigator, based on the WHO (WHO Uppsala Monitoring Centre) method, is based on the following 4 causality terms:

- Certain,
- Probable/plausible,
- Possible,
- Unlikely (not excluded).

Their definition is presented in the following table (taken from WHO-UMC causality categories, version of 17/04/2012).

Certain

- Event or laboratory test abnormality, with plausible time relationship to drug intake **
- It cannot be explained by disease or other drugs
- Respons to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

Probable / Likely

- Event or laboratory test abnormality, with reasonable time relationship to drug intake**
- Unlikely to be attributed to disease or other drugs
- ·Response to withdrawal clinically reasonable
- Rechallenge not required

Possible

- Event or laboratory test abnormality, with reasonable time relationship to drug intake **
- Could also be explained by disease or other drugs
- information on drug withdrawal may be lacking or unclear

Unlikely

- Event or laboratory test abnormality, with a time to drug intake **
- that makes a relationship improbable (but not impossible)
- disease or other drugs provide plausible explanations

*All points should be reasonably complied with
** Or study procedures

10.3.3 Specific features of the protocol

All serious and non-serious adverse events must be reported in the CRF.

10.3.3.1 Serious adverse events that do not require the investigator to notify the sponsor immediately

- Death
- Grade Neutropenia ≥ 3 according to the CTCAE scale
- Renal insufficiency stage KDIGO 3 (see appendix 2)
- Suspicion of TRALI
- Radiologically proven venous thrombosis or pulmonary embolism

These serious adverse events are only collected in the case report form. Extraction of these serious adverse events from the case report will be made at the end of the study.

● Natural and habitual evolution of the pathology:

Patients admitted to ICU for COVID-19-related ARDS have hypoxic major respiratory failure in the foreground, often leading to the use of mechanical ventilation. After initiation of mechanical ventilation, patients may experience circulatory failure requiring vasopressor treatment in more than 75% of cases, renal failure in approximately 25% of cases, pulmonary embolism or other thromboembolic events in more than 50% of cases.
Patients may present in ICU a complication increasing morbi-mortality such as nosocomial infection (ventilator acquired pneumonia, catheter-related infection), complications related to invasive procedures (pneumothorax...). After sedation withdrawal, patients may develop delirium or ICU neuromyopathy, probably very frequently.

The mortality of ARDS related to COVID-19 in ICU is 50%. It is related to uncontrolled respiratory failure leading to hypoxia and cardiac arrest, uncontrolled circulatory failure, limitations, and cessation of therapy or complications of ICU.

The main objective of the research is to show an increase in the number of days living without mechanical ventilation. The mortality rate related to the pathology studied approaches 50% at one month.
Deaths are not to be notified immediately to the promoter but to be collected in the case report as they are linked to the natural and usual evolution of the pathology.
An extraction of deaths from the CRF will be performed after 3 weeks from the beginning of the study. The extraction of the deaths will be transmitted to the members of the Independent Supervisory Committee.
In the event of an imbalance between groups/mortality rate higher than the expected 20% frequency having an impact on the safety of the participants and requiring an urgent safety measure from the sponsor, a safety development will be transmitted to ANSM without delay.

● Adverse events that may be related to treatments prescribed as part of care during research follow-up
These adverse reactions should be reported by the investigator to the regional pharmacovigilance center to which the investigator belongs.
- So-called allergic reactions, which are rare with new products and which generally improve with appropriate symptomatic treatment;
- An increased risk of thromboembolism, monitored by the occurrence of deep vein thrombosis or pulmonary embolism;
- The occurrence of acute renal failure; defined by a KDIGO 3 stage
- Other effects include aseptic meningitis, hemolytic anemia, leuko-neutropenia, TRALI.

10.3.3.2 Serious adverse events that require the investigator to immediately notify the sponsor

The investigator must report all adverse events that meet one of the seriousness criteria below, except for events listed in section 10.3.3.1 as not requiring notification:
1- Death
2- Life-threatening situation
3- Requiring hospitalization or prolonging hospitalization
4- Persistent or significant disability or incapacity
5- Congenital abnormality or congenital disability
6- Or any other adverse event considered "medically significant."

10.3.3.3 Other events that require the investigator to immediately notify the sponsor

Adverse events considered "medically significant," i.e., events that could endanger the trial subject or require intervention to prevent one of the defining characteristics or consequences of a severe adverse event (SAE): none

These adverse events should be notified to the sponsor by the investigator without delay from the day on which they become known to the sponsor, in the same way, and within the same timeframe as serious adverse events.

10.3.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE shall be the subject of a written report signed by the investigator using the SAE notification form specific to the research and provided for this purpose (in the observation notebook).
Each item in this document should be completed by the investigator to allow the sponsor to perform a relevant analysis, including the nature of the severity endpoint and the causal link between the reported event and the study product/research added procedures (this implies that follow-up by the investigator may continue after the participant's exit from the trial).
The initial notification of a severe adverse event to the sponsor should be followed promptly by a detailed written follow-up report(s) to monitor the case's progress vigilantly or supplement the information.
The investigator should provide the sponsor with any documents that may be useful to the sponsor (medical reports, biological results, results of additional tests, etc.), whenever possible. These documents should be made anonymous. Also, they must be completed with the following information: research acronym, participant number, and initials.
Any adverse event will be monitored until it is fully resolved (stabilized at a level acceptable to the investigator or returned to the previous state) even if the participant has left the research.
The initial notification, the SAE follow-up reports, and any other document will be sent to the promoter exclusively by fax to 01 445 65 76 09.
In the case of a search with e-CRF :
- the investigator completes the ISG notification form in the e-CRF, validates it, prints it, signs it, and sends it by fax ;
- if it is impossible to connect to the e-CRF, the investigator shall complete, sign and send the ISG notification form to the Vigilance Sector. As soon as the connection is re-established, he will regularize by completing the ISG notification form in the e-CRF.
The investigator should respond to any request for additional information from the sponsor.

10.3.5 Period for notifying the sponsor

The investigator should immediately notify the sponsor of serious adverse events as defined in the relevant section:
- from the date of the start of treatment with an investigational drug,
- for the duration of the participant's follow-up, as provided for by the research,
- up to 28 days after taking IVIG following the completion of treatment with the participant's investigational drug.

10.3.6 The sponsor's roles

The sponsor, represented by its DRCI, continuously assesses the safety of each experimental medication throughout the research.

10.3.6.1 Analysis and declaration of serious adverse events

The sponsor assesses:
- the seriousness of all adverse events reported
- the causal relationship of these events with each experimental medication and/or specific medical procedures/exams added by the research and with other possible treatments
- the expected or unexpected nature of these adverse reactions

All serious adverse events which the investigator and/or the sponsor believe could reasonably have a causal relationship with the experimental medication are considered as suspected adverse reactions.

All suspected unexpected serious adverse reactions are declared by the sponsor, within the legal time frame, to the Agence Nationale de Sureté du Médicament and to the relevant Comité de Protection des Personnes (CPP, ethical committee).

● The initial declaration must be made with no delay after the date on which the serious adverse event occurs in the case of death or of a life-threatening diagnosis.

● The initial declaration must be made with no delay after the date on which the serious adverse event occurs in the case of other serious situations.

● The follow-up declaration must be made with no delay.

Any suspected unexpected serious adverse reaction must also be declared electronically in the Eudravigilance European database for adverse events due to medications established by the European Medicines Agency (EMA).

The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the research subjects.

Specific cases of serious adverse events of special interest:
At the request of ANSM, the sponsor may be asked to declare serious adverse events of special interest, in accordance with the same procedures and deadlines as suspected unexpected serious adverse reactions.

Specific case of double-blind trials:
After unblinding by the sponsor, if the administered product is the investigational product: the related and unexpected case will therefore be reported immediately as a suspected unexpected serious adverse reaction within the regulatory timeframe mentioned above). If the product administered is the placebo, any unexpected events that may be related to it (allergy to excipients, etc.).

10.3.6.2 Analysis and declaration of other safety data

This relates to any safety data or the new fact that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the

research, or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the research.

New facts must be declared to the competent authorities within 15 calendar days of the sponsor becoming aware. Additional relevant information must be sent within an additional 8 days after the 15 day deadline.

10.3.6.3 Annual safety report

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- an analysis of the safety of the research subjects
- a description of the patients included in the trial (demographic characteristics, etc.)
- a line listing of suspected serious adverse reactions that occurred during the period covered by the report
- a cumulative summary tabulation of serious adverse events that have occurred since the start of the research

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorized the trial.

10.3.7 Data Safety Monitoring Board

For this biomedical research, it has not been considered beneficial to convene a DSMB.

11. DATA MANAGEMENT

11.1 Data collection methods

Trial data will be collected in the trial's electronic CRF as inclusions, and patient follow-up visits by the investigator or collaborators occur.

11.2 Identification of data collected directly in the CRFs and that will be considered as source data

None.

11.3 Right to access source data and documents

11.3.1 Access to data

In accordance with GCPs (Good Clinical Practice) :
- the sponsor is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research will be carried out, to the source data, to the source documents and the reports, with the goal of quality control and audit by the sponsor
- the investigators will make available to those in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.3.2 Source documents

Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during the research. These documents will be kept for 15 years by the investigator or by the hospital in the case of a hospital medical file.

11.3.3 Data confidentiality

Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research subjects, and in particular, the identity of the participants and the results obtained.
These individuals, as well as the investigators themselves, are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).
During or after the biomedical research, the data collected about the research subjects and sent to the sponsor by the investigators (or any other specialized parties) will be made non-identifying.

Under no circumstances should the names and addresses of the subjects involved be shown.
The sponsor will ensure that each research subject has given permission in writing for access to personal information about him or her, which is strictly necessary for the quality control of the research.

11.4 Data processing and storage of documents and data

11.4.1 Identification of the manager and the location(s) for data processing

The GHU DRCI biostatistician will analyze the data collected in the trial.

11.4.2 Data entry

Data entry will be carried out by the investigator and his collaborators in the eCRF.

11.4.3 Data processing (CNIL, the French Data Protection Authority) in France

This research falls under the "Méthodologie de référence" (MR-001) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978 relating to information technology data files and privacy. This change was approved in a decision made on 5 January 2006. Le GHU Paris Psychiatrie et Neurosciences, the research sponsor, has signed a commitment to comply with this " Méthodologie de référence "

11.4.4 Data processing (CNIL) outside of France

The data collected in the trial will not be sent to the European Union or a "suitable" country.

11.4.5 Archival

Specific documents for biomedical research relating to medication for human use will be archived by the investigator and the sponsor for a period of 15 years after the end of the study.

This indexed archival includes, in particular:

- A sealed envelope containing the original copies of all information sheets and consent forms signed for all individuals at the center that participated in the research for the investigator
- A copy of all the information notes and consent forms signed for all subjects at the center that participated in the research for the sponsor
- "Research" binders for the Investigator and the sponsor, including:

- the successive versions of the protocol (identified by the version no. and date), and the appendices
- the ANSM authorizations and CPP favorable opinions
- letters of correspondence
- the inclusion list or register
- the appendices specific to the research
- the final research report
- The data collection documents

11.05 Ownership of the data

Le GHU Paris Psychiatrie et Neurosciences is the owner of the data, which cannot be used or disclosed to a third party without its prior approval.

12. STATISTICAL ASPECTS

12.1 Description of statistical methods to be used, including the timetable for the planned interim analyses

The statistical analysis plan will be developed and finalized before the database is locked and will describe the participating populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary objectives.

The primary and secondary analyses will be stratified by age categories, sex, and other clinically relevant factors (comorbidities). Demographic characteristics and parameters identified at enrolment will be summarized using descriptive statistical methods.

Demographic summaries will include gender, race/ethnicity, and age. For demographic and categorical background characteristics, a Cochran-Mantel-Haenszel test will be used to compare treatment groups. For continuous demographic and baseline characteristics, a Wilcoxon test will be used to compare treatment groups.

The number of days without mechanical ventilation will be presented as a mean with standard deviation and 95% confidence interval. The groups will be analyzed in terms of intention to treat. The difference between the two groups will be analyzed by a non-parametric test of comparison of means, stratified for the primary endpoint. The point estimate of the difference between treatments and the associated 95% confidence interval will be provided.

A regression model for censored data (Cox model) will explore prognostic factors. The IGIV immunological and pathological related efficacy endpoints will also be compared according to their distribution and analyzed using Student, Mann-Whitney, and Fisher tests.

Other variables will be presented as means and standard deviations or medians and interquartile ranges according to their distribution and analyzed by Student, Mann-Whitney, and Fisher tests.

Parameters measured on a time scale from randomization or start of administration will be compared between treatment groups using the Log-Rank test.

The choice of statistical tests and multivariate models (parametric or non-parametric) will be made for each variable based on observed characteristics (normality of distributions and residuals, collinearity).

The statistical analyses relating to the main objective will be carried out as intention to treat. Secondary analyses on the population per-protocol may also be carried out.

For the main objective, both general and subgroups, the following evidence-based medicine statistics (effect size) will be provided: confidence intervals, numbers needed to treat, and absolute risk reduction.

All tests will be bilateral with a significance threshold of 5% *(adjusted for interim analyses).*

The software used will be SPSS v26 (SPSS Inc., Chicago, IL, USA).

12.2 Interim Analysis

One interim analysis will be performed.
The interim an analysis will be conducted when about 50 participants (25 participants in the IgIV arm and 25 participants in the SOC arm) have completed the Day 28 assessment. The purpose of this analysis is to evaluate efficacy of IgIV with the application of a futility criterion based on the results on VFDs change from baseline on Day 28. The following futility criterion will be used for this first interim analysis:
If the difference in the VFDs is less than 3 days improvement between both treatment arms, benefit of IgIV treatment is not expected. For a final decision to stop the study for futility, the results on other endpoints will be considered as well.
For the primary objective (VFDs) to account for multiple testing due to the interim analysis, an adjustment for type I error alpha will be applied using the O'Brien-Fleming spending function, which would expend two-sided alpha = 0.003 at the interim analysis (critical value = ±3.6128) and leave nominal two-sided alpha of 0.0497 for the final analysis (critical value = ±1.9601).

12.2 Calculation hypotheses for the number of subjects required and the result

We hypothesize that the number of days without IMV is 10 days in the placebo group and 15 days in the experimental group with a standard deviation of 6 days, considering mortality of 50% and 40% in the placebo and experimental groups, respectively (26, 27). The number of days without IMV in the placebo group is (50% x 10 D) + (50% x 0 D) or 5 D on average, and following the same calculation for the experimental group of (60% x 15 D) + (40% x 0 D) or 9 D.

Therefore, a mean value of 5 days without ventilation in the placebo group versus 9 in the experimental group is assumed, and the 6-day standard deviation is assumed to be stable. Given the uncertainty regarding the assumption of normality of distributions, the non-parametric Wilcoxon-Mann-Whitney test (U-test) was used for the estimation of the sample size. Considering a bilateral alpha risk of 5% and a power of 90% and

an effect size of 0.6, the number of subjects to be included is 138 patients, 69 in each arm.

A 4-day reduction in IMV duration is a reasonable clinical objective. A total of 138 patients is achievable as each of the 36 participating units is able to accommodate more than 40 ARDS patients over one month.

12.3 Specify if subjects who leave the research prematurely will be replaced and in what proportion.

No subject replacement. No premature exit or predictable loss of sight.

12.4 Anticipated level of statistical significance

All tests will be bilateral with a significance threshold of 5% *(adjusted for interim analisys).*

12.5 Statistical criteria for termination of the research.

The study may be discontinued for reasons of futility according to the IDCM reasoned opinion.

12.6 Method for taking into account missing, unused or invalid data

Given the ICU setting, no missing data on the primary outcome are expected, even in the case of off-duty transfers, as these transfers are from ICU to ICU and are traced. Missing data on important confounding factors will be valued using a multiple chain equation imputation (MICE) method as part of robustness analysis.

12.7 Management of modifications made to the analysis plan for the initial strategy.

Any changes to the analysis plan in response to protocol amendments or changes in the study process will be defined prior to database freezing and documented in a protocol amendment. Any unplanned analysis will be considered a posthoc analysis in the scientific report.

12.8 Selection of populations

This population is representative of the general population, and positive results from the ARDS linked to COVID could be rapidly extrapolated to the general population. A positive result will be quickly disseminated.

13. QUALITY CONTROL AND ASSURANCE

Each biomedical research project managed by Le GHU Paris Psychiatrie et Neurosciences is ranked from A to D according to the projected risk incurred by research subjects using the classification of biomedical research sponsored by Le GHU Paris Psychiatrie et Neurosciences

13.1 General organization

The sponsor must be responsible for the safety and respect of those subjects who have agreed to participate in the research. The sponsor must implement a quality assurance system to best monitor the conduct of the study in the investigation centers.

