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.

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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

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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

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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.

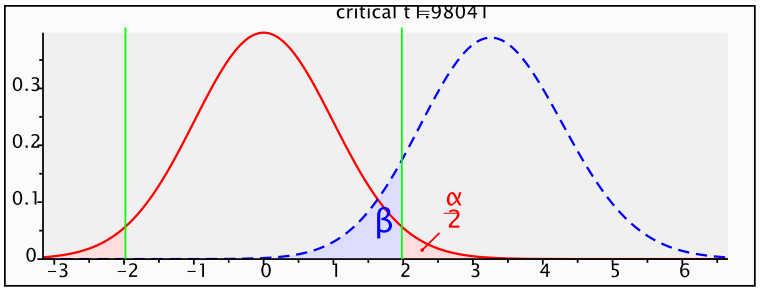
Therefore, a mean value of 5 days without ventilation in the placebo group versus 9 in the experimental group is assumed, and the 6-day standard deviation is assumed to be stable. Given the uncertainty regarding the assumption of normality of distributions, the non-parametric Wilcoxon-Mann-Whitney test (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).

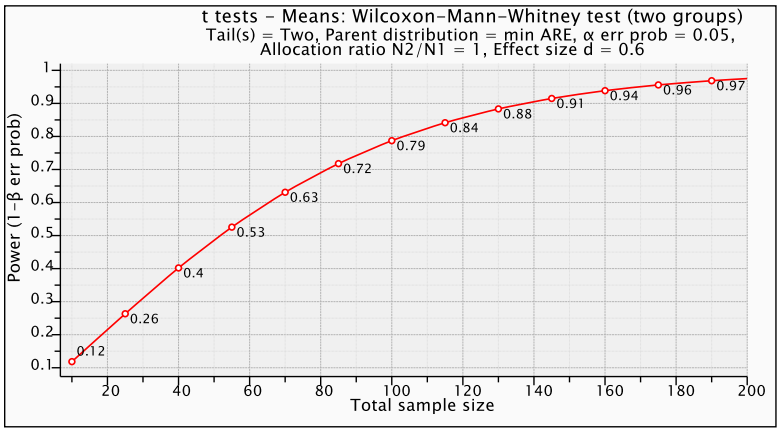
Table 1

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).

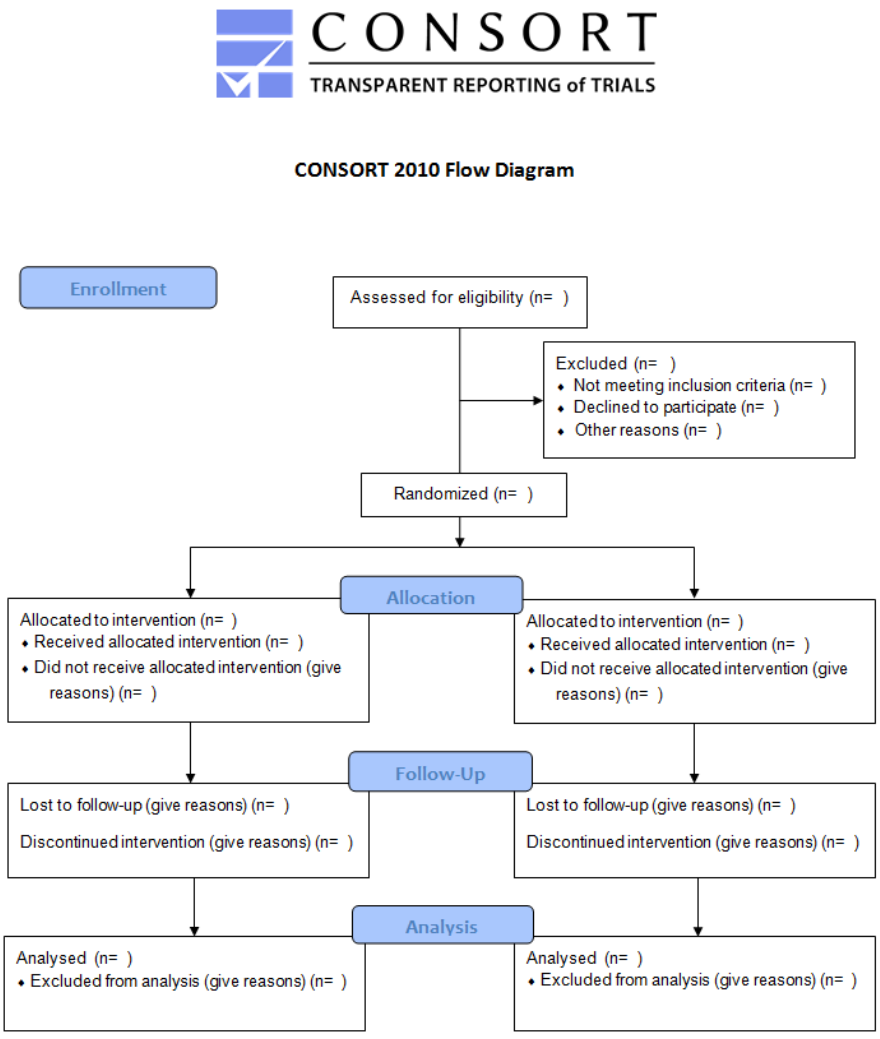


Figure 1. CONSORT Flow Diagram of trial participants

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 96 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 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