



## Early View

Original research article

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## **Prolonged higher dose methylprednisolone vs. conventional dexamethasone in COVID-19 pneumonia: a randomized controlled trial (MEDEAS)**

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### **Take-home message**

Infusive methylprednisolone did not show major advantages over dexamethasone in severe COVID-19 pneumonia, confirming the favorable drug class effect of prolonged, low-dose glucocorticoids postulated by current guidelines.

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## **Abstract**

### Introduction

Dysregulated systemic inflammation is the primary driver of mortality in severe COVID-19 pneumonia. Current guidelines favor a 7-10-day course of any glucocorticoid equivalent to dexamethasone 6 mg/day. A comparative RCT with a higher dose and a longer duration of intervention was lacking.

### Methods

We conducted a multi-center, open-label RCT to investigate methylprednisolone 80 mg as a continuous daily infusion for 8 days followed by slow tapering vs. dexamethasone 6 mg daily for up to 10 days in adult patients with COVID-19 pneumonia requiring oxygen or noninvasive respiratory support. Primary outcome: reduction in 28-day mortality. Secondary outcomes: mechanical ventilation-free days at 28 days, need for ICU referral, length of hospitalization, need for tracheostomy, changes in PaO<sub>2</sub>:FiO<sub>2</sub> ratio, C-reactive protein levels and WHO clinical progression scale at days 3, 7, and 14.

### Results

677 randomized patients were included. Findings are reported as methylprednisolone (n=337) vs dexamethasone (n=340). By day 28, there were no significant differences in mortality (35[10.4%] vs. 41[12.1%];  $p=0.49$ ), nor in the median mechanical ventilation-free days (23[14] vs. 24[16];  $p=0.49$ ). ICU referral was necessary in 41[12.2%] vs. 45[13.2%];  $p=0.68$  and tracheostomy in 8[2.4%] vs. 9[2.6%];  $p=0.82$ . Survivors in the methylprednisolone group required a longer median hospitalization (15[11] vs. 14[11] days;  $p=0.005$ ) and experienced an improvement in C-reactive protein levels, but not in PaO<sub>2</sub>:FiO<sub>2</sub> ratio, at days 7 and 14. There were no differences in disease progression at the prespecified timepoints.

### Conclusion

Prolonged, higher dose methylprednisolone did not reduce mortality at 28 days compared to conventional dexamethasone in COVID-19 pneumonia.

## Introduction

A substantial percentage of COVID-19 cases experience severe pneumonia associated with an acute respiratory decompensation requiring supplemental oxygen and mechanical ventilation (MV). The overall fatality rate approximates 40% in patients undergoing invasive MV.[1] Glucocorticoid (GC) treatment is the intervention associated with the highest mortality reduction in COVID-19 pneumonia.[2] The randomized controlled trial (RCT) RECOVERY firstly demonstrated the efficacy of dexamethasone (DM) once daily for up to 10 days, with a greater impact in those receiving MV (-36%) than oxygen alone (-18%).[1] Several other RCTs confirmed the rationale for the use of GCs in severe COVID-19 pneumonia.[3] Current guidelines favor a 7-10-day course of any GC equivalent to DM 6 mg/day (e.g. hydrocortisone 50 mg every 8 hours) in severe COVID-19.[4, 5] However, the lack of detailed indications about a preferable GC molecule and administration schedule led to a heterogeneity of treatment protocols and misinterpretation of findings.[3]

Glucocorticoids exert their effects binding to the glucocorticoid receptor alpha ( $GR\alpha$ ), but different compounds have different pharmacological properties.[6] Clinical efficacy in ARDS depends on the magnitude and duration of exposure to GC, including genomic and non-genomic effects.[7, 8] Theoretically, optimal results are achievable with an initial bolus to reach close-to-maximal  $GR\alpha$  saturation, followed by a prolonged low-dose infusion to maintain high levels of response, and a dose-tapering period to favor recovery of the physiological hypothalamic-pituitary-adrenal axis.[8] According to these principles, the 2017 SCCM/ESICM consensus for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) proposed a protocol involving a bolus followed by a continuous infusion of 80 mg of methylprednisolone (MP).[9] The same protocol has proven safe and effective in reducing both mortality and the duration of invasive MV among patients affected by severe COVID-19 pneumonia.[10] At present, however, there is poor evidence of the superiority of one GC protocol. Indeed, two small RCTs reported better outcomes with MP compared to DM in COVID-19, but their results are poorly generalizable.[11, 12] Furthermore, molecular target-based bioinformatic studies supported the theoretical advantage of MP.[13]

The lack of comparative studies on prolonged low dose GCs prompted us to perform a RCT comparing MP 80 mg bolus followed by 80 mg/day continuous infusion for eight days followed by slow tapering vs. DM 6 mg once daily for up to 10 days, in COVID-19 pneumonia requiring oxygen or noninvasive respiratory support.

## **Methods**

### Trial design, setting and participants

This is a multi-center, open-label RCT (2 parallel arms, allocation ratio 1:1) conducted in 26 Italian centers including internal medicine units, infectious diseases units, emergency medicine departments, and respiratory high-dependency units. The study was registered on ClinicalTrials.gov (NCT04636671) and approved by the National Ethics Committee (2020-006054-43) and the Italian Medicines Agency (AIFA). The protocol and trial conduct complied with the Declaration of Helsinki, ICH E6 Guideline for Good Clinical Practice, and European Regulations.

The inclusion criteria were: a) able to understand and sign the written informed consent; b) real-time polymerase chain reaction-positive for SARS-CoV-2 on at least one upper respiratory swab or bronchoalveolar lavage; c)  $\text{PaO}_2 \leq 60$  mmHg or  $\text{SpO}_2 \leq 90\%$  or on high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV); d) age  $\geq 18$  years. The exclusion criteria were: a) requiring invasive MV; b) heart failure as the main cause of acute respiratory failure; c) on long-term oxygen or home MV; d) decompensated liver cirrhosis; e) immunosuppression (i.e., cancer on treatment, post-organ transplantation, HIV-positive, on immunosuppressant therapy); f) on chronic steroid therapy or other immunomodulant therapy; g) dialysis dependence; h) neurodegenerative conditions; i) dementia or decompensated psychiatric disorder; j) quadriplegia/hemiplegia or quadriparesis/hemiparesis; k) do-not-resuscitate order; l) use of any other investigational drug for COVID-19 treatment; m) any other condition that in the opinion of the investigator might significantly impact with the patient's capability to comply with the protocol intervention.

### Interventions

All patients meeting the above entrance criteria were randomized to one of the following treatment protocols. Arm 1 (methylprednisolone, MP): on day 1, a loading dose of MP 80 mg was administered intravenously (IV) in 30 minutes, followed by a continuous infusion of MP 80 mg in 240 mL of normal saline at 10 mL/h for eight days. From day nine and beyond: a) if the patient was not intubated and  $\text{PaO}_2:\text{FiO}_2$  was  $> 200$ , the treatment was tapered to MP 20 mg IV in 30 minutes three times a day for three days, then MP 20 mg IV twice daily for three days, then MP 20 mg IV once daily for two days, then MP 16 mg/day per os (PO) for two days, then MP 8mg/day PO for two days, then MP 4mg/day PO for two days; b) If the patient required invasive mechanical ventilation (IMV) or  $\text{PaO}_2:\text{FiO}_2$  was  $\leq 200$  with at least 5 cmH<sub>2</sub>O CPAP, an infusion of MP 80 mg/day in 240 mL of normal saline at 10 mL/h was continued until  $\text{PaO}_2:\text{FiO}_2$  reached  $> 200$ , then it was tapered as in a). Arm 2 (dexamethasone, DM): DM 6 mg IV in 30 minutes or PO from day one to day ten or until hospital discharge (if sooner). Figure S1 summarizes the treatment schedule

in both arms. Patients in both study groups had access to the same standard of care, comprising NIV, IMV, extracorporeal membrane oxygenation (ECMO), antibiotics, antivirals, vasopressors, renal replacement therapy, and anticoagulation according to clinical needs.

#### Outcome measures

The primary endpoint was mortality proportion at day 28. The secondary endpoints were: a) number of days free from MV (either NIV or IMV) by study day 28; b) proportion of patients requiring admission to an intensive care unit (ICU); c) number of days of hospitalization among survivors; d) proportion of patients requiring tracheostomy; e) C-reactive protein level (CRP, mg/L) at study day three, seven, and fourteen; f) PaO<sub>2</sub>:FiO<sub>2</sub> ratio (mmHg) at study days three, seven, and fourteen; g) WHO clinical progression scale at study days three, seven, and fourteen.[14]

#### Randomization and data collection

The randomization list was generated by the study statisticians with Stata 14.2 using blocks of variable size of 2, 4 or 6 in a random order. The list was implemented in the REDCap® randomization module allowing for centralized allocation of patients through the REDCap® platform embedded in a web hosting facility, which granted allocation concealment. Electronic case report forms were developed to collect all relevant information. At each participating Centre, one assigned investigator who had secure access to the platform was in charge for the randomization and data entry. Three independent physicians checked the data.

#### Statistical methods

This trial was designed as a sequential RCT with two interim analyses, unblinded sample size recalculation, and stopping rules for either early efficacy or futility (O'Brien-and-Fleming design). The experimental hypothesis was that MP treatment would have improved 28-day survival from 77% in arm 2 to 87% in arm 1 (10% risk difference). If this hypothesis had been true, the study would have had a one tail alpha-error < 0.025 and an overall power > 90% using a Fisher's exact test, with a sample size varying between 200 to 680 participants according to the observed effect within the trial sample at each stage (see supplementary material for details). The actual sample size is 680 patients. A list of 690 patients was generated to account for randomization of not eligible patients.