For this purpose, the sponsor shall delegate Clinical Research Associates (CRA), whose primary role is to carry out regular follow-up visits at the research locations after having carried out initial visits.
The objectives of monitoring the research, as defined in the French Good Clinical Practices (BPC section 5.18.1), are to verify that:

- the rights, safety, and protection of the research subjects are met
- the data reported is exact, complete, and consistent with the source documents
- the research is carried out in accordance with the protocol in force, with the French GCPs, and with the legislative and regulatory provisions in force

13.1.1 Strategy for opening the centers

The strategy for opening the centers set up for this research is massive and urgent, as called for in response to the health crisis at COVID-19.

13.1.2 Level of center monitoring

In the case of this Phase III research, the choice of an appropriate level of monitoring was weighted according to the complexity, impact, and budget of the study. To this end, the promoter, in agreement with the coordinating investigator, determined the logistic and impact score that made it possible to obtain the high level of monitoring to be implemented on the research.

13.2 Quality control

A CRA appointed by the sponsor will be responsible for the proper conduct of the research, for collecting and documenting, recording and reporting the data generated in writing, in accordance with the Standard Operating Procedures applied within the DRCI and in accordance with the French Good Clinical Practices as well as with the legislative and regulatory provisions in force.

The investigator and the members of the investigator's team agree to make themselves available during Quality Control visits carried out at regular intervals by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the research protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

13.3 Case Report Form

Electronic CRF:
All information required according to the protocol must be entered in the case report forms. The data must be collected as and when they are obtained and clearly recorded in these case report forms. Each missing data item must be coded.
This digital case report form will be implemented in each center's thanks to a web-based data collection medium. Investigators will be given a document offering guidance in using this tool.
When the investigators complete the case report via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality, and relevance of all the data entered. Also, the data are immediately verified as they are entered, thanks to consistency checks. Thus, the investigator must validate any changes to the values in the case report form. These modifications will be subject to an audit trail. A justification can be added when applicable as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the research. The investigator must archive a copy of the certified document that was delivered to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance by the investigator or any other individual involved in conducting the research, with the protocol, with the standard operating procedures, with the good clinical practices, or with the legislative and regulatory provisions in force must be noted in a declaration of non-compliance addressed to the sponsor. As a first step, major or critical non-compliances will be reviewed and processed by the DRCI's medical coordinator in order to implement the necessary corrective or preventive actions. Next, the non-compliances will be sent to the Quality - Risk Management Division of the DRCI for verification and analysis. These verifications could result in the investigator in charge of the research location in question being asked for information or could lead to compliance or audit visits.

13.5 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data,

documents, and reports may be subject to regulatory audits and inspections. Medical secrecy cannot be invoked in opposition to these audits and inspections.

An audit can be carried out at any time by individuals appointed by the sponsor and who are not associated with the research directors. The objective of the audit is to ensure the quality of the research, the validity of the results, and compliance with the legislation and regulations in force.

The individuals who lead and monitor the research agree to comply with the sponsor's requirements and with the competent authority regarding research audits or inspections.

The audit may be applicable to all stages of the research, from the development of the protocol to the publication of the results and the organization of the data used or produced as part of the research.

13.6 Primary investigator's commitment to assume responsibility

Before starting the research, each investigator will give the sponsor’s representative a copy of his/her personal curriculum vitæ, signed and dated, with his/her number in the RPPS (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will undertake to comply with the legislation and to carry out the research according to French GCP, adhering to the Declaration of Helsinki terms in force.

The primary investigator at each participating center will sign a responsibility commitment (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their employees will sign a delegation of duties form specifying each person's role.

13.7 Pharmacist's commitment to assume responsibility

Pharmacists from the various recruiting centers will each sign a commitment of responsibility for the trial. They will be responsible for all their collaborators who will be involved in the preparation of the UTs and their dispensing.

14. ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for obtaining information and consent from research participants

In accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research can be carried out on a person without free and informed consent, obtained

in writing after the person has been given the information specified in Article L.1122-1 of said Code.

An initial consent for the patient may be requested in the event that the patient is able to provide informed consent, which is unlikely given the seriousness of COVID-19 and the emergency situation.
The second permits, in the event that it is impossible for the person sought to consent in writing, the collection of the consent in order of priority by the trusted person, a family member, or, failing that, by a close relative. These should be completely independent of the investigator and sponsor.
The third permits the patient's consent, as soon as his or her condition permits, for the continuation of the research.
However, if no consent could be obtained for the inclusion of the patient, in this particular context of a medical emergency, the law allows the inclusion of the patient without his or her consent or that of a trusted person or family member (in the absence of the latter). Patients with ARDS related to COVID-19 are unable to receive information and give written consent in the initial phase. They are sometimes urgently ventilated invasively and sedated to treat life-threatening distress. It is likely that most subjects will not be in a position to give consent at the time of inclusion. The possibility of emergency consent is therefore provided for. The patient is informed as soon as possible, and his consent is requested for the continuation of the research and the use of the data (Law 2004-806 of 09 August 2004, Art L1122-1-2 and Art L 1111-6).
The briefing note and a copy of the consent form, dated and signed by the individual who participates in the research and by the investigator or the physician representing him or her, shall be given to the individual before participation in the study.
Also, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his or her consent, or the consent of any other person in the cases provided for in Articles L. 1122-1-1 to L. 1122-2 of the CSP and the procedures for providing the information to collect it. He or she shall retain the original copy of the dated and signed consent form.
A copy of this document is given to the research participant. The investigator should keep the original copy in his/her archives for a minimum of 15 years. The third copy is archived by the promoter.

14.2 Subject prohibited from participating in another research or an exclusion period anticipated after the study, if applicable

At the end of the subject's participation, a period of exclusion of 28 days is defined within the framework of this research.
During participation, the subject may not participate in any other intervention research protocol involving the human subject without first discussing the matter with the physician who is following him or her in the research.

14.3 Compensation for subjects

There is no anticipated compensation for subjects.

14.4 Registration on the national register of subjects participating in biomedical research relating to the products listed in Article L. 5311-1 of the French Public Health Code

Patients included in the trial will not be included in the national register of subjects participating in biomedical research.

14.5 Legal obligations

14.5.1 The sponsor's role

Assistance Publique - Hôpitaux de Paris (Le GHU Paris Psychiatrie et Neurosciences) is the sponsor of this research, and by delegation, the Clinical Research and Innovation Office (DRCI) carries out the research's missions in accordance with Article L.1121-1 of the French Public Health Code. Assistance Publique - Hôpitaux de Paris reserves the right to halt the research at any time for medical or administrative reasons. In this case, notification will be sent to the investigator

14.6 Request for an opinion from the Comité de Protection des Personnes (CPP, ethical review board)

Le GHU Paris Psychiatrie et Neurosciences, as sponsor, obtains for this biomedical research relating to medication for human use and prior to starting the study, the favorable opinion of the appropriate CPP, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

14.7 Request for authorization to ANSM

Le GHU Paris Psychiatrie et Neurosciences, as sponsor, obtains for this biomedical research relating to medication for human use and, prior to starting the study, authorization from the ANSM, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

14.8 Commitment to compliance with the MR 001 "Méthodologie de Reference"

Le GHU Paris Psychiatrie et Neurosciences, the research sponsor, has signed a commitment to comply with this "Méthodologie de reference".

14.9 Request for the opinion of the CCTIRS (advisory committee on the processing of research information in the area of health) and request for authorization from CNIL (French data protection authorities)

Not applicable.

14.10 Standard declaration to the CNIL

Not applicable.

14.11 Modifications to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain a favorable opinion from the CPP and authorization from the ANSM within the scope of their respective authorities prior to starting the research.
The information sheet and the consent form can be revised if necessary, in particular, if there is a substantial modification to the research or if adverse reactions occur.

14.12 Final research report

The final biomedical research report referred to in Article R1123-60 of the French Public Health Code is drawn up and signed by the sponsor and the investigator. A summary of the report written according to the competent authority's reference plan will need to be sent to the competent authority and ethical review board within one year after the end of the research, meaning the end of the participation of the last research subject.

15. FUNDING AND INSURANCE

15.1 Funding source

GHU Paris Psychiatrie et Neurosciences.

15.2 Insurance

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide total compensation for all harmful consequences of the research for the research subjects and their beneficiaries unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against said compensation.

The GHU Paris - Psychiatry and Neurosciences has taken out an insurance policy with the SHAM company, guaranteeing its civil liability as well as that of any participant (doctor or staff involved in carrying out the research), in accordance with the article L.1121-10 of the CSP.

16. PUBLICATION RULES

The GHU Paris must obligatorily be mentioned in the affiliations of the author(s) of the publications resulting from this research and cite the promoter GHU Paris (DRCI).

16.1 Mention of the affiliation of Le GHU Paris Psychiatrie et Neurosciences for projects sponsored or managed by Le GHU Paris Psychiatrie et Neurosciences

The institution GHU Paris must appear under the acronym "GHU Paris" first in the address.

16.2 Mention of the Le GHU Paris Psychiatrie et Neurosciences manager (DRCI) in the acknowledgments of the text

- ”The sponsor was GHU Paris – Psychiatrie et Neurosciences.

16.3 Mention of the financier in the acknowledgments of the text

”The research was funded by a grant from le GHU Paris Psychiatrie et Neurosciences.”

This research has been registered on the website http://clinicaltrials.gov/ under number *registration number*. NCT04350580

List of abreviations

COVID-19 Coronavirus Disease due to SARS-CoV-2
ARDS Acute respiratory distress syndrom
IVIG Intravenous Immunoglobulin
SARS-CoV-2 severe acute respiratory syndrome virus number. 2
ACE2 AngiotensinII converting enzyme
IL Interleukin
PaO2 partial pressure of oxygen in arterial blood
FiO2 fraction of oxygen in inhaled. Gaz
PEEP positive end expiratory pressure
IMV invasive mechanical ventilation
SOFA Sequential Organ Failure Assessment (SOFA
CTCAE Common Terminology Criteria for Adverse Events
ADL Activities of daily living
IADL Instrumental activities of daily living
CT computed tomography
CAM-ICU Confusion assessment method for the intensive care unit
ICU Intensive Care Unit
VAP ventilator acquired pneumonia
D Day
PCR Polymerase Chain Reaction
CRF Clinical report Form
ANSM Agence nationale de sureté du médicament
CPP Comité de protection des personnes
TRALI Transfusion associated Lung Injury
DSMB Data safety monitoring board
SAE Severe Adverse. Event
CNIL Commission national de l'informatique et des libertés
CRA Clinical Research Associates
BPC Bonnes pratiques cliniques

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LIST OF ADDENDA

Each addendum and the addendum version record are attached, independent of the protocol. Each addendum can be modified (change of addendum version) without changing the protocol version.

Annexe 1 Score des défaillances viscérales SOFA[34]

SOFA SCORE	**1**	**2**	**3**	**4**
Respiration *PaO2 :FiO2*	<400	<300	<200*	<100*
Coagulation *Plaquettes* *x10^3/mm^3*	<150	<100	<50	<20
Foie *Bilirubine, mg/dl (µmol/l)*	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (>204)
Cardiovasculaire *Hypotension*	MAP<70 mm Hg	Dopamine ≤5 γ/kg/min ou Dobutamine	Dopamine >5 γ/kg/min ou adrénaline ou noradrénaline ≤0.1 γ/kg/min	Dopamine >15 γ/kg/min ou adrénaline ou noradrénaline >0.1 γ/kg/min
Neurologique *Glasgow*	13-14	10-12	6-9	>6
Rénal *Créatinine, mg/dl (µmol/l) ou diurèse*	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or < 500 ml/jour	>5.0 (>440) or <200 ml/jour

*** avec assistance respiratoire**

Annexe 2 Lung injury score

	Score
Chest radiograph	
No alveolar consolidation	0
Alveolar consolidation confined to 1 quadrant	1
Alveolar consolidation confined to 2 quadrants	2
Alveolar consolidation confined to 3 quadrants	3
Alveolar consolidation confined to 4 quadrants	4
Hypoxaemia score	
PaO_2/FiO_2 ⩾300	0
PaO_2/FiO_2 225–299	1
PaO_2/FiO_2 175–224	2
PaO_2/FiO_2 100–174	3
PaO_2/FiO_2 <100	4
PEEP score (when mechanically ventilated)	
⩽5 cm H_2O	0
6–8 cm H_2O	1
9–11 cm H_2O	2
12–14 cm H_2O	3
⩾15 cm H_2O	4
Respiratory system compliance score (when available)	
⩾80 ml/cm H_2O	0
60–79 ml/cm H_2O	1
40–59 ml/cm H_2O	2
20–39 ml/cm H_2O	3
⩽19 ml/cm H_2O	4
The score is calculated by adding the sum of each component and dividing by the number of components used.	
No lung injury	0
Mild to moderate lung injury	0.1–2.5
Severe lung injury (ARDS)	>2.5

Annexe 3

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

_____

† CTCAE v4.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

Annexe 4 Activities of a daily living scale

ECHELLE A.D.L **(Aide-soignante Infirmière)**	**1ère évaluation** **Date :** **Score:**	**2ème évaluation** **Date :** **Score:**	**3ème évaluation** **Date :** **Score:**
HYGIENE CORPORELLE			
. autonomie	**1**	**1**	**1**
. aide	**½**	**½**	**½**
. dépendant(e)	**0**	**0**	**0**
HABILLAGE			
. autonomie pour le choix des vêtements et l'habillage	**1**	**1**	**1**
. autonomie pour le choix des vêtements, l'habillage mais a besoin d'aide pour se chausser	**½**	**½**	**½**
. dépendant(e)	**0**	**0**	**0**
ALLER AUX TOILETTES			
. autonomie pour aller aux toilettes, se déshabiller et se rhabiller ensuite	**1**	**1**	**1**
. doit être accompagné(e) ou a besoin d'aide pour se déshabiller ou se rhabiller	**½**	**½**	**½**
. ne peut aller aux toilettes seul(e)	**0**	**0**	**0**
LOCOMOTION			
. autonomie	**1**	**1**	**1**
. a besoin d'aide	**½**	**½**	**½**
. grabataire	**0**	**0**	**0**
CONTINENCE			
. continent(e)	**1**	**1**	**1**
. incontinence occasionnelle	**½**	**½**	**½**
. incontinent(e)	**0**	**0**	**0**
REPAS			
. mange seul(e)	**1**	**1**	**1**
. aide pour couper la viande ou peler les fruits	**½**	**½**	**½**
. dépendant(e)	**0**	**0**	**0**
TOTAL			

Annexe 5 - IADL-4

Echelle d'activités instrumentales de la vie quotidienne : version courte à 4 items (d'après Lawton & Brody)

MODE D'EMPLOI

Cette échelle doit être remplie par un membre du personnel médico-social en utilisant une ou plusieurs des sources d'informations suivantes : le malade, sa famille, ses amis. Choisir la réponse qui correspond le mieux aux capacités du sujet. On peut s'aider du questionnaire situé au verso.
Les 4 activités font l'objet d'une cotation en 3, 4 ou 5 points selon les items. Dans un deuxième temps, la cotation de chacun des items est transformée en codage binaire 0 ou 1.
Codez 0 tout item pour lequel le sujet est autonome (la cotation ne dépasse pas 1).
Codez 1 tout item pour lequel le sujet est dépendant (la cotation est supérieure ou égale à 2)
Nom : Prénom :
Date :

CAPACITÉ À UTILISER LE TÉLÉPHONE

1. Utilise le téléphone de sa propre initiative, cherche et compose les numéros, etc.
2. Compose un petit nombre de numéros bien connus.
3. Répond au téléphone, mais n'appelle pas.
4. Incapable d'utiliser le téléphone.

MOYEN DE TRANSPORT

1. Peut voyager seul(e) et de façon indépendante (par les transports en commun ou avec sa propre voiture).
2. Peut se déplacer seul(e) en taxi, pas en autobus.
3. Peut prendre les transports en commun si accompagné(e).
4. Transport limité au taxi ou à la voiture, en étant accompagné(e).
5. Ne se déplace pas du tout.

RESPONSABILITÉ POUR LA PRISE DES MÉDICAMENTS

1. S'occupe lui (elle)-même de la prise : dosage et horaire.
2. Peut les prendre lui (elle)-même, s'ils sont préparés et dosés à l'avance.
3. Incapable de les prendre lui (elle)-même.

CAPACITÉ À GÉRER SON BUDGET

1. Totalement autonome (gérer le budget, faire des chèques, payer des factures, ...).
2. Se débrouille pour les dépenses au jour le jour, mais a besoin d'aide pour gérer son budget à long terme (pour planifier les grosses dépenses).
3. Incapable de gérer l'argent nécessaire à payer ses dépenses au jour le jour

Guide d'utilisation pratique des 4 IADL

1) Répondez-vous au téléphone sans difficulté ? ☐ OUI ☐ NON

2) Appelez-vous seul au téléphone quelques numéros connus ? ☐ OUI ☐ NON

3) Cherchez-vous vous–même des numéros dans l'annuaire (ou 118 ou Internet) ? ☐ OUI ☐ NON

4) Conduisez-vous votre voiture ? ☐ OUI ☐ NON

5) Utilisez-vous seul les transports en commun ? (bus, train, avion)? ☐ OUI ☐ NON

6) Allez-vous sans problème dans des endroits inconnus ? ☐ OUI ☐ NON

7) Comment vous organisez-vous pour la prise de vos médicaments ?
Je les prépare et les prends moi-même (dosage et horaire corrects)
On me les prépare d'avance
On doit me faire penser à les prendre

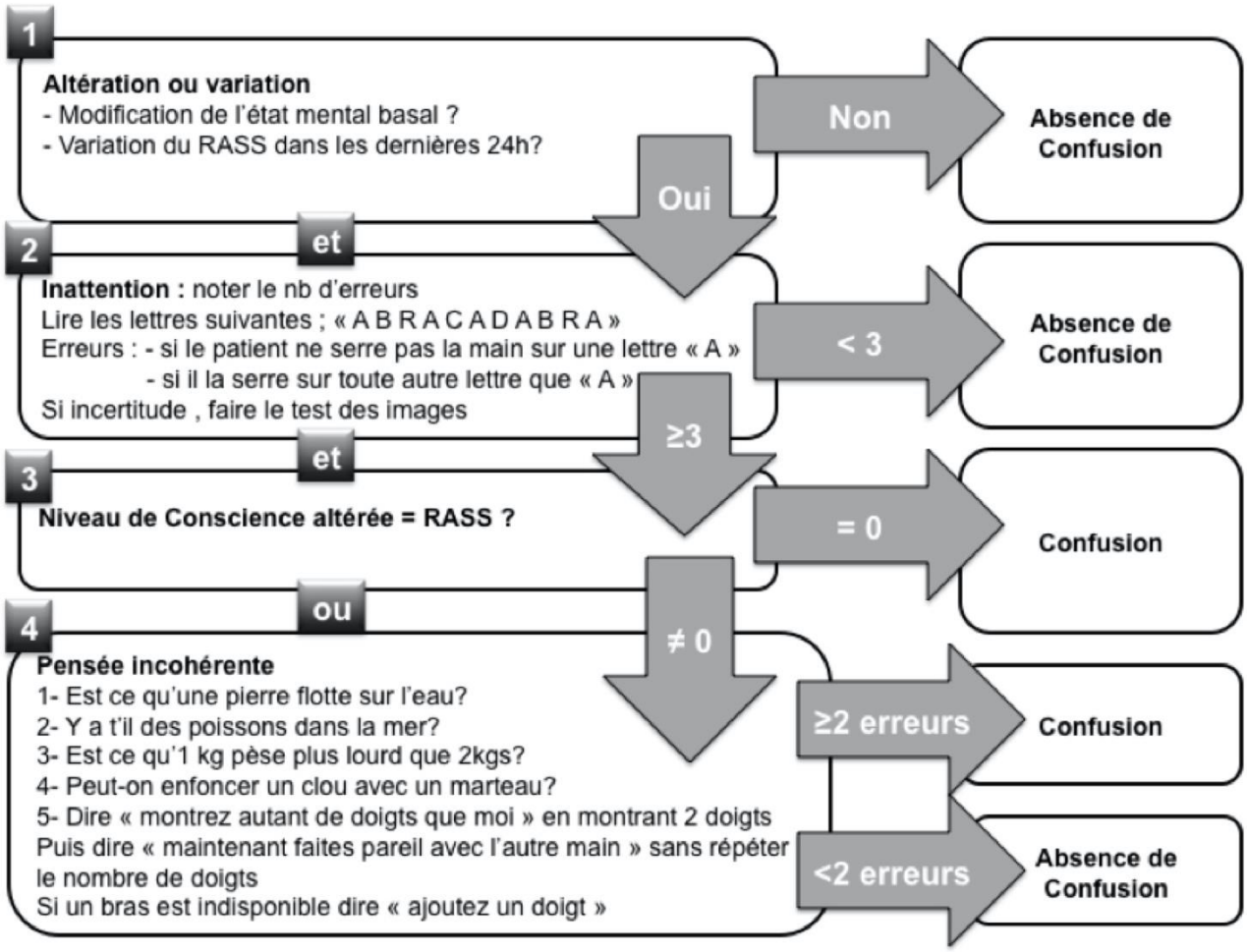
8) Les oubliez-vous souvent ? ☐ OUI ☐ NON

9) Comment réglez-vous vos achats ?
J'utilise des chèques, ma carte bancaire ou l'argent liquide sans problème
Je ne règle jamais moi-même aucun achat

10) Est-ce que vous payez vous-même vos factures ? ☐ OUI ☐ NON

11) Est-ce que vous avez besoin d'aide pour gérer votre budget ? ☐ OUI ☐ NON
OUI (gère seulement les dépenses au jour le jour) NON

Annexe 6 Score *Confusion Assessment Method for Intensive Care Unit* CAM-ICU



Le score de CAM-ICU[2] permet un diagnostic rapide de syndrome confusionnel en réanimation à l'aide de 4 critères: 1) Rapidité d'installation ou fluctuation 2) Inattention 3) La désorganisation de la pensée 4) Altération du niveau de conscience. La présence des critères 1 et 2 puis 3 ou 4 est nécessaire au diagnostic de syndrome confusionnel. C'est un outil diagnostique consensuel de syndrome confusionnel présentant une sensibilité et spécificité élevés, une faible variabilité inter-observateur et une valeur clinique majeure. Dans une étude réalisée par Ely *et al.* la présence d'une confusion attestée par ce score montrait une mortalité à 6 mois après sortie de réanimation plus élevée dans le groupe de patient présentant une confusion (hazard ratio, 3.2; 95% intervalle de confiance a 95%, 1.4 à 7.7; p = .008)[2].

Annexe 7 Medical Research Council score

Muscle group evaluated

- Wrist extension
- Elbow flexion
- Shoulder abduction
- Dorsiflexion foot
- Knee extension
- Hip flexion

Appointed score

- 0, no visible/palpable contraction
- 1, visible/palpable contraction without movement of the limb
- 2, movement of the limb, but not against gravity
- 3, movement against gravity
- 4, movement against gravity and some resistance
- 5, normal

Each muscular group from each side is evaluated. The quotations are added to each other. The MRC sum score ranges from 0 to 6, 48 being the threshold for ICU acquired weakness.

<u>Annexe 8</u> : tableau de calcul du score de IGS II *(indice de gravité simplifié)*

Entrée	Chir urgente :8 pts		Médecine : 6 pts		Chir programmée	
Age (ans)	<40 :0 pt	40 – 59 :7 pts	60 – 69 : 12 pts	70 – 74 : 15	75 – 79 : 16 pts	>80 :18
Température (°c)	<39 :0 pt				>39 : 3 pts	
Urée (mmol/L)	<10 :0 pt	10 – 29,9 :6pts	>30 : 10 pts			
Na (mEqL)	125 _ 144 : 0 pt	>145 : 1 pt	<125 :5 pts			
Maladie chronique	Aucune :0 pt	Cancer métastasé :9	Mal hémato :10	SIDA : 17 pts		
PAs (mmHg)	<70 : 13 pts	70 – 99 : 5 pts	100 – 199 : 0 pt	>200 : 2 pts		
GB / mm^3	<1000 :12 pts	1000 – 19000 :0 pt	>20000 : 3 pts			
Bicar (mEq/L)	>20 :0 pt	15 – 19 :3 pts	<15 :6 pts			
Glasgow	<6 :26 pts	6 – 8 :13 pts	9 – 10 : 7 pts	11 – 13 : 5 pts	14 – 15 : 0 pt	
FC / mn	<40 : 11 pts	40 – 69 :2 pts	70 – 119 :0	120 – 159 : 4 pts	>160 : 7 pts	
Diurèse (L/24h)	<0,5 :11 pts	0,5 – 0,99 : 4 pts	>1 :0 pt			
K+ (mEq/l)	<3 :3 pts	3 – 4,9 :0 pt	>5 :3 pts			
Bilirubine (µom/L)	<68,4 : 0 pts	68,4 – 102,6 : 4 pts	>102,6 : 9 pts			

Annexe 9 Kidney Disease: Improving Global Outcomes – Grading of Acute Kidney Injury

Stage	Serum creatinine	Urine output
1	1.5-1.9×baseline or ≥0.3 mg/dl (≥26.5 mmol/l) increase	<0.5 ml/kg/h for 6-12 h
2	2.0-2.9×baseline	<0.5 ml/kg/h for >12 h
3	3.0×baseline, or increase in serum creatinine ≥4.0 mg/dl (≥353.6 mmol/l), or initiation of RRT, or decrease in eGFR <35 ml/min/1.73 m^2 for patients <18 years	<0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

KDIGO: Kidney disease: Improving global outcomes; RRT: Renal replacement therapy; eGFR: Estimated glomerular filtration rate

Annexe 10 Response to reviewers

We thank the reviewers for their evaluation of the project. The reviewers suggested us to link our study to other existing trials such as CORIMMUNO or DISCOVERY. We would have been delighted to participate to these trials. Unfortunately, our solicitations did not allow us to participate to the trial.

Concerning the inclusion criteria, the reviewer number 2 suggested that the ARDS criteria should be homogenized. We propose to study patients with COVID-19 related ARDS. The IGIV could present beneficial effects on the late phase of SARS-CoV-2 when the immune response is overwhelming to lower the intensity of the cytokinic storm. Based on the availability and cost of IgIV, such treatment could not be evaluated in the entire population of patients presenting COVID-19. We thus chose to focus on a subpopulation of patients with a severe COVID-19.
The 2012 "Berlin" definition of acute respiratory distress syndrome (ARDS) distinguishes, according to the PaO_2/FiO_2 ratio measured in the presence of a positive external expiratory pressure (PEEP) of at least 5 cmH2O, three levels of severity of ARDS: minimal (200 < PaO2/FiO2 ≤ 300 mmHg), moderate (100 < PaO2/FiO2 ≤ 200 mmHg) and severe (PaO2/FiO2 ≤ 100 mmHg).
We therefore determined that the effectiveness of IVIG should be evaluated when mechanical ventilation for moderate to severe ARDS is introduced. We will use a PCR technique to diagnose an SARS-CoV-2 infection and the conventional Berlin definition of adult respiratory distress syndrome.

The benefits of a new therapy in COVID-19 are to increase the survival rate and to reduce the duration of mechanical ventilation, which is associated with is also significant morbidity. On a collective scale, reducing the duration of mechanical ventilation will increase the availability of ventilators and ICU beds to limit the shortage observed during the SARS-CoV-2 pandemic. We chose the ventilation free days at day 28 as a main outcome for two main reasons. (1) This outcome has been used in the evaluation of treatment of the ARDS by corticosteroids. (2) This outcome is composite integrating both mortality and the duration of mechanical ventilation. This outcome is then important both on an individual but also collective point of view. The risk of evaluation bias concerning the number of ventilation free days at day 28 is low as both its components are objectively collected, i.e. the duration of mechanical ventilation and survival. As a secondary analysis, each component will be evaluated independently. The duration of mechanical ventilation could depend on clinical judgement as the moment of mechanical weaning and extubation may show inter-operator variability. To prevent this, the attending physicians will be blind to the arm allocation. Also, to prevent imbalance across centers with slightly different standards for mechanical ventilation weaning, the randomization will be stratified on centers.

Reviewer number 4 did not raise any question

We thank the reviewer number 7 for his suggestions and questions. Reviewer 7 raised the question of the size of the expected effect IVIG, the fact to include de novo 126 patients and raised the issue of the use of corticosteroids.

The reviewer 7 suggested us to link our study to other existing trials such as CORIMMUNO or DISCOVERY so as not to include de novo 126 patients. We would have been delighted to participate to these trials. Unfortunately, our solicitations did not allow us to participate to these trials.
Concerning the number of patients to be included according to the size effect, we hypothesize that the number of days without IMV is 10 days in the placebo group and 15 days in the experimental group with a standard deviation of 6 days, considering a mortality of 50% and

40% in the placebo and experimental groups respectively (26, 27). The number of days without IMV in the placebo group is (50% x 10 D) + (50% x 0 D) or 5 D on average, and following the same calculation for the experimental group of (60% x 15 D) + (40% x 0 D) or 9 D.

Therefore, a mean value of 5 days without ventilation in the placebo group versus 9 in the experimental group is assumed, and the 6-day standard deviation is assumed to be stable. Given the uncertainty regarding the assumption of normality of distributions, the non-parametric Wilcoxon-Mann-Whitney test (U-test) was used for the estimation of the sample size. Considering a bilateral alpha risk of 5% and a power of 90% and an effect size of 0.6, the number of subjects to be included is 138 patients, 69 in each arm.

In our opinion, a 4-day reduction in IMV duration is a reasonable clinical objective. Showing a more modest effect on the number of ventilation free days at day 28 could raise the question clinical relevancy of such effect. More recently, one multicentric retrospective study including 325 patients has been submitted to the MedRxiv repository suggesting that a high dose (>15g/day) initiated in the first 7 days of mechanical ventilation could reduce COVID-19 mortality from 53% to 27% (p=0.009, 13). Besides the fact that such publication has not been peer-reviewed, these results support the size of the effect of IVIG we hypothesized in the ICAR Trial.

Finally, a recent trial suggests that corticosteroids could present a survival benefit of ARDS before the COVID-19 crisis. We therefore considered that corticosteroids could represent a standard of care of ARDS. Thus, the administration of corticosteroids will be allowed concomitantly with the use of IGIV and will be collected through the study. Recently, it has been mentioned in a news release that corticosteroids could present a survival benefit on COVID-19 related ARDS. If this would be verified, we would include steroids as a standard of care and evaluate the use of IVIG as an adjunctive treatment to corticosteroids. A post-hoc analysis will be conducted evaluating the interaction between the effects of corticosteroids and the effects of IVIG.

Study Protocol

Effect of early treatment with polyvalent immunoglobulin on acute respiratory distress syndrome associated with SARS-CoV-2 infections

ICAR (IgIV in Covid-related ARds)

Summary of Changes

The substantive changes to the protocol are reported; additional non-substantive changes have been made and highlighted in italics and blue color in the latest protocol version.

Amendment	**Modifications**	**Justification**	**Modified sections**
Amendment No. 1 (04/05/2020)	Two-Month Lengthening of the Inclusion Period	A slowdown in enrollment rate was observed in the study because of decreasing COVID-19 patients admitted to the intensive care unit. The initial duration of one month planned for the inclusions is becoming insufficient to reach the objective of inclusions.	5.4 6.3
	Extending the patient's duration of mechanical ventilation before inclusion to 72 hours instead of the originally planned 36 hours	The maximum IMV duration of 36 hours for patient inclusion does not appear compatible with the study treatment's hospital pharmacies' provision. This duration is therefore extended to 72	4.2.4 6.1 7.1.1
	Clarification on the non-inclusion criterion related to renal failure	In order to avoid any ambiguity about this non-inclusion criterion, it has been specified that the patients suffering from acute renal failure will not be included in the trial. However, patients suffering from chronic renal failure on dialysis may be included.	6.2

Amendment	Modifications	Justification	Modified sections
Amendment No. 2 (29/05/2020)	Clarification Regarding Use of Deceased Patient Data Included in an Emergency Clause	It was verified during the trial that some patients included with an "emergency clause" died without being able to give their consent. Therefore, a protocol section was added to specify the conditions under which data from these patients could be used.	13.1
	Inclusion also of protected patients (under tutorship and curatorship)	In response to questions from participating centers, it was clarified that protected patients who meet the eligibility criteria would also be included in the study. The tutor will collect the informed consent developed for this purpose for the protected patients and, if necessary, used it to regularize the protected patients' inclusion. In the case of patients under tutelage, the patient's consent will be obtained, and the tutor will be informed using a letter mentioning the inclusion of his/her protégé in the trial.	13.1
	Modification of the Flow Cytometry Loading Center and Cytokine Profile related to the Ancillary Study	The center in charge will be the Cochin Hospital and no the Pasteur Institute	4.7

Amendment	Modifications	Justification	Modified sections
Amendment No.3 (11/06/2020)	Change in the study design with the addition of the "Sequential Methodology." Scheduling an interim futility analysis on the first 50 patients with a 28-day assessment performed. A Data Monitoring Committee (DMC) was constituted to evaluate the interim analysis safety and efficacy results and provide recommendations for the continuation of the study.	The sponsor promoted the amendment in the evidence of the difficulties in recruiting patients. At the end of the first pandemic wave, the rate of inclusion in the study was less than one patient per week. For this reason, it was considered necessary to verify the futility of the hypotheses to discontinue or not prematurely the study.	3.2.1 4.8.4 9.4 11.1 11.2 11.6
Amendment No.4 (10/08/2020)	Extension of the inclusion period to 12 months	An increase in the inclusion period to 9 months (12 months in total) was requested considering the progressive growth in the number of inclusions, suggesting a possible second pandemic wave in the fall. This extension of the inclusion period will allow the number of patients envisioned in the protocol to be reached.	4.4
Amendment No.5 (07/10/2020)	Three further experimental centers added		3.2.2
	A second interim analysis when 100 patients (50 in the IVIG group and 50 in the placebo group) have completed their 28-day assessment	The amendment was carried out in accordance with the recommendations of the Data Monitoring Committee members	Not implemented(*)

Amendment	Modifications	Justification	Modified sections
Amendment No.6 (07/10/2020)	Inclusion continuation until at least 69 patients will be randomized in each arm (experimental arm and placebo arm) as planned in the study.	The Data Manager in charge of the ICAR study monitoring reported that in the last two weeks, patient enrollment in the ICAR study increased significantly due to the health situation regarding COVID 19. However, the data manager notes that this significant increase in inclusions occurred simultaneously in a large number of centers. The data manager also reported that the last 20 inclusions were mainly concentrated in one of the two experimental arms, causing a significant imbalance. Although rare, given the randomized block design of random size (2 and 4), this situation can occur. There was an imbalance of 14 patients between the two experimental arms (62 patients versus 76). A total of 137 patients had been randomized out of the 138 planned in the protocol. In order to ensure the protocol-predicted power of the test, continued enrollment was requested to reach at least 69 patients in both arms as planned. It is understood that all recruited and randomized patients will be included in the outcome analysis.	12.1

(*) The amendment had been submitted to the CPP after the DMC's report following the results of the first interim analysis (document shown in Annex 1). After the amendment submission, there was a significant acceleration of the study inclusions due to the second critical pandemic peak recorded in France, beginning in the second half of October. When consulted about the usefulness of proceeding with the second interim analysis, the DMC recommended that it not be carried out and that the study should continue according to the protocol. The DBM's response is attached as Annex 2.