Data were described using absolute and relative frequencies (percentage) or position indices (mean or median) and relative dispersion indices (standard deviation, SD or interquartile range, IQR), according to the type and distribution of the variables. Odds ratio and relative 95% Confidence Interval (95% CI) were calculated. The difference in numerical variables between groups was calculated using the Student t-test or Wilcoxon rank-sum test, as appropriate. Differences between study groups concerning categorical and dichotomous variables were evaluated with chi-square test



or Fisher exact test, as appropriate. Time at risk for all-cause death was computed from the date of study enrollment up to the date of death, hospital discharge, or 28 days, whichever came first. Event-free probabilities were estimated by the Kaplan-Meier method, and differences between groups were assessed by the log-rank test. Prespecified subgroups analyses were performed by the severity of respiratory impairment at randomization ( $\text{PaO}_2\text{:FiO}_2 < 200$  or  $> 200$ ) and by the level of respiratory support required at randomization (low-flow oxygen therapy; HFNC; NIV). Available case analysis was performed for the variation of CRP and  $\text{PaO}_2\text{:FiO}_2$  levels over time. Multivariable logistic regression was used to adjust for imbalance between the two arms and for possible confounders. All tests were 2-sided, and a p-value of  $< 0.05$  was considered statistically significant. All analyses were conducted according to the *intention to treat* principle, but sensitivity *per protocol* sub-analyses were then carried out.

## Results

### Patients

Of the 690 patients who underwent randomization from April 14, 2021 to May 4, 2022, 677 patients were eligible to receive one of the study treatments, while 13 were excluded because they were incorrectly enrolled in the trial despite meeting exclusion criteria. Of these 677 patients, 337 received MP, while 340 received DM (Figure 1).

Findings are reported as MP vs. DM. The two groups had similar baseline characteristics (Table 1), except for a lower median [IQR]  $\text{PaO}_2\text{:FiO}_2$  ratio in the MP group (178.6 [135.0] vs. 202 [130.9] mmHg). Accordingly, more patients in the MP group were undergoing HFNC as compared to low-flow oxygen therapy and NIV at randomization. All patients included in the analysis received at least one dose of the assigned treatment. The median [IQR] duration of GC treatment was 20.0 [6.2] vs. 9.0 [4.0] days. A similar number of patients (58 [17.2%] vs. 54 [15.9%];  $p = 0.64$ ) did not comply with the assigned protocol, detailed as: a) earlier discontinuation due to adverse events (4 [1.2%] vs 0 [0.0%]); b) earlier discontinuation due to physician's decision (35 [10.4%] vs. 20 [5.8%]); c) switch to the other arm (10 [3.0%] vs. 10 [2.9%]); d) increase in the treatment dosage or duration due to clinical worsening (9 [2.7%] vs. 24 [7.1%]). Patients who complied with the assigned protocol (279 [82.8%] vs. 286 [84.1%]) were included in the *per-protocol* analysis. The number of patients requiring either NIV (205 [60.8%] vs. 204 [60%];  $p = 0.82$ ) or IMV (32 [9.5%] vs. 33 [9.7%];  $p = 0.93$ ) within day 28 did not differ. The use of concomitant medications was similar between the two groups (Table S1).

### Primary outcome

Mortality at 28 days (Table 2) did not significantly differ between groups either in the *intention-to-treat* analysis (35 [10.4%] vs. 41 [12.1%];  $p = 0.49$ ) or in the *per-protocol* analysis (24 [7.1%] vs. 19 [5.6%];  $p = 0.38$ ). Mortality at 60 days was also similar between groups, though it was not a prespecified outcome. Figure 2 shows the Kaplan-Meier curves of the survival probability at 28 days and 60 days. We observed no difference in the primary endpoint even when stratifying for the severity of respiratory impairment or for the type of respiratory support received at randomization (Table 3). These results did not substantially change when other variables (e.g., baseline PaO<sub>2</sub>:FiO<sub>2</sub>, GC use before randomization, vaccination status, age) were included in the logistic regression models.

### Secondary outcomes

The secondary outcome results are summarized in Table 4. The median [IQR] MV-free days by day 28 were similar (23.0 [14.0] vs. 24.0 [16.0];  $p = 0.49$ ), as well as they were IMV-free days by day 28 (28.0 [0.0] vs. 28.0 [0.0];  $p = 0.92$ ). These results did not significantly change in the *per-protocol* analysis, nor after stratification for baseline severity (Table S2). The number of patients who required referral to an ICU was comparable (41 [12.2%] vs. 45 [13.2%];  $p = 0.68$ ), though it was significantly lower in the MP group according to the *per-protocol* analysis (7 [2.1%] vs. 19 [5.6%];  $p = 0.02$ ). In the stratified analysis (Table S3), statistical significance was only reached in the subgroup of patients who had a PaO<sub>2</sub>:FiO<sub>2</sub> < 200 mmHg at randomization. Survivors in the MP group required a longer median [IQR] duration of hospitalization (15.0 [11.0] vs. 14.0 [11.0] days;  $p = 0.005$ ), which was confirmed in the *per-protocol* analysis (15.0 [10.0] vs. 13.0 [10.0];  $p = 0.001$ ). However, this result was only consistent in patients with a less severe respiratory involvement (i.e. those with a PaO<sub>2</sub>:FiO<sub>2</sub> ≥ 200 mmHg and those requiring oxygen alone, but not HFNC and NPPV) at randomization (Table S4). No differences were observed in the need for tracheostomy between groups (8 [2.4%] vs. 9 [2.6%] patients;  $p = 0.82$ ). The median [IQR] levels of CRP was significantly lower in the MP group at days 7 (8.6 [21.9] vs. 12.4 [28.9];  $p = 0.006$ ) and 14 (5.0 [21.8] vs. 11.5 [36.2];  $p = 0.0001$ ) but not at day 3 (Figure S2). There were no significant differences in the median PaO<sub>2</sub>:FiO<sub>2</sub> ratio at days 3, 7 and 14 (Figure S2). Patients in both groups did not show significant changes in the WHO clinical progression scale at days 3, 7 and 14 (Tables S5-S6).

### Adverse events

As detailed in tables S7-S8, there were no differences between groups in the occurrence of adverse events related to the study treatment (147 [43.6%] vs. 126 [37.0%];  $p = 0.08$ ), nor in that of in-hospital complications of any type (169 [50.1%] vs. 158 [46.5%];  $p = 0.36$ ). The most frequent adverse event was hyperglycemia (113 [33.5%] vs. 93 [27.4%];  $p = 0.15$ ). In four cases the

treatment was interrupted due to adverse events, reported as: agitation (two cases), hyperglycemia and GI bleeding. There were no reports of serious adverse reactions related to the study treatment.

## **Discussion**

In our study there were no statistically significant differences in 28-day mortality between patients affected by SARS-CoV-2-related pneumonia treated with MP and those treated with DM. While the duration of MV and IMV was similar between groups, patients in the MP group with  $\text{PaO}_2:\text{FiO}_2 < 200$  mmHg at randomization who completed the assigned treatment protocol experienced a lower rate of ICU admission. Conversely, patients in the DM group with a less severe respiratory involvement at randomization had a shorter median length of hospital stay. MP was associated with a significant reduction of CRP at days 7 and 14. Previous data associated a faster reduction of CRP with a lower 1-year mortality after severe pneumonia and sepsis [15, 16], and there is evidence that persistently elevated CRP and need for ICU admission are independent risk factor for the development of post-COVID conditions, which were not followed-up in this trial.[17, 18] Both treatment protocols were equally safe as we observed a similar incidence of adverse events and no serious adverse reactions, consistently with previous data.[19, 20]

Two smaller RCTs compared methylprednisolone with dexamethasone in COVID-19 to date. Both studies investigated a single bolus of methylprednisolone 2 mg/Kg daily for five days followed by 1 mg/Kg for other five days vs. dexamethasone 6 mg daily for ten days.[11, 12] A statistically significant reduction in mortality was only observed in the study by Saeed et al. (n=414), in which mechanically ventilated patients were selectively included.[12] This inclusion criterion could explain the discordant result with our study. Indeed, there is strong evidence of a proportional benefit of GCs among patients who require mechanical ventilation rather than other lower-intensity respiratory support modalities [3]. The duration of MV was lower in the MP group in both studies, while Ranjbar et al. (n=86) also found a significant reduction in the length of hospitalization.[11]

One recent RCT found no benefit of 1g MP boluses for 3 consecutive days vs. placebo in addition to DM 6 mg/day for 10 days on the duration of hospitalization, nor on survival.[21] Despite this study design is not comparable with ours, pulsed high-dose MP had already proven detrimental.[8]

Our results are also concordant with those of both the COVID STEROID 2 trial and the recent RCT by Taboada et al on the effect of higher vs. lower doses of DM on clinical worsening.[22, 23]

We believe there are two leading causes underlying the longer duration of hospitalization among patients treated with MP in our study: first, the MP protocol had a more extended administration schedule due to both titration based on clinical response and an intravenous de-escalation phase. Indeed, the differential length of hospital stay was even larger among patients who completed the

assigned treatments (Table 4). Second, patients in the MP group suffered from a more severe respiratory involvement at randomization. Furthermore, we observed an inversely proportional trend between the severity of respiratory status at baseline and the difference in the duration of hospitalization between groups, which is consistent with a possible higher benefit of MP treatment in the most severe subgroups.

One major finding was the lower ICU admission incidence in the MP group, which reached statistical significance in patients who had a  $\text{PaO}_2:\text{FiO}_2 < 200$  mmHg at randomization and completed the assigned treatment protocol. This could be apparently discordant with the similar number of days free from IMV at 28 days between groups; however, it is important to observe that this was a multicenter study involving different types of hospital units, and that not all of them were able to provide MV. Therefore, in several centers, patients who deteriorated were moved to the ICU regardless of the need for IMV. The MEDEAS trial was implemented to provide a rapid assessment of a potentially higher benefit of the infusive MP protocol over the widely used DM administration schedule. An open-label design was best suitable for the purposes of this study, as it also is accepted from previous reports in similar settings [3]. However, one major limitation pertains to study design itself. Indeed, we calculated the sample size hypothesizing 23% mortality in patients treated with DM. While this data was extrapolated from previous literature and primarily from the RECOVERY trial, the actual 28-day mortality in the DM group was halved (12.1%) as a result of the different pandemic moments, different viral strains, and the increasingly better knowledge of COVID-19 and its management. Figure S3 shows the number of enrolled patients per month and the corresponding incidence of new COVID-19 cases in Italy. For this reason, interim analyses were not performed, as we deemed necessary to reach the highest preplanned sample size. Nevertheless, it is likely that the overestimation of overall mortality was of minor relevance, given the closeness of agreement between the primary outcome results in the two groups. Although the same standard of care was used among the 26 participating centers, it is possible that some centers experienced variations in internal protocols, limitations in the availability of ICU beds or delays in the initiation of MV due to the variable pressure on the hospitals in different pandemic moments. A further limitation pertains to the use of GCs in the home care setting, which was contraindicated at the time this trial was designed, but became increasingly frequent during the following months.[24] As this was not a prespecified exclusion criterion, the dose, type and duration of GC were recorded, and the median cumulative prednisone-equivalent dose before randomization was calculated, finding no differences between groups (Table 1). The proportion of vaccinated in our study was lower than that of the general population in the same time frame. However, it is concordant with the literature reporting on hospitalized patients affected by moderate to severe COVID-19, and we did not find differences

in death rates between groups within vaccinated and non-vaccinated.[25] One least potential limitation relates to the predictability of the randomization list that may result from block randomization. To avoid this, blocks of different sizes were used in a random order.

In conclusion, a protocol of infusive, prolonged, higher dose methylprednisolone did not show major advantages over conventional dexamethasone in COVID-19 pneumonia, confirming the favorable drug class effect of prolonged low-dose GCs postulated by current guidelines.

### **Registration**

ClinicalTrials.gov Identifier: NCT04636671.

### **Data availability**

Deidentified participant data will be made available upon motivated request to the Corresponding Author. The proposed use of the data and analyses must be approved by the Scientific Committee.

### **Author contributions**

FS conceived and designed the study, analyzed and interpreted the data, drafted, revised and approved the work; PC designed the study, collected and interpreted the data, revised and approved the work; SC collected and interpreted the data, revised and approved the work; MM collected and interpreted the data, revised and approved the work; NP conceived and designed the study, collected the data, revised and approved the work; PB collected and interpreted the data, revised and approved the work; GL collected and interpreted the data, revised and approved the work; DL collected and interpreted the data, revised and approved the work; AV collected and interpreted the data, revised and approved the work; NC collected and interpreted the data, revised and approved the work; MM designed the study, analyzed and interpreted the data, drafted, revised and approved the work; NR analyzed and interpreted the data, drafted, revised and approved the work; GUM conceived and designed the study, interpreted the data, revised and approved the work; BR collected and interpreted the data, revised and approved the work; MC conceived and designed the study, interpreted the data, drafted, revised and approved the work. All Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Conflict of interest**

Francesco Salton, Paola Confalonieri, Stefano Centanni, Michele Mondoni, Nicola Petrosillo, Donato Lacedonia, Antonio Voza, Nicoletta Carpenè, Marcella Montico, Nicolò Reccardini, Gianfranco Umberto Meduri, Barbara Ruaro, Marco Confalonieri have no conflicts of interest to disclose. Paolo Bonfanti received personal fees from ViiV Healthcare Gilead, Janssen, Merck and Pfizer, not related to this work. Giuseppe Lapadula received personal fees from ViiV Healthcare and Pfizer, not related to this work.

**Table 1.** Baseline characteristics of the study population

	MP (n=337)	DM (n=340)
Age, mean (SD)	64.4 (13.6)	63 (14.1)
Sex, No. (%)		
Male	237 (70.3)	233 (68.5)
Female	100 (29.7)	107 (31.5)
BMI, mean (SD)*	28.4 (5.2)	28.1 (5.1)
Ever smoker, No. (%)	132 (39.2)	150 (44.1)
Previous coexisting disease, No. (%)		
Any of the listed conditions	247 (73.3)	225 (66.2)
Diabetes <sup>†</sup>	60 (17.8)	58 (17.1)
Previous cancer <sup>‡</sup>	23 (6.8)	28 (8.2)
Arterial hypertension <sup>§</sup>	161 (47.8)	154 (45.3)
Asthma <sup>  </sup>	17 (5.0)	17 (5.0)
COPD <sup>¶</sup>	25 (7.4)	26 (7.7)
Bronchiectasis <sup>**</sup>	4 (1.2)	3 (0.9)
Pulmonary embolism <sup>††</sup>	3 (0.9)	10 (2.9)
Chronic kidney disease <sup>‡‡</sup>	17 (5.0)	16 (4.7)
Atrial fibrillation <sup>§§</sup>	20 (5.9)	23 (6.8)
Ischemic heart disease <sup>   </sup>	27 (8.0)	26 (7.7)
Heart failure <sup>¶¶</sup>	23 (6.8)	22 (6.5)
Chronic liver disease	6 (1.8)	6 (1.8)
Vasculopathy	11 (3.3)	8 (2.4)
Use of glucocorticoids before enrollment, No. (%) <sup>***</sup>	158 (46.9)	160 (47.3)
No. of days of glucocorticoid use, median (IQR)	2 (3.0)	3 (4.0)
Prednisone-equivalent cumulative dose (mg), median (IQR) <sup>†††</sup>	75 (112.5)	100 (118.7)
Anticoagulation before enrollment, No. (%) <sup>‡‡‡</sup>	33 (9.8)	40 (11.8)
Days of hospitalization before randomization, median (IQR)	1 (1.0)	1 (1.0)
Respiratory support at randomization, No. (%) <sup>§§§</sup>		
Low-flow oxygen	142 (42.3)	174 (51.6)
High-flow nasal cannula	74 (22.0)	45 (13.3)
Noninvasive mechanical ventilation	120 (35.7)	118 (35.0)
Anti SARS-CoV-2 vaccination (at least one dose), No. (%) <sup>    </sup>	80 (23.7)	76 (22.4)
PaO <sub>2</sub> :FiO <sub>2</sub> (mmHg), median (IQR)	178.6 (135.0)	202 (130.9)
C-reactive protein (mg/L), median (IQR)	69.7 (81.8)	74 (87.1)

**Table 1.** Baseline characteristics of the study population

	MP	DM
Abbreviations: SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range, PaO <sub>2</sub> :FiO <sub>2</sub> , ratio of partial pressure of arterial oxygen (PaO <sub>2</sub> in mmHg) to fractional inspired oxygen (FiO <sub>2</sub> )		
††† Calculated as [(daily mg of MP x 1.25 x days) + (daily mg of DM x 6.25 x days) + (daily mg of prednisolone x days)].		
*	Missing data: 35 MP, 23 DM.	
†	Missing data: 3 MP, 7 DM.	
‡	Missing data: 4 MP, 2 DM.	
§	Missing data: 2 MP, 1 DM.	
	Missing data: 4 MP, 3 DM.	
¶	Missing data: 7 MP, 6 DM.	
**	Missing data: 6 MP, 4 DM.	
††	Missing data: 21 MP, 20 DM.	
‡‡	Missing data: 2 MP, 2 DM.	
§§	Missing data: 2 MP, 1 DM.	
	Missing data: 5 MP, 2 DM.	
¶¶	Missing data: 5 MP, 5 DM.	
***	Missing data: 8 MP, 13 DM.	
†††	Missing data: 13 MP, 8 DM.	
§§§	Missing data: 1 MP, 3 DM.	
	Missing data: 129 MP, 126 DM.	



**Table 2.** Primary endpoints.

	Intention-to-treat analysis			Per-protocol analysis		
	MP (n=337)	DM (n=340)	p-value*	MP (n=279)	DM (n=286)	p-value*
Death at 28 days, No. (%)	35 (10.4)	41 (12.1)	0.49	24 (7.1)	19 (5.6)	0.38
Death at 60 days, No. (%)	44 (13.1)	44 (12.9)	0.96	28 (8.3)	21 (6.2)	0.26

Abbreviations: ITT, intention-to-treat; PP, per-protocol.

\* P-value of Chi-square or Fisher exact test for dichotomous variables

**Table 3.** Odds of death at 28 days according to the severity of respiratory impairment at randomization.

Stratification variable	Intention-to-treat analysis				Per-protocol analysis			
	MP <i>no. of events/total no. (%)</i>	DM <i>no. of events/total no. (%)</i>	OR (95% CI)	p-value*	MP <i>no. of events/total no. (%)</i>	DM <i>no. of events/total no. (%)</i>	OR (95% CI)	p-value*
None	35/337 (10.4)	41/340 (12.1)	0.84 (0.52-1.36)	0.49	24/279 (7.1)	19/286 (5.6)	1.32 (0.71-2.47)	0.38
PaO <sub>2</sub> :FiO <sub>2</sub> ≥ 200 mmHg	10/150 (6.7)	10/174 (5.7)	1.17 (0.47-2.89)	0.73	5/123 (4.1)	3/156 (1.9)	2.16 (0.51-9.22)	0.30
PaO <sub>2</sub> :FiO <sub>2</sub> < 200 mmHg	23/184 (12.5)	31/163 (19.0)	0.61 (0.34-1.09)	0.10	18/154 (11.7)	16/128 (12.5)	0.93 (0.45-1.90)	0.84
Low-flow oxygen	7/142 (4.9)	13/174 (7.5)	0.64 (0.25-1.65)	0.36	5/122 (4.1)	6/157 (3.8)	1.07 (0.32-3.61)	0.91
HFNC	6/74 (8.1)	6/45 (13.3)	0.57 (0.17-1.90)	0.36	4/66 (3.1)	5/38 (13.2)	0.42 (0.10-1.69)	0.23
NIV	22/120 (18.3)	21/118 (17.8)	1.04 (0.54-2.00)	0.91	15/90 (16.7)	7/89 (7.9)	2.34 (0.91-6.06)	0.08

Abbreviations: PaO<sub>2</sub>:FiO<sub>2</sub>, ratio of partial pressure of arterial oxygen (PaO<sub>2</sub> in mmHg) to fractional inspired oxygen (FiO<sub>2</sub>); HFNC, high-flow nasal cannula; NIV, noninvasive ventilation.