Data monitoring committee (DMC)
November 9, 2020 – closed session

To the Chair of the Trial Steering Committee

Subject: "Polyvalent Immunoglobulin in COVID-19 Related ARds (ICAR)" protocol NCT #04350580

The objective of the ICAR study is to evaluate the efficiency of an early treatment (within 72h of mechanical ventilation) with polyvalent immunoglobulin in the management of Acute Respiratory Distress Syndrome associated with SARS-CoV-2 infections on ventilator-free days in comparison to placebo.

As requested, and in order to respond quickly to the sponsor's solicitation, the DMC met on November 9, 2020 to review the study progress. Dr Guillaume Turc, chair, Dr Franck Verdonk, secretary, Prof. Raphaël Porcher, statistician and Prof. Antoine Roquilly, clinician attended the meeting and reviewed the report.

During its last meeting, the DMC recommended an additional interim analysis after the inclusion of 100 patients. However, due to a steep increase in enrollment related to the epidemic situation in France, the target recruitment of ICAR (148 patients) has already been achieved at the time of the present DMC meeting.

On the question: "*Does it make sense to maintain the second interim analysis on D28 of the 100th patient included following the DSMB recommendations?"* and considering the completion of the recruitment, the DMC recommends to skip this interim analysis (which was previously suggested owing to the slow accrual rate), and to only perform the final analysis as soon as all included patients have reached their D28 evaluation.

On the question: "*Should the second interim analysis be postponed until D28 of the last patient included in the trial",* the DMC recommend continuation of the current version of the protocol with no changes.

From a statistical point of view, the DMC recommends to analyze time-to-event data using appropriate methods for censored data (e.g., Cox model), adjusted for relevant factors, and to avoid computing odds ratios for event rates when follow-up is different among trial participants.

Sincerely,

The DMC members:
Dr Guillaume Turc, chair,
Dr Franck Verdonk, secretary,
Prof. Raphaël Porcher, statistician
Prof. Antoine Roquilly, clinician

ICAR trial Data monitoring committee (DMC)
September 1st, 2020 – closed session

To the Sponsor and the Chair of the Trial Steering Committee

Subject: "Polyvalent Immunoglobulin in COVID-19 Related ARds (ICAR)" protocol NCT #04350580

The objective of the ICAR trial is to evaluate the efficiency of an early treatment (within 72h of mechanical ventilation) with polyvalent immunoglobulin in the management of Acute Respiratory Distress Syndrome associated with SARS-CoV-2 infections on ventilator-free days in comparison to placebo.

As requested, the DMC met on September 1, 2020 for an interim review of the trial's progress and the results. Dr Guillaume Turc, chair, Dr Franck Verdonk, secretary, Prof. Raphael Porcher, statistician and Prof. Antoine Roquilly, clinician attended the meeting and reviewed the report.

On the question: "*does it make sense to continue the study in view of the results of the interim analysis?*", and after evaluation of unblinded data about safety and adverse events, the DMC recommends continuation of the trial, without modification of the methodology.

On the question: "*due to longer mechanical ventilation time than initially expected, should the investigators change the primary outcome: "number of ventilator-free days" until day 28?*", the DMC recommends continuation of the trial with no changes regarding the primary outcome.

On the question: "*does the calculated mortality constitute a deviation from standard care?*", the DMC considered that a mortality from 35.7% to 19.2% at 28d and from 26.9% to 50% at 90d is not a deviation from standard of care in this context.

On the question: "*should the investigators unblind the data for safety reasons?*", the DMC recommend continuation of the current version of the trial protocol with no changes.

On the question: "*should the trial design be adapted by changing the randomization ratio from 1:1 to 2:1?*", the DMC recommend continuation of the current version of the trial protocol with no changes.

On the question: "*can the sponsor communicate on the basis of the first results of the intermediate analysis*?", the DMC recommend no communication before the end of the trial.

We suggest that a formal interim analysis be performed and only disclosed to the DMC after the inclusion of 100 patients. To this aim, we recommend that the statistical analysis plan be updated, mentioning the choice of the alpha spending function.

Sincerely,

The DMC members:

Dr. Guillaume Turc, chair
Dr. Franck Verdonk, secretary
Prof. Raphael Porcher, statistician
Prof. Antoine Roquilly, clinician

Statistical Analysis Plan (SAP)
ver. 1.0

EFFECT OF EARLY TREATMENT WITH POLYVALENT IMMUNOGLOBULIN ON ACUTE RESPIRATORY DISTRESS SYNDROME ASSOCIATED WITH SARS-COV-2 INFECTIONS
ICAR (IGIV IN COVID-RELATED ARDS)

Paris 30.06.2020

This statistical analysis plan has been drawn up in accordance with the following guidelines: Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337–2343. doi:10.1001/jama.2017.18556.

Index

1. Administrative information

1.1 Title, trial registration, version and revision

Full study title	Effect of early treatment with polyvalent immunoglobulin on acute respiratory distress syndrome associated with SARS-CoV-2 infections
Acronym	ICAR (IgIV in Covid-related ARds)
Local project number	D20 – P013
Human Subjects Protection Review Board	Approved by Comité de Protection des Personnes (CPP) Ile de France X – GHT Grand Paris Nord Est
EudraCT number	2020-001570-30
Clinicaltrials.gov id	NCT04350580
Study protocol version	3.0, dated 29/05/2020
SAP version	1.0, dated 30/06/2020

1.2 Roles and Responsibility

Author, Statistician	Rossella Letizia Mancusi[1], MD
Senior Statistician	Philippe Aegerter[2], MD, PhD
Principle investigator	Aurélien Mazeraud[3, 4], MD, PHD
Study Chair	Tarek Sharshar [3 4], MD, PHD
Sponsor	Khaoussou SYLLA[1], MD, PHD
Affiliation	1. Délégation à la Recherche Clinique et à l'Innovation – GHU Paris Psychiatrie & Neurosciences 2. GIRCI-IdF, Paris - Université Paris-Saclay, UVSQ, U1018 CESP, Villejuif, France 3. Service de Neuroanesthésie Neuroréanimation, Paris, France. -GHU Paris Psychiatrie & Neurosciences 4. Univeristé de Paris, Paris, France

1.3 Signatures

We, the undersigned, certify that we read this SAP and approve it is adequate in the scope of the main analyses of the ICAR (IgIV in Covid-related ARds) study

Author

Name: MANCUSI Rossella Letizia

…….

Date: 30/06/2020

Senior Statistician

Name: AEGERTER Ph

Date: 30/06/2020

Principle Investigator

Name: MAZERAUD Aurélien

……

Date: 30/06/2020

Study Chair

Name: SHARSHAR Tarek

……

Date: 30/06/2020

Sponsor

Name: SYLLA Khaoussou

……

Date: 30/06/2020

2. Introduction

2.1 Background and rationale

Mid-June 7 500 000 people were infected with coronavirus disease 2019 (COVID-19) worldwide, and 420 000 people died, mainly from acute respiratory distress syndrome (ARDS). No specific pharmacological treatment of COVID-19-related-ARDS is currently available (1).

Pulmonary lesions are related to both the viral infection and an inflammatory reaction. Patients admitted to intensive care unit (ICU) have a cytokinetic inflammatory response and higher plasma concentrations of interleukin (IL) 2, IL 7, IL 10, Granulocyte Colony Stimulating Factor, interferon-inducible protein 10, Monocyte chemoattractant protein-1, macrophage inflammatory protein 1α, and tumor necrosis factor-alpha (2). In the blood, the Number of peripheral CD4 and CD8 T cells appears to be significantly reduced, while their status is hyperactivated. This is evidenced by immunoreactive cytometric profiles for HLA-DR (CD4 3-47%) and CD38 (CD8 39-4%) or by an increase in the proportion of highly pro-inflammatory Th17 CCR6+ lymphocytes. Besides, CD8 T cells would exhibit a highly cytotoxic profile characterized by high concentrations of cytotoxic granules (perforin+, granulysin+ or double-positive) (3).

Because of their immunomodulatory effect that may both attenuate the inflammatory response and enhance antiviral defense, we propose to evaluate the efficacy and safety of intravenous immunoglobulin (IVIG) administration in patients developing COVID-19 related ARDS. IVIG modifies T cells functions but also dendritic cell function and ultimately cytokine and chemokine networks. IVIG stimulates regulatory T cells proliferation that regulates CD4 and CD8 T cell activity (3-5). Also, IVIG restores regulatory T cells functions and modulate lymphocyte populations specifically altered during COVID-19 (3).

In addition, IVIG can modulate humoral acquired immunity through its effect on the idiotypic network and antibody production. IVIG also act on innate immunity by antigen

neutralization and modulation of phagocytic cells. These effects lead to a decrease in the production of pro-inflammatory cytokines and complement activation, key factors in COVID-19 related ARDS (4-7). It should be noted that IVIG is used as a treatment for a variety of autoimmune and inflammatory diseases. Both standard and polyclonal IVIG have significantly reduced mortality in patients with Kawasaki disease (10) and improve outcomes in patients with polyneuropathy (DOI 10.1016/S1474-4422(07)70329-0). More recently, it has been shown that IVIG may have a beneficial effect in diffuse interstitial lymphocytic pneumonitis (6) and post-influenza ARDS (11).

Few low-level of evidence data support the effect of IVIG during COVID-19, this treatment has been described as favorable in 3 cases of COVID-19 related ARDS and one with COVID-19-related myocarditis who received a high dose of intravenous immunoglobulin IVIG at the time of onset of distress, with a favorable clinical course (12, 20). A retrospective study showed a decrease in mortality and ventilation time in patients with ARDS receiving invasive mechanical ventilation (IMV) treated early with a high dose of IVIG (https://doi.org/10.1101/2020.04.11.20061739). Notably, there were no adverse events reported, including no renal impairment or allergic reactions. IVIG is a treatment option if it is well-tolerated, particularly concerning renal function (13). In adults, adverse events reported as possibly related to polyclonal IVIG during septic shock were allergic reactions (14, 15); skin reactions such as erythema and exanthema; pruritus; nausea and vomiting; dyspnea; congestion; shock; and fever (14-18). Two trials reported no adverse events attributable to IVIG, and one trial reported adverse events, but none were ascribed to IVIG, but the cohort size was limited (16, 17, 19).

This promising benefits-risks balance encourages us to rapidly carry out a multicenter, placebo-controlled therapeutic trial testing the benefit of IVIG in COVID-19 related ARDS.

Research hypothesis

The null hypothesis is that there are no differences in Ventilator Free Days at 28 days between the standard of care plus placebo (SOC+placebo) and standard of care plus IGIV (SOC+IVIG) groups. The alternative hypothesis is that there is a difference between the two groups.

2.2. Objectives

2.2.1. Objectives and research questions

Study Objectives

The main objective is to verify if the administration of IVIG at a dose of 2g/kg over four consecutive days up 24-72 hours after the start of IMV, in patients with COVID-19 related ARDS, increases the number of days alive without IMV (ventilator-free days) up to day 28 (D28) after IMV initiation.

VFDs at 28 days is defined as follows:

- VFDs = 0 if subject dies within 28 days of mechanical ventilation
- VFDs = 28-x if the subject is successfully liberated from ventilation x days after initiation
- VFDs = 0 if the subject is mechanically ventilated for 28 days or more

Secondary objectives are:

- Overall Mortality Rate at 28 and 90 days
- Total duration of mechanical ventilation, ventilatory withdrawal, curarization, use of non-invasive ventilation (NIV), high flow oxygen therapy (HFO.) WHO ordinal severity scale
- WHO ordinal scale of severity of COVID impairment

- Organ failures according to the SOFA score achieved at D1, D7, D14, D21, and D28, according to Appendix 6
- Clinical Efficacy Criteria: Radiological score according to the quadrant method, the chest x-ray is divided into 4 quadrants. The existence of alveolar-interstitial opacities in one quadrant adds 1 point to the score. P/F ratio value, lung compliance at D1, D7, D14, D21, and D28
- Biological efficacy endpoints: inflammatory syndrome at D1, D3, D7, D14, D21, and D28 by measuring serum C-reactive protein, procalcitonin, white blood cell count, and d-dimer levels.
- Occurrence of ventilator-associated pneumonia.
- Occurrence of an adverse event related to immunoglobulins (D1, D2, D3, D4, D5, D6 and D7, D14, D21, and D28: KDIGO 3 stage renal failure, hypersensitivity manifestations with cutaneous or hemodynamic manifestations, aseptic meningitis defined by a clinically objectified meningeal syndrome upon awakening, hemolytic anemia (defined by hemoglobin less than 8 g/dL, non-detectable haptoglobin, and a positive direct Coombs test), leukoneutropenia (according to the WHO classification in Appendix X), Transfusion-Related Respiratory Distress Syndrome (TRALI) due to immunoglobulin
- KDIGO score (D1, D7, D14, D21, and D28) and the need for extrarenal purification, the occurrence of clinically detected deep vein thrombosis proven by Doppler ultrasound. Occurrence of a pulmonary embolism detected by a pulmonary angioscan.

Biological efficiency study through the in-depth study of IGIV impact on cytokines, immune cells transcriptome, and lymphocytes activation in an ancillary study

3. Trial Methods

Trial design

The ICAR trial is a Phase III double-blind, multicenter, randomized in parallel-group, placebo-controlled study in hospitalized participants with COVID-19 requiring mechanical ventilation. Patients will be randomized 1:1 to the Investigational arm or the Control arm. Participants randomized to the Investigational arm will receive Ig 2g/Kg administered IV for up to 4 days in addition to the standard of care (SOC), while participants in the Control arm will receive placebo plus SOC. The Sponsor intends to enroll approximately 138 patients that have been diagnosed with SARS-CoV-2 pneumonia and meet the entry criteria in centers globally.

Patients must be at least 18 years of age develop moderate to severe ARDS: according to Berlin classification (REF), with confirmed SARS-CoV-2 infection (by polymerase chain reaction), and receiving invasive mechanical ventilation for less than 72 hours.

Patients with acute renal failure, allergy to polyvalent immunoglobulins, or known Immunoglobulin-A deficiency will be excluded from the study.

Randomization

Patients will be randomly assigned to one of the two treatment arms: IVIG in combination with SOC or placebo in combination with SOC. Randomization will occur in a 1:1 ratio through the use a balanced permuted-block randomization method. The randomization list will be stratified by center and IMV at randomization (<=12 hours, >12 and <=24 hours; >24 and <=72 hours). The randomization list will be carried out by the GHU biostatistician using the R software and incorporated into the e-CRF. A document describing the randomization procedure will be kept confidentially in the DRCI of the GHU Paris.