\* Odds-ratio of event among MP group vs DM group, estimated using logistic regression model.

**Table 4.** Secondary endpoints.

	Intention-to-treat analysis			Per-protocol analysis		
	MP (n=337)	DM (n=340)	p-value*	MP (n=279)	DM (n=286)	p-value*
Mechanical ventilation-free days at 28 days, median (IQR)	23.0 (14.0)	24.0 (16.0)	0.49	24.0 (10.0)	26.0 (8.0)	0.09
Invasive mechanical ventilation-free days at 28 days, median (IQR)	28.0 (0.0)	28.0 (0.0)	0.92	28.0 (0.0)	28.0 (0.0)	0.93
Days of hospitalization among survivors, median (IQR)	15.0 (11.0)	14.0 (11.0)	0.005	15 (10.0)	13 (10.0)	0.001
Tracheostomy, No. (%)	8.0 (2.4)	9.0 (2.6)	0.82	3.0 (1.1)	6.0 (2.1)	0.33
C-reactive protein (mg/L), median (IQR)						
Day 3	32.0 (57.5)	37.7 (56.6)	0.16			
Day 7	8.6 (21.9)	12.4 (28.9)	0.006			
Day 14	5.0 (21.8)	11.5 (36.2)	0.0001			
PaO <sub>2</sub> :FiO <sub>2</sub> (mmHg), median (IQR)						
Day 3	187.0 (132.0)	192.0 (138.0)	0.40			
Day 7	213.0 (146.0)	227.4 (151.0)	0.20			
Day 14	253.2 (159.0)	264.4 (165.5)	0.67			
ICU referral, No. (%)	41.0 (12.2)	45.0 (13.2)	0.68	7.0 (2.1)	19.0 (5.6)	0.02

Abbreviations: IQR, interquartile range; PaO<sub>2</sub>:FiO<sub>2</sub>, ratio of partial pressure of arterial oxygen (PaO<sub>2</sub> in mmHg) to fractional inspired oxygen (FiO<sub>2</sub>).

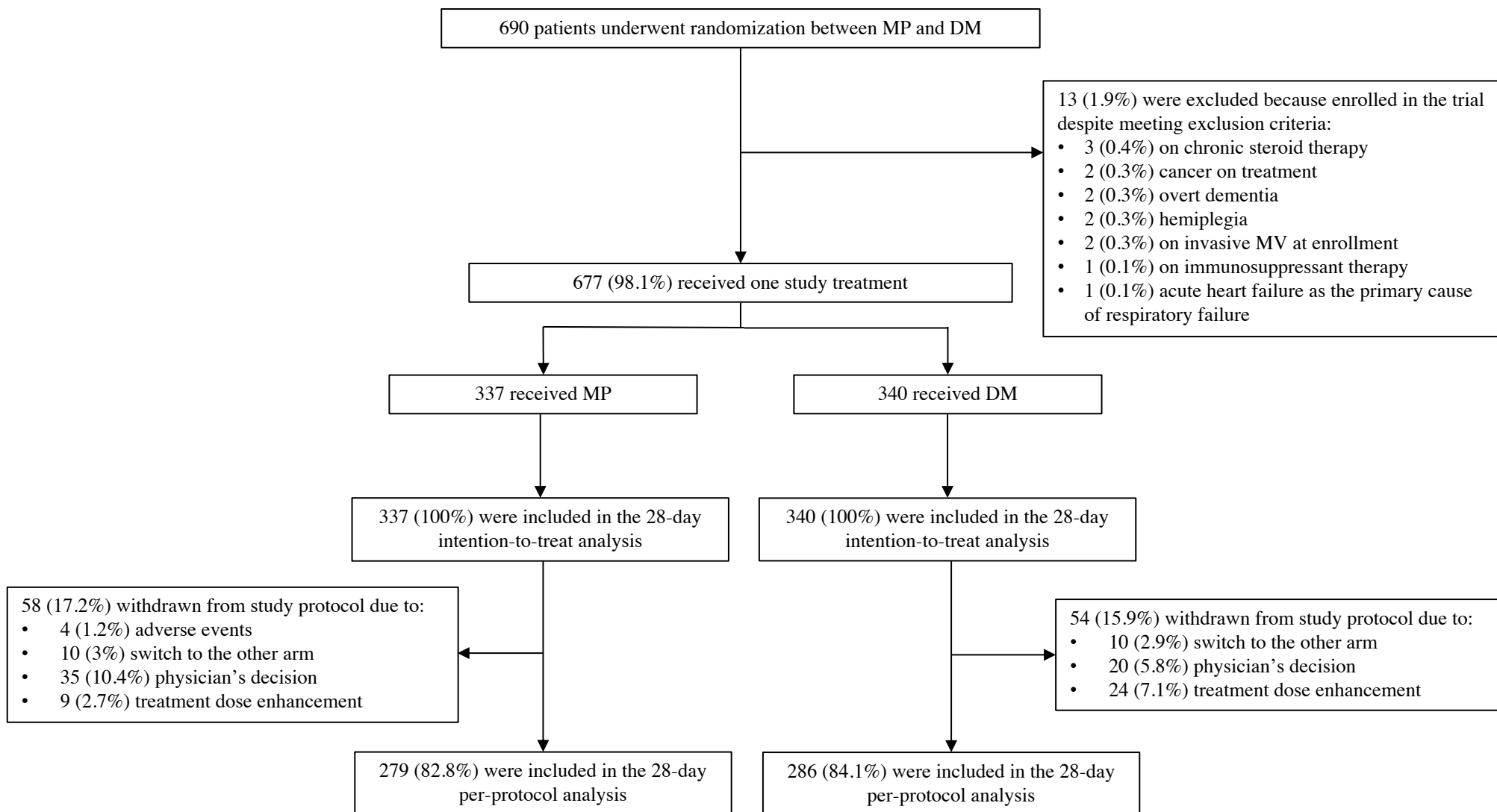
\* p-value of the Mann-Whitney for numerical variables; Chi-square or Fisher exact test for dichotomous variable, as appropriate.