Sample size

We hypothesize that the number of days without IMV is 10 days in the placebo group and 15 days in the experimental group with a standard deviation of 6 days for discharged alive patients, considering mortality of 50% and 40% in the placebo (i.e., 0 D according to the

definition of VFD) and investigational groups respectively. The number of days without IMV in the placebo group is (50% x 10 D) + (50% x 0 D) or 5 D on average, and following the same calculation for the experimental group of (60% x 15 D) + (40% x 0 D) or 9 D.

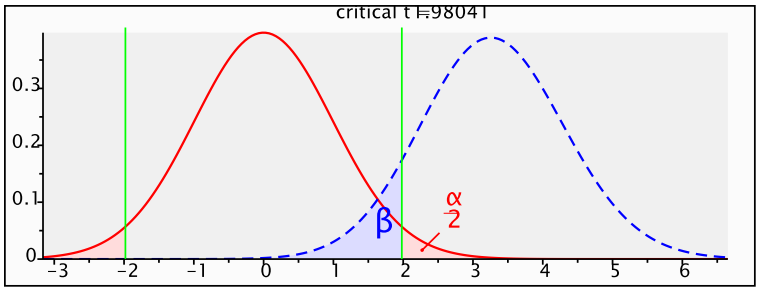
Therefore, a mean value of 5 days without ventilation in the placebo group versus 9 in the experimental group is assumed, and the 6-day standard deviation is assumed to be stable. Given the uncertainty regarding the assumption of normality of distributions, the non-parametric Wilcoxon-Mann-Whitney test (U-test) was used for the estimation of the sample size. Considering a bilateral alpha risk of 5% and a power of 90%, and an effect size of 0.6, the number of subjects to be included is 138 patients, 69 in each arm (Table 1).

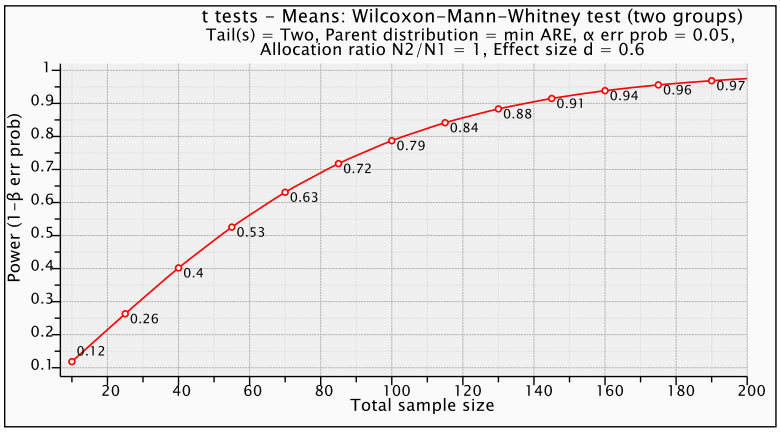
Table 1

Tests - Means: Wilcoxon-Mann-Whitney test (two groups)[1]
Options: ARE method
Analysis: A priori: Compute required sample size

Input:		
Tail(s)	=	Two
Parent distribution	=	min ARE
Effect size d	=	0.6
α err prob	=	0.05
Power (1-β err prob)	=	0.90
Allocation ratio N2/N1	=	1
Output:		
Noncentrality parameter δ	=	3.28
Critical t	=	1.980
Df	=	117.232
Sample size group 1	=	69
Sample size group 2	=	69
Total sample size	=	138
Actual power	=	0.90

1 The estimate using G*Power Ver. 3.1.9.4. (Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods, 39, 175-191)





Framework

All efficacy outcomes will be tested for superiority in ITT.

Statistical Interim analysis and stopping guidance

No interim analysis is planned

Timing of final analysis

The final analysis of 28D VFDs is scheduled 90 days after the last randomization.

Timing of outcome assessment

The schedule of study procedures is given in table 2.

Timepoint	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D1 4	D15-20	D2 1	D22-27	D2 8	D9 0
Consent collection													
Pursuit consent collection	x	x	x	x	x	x	x	x	x	x	x	x	
Demographics, medical history, disease characteristics													
Administration of IVIG or Placebo Therapy	x	x	x	x									
Main outcome measurement	x	x	x	x	x	x	x	x	x	x	x	x	
Collection of clinical data	x	x	x	x	x	x	x	x	x	x	x	x	
Complete blood count, blood gas, creatinine	x						x	x		x		x	
Leukocytosis, C-reactive protein, biobank collection	x						x			x			
SOFA score	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x
Final assessment of the primary outcome												x	
Final assessment of secondary outcomes												x	x

4. Statistical principles

Confidence interval and p-values

All applicable statistical tests will be 2-sided and will be performed using a 0.05 significance level, and all confidence interval reported will be 95% and 2-sided.

Adherence and Protocol deviations

Compliance per patient is defined as the ratio of the administered dose to the protocol dose.

Compliance will be assessed based on the percent of patients of scheduled treatment administration.

A total dose of IVIG administered over four days of at least 75% of the intended dose is considered adherent to the protocol.

Non-adherence is defined as the administration of less than 75% of the protocol dose (protocol deviation).

All deviations in treatment administration will be described, in particular: reduction in the total dose administered (with reasons), the correct start of treatment at day 1

Analysis population

For the statistical analysis, the following populations are defined:

Population (Analysis Set)	**Description**
Intent-To-Treat (ITT.) Population	The ITT Population will include all randomized participants. The ITT participants will be analyzed according to randomized treatment, irrespective of the actual treatment received. All efficacy analyses will be performed using the ITT Population.
Modified Intent-To-Treat (mITT) Population	The mITT population will include all randomized participants. According to randomized treatment, the ITT participants will be analyzed and received at least one treatment dose. The mITT Population will be used for supportive analyses of the efficacy measurements.
Per Protocol (PP.) Population	The PP Population will include all participants in the ITT Population with no significant protocol deviations that may significantly impact data integrity or patient safety. The PP

	Population will be used for supportive analyses of the efficacy measurements.
Safety Population (SP.)	The SP will include all randomized participants who have received at least one treatment dose (IGIV or placebo). The SP will be analyzed according to the actual treatment received. This set will be used for the safety analyses

5. Trial Population

Screening and eligibility data (Day 0)

- Patient's initials, gender, date of birth
- Verification of inclusion and exclusion criteria
  - Mechanical ventilation initiation time
  - PaO2/FiO2 value
  - Positive end-expiratory pressure (PEEP) Value
  - Chest X-ray or lungs CT scan
  - Specimen positive for SARS-CoV-2 in PCR
  - Informed consent or emergency clause
  - Creatininemia and diuresis

Summary of eligibility criteria

Inclusion Criteria:

1) Receiving invasive mechanical ventilation for less than 72 hours

2) Develops moderate to severe ARDS according to Berlin classification (REF)

3) Has a proven SARS-CoV-2 infection (by polymerase chain reaction)

4) Given consent by the patient, family, or deferred consent (emergency clause)

5) Is affiliated to a social security scheme (or exemption from affiliation)

Exclusion Criteria (any of the following):

- Allergy to polyvalent immunoglobulins
- Pregnancy or minor patient
- Known Immunoglobulin A deficiency
- Patient with acute renal failure on admission defined by a creatinine 3 times higher than baseline or creatinine >354 micromole/L or a diuresis of less than 0.3 mL/Kg for 24 hours or anuria for 12 hours
- Participation in another interventional trial

Information to be included in the CONSORT flow diagram

A CONSORT flow diagram (Figure 1) will illustrate patient progression through the trial from initial screening for eligibility to completion of the primary outcome assessment (28d) and follow-up (90d).

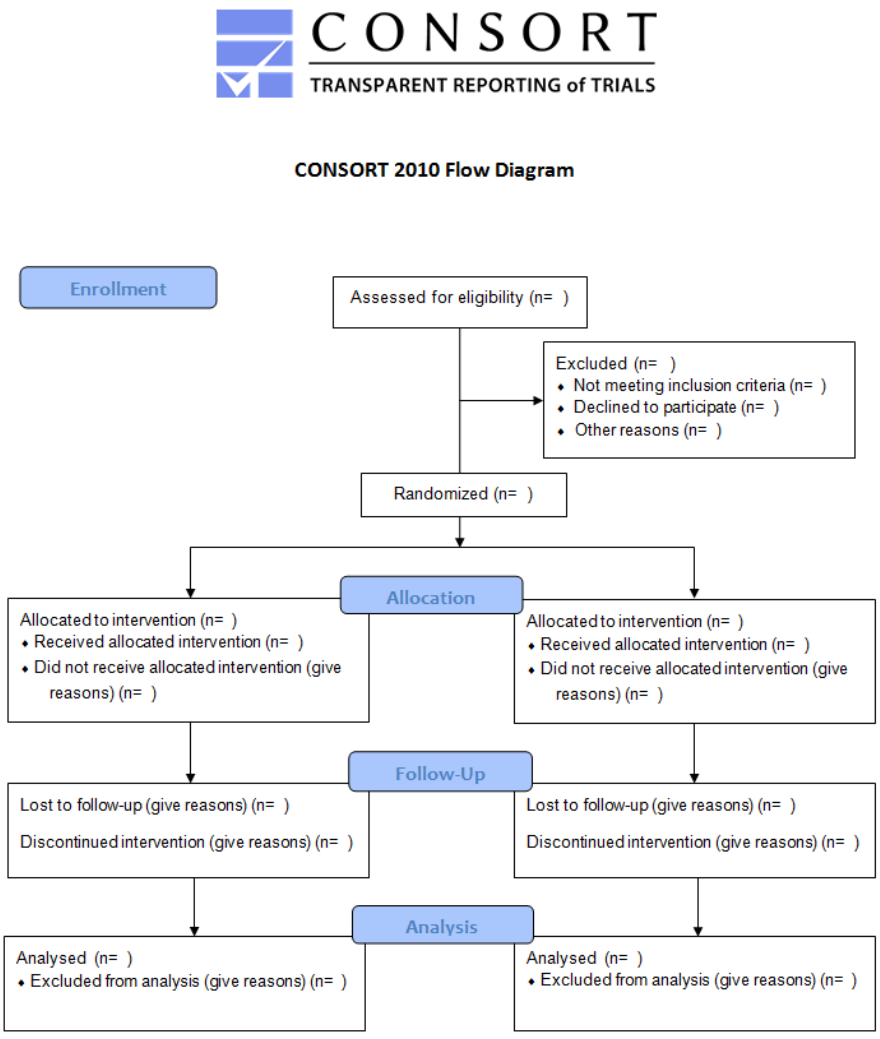


Figure 1. CONSORT Flow Diagram of trial participants

The number of patients losses to follow-up (with reasons) (for patients discharged before 28D and 90D visit) will be summarized by the treatment arm.

Withdrawal or loss to follow-up

Any subject may discontinue participation in the research at any time for any reason. The investigator may temporarily or permanently discontinue a subject's participation in the research for any reason that affects the subject's safety or is in the participant's best interests. In the event of premature termination of the research or withdrawal of consent, data collected before the premature termination may be used. The reasons for discontinuing participation in the research should be registered in the participant's file.

The number of patients withdrawals or losses to follow-up (with reasons) (for patients discharged before 28D and 90D visit) will be summarized by the treatment arm.

Baseline data (Day 0)

The following data will be recorded at the baseline visit:

- Weight (measures with a weighing scale) in Kg
- Height in cm
- COVID-19 characteristics, symptoms onset, severity at pulmonary CT, previous treatment of COVID-19 with antiviral, corticosteroids, interleukin inhibitors, antibiotics, and chloroquine derivatives
- Pulmonary embolism on chest CT angiogram
- ICU. admission and invasive mechanical ventilation initiation date and time
- Simplified Acute Physiology Score (SAPS) 2 at ICU. admission
- Respiratory variables*:* Tidal volume, Plateau pressure, compliance, PaO2/FiO2 Weaning initiation defined as the first use of spontaneous breathing trial or T-tube trial, use of spontaneous breathing ventilator mode
- Complementary tests: leukocytes and lymphocytes count, platelet count, fibrinogen, D-Dimer, procalcitonin, and C reactive protein.
- Radiological score
- SOFA score and Kidney Disease: Improving Global Outcomes score (KDIGO)

- CAM-ICU

These parameters will be used to calculate Charlson's comorbidity score and performance status.

The baseline characteristics will be summarized by the treatment arm. For continuous measures, the mean and standard deviation (SD) will be summarized or median and interquartile range for asymmetric distribution. Categorical variables will be described by the proportion in each category. In addition, 95% confidence intervals (CIs) will be computed as indicated

Daily Follow-Up D0-D28

- Vital status, extubation, re-intubation, tracheostomy, I.C.U. discharge
- The supportive treatment administered: Continuous intravenous sedation, neuromuscular blocker, prone position initiated in the last 24 hours, nitric oxide, almitrine, extracorporeal life-sustaining support
- Respiratory variables: Tidal volume, Plateau pressure, compliance, PaO2/FiO2
- Weaning initiation defined as the first use of spontaneous breathing trial or T-tube trial, use of spontaneous breathing ventilator mode
- COVID-19 treatment: hydroxychloroquine, azithromycin, other antibiotics, corticosteroids, interleukin inhibitors, antiretroviral therapy
- Complementary tests: leukocytes and lymphocytes count, platelet count, fibrinogen, D-Dimer, procalcitonin, and C reactive protein.
- Radiological score
- SOFA score and Kidney Disease: Improving Global Outcomes score (KDIGO)
- CAM-ICU
- IVIG adverse event occurrence:
- Manifestations of cutaneous hypersensitivity
- After IVIG administration, the occurrence of hypersensitivity or hypotension after IVIG administration (defined as a mean blood pressure of less than 65 mmHg for 30 minutes, after correction for hypovolemia).

- Doppler ultrasound evidence of deep venous thrombosis
- Existence of a pulmonary embolism proven but CT-scan
- possible transfusion-associated lung injury
- Aseptic meningitis defined by a clinically objectified meningeal syndrome upon awakening
- Hemolytic anemia (defined as hemoglobin less than 8 g/dL, not-evaluable haptoglobin, and a positive direct Coombs test)

D28 and D90 follow-up

- Days on mechanical ventilation
- Vital status and date of death (for patients who died)
- Days on tracheostomy if realized.
- ICU complications: Catheter-related infection, Number of the episode of ventilator-associated pneumonia (VAP), digestive hemorrhage, pressure sores (>grade 2), confusion according to the CAM-ICU, focal neurological deficit, toxidermia
- Functional status: MRC Score at discharge, ADL value, IADL value

6. Analysis

Exposure to study drugs by the treatment arm will be summarized, including the number of patients with dose modification.

All of the continuous variables, including the changes from baseline, will be summarized by treatment with the means, SD, or medians and the interquartile ranges for asymmetric variables. All the categorical variables will be summarized by treatment with the numbers and percentages of the patients. In addition, 95% confidence intervals (CIs) will be computed as indicated.

The normality check of the distributions for all quantitative variables will be done through the Kolmogorov-Smirnov test (with the Lillefors correction) and the Shapiro-Wilk test.

For each variable, If not otherwise pre-specified, the choice of statistical tests and multivariate models (parametric or non-parametric) will be carried out based on observed characteristics (normality of distributions and residuals, collinearity).

Primary endpoint

According to recommendations in Yehya et al. (20), 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.

The Wilcoxon rank-sum test stratified by center and IMV duration will be used for the primary analysis of the principal endpoint. The hypothesis of equality of treatment arms for VFD will be tested at a two-sided significance level of 0.05.

Secondary endpoints for efficacy

The primary outcome composite components will also be analyzed as time-to-event censored at 28D, within a competing risk framework, where extubation is the main event and death before extubation a competing one, as recommended byYehya et al. (20). Time to each event, i.e., subdistribution hazards, will be modeled by a Fine&Gray model, with the treatment arm included as a covariate and center as strata. This analysis provides a subdistribution of the hazard ratio (SHR), where the size is influenced by both times to extubation and probability of death.

In addition, the effect size and number needed to treat (NNT) will be computed as indicated.

Other multi-state models can be used to explore the primary endpoint.

The 28 and 90 days overall survival probability will be estimated by the Kaplan-Meier method. The Kaplan-Meier curves will be presented by treatment

If the assumptions for appropriate use of the Cox proportional hazards regression model and Fine&Gray model will be respected, in particular:

- independence of survival times between distinct individuals in the sample,
- a multiplicative relationship between the predictors and the hazard

Comparing the treatment arms will be performed with the Cox model by estimating the hazard ratio with a 95% confidence interval; treatment, participant's risk factors (age, sex, and BMI) at baseline as covariates. Center will be included as strata in this model.

For mortality at 28 and 90 days, effect size and numbers needed to treat (NNT) will be computed.