## References

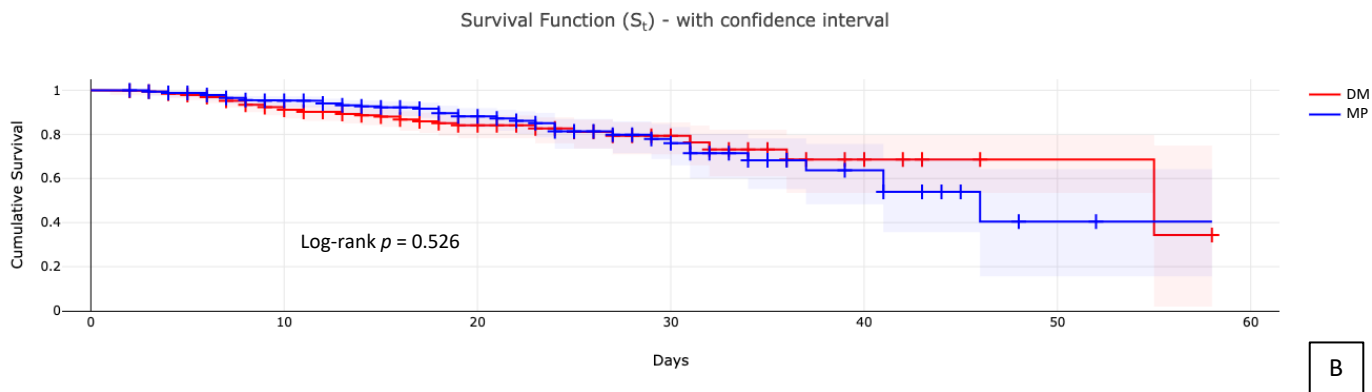
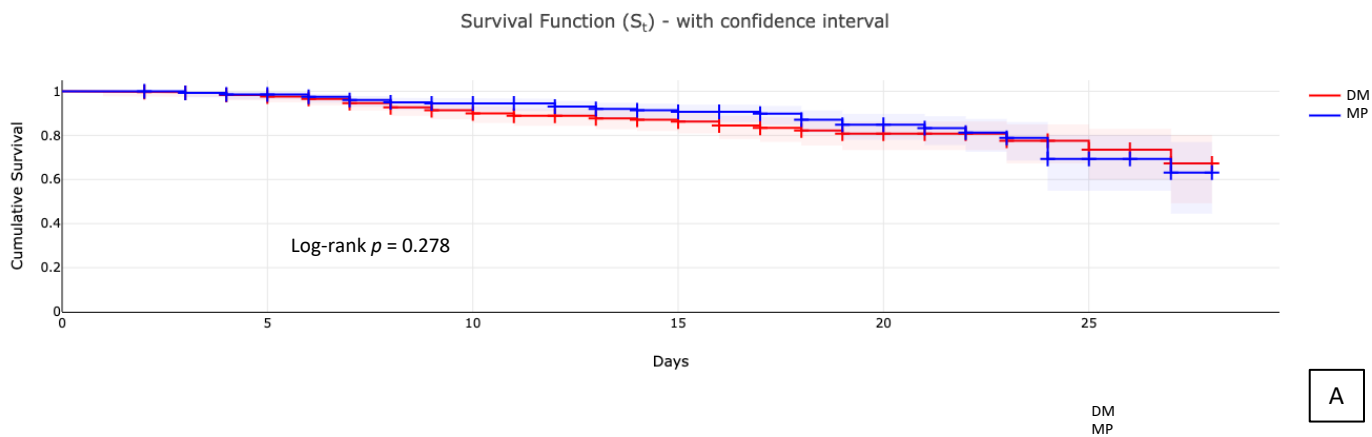
1. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. doi:10.1056/NEJMoa2021436
2. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA*. 2020;324(13):1330-1341. doi:10.1001/jama.2020.17023
3. Wagner C, Griesel M, Mikolajewska A, et al. Systemic corticosteroids for the treatment of COVID-19. *Cochrane Database Syst Rev*. 2021;8(8):CD014963. doi:10.1002/14651858.CD014963
4. Chalmers JD, Crichton ML, Goeminne PC, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. *Eur Respir J*. 2021;57(4):2100048. doi:10.1183/13993003.00048-2021
5. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at <https://www.covid19treatmentguidelines.nih.gov/>.
6. Meduri GU, Chrousos GP. General Adaptation in Critical Illness: Glucocorticoid Receptor-alpha Master Regulator of Homeostatic Corrections. *Front Endocrinol (Lausanne)*. 2020;11:161. doi:10.3389/fendo.2020.00161
7. Salton F, Confalonieri P, Campisciano G, et al. Cytokine Profiles as Potential Prognostic and Therapeutic Markers in SARS-CoV-2-Induced ARDS. *J Clin Med*. 2022;11(11):2951. doi:10.3390/jcm11112951
8. Meduri GU, Annane D, Confalonieri M, et al. Pharmacological principles guiding prolonged glucocorticoid treatment in ARDS. *Intensive Care Med*. 2020;46(12):2284-2296. doi:10.1007/s00134-020-06289-8.
9. Annane D, Pastores SM, Rochweg B, et al. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med*. 2017;45(12):2078-2088. doi:10.1097/CCM.0000000000002737.
10. Salton F, Confalonieri P, Meduri GU, et al. Prolonged Low-Dose Methylprednisolone in Patients With Severe COVID-19 Pneumonia. *Open Forum Infect Dis*. 2020;7(10):ofaa421. doi:10.1093/ofid/ofaa421.

11. Ranjbar K, Moghadami M, Mirahmadizadeh A, et al. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial [published correction appears in *BMC Infect Dis*. 2021 May 11;21(1):436]. *BMC Infect Dis*. 2021;21(1):337. doi:10.1186/s12879-021-06045-3.
12. Saeed MAM, Mohamed AH, Owaynat AH. Comparison between methylprednisolone infusion and dexamethasone in COVID-19 ARDS mechanically ventilated patients. *Egypt J Intern Med*. 2022;34(1):19. doi:10.1186/s43162-022-00113-z.
13. Draghici S, Nguyen TM, Sonna LA, et al. COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases. *Bioinformatics*. 2021;btab163. doi:10.1093/bioinformatics/btab163.
14. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192-e197. doi:10.1016/S1473-3099(20)30483-7.
15. Yende S, D'Angelo G, Kellum JA, et al. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med*. 2008;177(11):1242-1247. doi:10.1164/rccm.200712-1777OC.
16. Restrepo MI, Faverio P, Anzueto A. Long-term prognosis in community-acquired pneumonia. *Curr Opin Infect Dis*. 2013;26(2):151-158. doi:10.1097/QCO.0b013e32835ebc6d.
17. Maamar M, Artime A, Pariente E, et al. Post-COVID-19 syndrome, low-grade inflammation and inflammatory markers: a cross-sectional study. *Curr Med Res Opin*. 2022;38(6):901-909. doi:10.1080/03007995.2022.2042991.
18. Mandal S, Barnett J, Brill SE, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax*. 2021;76(4):396-398. doi:10.1136/thoraxjnl-2020-215818.
19. Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med*. 2005;171(3):242-248. doi:10.1164/rccm.200406-808OC.
20. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276. doi:10.1016/S2213-2600(19)30417-5.
21. Salvarani C, Massari M, Costantini M, et al. Intravenous methylprednisolone pulses in hospitalised patients with severe COVID-19 pneumonia, A double-blind, randomised,

- placebo-controlled trial. *Eur Respir J.* 2022;2200025. doi:10.1183/13993003.00025-2022.
22. COVID STEROID 2 Trial Group, Munch MW, Myatra SN, et al. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. *JAMA.* 2021;326(18):1807-1817. doi:10.1001/jama.2021.18295.
  23. Taboada M, Rodríguez N, Varela PM, et al. Effect of high *versus* low dose of dexamethasone on clinical worsening in patients hospitalised with moderate or severe COVID-19 pneumonia: an open-label, randomised clinical trial. *Eur Respir J.* 2022;60(2):2102518. doi:10.1183/13993003.02518-2021.
  24. Agarwal A, Rochwerg B, Lamontagne F, et al. A living WHO guideline on drugs for covid-19. *BMJ.* 2020;370:m3379. Published 2020 Sep 4. doi:10.1136/bmj.m3379
  25. Havers FP, Pham H, Taylor CA, et al. COVID-19-Associated Hospitalizations Among Vaccinated and Unvaccinated Adults 18 Years or Older in 13 US States, January 2021 to April 2022. *JAMA Intern Med.* 2022;10.1001/jamainternmed.2022.4299. doi:10.1001/jamainternmed.2022.4299.



**Figure 1.** Randomization and inclusion in the primary analysis.



**Figure 2.** Kaplan-Meier estimates of 28-day survival probability (panel A) and 60-day survival probability (panel B). Abbreviations: DM, dexamethasone; MP, methylprednisolone.

## Supplementary Materials

**Table S1.** In-hospital use of anticoagulants and other treatments.

	MP (n=337)	DM (n=340)	p-value*
<b>Anticoagulants, No. (%)</b>			
LMWH prophylactic dose <sup>†</sup>	271 (80.4)	266 (78.2)	0.36
LMWH therapeutic dose <sup>‡</sup>	88 (26.1)	74 (21.8)	0.38
UFH prophylactic dose <sup>§</sup>	1 (0.3)	2 (0.6)	0.85
UFH therapeutic dose <sup>  </sup>	1 (0.3)	1 (0.3)	0.98
Warfarin <sup>¶</sup>	2 (0.6)	4 (1.2)	0.56
DOAC <sup>**</sup>	13 (3.9)	12 (3.5)	0.87
<b>Other treatments, No. (%)</b>			
Tocilizumab	30 (8.9)	24 (7.1)	0.38
Remdesivir	75 (22.3)	66 (19.4)	0.36
Baricitinib	14 (4.2)	17 (5.0)	0.60
Anakinra	2 (0.6)	3 (0.9)	0.67
Casirivimab + Imdevimab	9 (2.7)	12 (3.5)	0.52
Sarilumab	0 (0.0)	2 (0.6)	0.16
Monoclonal antibodies	0 (0.0)	1 (0.3)	0.32

Abbreviations: LMWH, low molecular weight heparin; UFH, unfractionated heparin; DOAC, direct oral anticoagulants.

\* P value of the Fisher exact test for dichotomous variables, unpaired Student t test or Wilcoxon; rank-sum test for numerical variables, as appropriate.

<sup>†</sup> Missing data: 5 MP, 9 DM.

<sup>‡</sup> Missing data: 9 MP, 10 DM.

<sup>§</sup> Missing data: 12 MP, 11 DM.

<sup>||</sup> Missing data: 13 MP, 12 DM.

<sup>¶</sup> Missing data: 9 MP, 10 DM.

<sup>\*\*</sup> Missing data: 10 MP, 9 DM.



**Table S2.** Stratification of MV-free days at 28 days according to the severity of respiratory impairment at randomization.

Stratification variable	Intention-to-treat analysis			Per-protocol analysis		
	MP	DM	p-value*	MP	DM	p-value*
	<i>Median (IQR)</i>			<i>Median (IQR)</i>		
None	23.0 (14.0)	24.0 (16.0)	0.49	24.0 (10.0)	26.0 (8.0)	0.09
PaO <sub>2</sub> :FiO <sub>2</sub> ≥ 200 mmHg	28.0 (7.0)	28.0 (6.0)	0.96	28.0 (6.0)	28.0 (5.0)	0.93
PaO <sub>2</sub> :FiO <sub>2</sub> < 200 mmHg	19.0 (25.0)	19.5 (26.0)	0.70	21.0 (10.0)	22.0 (13.0)	0.39
Low-flow oxygen	28.0 (6.0)	28.0 (5.0)	0.80	28.0 (4.0)	28.0 (3.0)	0.78
HFNC	22.0 (11.0)	21.5 (28.0)	0.40	22.5 (10.0)	24.0 (14.0)	0.98
NIV	16.5 (23.0)	19.0 (23.0)	0.41	20.0 (14.0)	21.0 (9.0)	0.19

Abbreviations: IQR, interquartile range; PaO<sub>2</sub>:FiO<sub>2</sub>, ratio of partial pressure of arterial oxygen (PaO<sub>2</sub> in mmHg) to fractional inspired oxygen (FiO<sub>2</sub>); HFNC, high-flow nasal cannula; NIV, noninvasive ventilation.

\* P-value of the Wilcoxon rank-sum test.

**Table S3.** Odds of ICU referral according to the severity of respiratory impairment at randomization.

Stratification variable	Intention-to-treat analysis				Per-protocol analysis			
	MP	DM	OR	p-value*	MP	DM	OR	p-value*
	<i>no. of events/total no. (%)</i>		<i>(95% CI)</i>		<i>no. of events/total no. (%)</i>		<i>(95% CI)</i>	
None	41/337 (12.2)	45/340 (13.2)	0.91 (0.58-1.43)	0.68	7/279 (2.1)	19/286 (5.6)	0.36 (0.15-0.87)	0.02
PaO <sub>2</sub> :FiO <sub>2</sub> ≥ 200 mmHg	11/150 (7.3)	12/174 (6.9)	1.07 (0.46-2.50)	0.88	2/123 (1.6)	5/156 (3.2)	0.50 (0.10-2.62)	0.41
PaO <sub>2</sub> :FiO <sub>2</sub> < 200 mmHg	29/184 (15.8)	32/163 (19.6)	0.77 (0.44-1.33)	0.34	5/154 (3.2)	13/128 (10.2)	0.30 (0.10-0.86)	0.03
Low-flow oxygen	9/142 (6.3)	12/174 (6.9)	0.91 (0.37-2.23)	0.84	2/122 (1.6)	5/157 (3.2)	0.51 (0.97-2.66)	0.42
HFNC	6/74 (8.1)	8/45 (17.8)	0.41 (0.13-1.26)	0.12	2/66 (3.0)	5/38 (13.16)	0.21 (0.04-1.12)	0.07
NIV	26/120 (21.7)	25/118 (21.2)	1.03 (0.55-1.91)	0.93	3/90 (3.3)	9/89 (10.1)	0.31 (0.08-1.17)	0.08

Abbreviations: PaO<sub>2</sub>:FiO<sub>2</sub>, ratio of partial pressure of arterial oxygen (PaO<sub>2</sub> in mmHg) to fractional inspired oxygen (FiO<sub>2</sub>); HFNC, high-flow nasal cannula; NIV, noninvasive ventilation.

\* Odds-ratio of event among MP group vs DM group, estimated using logistic regression model.

**Table S4.** Stratification of the number of hospitalization days among survivors, according to the severity of respiratory impairment at randomization.

Stratification variable	Intention-to-treat analysis			Per-protocol analysis		
	MP	DM	p-value*	MP	DM	p-value*
	<i>Median (IQR)</i>			<i>Median (IQR)</i>		
None	15.0 (11.0)	14.0 (11.0)	0.005	15.0 (10.0)	13.0 (10.0)	0.001
PaO <sub>2</sub> :FiO <sub>2</sub> ≥ 200 mmHg	14.0 (10.0)	12.0 (9.0)	0.006	14.0 (10.0)	12.0 (9.0)	0.009
PaO <sub>2</sub> :FiO <sub>2</sub> < 200 mmHg	17.0 (13.0)	16.0 (14.0)	0.55	18.0 (11.0)	15.5 (13.0)	0.21
Low-flow oxygen	14.0 (10.0)	12.0 (9.0)	0.003	14.0 (9.0)	12.0 (8.0)	0.001
HFNC	17.0 (12.0)	12.0 (14.0)	0.09	17.0 (11.0)	12.0 (12.0)	0.06
NIV	18.0 (11.0)	18.0 (12.0)	0.78	17.0 (9.0)	17.0 (8.0)	0.96

Abbreviations: IQR, interquartile range; PaO<sub>2</sub>:FiO<sub>2</sub>, ratio of partial pressure of arterial oxygen (PaO<sub>2</sub> in mmHg) to fractional inspired oxygen (FiO<sub>2</sub>); HFNC, high-flow nasal cannula; NIV, noninvasive ventilation.

\* P-value of the Wilcoxon rank-sum test.

**Table S5.** Score of the WHO clinical progression scale at days 3, 7 and 14, median (IQR)

	MP (n=325)	DM (n=326)	p-value*
Day 3	6 (1)	6 (1)	0.19
Day 7	6 (1)	6 (1)	0.05
Day 14	5 (5)	4 (5)	0.09

\*P-value of the Mann-Whitney test

**Table S6.** Description of the WHO clinical progression scale by score at days 3, 7 and 14, No. (%)

	Day 3		Day 7		Day 14	
	MP (n=325)	DM (n=326)	MP (n=300)	DM (n=303)	MP (n=298)	DM (n=305)
< 4	0 (0.0)	2 (0.6)	10 (3.3)	23 (7.6)	93 (31.2)	131 (43.0)
4	6 (1.9)	13 (4.0)	16 (5.3)	33 (10.9)	46 (15.4)	36 (11.8)
5	88 (27.1)	94 (28.8)	105 (35.0)	95 (31.4)	83 (27.9)	56 (18.4)
6	225 (69.2)	210 (64.4)	149 (49.7)	127 (41.9)	44 (14.8)	42 (13.8)
7	3 (0.9)	1 (0.3)	4 (1.3)	6 (2.0)	5 (1.7)	5 (1.6)
8	1 (0.3)	2 (0.6)	5 (1.7)	3 (1.0)	4 (1.3)	3 (1.0)
9	0 (0.0)	2 (0.6)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)
10	2 (0.6)	2 (0.6)	11 (3.7)	15 (5.0)	22 (7.4)	31 (10.2)

Legend to the WHO clinical progression scale:

< 4 = non hospitalized

4 = hospitalized, no oxygen therapy

5 = hospitalized, oxygen by mask or nasal prongs

6 = hospitalized, oxygen by NIV or high flow

7 = intubation and mechanical ventilation,  $\text{PaO}_2:\text{FiO}_2 \geq 150$

8 = mechanical ventilation,  $\text{PaO}_2:\text{FiO}_2 < 150$  or vasopressors

9 = mechanical ventilation,  $\text{PaO}_2:\text{FiO}_2 < 150$  and vasopressors, dialysis or ECMO

**Table S7.** Adverse events related to the study treatment, No. (%)

	MP (n=337)	DM (n=340)	p-value*
Anaphylaxis <sup>†</sup>	0 (0.0)	0 (0.0)	1.00
Agitation <sup>‡</sup>	34 (10.1)	30 (8.8)	0.73
Psychosis <sup>§</sup>	11 (3.3)	5 (1.5)	0.30
Insomnia <sup>  </sup>	47 (13.9)	40 (11.8)	0.47
Hyperglycemia <sup>¶</sup>	113 (33.5)	93 (27.4)	0.15
Any of the above <sup>**</sup>	147 (43.6)	126 (37.0)	0.08

\* P value of the Fisher exact test for dichotomous variables.

<sup>†</sup> Missing data: 8 MP, 9 DM.

<sup>‡</sup> Missing data: 12 MP, 14 DM.

<sup>§</sup> Missing data: 14 MP, 13 DM.

<sup>||</sup> Missing data: 19 MP, 13 DM.

<sup>¶</sup> Missing data: 20 MP, 16 DM.

\*\* Missing data: 1 MP, 0 DM.

**Table S8.** In-hospital complications, No. (%)

	MP (n=337)	DM (n=340)	p-value*
Bradycardia <sup>†</sup>	31 (9.2)	24 (7.1)	0.51
Diarrhea <sup>‡</sup>	13 (3.9)	16 (4.7)	0.82
Elevation of liver enzymes <sup>§</sup>	85 (25.2)	89 (26.2)	0.89
Hypokalemia <sup>  </sup>	19 (5.6)	17 (5.0)	0.67
Shock requiring vasopressors <sup>¶</sup>	3 (0.9)	5 (1.5)	0.59
Acute kidney injury <sup>**</sup>	23 (6.8)	26 (7.6)	0.67
Disseminated intravascular coagulation	15 (4.5)	14 (4.1)	0.83
Acute myocardial infarction <sup>††</sup>	0 (0.0)	1 (0.3)	0.61
Stroke <sup>‡‡</sup>	1 (0.3)	0 (0.0)	0.50
Atrial fibrillation <sup>§</sup>	9 (2.8)	5 (1.5)	0.39
Pulmonary embolism <sup>    </sup>	21 (6.2)	18 (5.3)	0.73
Bacterial superinfection <sup>¶¶</sup>	46 (13.6)	49 (14.4)	0.94
Pneumothorax	2 (0.6)	2 (0.6)	0.99
Pneumomediastinum	7 (2.1)	4 (1.2)	0.35
Deep vein thrombosis	1 (0.3)	0 (0.0)	0.32
Bleeding	8 (2.4)	3 (0.9)	0.12
Any of the above	169 (50.1)	158 (46.5)	0.36

\* P value of the Fisher exact test for dichotomous variables.

<sup>†</sup> Missing data: 19 MP, 22 DM.

<sup>‡</sup> Missing data: 18 MP, 20 DM.

<sup>§</sup> Missing data: 15 MP, 13 DM.

<sup>||</sup> Missing data: 16 MP, 12 DM.

<sup>¶</sup> Missing data: 17 MP, 13 DM.

<sup>\*\*</sup> Missing data: 15 MP, 11 DM.

<sup>††</sup> Missing data: 15 MP, 15 DM.

<sup>‡‡</sup> Missing data: 15 MP, 13 DM.

<sup>§§</sup> Missing data: 16 MP, 12 DM.

<sup>||||</sup> Missing data: 20 MP, 16 DM.

<sup>¶¶</sup> Missing data: 15 MP, 15 DM.