The other efficacy outcome such as:

- Evolution of SOFA score (presented as percentage variation from the baseline score at 14 and 28 days)
- Lung injury score: the LI score will be calculated by adding the sum of each component and dividing by the number of components used (21;22)
- ADL and IADL score at 28 and 90 days

Will be presented as medians and interquartile ranges. According to their distribution, a Student or Mann-Whitney test will be performed for the treatment arms comparisons.

Finally, the length of the ICU stay (in days) and length of hospital stay up to the 90th day will be analyzed according to discharge using the Log-Rank test.

Exploratory objectives

Exploratory objectives will be evaluated the impact of the experimental on:

- the incidence of pulmonary embolism
- the number of delirium free days according to the CAM-ICU up to 28D
- the occurrence of ICU-acquired weakness defined by an MRC sum score < 48 at ICU. discharge
- the occurrence of ventilator-associated pneumonia
- biological efficiency study through the in-depth study of IGIV impacts cytokines, immune cells transcriptome, and lymphocytes activation in an ancillary study.

Safety parameters

All safety analyses will be performed on the Safety Population.

Safety and tolerability will be assessed by clinical safety laboratory measurements, physical examinations, vital signs, concomitant medications. The cumulative incidence of AEs and SAEs will be reported.

Exposure

Exposure to study treatment will be performed on mITT Population and summarized by the following using descriptive statistics:

- Duration of treatment
- Starting dose
- Cumulative dose
- Dose intensity (%) (defined as the total amount of study treatment received relative to the total amount of study treatment planned per protocol)

Dose modification (dose reduction or interruption) will be summarized as follows:

Dose modification:

- n (%) of patients with any dose modification (reduction or interruption)

Dose reduction:

- n (%) of patients with at least one dose reduction
- Number of dose reductions per patient (mean, median, range)
- Reason for change in dose

Dose interruptions:

- n (%) of patients with at least one dose interruption
- Number of interruptions per patient (mean, median, range)

Adverse Events

Adverse Events will be coded using the MedDRA coding dictionary.

The number and percentage of patients with any AE, any related AE, any SAE, any related SAE, any severe AE, and related severe AE and the total number of events for each category will be summarized. The number of deaths due to an AE and study discontinuation due to an AE will be summarized.

Listing of all Serious Adverse Events will be provided. Patient listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs, related AEs, and severe AEs will be produced.

Clinical laboratory evaluation

Baseline is defined as the last non-missing value obtained at the screening visit and before the first exposure to the study drug. Actual values and changes from Baseline clinical laboratory tests will be summarized by study day.

Laboratory test results will be classified according to the reference ranges and clinical significance determined by the investigator. The number of patients with a non-missing result, the number and percentage of patients with a clinically significant result more minor than the lower limit of normal, non-clinically significant result more than the upper limit of normal (ULN), and clinically significant result more than the ULN will be summarized by study visit.

Categorical laboratory test results will be summarized by study visit.

Patients with clinically significant abnormal laboratory test results will be listed. This listing will include all laboratory results that were abnormal and determined to be clinically significant by the investigator for a patient across study visit.

Vital Sign

Baseline is defined as the last non-missing value obtained in screening and before the first exposure to study drug. Actual values and changes from baseline in vital signs will be summarized by study day and study time point. All vital sign data will be presented in patient listings.

Vital sign values will be classified according to the clinical significance as determined by the investigator. The number of patients with a non-missing result, the number and percentage of patients with a non-clinically significant result, and clinically significant result will be summarized by study visit and study time point.

Patients with clinically significant vital sign values will be listed. This listing will include all the vital sign parameter results that the investigator determined to be clinically significant for a patient across study time points.

Subgroup analysis

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints (and its composite components), overall survival at 28 and 90 days and mortality, will be estimated and plotted within each category of the following classification variables:

- Time of IMV at randomization: less than 12 hours, between 12 and 24 hours, and between 24 and 72 hours
- Age: <=65 years; >65 years
- BMI (kg/m^2): >= 30; <30
- Concomitant treatment with corticosteroids: Y vs N

A subgroup analysis by age, with a threshold >= 65, in the subgroup of patients alive at day seven will be performed.

In addition, a Forest plot will be produced, which provides the estimated point and confidence intervals for the treatment effect across the subgroups categories listed above. If there are a small number of responses/events in one or more strata, for analysis, strata will be combined to ensure a sufficient number of responses/events in each stratum.

Missing data

- For the primary endpoint (VFDs)

Patients discharged from the hospital before day 28 after randomization will have a telephone interview regarding their actual and past ventilation status on day 28, so information on ventilation status can be completed.

Given the type of patient and pathology, it is expected that the number of patients lost to follow-up before day 28 is very small.

In the primary analysis, for these very few patients (withdrawn early from the study but not discharged), we assume:

- if the patients were on invasive-mechanical ventilation at the discontinuation point, the remaining days to Week 4 with missing data on ventilation status would be counted as no VFDs
- If the patients were not in invasive ventilation at the point of withdrawal will be assumed the days from withdrawal to Week 4 as VFDs

If ventilator status is missing for patients that have not withdrawn, died, or discharged, then the last ventilator status observed post-baseline would be carried forward until the following observation.

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

In the case of missing data on individual SOFA components, 0 (normal) value was imputed for that component (23).

Statistical software

All statistical analyses will be conducted using SPSS, Version 26 (IBM Corp., Armonk, NY, USA).

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Appendix 1. ARDS Berlin Definition

Criterion	Mild	Moderate	Severe
Timing	Acute onset within one week of a known clinical insult or new or worsening respiratory symptoms		
Hypoxemia (PaO_2/FIO_2)	201-300 with PEEP/CPAP ≥5	101-200 with PEEP ≥5	≤100 with PEEP ≥5
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload		
Chest imaging	Bilateral opacities	Bilateral opacities	Bilateral opacities

PaO_2/FIO_2 - relationship between oxygen partial pressure and fraction of inspired oxygen; PEEP - positive end-expiratory pressure; CPAP - continuous positive airway pressure.

Appendix 2. Kidney Disease: Improving Global Outcomes (KDIGO)

Stade	Créatinine	Diurèse
1	1.5-1.9 x la baseline ou Augmentation ≥ 26.5 µmol/l	< 0.5 ml/kg/h pour 6-12h
2	2.0-2.9 x la baseline	< 0.5 ml/kg/h pour ≥ 12h
3	3.0 x la baseline ou Augmentation ≥ 353.6 µmol/l ou Début de l'épuration extra-rénale ou Chez patient < 18 ans, diminution du DFGe < 35 ml/min/1.73 m^2	< 0.3 ml/kg/h pour ≥ 24h ou Anurie pour ≥ 12h

Appendix 3. The Medical Research Council (MRC.)

Scale for Muscle Strength is a commonly used scale for assessing muscle strength from Grade 5 (normal) to Grade 0 (no visible contraction). This score was defined as the sum of MRC scores from six muscles in the upper and lower limbs on both sides so that the score ranged from 60 (normal) to zero (quadriplegic).

The Criteria requires that each of the six muscle groups listed in the table be examined bilaterally, each with a score from zero to five according to the scale in the right-hand column.

MRC Sum score

Muscle		Score 0 - 5	MRC scale for muscle strength (0-5)
Shoulder abductors	Left		Grade 5: Normal
	Right		Grade 4: Movement against gravity and resistance
Elbow flexors	Left		Grade 3: Movement against gravity over (almost) the full range
	Right		Grade 2: Movement of the limb but not against gravity
Wrist extensors	Left		Grade 1: Visible contraction without movement of the limb (not existent for hip flexion)
	Right		Grade 0: No visible contraction
Hip flexors	Left		MRC grade for each muscle given in full numbers: (4+/4.5 =4) (4-=3) (5- = 4)
	Right		
Knee extensors	Left		
	Right		
Foot dorsiflexors	Left		
	Right		
	Total (out of 60)		

Appendix 4. Charlson Comorbidity Index (CCI)

Condition	Assigned weight
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Liver disease, mild	1
Diabetes	1
Hemiplegia	2
Renal disease, moderate or severe	2
Diabetes with end organ damage	2
Any malignancy	2
Leukemia	2
Malignant lymphoma	2
Liver disease, moderate or severe	3
Metastatic solid malignancy	6
Acquired immunodeficiency syndrome (AIDS)	6

Appendix 5: IGS II score calculation table (simplified severity index)

Entrée	Chir urgente :8 pts		Médecine : 6 pts		Chir programmée	
Age (ans)	<40 :0 pt	40 – 59 :7 pts	60 – 69 : 12 pts	70 – 74 : 15 pts	75 – 79 : 16 pts	>80 :18 pts
Température (°c)	<39 :0 pt				>39 : 3 pts	
Urée (mmol/L)	<10 :0 pt	10 – 29,9 :6pts	>30 : 10 pts			
Na (mEqL)	125 _ 144 : 0 pt	>145 : 1 pt	<125 :5 pts			
Maladie chronique	Aucune :0 pt	Cancer métastasé :9	Mal hémato :10	SIDA : 17 pts		
PAs (mmHg)	<70 : 13 pts	70 – 99 : 5 pts	100 – 199 : 0 pt	>200 : 2 pts		
GB / mm^3	<1000 :12 pts	1000 – 19000 :0 pt	>20000 : 3 pts			
Bicar (mEq/L)	>20 :0 pt	15 – 19 :3 pts	<15 :6 pts			
Glasgow	<6 :26 pts	6 – 8 :13 pts	9 – 10 : 7 pts	11 – 13 : 5 pts	14 – 15 : 0 pt	
FC / mn	<40 : 11 pts	40 – 69 :2 pts	70 – 119 :0	120 – 159 : 4	>160 : 7 pts	
Diurèse (L/24h)	<0,5 :11 pts	0,5 – 0,99 : 4 pts	>1 :0 pt			
K+ (mEq/l)	<3 :3 pts	3 – 4,9 :0 pt	>5 :3 pts			
	<68,4 : 0 pts	68,4 – 102,6 : 4 pts	>102,6 : 9 pts			

Appendix 6: SOFA score

SOFA SCORE	1	2	3	4
Respiration *PaO2 :FiO2*	<400	<300	<200*	<100*
Coagulation *Plaquettes x10^3/mm^3*	<150	<100	<50	<20
Foie *Bilirubine, mg/dl (µmol/l)*	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (>204)
Cardiovasculaire *Hypotension*	MAP<70 mm Hg	Dopamine ≤5 γ/kg/min ou Dobutamine	Dopamine >5 γ/kg/min ou adrénaline ou noradrénaline ≤0.1 γ/kg/min	Dopamine >15 γ/kg/min ou adrénaline ou noradrénaline >0.1 γ/kg/min
Neurologique *Glasgow*	13-14	10-12	6-9	>6
Rénal *Créatinine, mg/dl (µmol/l) ou diurèse*	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or < 500 ml/jour	>5.0 (>440) or <200 ml/jour

Statistical Analysis Plan (SAP)
ver. 2.0

EFFECT OF EARLY TREATMENT WITH POLYVALENT IMMUNOGLOBULIN ON ACUTE RESPIRATORY DISTRESS SYNDROME ASSOCIATED WITH SARS-COV-2 INFECTIONS
ICAR (IGIV IN COVID-RELATED ARDS)

Paris 10.10.2020

This statistical analysis plan has been drawn up in accordance with the following guidelines: Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337–2343. doi:10.1001/jama.2017.18556.

Index

1. Administrative information

1.1 Title, trial registration, version and revision

Full study title	Effect of early treatment with polyvalent immunoglobulin on acute respiratory distress syndrome associated with SARS-CoV-2 infections
Acronym	ICAR (IgIV in Covid-related ARds)
Local project number	D20 – P013
Human Subjects Protection Review Board	Approved by Comité de Protection des Personnes (CPP) Ile de France X – GHT Grand Paris Nord Est
EudraCT number	2020-001570-30
Clinicaltrials.gov id	NCT04350580
Study protocol version	3.0, dated 29/05/2020
SAP version	2.0, dated 10/10/2020
SAP revision story	Ver. 1.0, dated 30/06/2020
SAP revision justification	SAP reviewed against protocol amendments, first interim analysis results and DSMB recommendation
SAP revision timing	No other revision is planned

1.2 Roles and Responsibility

Author, Statistician	Rossella Letizia Mancusi[1], MD
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Study Chair	Tarek Sharshar [3 4], MD, PHD
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1.3 Signatures

We, the undersigned, certify that we read this SAP and approve it is adequate in the scope of the main analyses of the ICAR (IgIV in Covid-related ARds) study

Author

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…….

Date: 30/10/2020

Senior Statistician

Name: AEGERTER Ph

Date: 30/10/2020

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Date: 30/10/2020

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Name: SYLLA Khaoussou

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Date: 30/10/2020

2. Introduction

2.1 Background and rationale

Mid-June 7 500 000 people were infected with coronavirus disease 2019 (COVID-19) worldwide, and 420 000 people died, mainly from acute respiratory distress syndrome (ARDS). No specific pharmacological treatment of COVID-19-related-ARDS is currently available (1).

Pulmonary lesions are related to both the viral infection and an inflammatory reaction. Patients admitted to intensive care unit (ICU) have a cytokinetic inflammatory response and higher plasma concentrations of interleukin (IL) 2, IL 7, IL 10, Granulocyte Colony Stimulating Factor, interferon-inducible protein 10, Monocyte chemoattractant protein-1, macrophage inflammatory protein 1α, and tumor necrosis factor-alpha (2). In the blood, the Number of peripheral CD4 and CD8 T cells appears to be significantly reduced, while their status is hyperactivated. This is evidenced by immunoreactive cytometric profiles for HLA-DR (CD4 3-47%) and CD38 (CD8 39-4%) or by an increase in the proportion of highly pro-inflammatory Th17 CCR6+ lymphocytes. Besides, CD8 T cells would exhibit a highly cytotoxic profile characterized by high concentrations of cytotoxic granules (perforin+, granulysin+ or double-positive) (3).

Because of their immunomodulatory effect that may both attenuate the inflammatory response and enhance antiviral defense, we propose to evaluate the efficacy and safety of intravenous immunoglobulin (IVIG) administration in patients developing COVID-19 related ARDS. IVIG modifies T cells functions but also dendritic cell function and ultimately cytokine and chemokine networks. IVIG stimulates regulatory T cells proliferation that regulates CD4 and CD8 T cell activity (3-5). Also, IVIG restores regulatory T cells functions and modulate lymphocyte populations specifically altered during COVID-19 (3).

In addition, IVIG can modulate humoral acquired immunity through its effect on the idiotypic network and antibody production. IVIG also act on innate immunity by antigen

neutralization and modulation of phagocytic cells. These effects lead to a decrease in the production of pro-inflammatory cytokines and complement activation, key factors in COVID-19 related ARDS (4-7). It should be noted that IVIG is used as a treatment for a variety of autoimmune and inflammatory diseases. Both standard and polyclonal IVIG have significantly reduced mortality in patients with Kawasaki disease (10) and improve outcomes in patients with polyneuropathy (DOI 10.1016/S1474-4422(07)70329-0). More recently, it has been shown that IVIG may have a beneficial effect in diffuse interstitial lymphocytic pneumonitis (6) and post-influenza ARDS (11).

Few low-level of evidence data support the effect of IVIG during COVID-19, this treatment has been described as favorable in 3 cases of COVID-19 related ARDS and one with COVID-19-related myocarditis who received a high dose of intravenous immunoglobulin IVIG at the time of onset of distress, with a favorable clinical course (12, 20). A retrospective study showed a decrease in mortality and ventilation time in patients with ARDS receiving invasive mechanical ventilation (IMV) treated early with a high dose of IVIG (https://doi.org/10.1101/2020.04.11.20061739). Notably, there were no adverse events reported, including no renal impairment or allergic reactions. IVIG is a treatment option if it is well-tolerated, particularly concerning renal function (13). In adults, adverse events reported as possibly related to polyclonal IVIG during septic shock were allergic reactions (14, 15); skin reactions such as erythema and exanthema; pruritus; nausea and vomiting; dyspnea; congestion; shock; and fever (14-18). Two trials reported no adverse events attributable to IVIG, and one trial reported adverse events, but none were ascribed to IVIG, but the cohort size was limited (16, 17, 19).

This promising benefits-risks balance encourages us to rapidly carry out a multicenter, placebo-controlled therapeutic trial testing the benefit of IVIG in COVID-19 related ARDS.

Research hypothesis

The null hypothesis is that there are no differences in Ventilator Free Days at 28 days between the standard of care plus placebo (SOC+placebo) and standard of care plus IGIV (SOC+IVIG) groups. The alternative hypothesis is that there is a difference between the two groups.

2.2. Objectives

2.2.1. Objectives and research questions

Study Objectives

The main objective is to verify if the administration of IVIG at a dose of 2g/kg over four consecutive days up 24-72 hours after the start of IMV, in patients with COVID-19 related ARDS, increases the number of days alive without IMV (ventilator-free days) up to day 28 (D28) after IMV initiation.