**Baseline (Day 1)**

- Screening
- Inclusion/exclusion criteria fulfillment
- Core data collection

**Randomization (Day 1)**

**Day 1**

MP 80 mg IV followed by MP  
80 mg/24h IV

**Day 1 to 10**

(or sooner if discharged)  
DM 6 mg IV/PO

**Day 2 to 8**

MP 80 mg/24h IV

**Day 9**

Intubated or  
 $\text{PaO}_2/\text{FiO}_2 \leq 200$   
with at least 5  
cmH<sub>2</sub>O CPAP?

**NO**

**YES**

**Taper:**

MP 80 mg/24h IV

- MP 20 mg IV three times a day  
for 3 days, then
- MP 20 mg IV twice daily for 3  
days, then
- MP 20 mg IV once daily for 2  
days, then
- MP 16 mg/day PO for 2 days,  
then
- MP 8mg/day PO for 2 days, then
- MP 4mg/day PO for 2 days

**Re-assess**

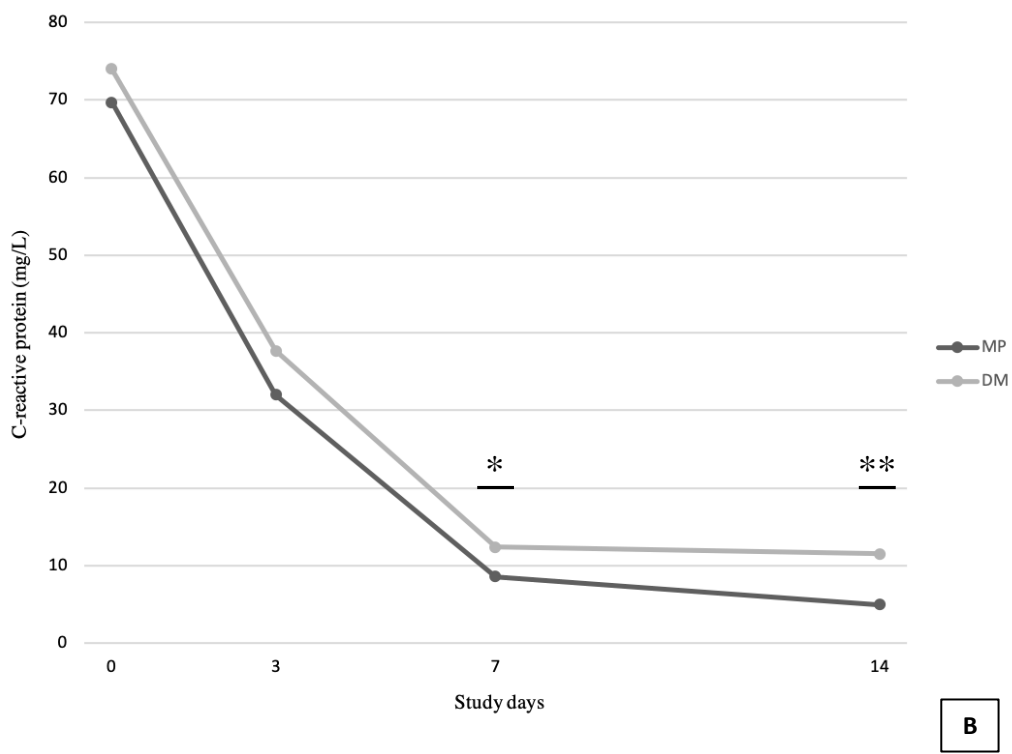
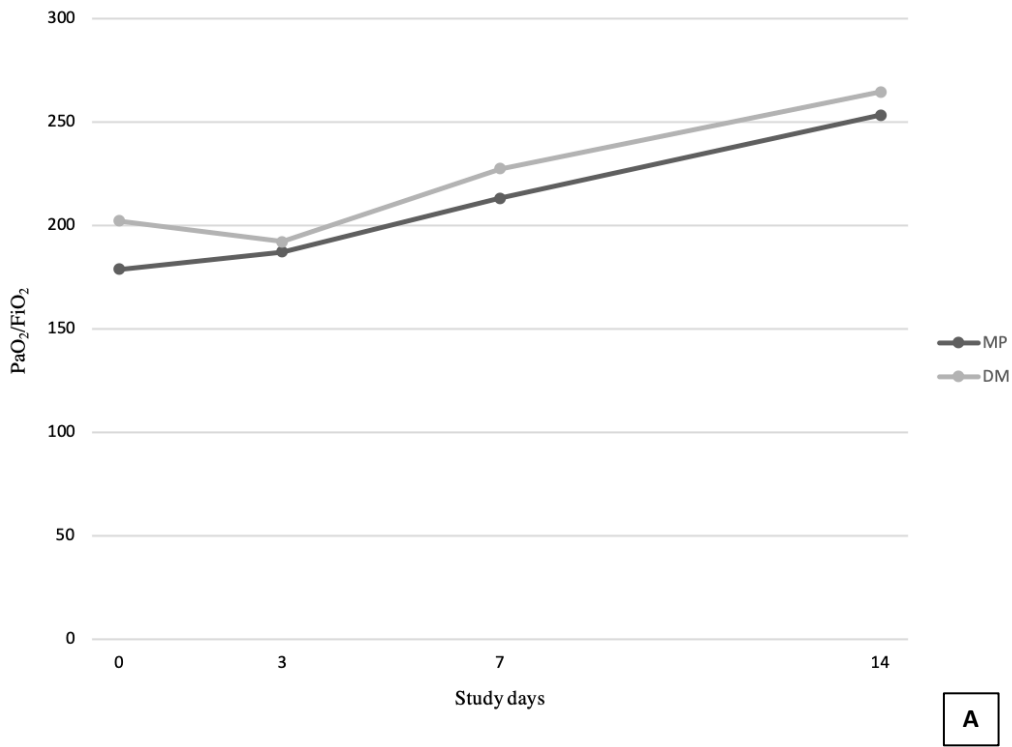
**daily**

Intubated or  
 $\text{PaO}_2/\text{FiO}_2 \leq 200$   
with  $\geq 5$  cmH<sub>2</sub>O  
CPAP?

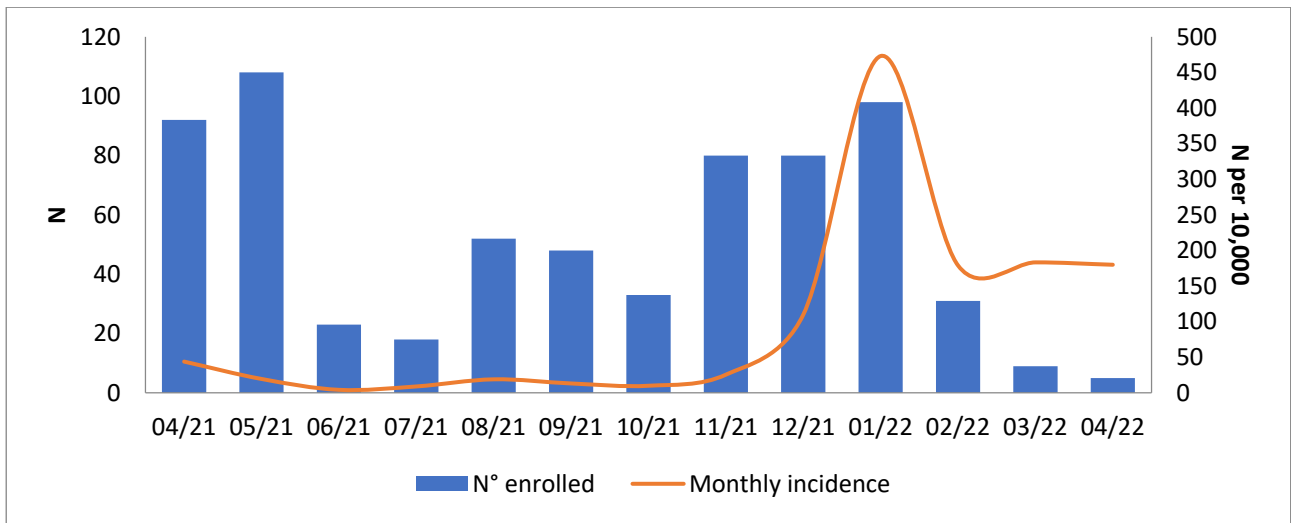
**YES**

**NO**

**Figure S1.** Flow-chart of the treatment schedule in both arms.



**Figure S2.** Panel A: time-course of PaO<sub>2</sub>:FiO<sub>2</sub> variation. Panel B: time course of C-reactive protein variation, showing significant differences at days 7 (\*,  $p = 0.006$ ) and 14 (\*\*,  $p = 0.0001$ ).



**Figure S3.** Distribution of the number of enrolled patients per month (blue bars) and incidence of new COVID-19 cases in Italy (orange line).