VFDs at 28 days is defined as follows:

- VFDs = 0 if subject dies within 28 days of mechanical ventilation
- VFDs = 28-x if the subject is successfully liberated from ventilation x days after initiation
- VFDs = 0 if the subject is mechanically ventilated for 28 days or more

Secondary objectives are:

- Overall Mortality Rate at 28 and 90 days
- Total duration of mechanical ventilation, ventilatory withdrawal, curarization, use of non-invasive ventilation (NIV), high flow oxygen therapy (HFO.) WHO ordinal severity scale
- WHO ordinal scale of severity of COVID impairment

- Organ failures according to the SOFA score achieved at D1, D7, D14, D21, and D28, according to Appendix 6
- Clinical Efficacy Criteria: Radiological score according to the quadrant method, the chest x-ray is divided into 4 quadrants. The existence of alveolar-interstitial opacities in one quadrant adds 1 point to the score. P/F ratio value, lung compliance at D1, D7, D14, D21, and D28
- Biological efficacy endpoints: inflammatory syndrome at D1, D3, D7, D14, D21, and D28 by measuring serum C-reactive protein, procalcitonin, white blood cell count, and d-dimer levels.
- Occurrence of ventilator-associated pneumonia.
- Occurrence of an adverse event related to immunoglobulins (D1, D2, D3, D4, D5, D6 and D7, D14, D21, and D28: KDIGO 3 stage renal failure, hypersensitivity manifestations with cutaneous or hemodynamic manifestations, aseptic meningitis defined by a clinically objectified meningeal syndrome upon awakening, hemolytic anemia (defined by hemoglobin less than 8 g/dL, non-detectable haptoglobin, and a positive direct Coombs test), leukoneutropenia (according to the WHO classification in Appendix X), Transfusion-Related Respiratory Distress Syndrome (TRALI) due to immunoglobulin
- KDIGO score (D1, D7, D14, D21, and D28) and the need for extrarenal purification, the occurrence of clinically detected deep vein thrombosis proven by Doppler ultrasound. Occurrence of a pulmonary embolism detected by a pulmonary angioscan.

Biological efficiency study through the in-depth study of IGIV impact on cytokines, immune cells transcriptome, and lymphocytes activation in an ancillary study

3. Trial Methods

Trial design

The ICAR trial is a Phase III double-blind, multicenter, randomized in parallel-group, placebo-controlled study in hospitalized participants with COVID-19 requiring mechanical ventilation. Patients will be randomized 1:1 to the Investigational arm or the Control arm. Participants randomized to the Investigational arm will receive Ig 2g/Kg administered IV for up to 4 days in addition to the standard of care (SOC), while participants in the Control arm will receive placebo plus SOC. The Sponsor intends to enroll approximately 138 patients that have been diagnosed with SARS-CoV-2 pneumonia and meet the entry criteria in centers globally.

Patients must be at least 18 years of age develop moderate to severe ARDS: according to Berlin classification (REF), with confirmed SARS-CoV-2 infection (by polymerase chain reaction), and receiving invasive mechanical ventilation for less than 72 hours.

Patients with acute renal failure, allergy to polyvalent immunoglobulins, or known Immunoglobulin-A deficiency will be excluded from the study.

Randomization

Patients will be randomly assigned to one of the two treatment arms: IVIG in combination with SOC or placebo in combination with SOC. Randomization will occur in a 1:1 ratio through the use a balanced permuted-block randomization method. The randomization list will be stratified by center and IMV at randomization (<=12 hours, >12 and <=24 hours; >24 and <=72 hours). The randomization list will be carried out by the GHU biostatistician using the R software and incorporated into the e-CRF. A document describing the randomization procedure will be kept confidentially in the DRCI of the GHU Paris.

Sample size

We hypothesize that the number of days without IMV is 10 days in the placebo group and 15 days in the experimental group with a standard deviation of 6 days for discharged alive patients, considering mortality of 50% and 40% in the placebo (i.e., 0 D according to the

definition of VFD) and investigational groups respectively. The number of days without IMV in the placebo group is (50% x 10 D) + (50% x 0 D) or 5 D on average, and following the same calculation for the experimental group of (60% x 15 D) + (40% x 0 D) or 9 D.

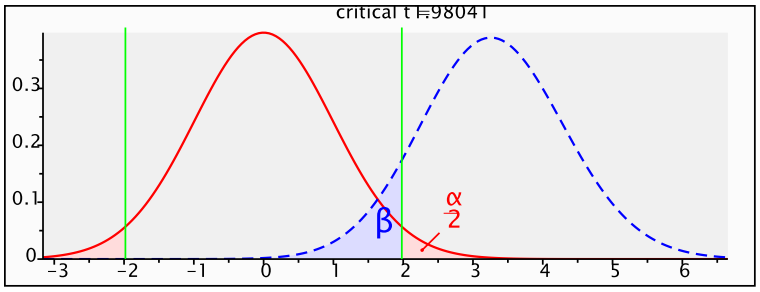
Therefore, a mean value of 5 days without ventilation in the placebo group versus 9 in the experimental group is assumed, and the 6-day standard deviation is assumed to be stable. Given the uncertainty regarding the assumption of normality of distributions, the non-parametric Wilcoxon-Mann-Whitney test (U-test) was used for the estimation of the sample size. Considering a bilateral alpha risk of 5% and a power of 90%, and an effect size of 0.6, the number of subjects to be included is 138 patients, 69 in each arm (Table 1).

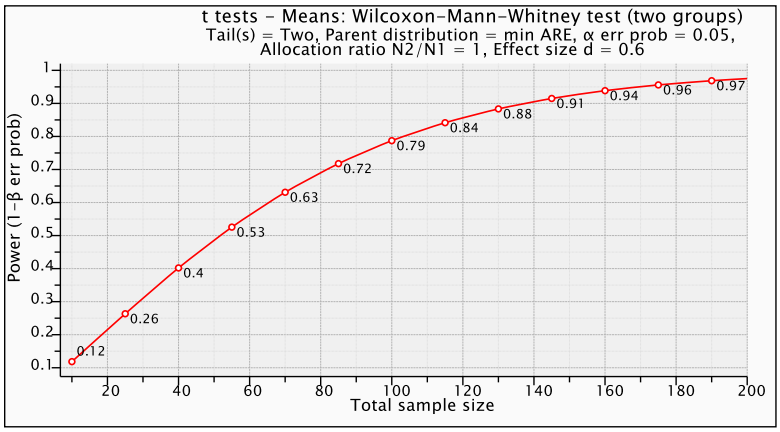
Table 1

Tests - Means: Wilcoxon-Mann-Whitney test (two groups)[1]
Options: ARE method
Analysis: A priori: Compute required sample size

Input:		
Tail(s)	=	Two
Parent distribution	=	min ARE
Effect size d	=	0.6
α err prob	=	0.05
Power (1-β err prob)	=	0.90
Allocation ratio N2/N1	=	1
Output:		
Noncentrality parameter δ	=	3.28
Critical t	=	1.980
Df	=	117.232
Sample size group 1	=	69
Sample size group 2	=	69
Total sample size	=	138
Actual power	=	0.90

1 The estimate using G*Power Ver. 3.1.9.4. (Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods, 39, 175-191)





Framework

All efficacy outcomes will be tested for superiority in ITT.

Statistical Interim analysis and stopping guidance

One formal interim statistical analysis will be carried out when 50 (25 participants in the IVIG arm and 25 participants in the placebo arm) have completed the D28 assessment.

The purpose of the first analysis will be to assess the futility of IVIG based on the results on change in VFDs at D28. The following futility criterion will be used for this interim analysis:

If the difference in the VFDs is less than 3-day improvement between both treatment arms, the benefit of IVIG treatment is not expected. For a final decision to stop the study for futility, the results on other endpoints will be considered as well.

For the primary objective (VFDs) to account for multiple testing due to the interim analysis, an adjustment for type I error alpha will be applied using the O'Brien-Fleming spending function, which would expend two-sided alpha = 0.0003 at the interim analysis (critical value = ±3.6128) and leave nominal two-sided alpha of 0.0497 for the final analysis (critical value = ±1.9601).

Timing of final analysis

The final analysis of 28D VFDs is scheduled 90 days after the last randomization.

Timing of outcome assessment

The schedule of study procedures is given in table 2.

Timepoint	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D1 4	D15-20	D2 1	D22-27	D2 8	D9 0
Consent collection													
Pursuit consent collection	x	x	x	x	x	x	x	x	x	x	x	x	
Demographics, medical history, disease characteristics													
Administration of IVIG or Placebo Therapy	x	x	x	x									
Main outcome measurement	x	x	x	x	x	x	x	x	x	x	x	x	
Collection of clinical data	x	x	x	x	x	x	x	x	x	x	x	x	
Complete blood count, blood gas, creatinine	x						x	x		x		x	
Leukocytosis, C-reactive protein, biobank collection	x						x			x			
SOFA score	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x
Final assessment of the primary outcome												x	

Final assessment of secondary outcomes												x	x

4. Statistical principles

Confidence interval and p-values

For the primary objective (VFDs) to account for multiple testing due to the interim analysis, an adjustment for type I error alpha will be applied using the O'Brien-Fleming spending function, which would expend two-sided alpha = 0.003 at the interim analysis (critical value = ±3.6128) and leave nominal two-sided alpha of 0.0497 for the final analysis (critical value = ±1.9601).

For the other objectives , all applicable statistical tests will be 2-sided and will be performed using a 0.05 significance level, and all confidence interval reported will be 95% and 2-sided.

Adherence and Protocol deviations

Compliance per patient is defined as the ratio of the administered dose to the protocol dose.
Compliance will be assessed based on the percent of patients of scheduled treatment administration.

A total dose of IVIG administered over four days of at least 75% of the intended dose is considered adherent to the protocol.

Non-adherence is defined as the administration of less than 75% of the protocol dose (protocol deviation).

All deviations in treatment administration will be described, in particular: reduction in the total dose administered (with reasons), the correct start of treatment at day 1

Analysis population

For the statistical analysis, the following populations are defined:

Population (Analysis Set)	**Description**
Intent-To-Treat (ITT.) Population	The ITT Population will include all randomized participants. The ITT participants will be analyzed according to randomized treatment, irrespective of the actual treatment received. All efficacy analyses will be performed using the ITT Population.
Modified Intent-To-Treat (mITT) Population	The mITT population will include all randomized participants. According to randomized treatment, the ITT participants will be analyzed and received at least one treatment dose. The mITT Population will be used for supportive analyses of the efficacy measurements.
Per Protocol (PP.) Population	The PP Population will include all participants in the ITT Population with no significant protocol deviations that may significantly impact data integrity or patient safety. The PP Population will be used for supportive analyses of the efficacy measurements.
Safety Population (SP.)	The SP will include all randomized participants who have received at least one treatment dose (IGIV or placebo). The SP will be analyzed according to the actual treatment received. This set will be used for the safety analyses

5. Trial Population

Screening and eligibility data (Day 0)

- Patient's initials, gender, date of birth
- Verification of inclusion and exclusion criteria
  - Mechanical ventilation initiation time
  - PaO2/FiO2 value
  - Positive end-expiratory pressure (PEEP) Value
  - Chest X-ray or lungs CT scan
  - Specimen positive for SARS-CoV-2 in PCR
  - Informed consent or emergency clause
  - Creatininemia and diuresis

Summary of eligibility criteria

Inclusion Criteria:

1) Receiving invasive mechanical ventilation for less than 72 hours

2) Develops moderate to severe ARDS according to Berlin classification (REF)

3) Has a proven SARS-CoV-2 infection (by polymerase chain reaction)

4) Given consent by the patient, family, or deferred consent (emergency clause)

5) Is affiliated to a social security scheme (or exemption from affiliation)

Exclusion Criteria (any of the following):

- Allergy to polyvalent immunoglobulins
- Pregnancy or minor patient
- Known Immunoglobulin A deficiency

- Patient with acute renal failure on admission defined by a creatinine 3 times higher than baseline or creatinine >354 micromole/L or a diuresis of less than 0.3 mL/Kg for 24 hours or anuria for 12 hours
- Participation in another interventional trial

Information to be included in the CONSORT flow diagram

A CONSORT flow diagram (Figure 1) will illustrate patient progression through the trial from initial screening for eligibility to completion of the primary outcome assessment (28d) and follow-up (90d).

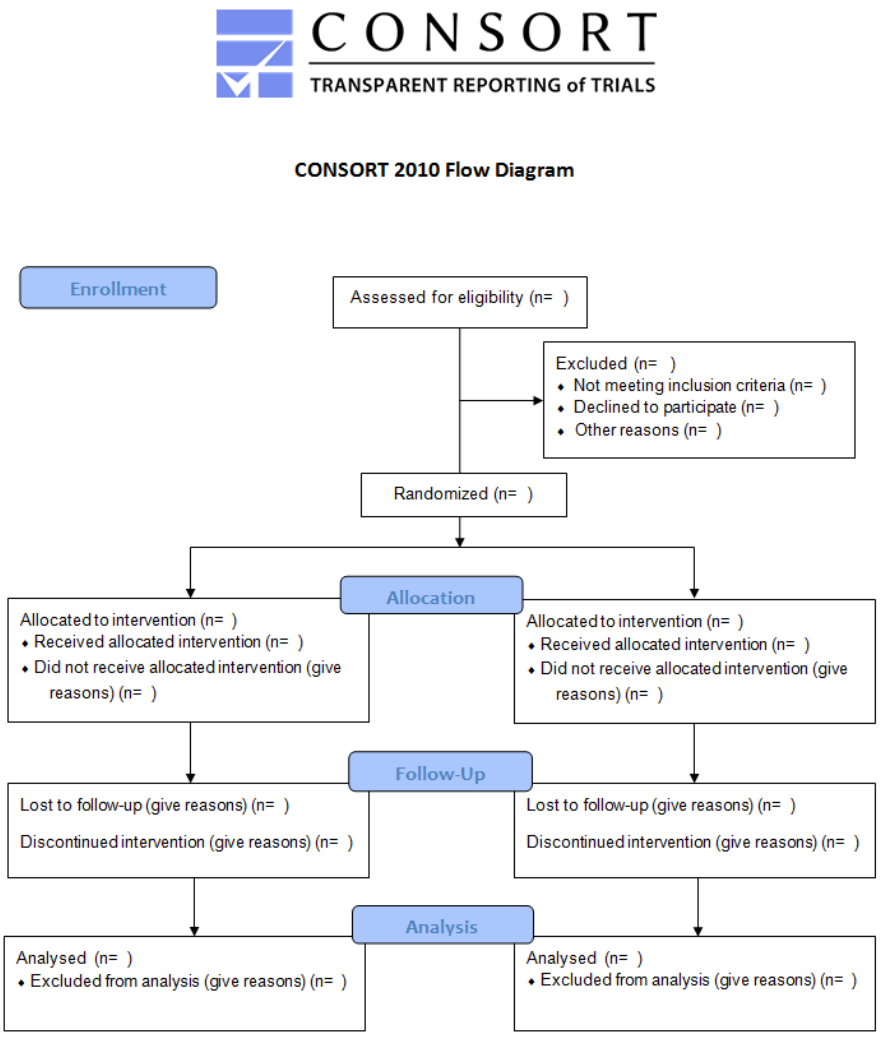


Figure 1. CONSORT Flow Diagram of trial participants

The number of patients losses to follow-up (with reasons) (for patients discharged before 28D and 90D visit) will be summarized by the treatment arm.

Withdrawal or loss to follow-up

Any subject may discontinue participation in the research at any time for any reason. The investigator may temporarily or permanently discontinue a subject's participation in the research for any reason that affects the subject's safety or is in the participant's best interests. In the event of premature termination of the research or withdrawal of consent, data collected before the premature termination may be used. The reasons for discontinuing participation in the research should be registered in the participant's file.

The number of patients withdrawals or losses to follow-up (with reasons) (for patients discharged before 28D and 90D visit) will be summarized by the treatment arm.

Baseline data (Day 0)

The following data will be recorded at the baseline visit:

- Weight (measures with a weighing scale) in Kg
- Height in cm
- COVID-19 characteristics, symptoms onset, severity at pulmonary CT, previous treatment of COVID-19 with antiviral, corticosteroids, interleukin inhibitors, antibiotics, and chloroquine derivatives
- Pulmonary embolism on chest CT angiogram
- ICU. admission and invasive mechanical ventilation initiation date and time
- Simplified Acute Physiology Score (SAPS) 2 at ICU. admission
- Respiratory variables*:* Tidal volume, Plateau pressure, compliance, PaO2/FiO2 Weaning initiation defined as the first use of spontaneous breathing trial or T-tube trial, use of spontaneous breathing ventilator mode
- Complementary tests: leukocytes and lymphocytes count, platelet count, fibrinogen, D-Dimer, procalcitonin, and C reactive protein.
- Radiological score
- SOFA score and Kidney Disease: Improving Global Outcomes score (KDIGO)

- CAM-ICU

These parameters will be used to calculate Charlson's comorbidity score and performance status.