## Supplementary methods

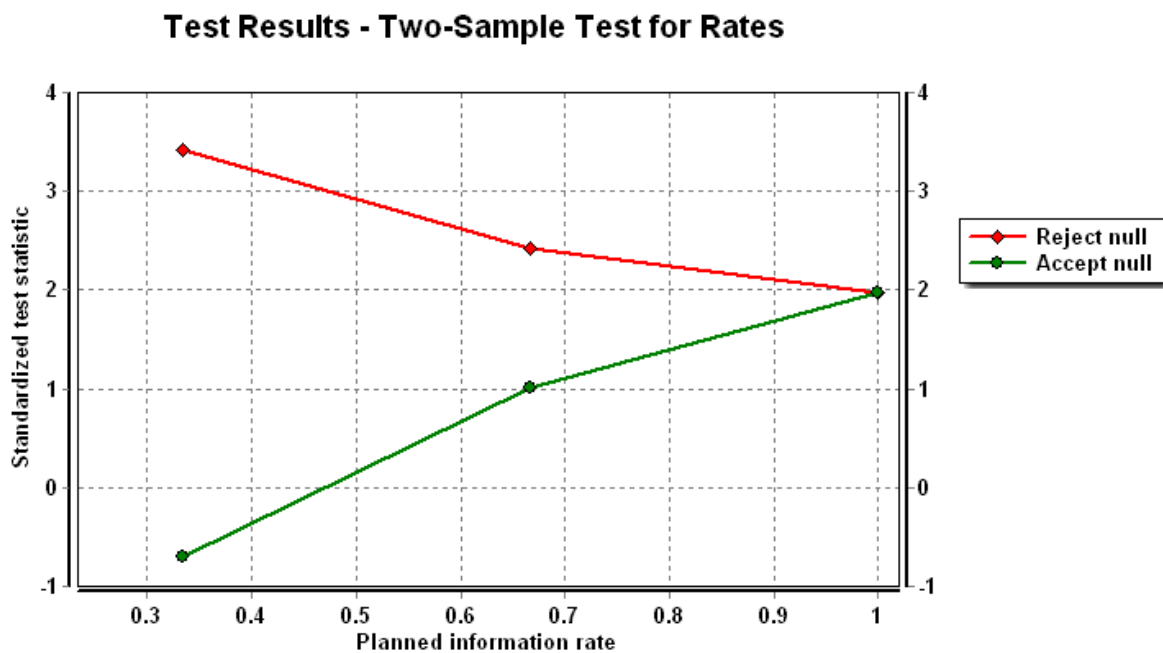
### Sequential design procedures

Stopping rules for either futility or efficacy are bound to specific error spending function according to a Fisher's exact test calculated on primary outcome. Preplanned critical values and plots are reported in table S9 and figure S4.

**Table S9.** Preplanned critical values (Fisher test) for application of early stopping rules.

$$H_0: \pi_T - \pi_C = 0$$

Critical values	Stage 1	Stage 2	Stage 3
Reject H0 (Efficacy)	3.421	2.419	1.975
Accept H0 (Futility)	-0.695	1.002	1.975
Information rate	0.333	0.667	1
alpha spent	0.0003	0.0079	0.025



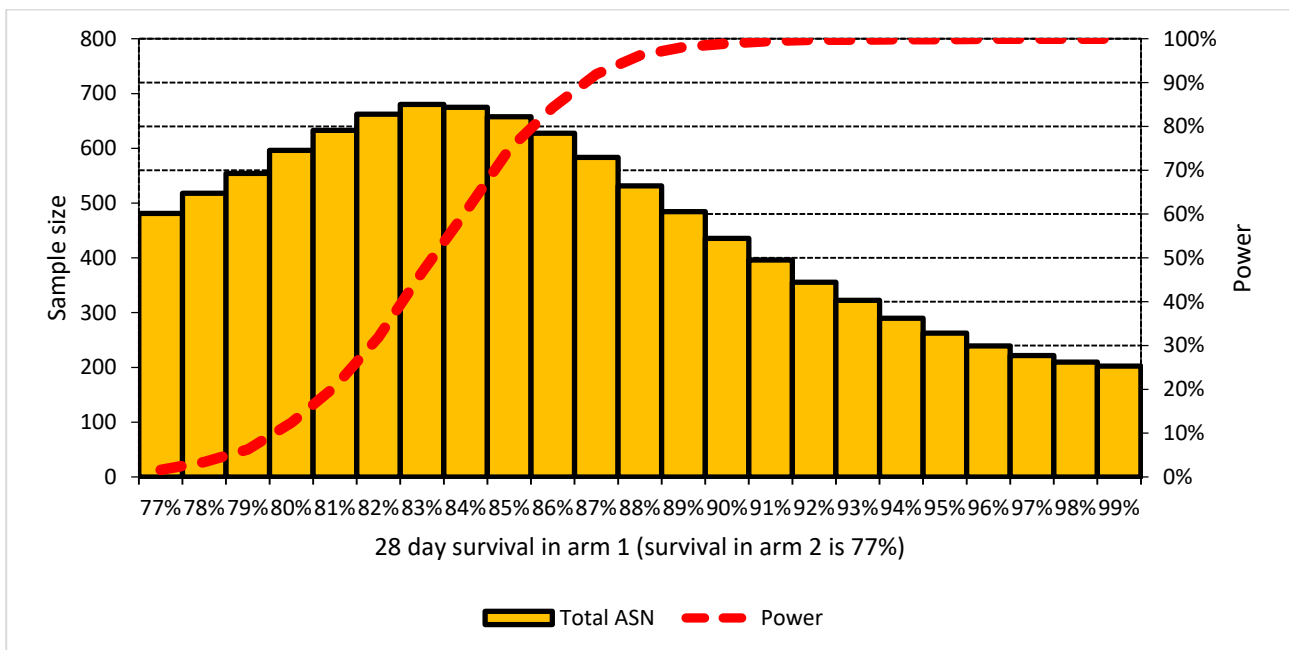
K = 3; alpha = 0.025, one-sided, binding futility = (-0.695, 1.002), Delta = 0 (O'Brien and Fleming design).

**Figure S4.** Plot for application of early stopping rule. Uncertainty area (i.e. H0 is neither accepted nor rejected) lies above the green line and below the red lines.

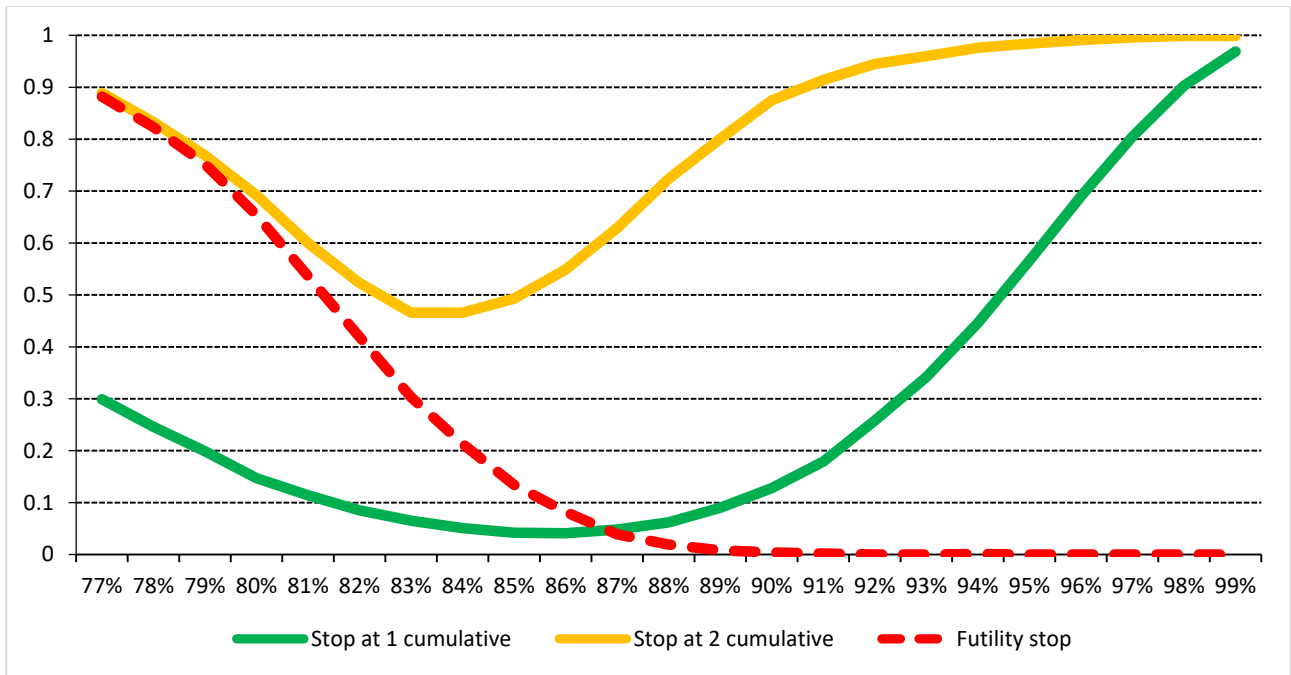
### Sample size

Minimum and maximum sample size will significantly change according to the observed effect within the trial sample (expected average sample size is between 200 and 680 participants. In particular, we expect to enroll 100 participants per arm at the first stage and then between 15 and 175 per arm for each eventual stage if the stopping rules were not met. The actual number of new

participants in each arm will be calculated according to the maximum likelihood estimates on observed efficacy at each interim analysis with an overall conditional power for next stage equal to 90%. This approach allows either to minimize the number of enrolled participants if the experimental hypothesis is too conservative or to have a good power level if the experimental hypothesis is too optimistic. The average sample size with relative power and the overall probability for meeting stopping rules according to different level of efficacy of arm 1 vs. arm 2 are reported in figures S5 and S6.



**Figure S5.** Adaptive sample size and power. The yellow bars represent the number of patients to be enrolled in the trial. Red dotted line shows the study power (i.e. the probability to detect a real difference between arm 1 and arm 2 if arm 1 is superior to arm2 is). Simulation has been carried out assuming 1:1 ratio between arms; first analysis is carried out at 200 patients; adaptive sample size between 30-350 and p-value calculated according Fisher exact statistics conditional power for next analysis 90%; K=3 (i.e. 2 interim analysis and one final analysis).



**Figure S6.** Cumulative probability of trial termination. Continuous lines show the cumulative probability of early termination either at first (green line) or second (yellow line) interim analysis. Early termination at both stages can be driven either by efficacy (i.e. reject H0) or futility (i.e. accept H0). The red dotted line shows the cumulative probability to termination for futility regardless the stage of analysis (i.e. at first interim, second interim or final analysis).