The baseline characteristics will be summarized by the treatment arm. For continuous measures, the mean and standard deviation (SD) will be summarized or median and interquartile range for asymmetric distribution. Categorical variables will be described by the proportion in each category. In addition, 95% confidence intervals (CIs) will be computed as indicated

Daily Follow-Up D0-D28

- Vital status, extubation, re-intubation, tracheostomy, I.C.U. discharge
- The supportive treatment administered: Continuous intravenous sedation, neuromuscular blocker, prone position initiated in the last 24 hours, nitric oxide, almitrine, extracorporeal life-sustaining support
- Respiratory variables: Tidal volume, Plateau pressure, compliance, PaO2/FiO2
- Weaning initiation defined as the first use of spontaneous breathing trial or T-tube trial, use of spontaneous breathing ventilator mode
- COVID-19 treatment: hydroxychloroquine, azithromycin, other antibiotics, corticosteroids, interleukin inhibitors, antiretroviral therapy
- Complementary tests: leukocytes and lymphocytes count, platelet count, fibrinogen, D-Dimer, procalcitonin, and C reactive protein.
- Radiological score
- SOFA score and Kidney Disease: Improving Global Outcomes score (KDIGO)
- CAM-ICU
- IVIG adverse event occurrence:
- Manifestations of cutaneous hypersensitivity
- After IVIG administration, the occurrence of hypersensitivity or hypotension after IVIG administration (defined as a mean blood pressure of less than 65 mmHg for 30 minutes, after correction for hypovolemia).

- Doppler ultrasound evidence of deep venous thrombosis
- Existence of a pulmonary embolism proven but CT-scan
- possible transfusion-associated lung injury
- Aseptic meningitis defined by a clinically objectified meningeal syndrome upon awakening
- Hemolytic anemia (defined as hemoglobin less than 8 g/dL, not-evaluable haptoglobin, and a positive direct Coombs test)

D28 and D90 follow-up

- Days on mechanical ventilation
- Vital status and date of death (for patients who died)
- Days on tracheostomy if realized.
- ICU complications: Catheter-related infection, Number of the episode of ventilator-associated pneumonia (VAP), digestive hemorrhage, pressure sores (>grade 2), confusion according to the CAM-ICU, focal neurological deficit, toxidermia
- Functional status: MRC Score at discharge, ADL value, IADL value

6. Analysis

Exposure to study drugs by the treatment arm will be summarized, including the number of patients with dose modification.

All of the continuous variables, including the changes from baseline, will be summarized by treatment with the means, SD, or medians and the interquartile ranges for asymmetric variables. All the categorical variables will be summarized by treatment with the numbers and percentages of the patients. In addition, 95% confidence intervals (CIs) will be computed as indicated.

The normality check of the distributions for all quantitative variables will be done through the Kolmogorov-Smirnov test (with the Lillefors correction) and the Shapiro-Wilk test.

For each variable, If not otherwise pre-specified, the choice of statistical tests and multivariate models (parametric or non-parametric) will be carried out based on observed characteristics (normality of distributions and residuals, collinearity).

Primary endpoint

According to recommendations in Yehya et al. (20), 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.

The Wilcoxon rank-sum test stratified by center and IMV duration will be used for the primary analysis of the principal endpoint. The hypothesis of equality of treatment arms for VFD will be tested at a two-sided significance level of 0.05 (*adjusted for interim analyses*).

Secondary endpoints for efficacy

The primary outcome composite components will also be analyzed as time-to-event censored at 28D, within a competing risk framework, where extubation is the main event and death before extubation a competing one, as recommended byYehya et al. (20). Time to each event, i.e., subdistribution hazards, will be modeled by a Fine&Gray model, with the treatment arm included as a covariate and center as strata. This analysis provides a subdistribution of the hazard ratio (SHR), where the size is influenced by both times to extubation and probability of death.

In addition, the effect size and number needed to treat (NNT) will be computed as indicated.

Other multi-state models can be used to explore the primary endpoint.

The 28 and 90 days overall survival probability will be estimated by the Kaplan-Meier method. The Kaplan-Meier curves will be presented by treatment

If the assumptions for appropriate use of the Cox proportional hazards regression model and Fine&Gray model will be respected, in particular:

- independence of survival times between distinct individuals in the sample,
- a multiplicative relationship between the predictors and the hazard

Comparing the treatment arms will be performed with the Cox model by estimating the hazard ratio with a 95% confidence interval; treatment, participant's risk factors (age, sex, and BMI) at baseline as covariates. Center will be included as strata in this model.

For mortality at 28 and 90 days, effect size and numbers needed to treat (NNT) will be computed.

The other efficacy outcome such as:

- Evolution of SOFA score (presented as percentage variation from the baseline score at 14 and 28 days)
- Lung injury score: the LI score will be calculated by adding the sum of each component and dividing by the number of components used (21;22)
- ADL and IADL score at 28 and 90 days

Will be presented as medians and interquartile ranges. According to their distribution, a Student or Mann-Whitney test will be performed for the treatment arms comparisons.

Finally, the length of the ICU stay (in days) and length of hospital stay up to the 90th day will be analyzed according to discharge using the Log-Rank test.

Exploratory objectives

Exploratory objectives will be evaluated the impact of the experimental on:

- the incidence of pulmonary embolism
- the number of delirium free days according to the CAM-ICU up to 28D
- the occurrence of ICU-acquired weakness defined by an MRC sum score < 48 at ICU. discharge
- the occurrence of ventilator-associated pneumonia
- biological efficiency study through the in-depth study of IGIV impacts cytokines, immune cells transcriptome, and lymphocytes activation in an ancillary study.

Safety parameters

All safety analyses will be performed on the Safety Population.

Safety and tolerability will be assessed by clinical safety laboratory measurements, physical examinations, vital signs, concomitant medications. The cumulative incidence of AEs and SAEs will be reported.

Exposure

Exposure to study treatment will be performed on mITT Population and summarized by the following using descriptive statistics:

- Duration of treatment
- Starting dose
- Cumulative dose
- Dose intensity (%) (defined as the total amount of study treatment received relative to the total amount of study treatment planned per protocol)

Dose modification (dose reduction or interruption) will be summarized as follows:

Dose modification:

- n (%) of patients with any dose modification (reduction or interruption)

Dose reduction:

- n (%) of patients with at least one dose reduction
- Number of dose reductions per patient (mean, median, range)
- Reason for change in dose

Dose interruptions:

- n (%) of patients with at least one dose interruption
- Number of interruptions per patient (mean, median, range)

Adverse Events

Adverse Events will be coded using the MedDRA coding dictionary.

The number and percentage of patients with any AE, any related AE, any SAE, any related SAE, any severe AE, and related severe AE and the total number of events for each category will be summarized. The number of deaths due to an AE and study discontinuation due to an AE will be summarized.

Listing of all Serious Adverse Events will be provided. Patient listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs, related AEs, and severe AEs will be produced.

Clinical laboratory evaluation

Baseline is defined as the last non-missing value obtained at the screening visit and before the first exposure to the study drug. Actual values and changes from Baseline clinical laboratory tests will be summarized by study day.

Laboratory test results will be classified according to the reference ranges and clinical significance determined by the investigator. The number of patients with a non-missing result, the number and percentage of patients with a clinically significant result more minor than the lower limit of normal, non-clinically significant result more than the upper limit of normal (ULN), and clinically significant result more than the ULN will be summarized by study visit.

Categorical laboratory test results will be summarized by study visit.

Patients with clinically significant abnormal laboratory test results will be listed. This listing will include all laboratory results that were abnormal and determined to be clinically significant by the investigator for a patient across study visit.

Vital Sign

Baseline is defined as the last non-missing value obtained in screening and before the first exposure to study drug. Actual values and changes from baseline in vital signs will be summarized by study day and study time point. All vital sign data will be presented in patient listings.

Vital sign values will be classified according to the clinical significance as determined by the investigator. The number of patients with a non-missing result, the number and percentage of patients with a non-clinically significant result, and clinically significant result will be summarized by study visit and study time point.

Patients with clinically significant vital sign values will be listed. This listing will include all the vital sign parameter results that the investigator determined to be clinically significant for a patient across study time points.

Subgroup analysis

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints (and its composite components), overall survival at 28 and 90 days and mortality, will be estimated and plotted within each category of the following classification variables:

- Time of IMV at randomization: less than 12 hours, between 12 and 24 hours, and between 24 and 72 hours
- Age: <=65 years; >65 years
- BMI (kg/m^2): >= 30; <30
- Concomitant treatment with corticosteroids: Y vs N

A subgroup analysis by age, with a threshold >= 65, in the subgroup of patients alive at day seven will be performed.

In addition, a Forest plot will be produced, which provides the estimated point and confidence intervals for the treatment effect across the subgroups categories listed above. If there are a small number of responses/events in one or more strata, for analysis, strata will be combined to ensure a sufficient number of responses/events in each stratum.

Missing data

- For the primary endpoint (VFDs)

Patients discharged from the hospital before day 28 after randomization will have a telephone interview regarding their actual and past ventilation status on day 28, so information on ventilation status can be completed.

Given the type of patient and pathology, it is expected that the number of patients lost to follow-up before day 28 is very small.

In the primary analysis, for these very few patients (withdrawn early from the study but not discharged), we assume:

- if the patients were on invasive-mechanical ventilation at the discontinuation point, the remaining days to Week 4 with missing data on ventilation status would be counted as no VFDs
- If the patients were not in invasive ventilation at the point of withdrawal will be assumed the days from withdrawal to Week 4 as VFDs

If ventilator status is missing for patients that have not withdrawn, died, or discharged, then the last ventilator status observed post-baseline would be carried forward until the following observation.

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

In the case of missing data on individual SOFA components, 0 (normal) value was imputed for that component (23).

Statistical software

All statistical analyses will be conducted using SPSS, Version 26 (IBM Corp., Armonk, NY, USA).

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Appendix 1. ARDS Berlin Definition

Criterion	Mild	Moderate	Severe
Timing	Acute onset within one week of a known clinical insult or new or worsening respiratory symptoms		
Hypoxemia (PaO_2/FIO_2)	201-300 with PEEP/CPAP ≥5	101-200 with PEEP ≥5	≤100 with PEEP ≥5
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload		
Chest imaging	Bilateral opacities	Bilateral opacities	Bilateral opacities

PaO_2/FIO_2 - relationship between oxygen partial pressure and fraction of inspired oxygen; PEEP - positive end-expiratory pressure; CPAP - continuous positive airway pressure.

Appendix 2. Kidney Disease: Improving Global Outcomes (KDIGO)

Stade	Créatinine	Diurèse
1	1.5-1.9 x la baseline ou Augmentation ≥ 26.5 µmol/l	< 0.5 ml/kg/h pour 6-12h
2	2.0-2.9 x la baseline	< 0.5 ml/kg/h pour ≥ 12h
3	3.0 x la baseline ou Augmentation ≥ 353.6 µmol/l ou Début de l'épuration extra-rénale ou Chez patient < 18 ans, diminution du DFGe < 35 ml/min/1.73 m^2	< 0.3 ml/kg/h pour ≥ 24h ou Anurie pour ≥ 12h

Appendix 3. The Medical Research Council (MRC.)

Scale for Muscle Strength is a commonly used scale for assessing muscle strength from Grade 5 (normal) to Grade 0 (no visible contraction). This score was defined as the sum of MRC scores from six muscles in the upper and lower limbs on both sides so that the score ranged from 60 (normal) to zero (quadriplegic).

The Criteria requires that each of the six muscle groups listed in the table be examined bilaterally, each with a score from zero to five according to the scale in the right-hand column.

MRC Sum score

Muscle		Score 0 - 5	MRC scale for muscle strength (0-5)
Shoulder abductors	Left		Grade 5: Normal
	Right		Grade 4: Movement against gravity and resistance
Elbow flexors	Left		Grade 3: Movement against gravity over (almost) the full range
	Right		Grade 2: Movement of the limb but not against gravity
Wrist extensors	Left		Grade 1: Visible contraction without movement of the limb (not existent for hip flexion)
	Right		Grade 0: No visible contraction
Hip flexors	Left		MRC grade for each muscle given in full numbers: (4+/4.5 =4) (4-=3) (5- = 4)
	Right		
Knee extensors	Left		
	Right		
Foot dorsiflexors	Left		
	Right		
	Total (out of 60)		

Appendix 4. Charlson Comorbidity Index (CCI)

Condition	Assigned weight
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Liver disease, mild	1
Diabetes	1
Hemiplegia	2
Renal disease, moderate or severe	2
Diabetes with end organ damage	2
Any malignancy	2
Leukemia	2
Malignant lymphoma	2
Liver disease, moderate or severe	3
Metastatic solid malignancy	6
Acquired immunodeficiency syndrome (AIDS)	6

Appendix 5: IGS II score calculation table (simplified severity index)

Entrée	Chir urgente :8 pts		Médecine : 6 pts		Chir programmée	
Age (ans)	<40 :0 pt	40 – 59 :7 pts	60 – 69 : 12 pts	70 – 74 : 15 pts	75 – 79 : 16 pts	>80 :18 pts
Température (°c)	<39 :0 pt				>39 : 3 pts	
Urée (mmol/L)	<10 :0 pt	10 – 29,9 :6pts	>30 : 10 pts			
Na (mEqL)	125 _ 144 : 0 pt	>145 : 1 pt	<125 :5 pts			
Maladie chronique	Aucune :0 pt	Cancer métastasé :9	Mal hémato :10	SIDA : 17 pts		
PAs (mmHg)	<70 : 13 pts	70 – 99 : 5 pts	100 – 199 : 0 pt	>200 : 2 pts		
GB / mm^3	<1000 :12 pts	1000 – 19000 :0 pt	>20000 : 3 pts			
Bicar (mEq/L)	>20 :0 pt	15 – 19 :3 pts	<15 :6 pts			
Glasgow	<6 :26 pts	6 – 8 :13 pts	9 – 10 : 7 pts	11 – 13 : 5 pts	14 – 15 : 0 pt	
FC / mn	<40 : 11 pts	40 – 69 :2 pts	70 – 119 :0	120 – 159 : 4	>160 : 7 pts	
Diurèse (L/24h)	<0,5 :11 pts	0,5 – 0,99 : 4 pts	>1 :0 pt			
K+ (mEq/l)	<3 :3 pts	3 – 4,9 :0 pt	>5 :3 pts			
	<68,4 : 0 pts	68,4 – 102,6 : 4 pts	>102,6 : 9 pts			

Appendix 6: SOFA score

SOFA SCORE	1	2	3	4
Respiration *PaO2 :FiO2*	<400	<300	<200*	<100*
Coagulation *Plaquettes x10^3/mm^3*	<150	<100	<50	<20
Foie *Bilirubine, mg/dl (µmol/l)*	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (>204)
Cardiovasculaire *Hypotension*	MAP<70 mm Hg	Dopamine ≤5 γ/kg/min ou Dobutamine	Dopamine >5 γ/kg/min ou adrénaline ou noradrénaline ≤0.1 γ/kg/min	Dopamine >15 γ/kg/min ou adrénaline ou noradrénaline >0.1 γ/kg/min
Neurologique *Glasgow*	13-14	10-12	6-9	>6
Rénal *Créatinine, mg/dl (µmol/l) ou diurèse*	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or < 500 ml/jour	>5.0 (>440) or <200 ml/jour

In the SAP, only one substantive change was made regarding the scheduling of an interim analysis.

Additional non-substantive changes have been made and highlighted in italics and blue color in the latest SAP version.

Statistical Interim analysis and stopping guidance No interim analysis is planned	Statistical Interim analysis and stopping guidance One formal interim statistical analysis will be carried out when 50 (25 participants in the IVIG arm and 25 participants in the placebo arm) have completed the D28 assessment. The purpose of the first analysis will be to assess the futility of IVIG based on the results on change in VFDs at D28. The following futility criterion will be used for this interim analysis: If the difference in the VFDs is less than 3-day improvement between both treatment arms, the benefit of IVIG treatment is not expected. For a final decision to stop the study for futility, the results on other endpoints will be considered as well. For the primary objective (VFDs) to account for multiple testing due to the interim analysis, an adjustment for type I error alpha will be applied using the O'Brien-Fleming spending function, which would expend two-sided alpha = 0.0003 at the interim analysis (critical value = ±3.6128) and leave nominal two-sided alpha of 0.0497 for the final analysis (critical value = ±1.9601).