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Progesterone in Addition to Standard of Care Versus Standard of Care Alone in the Treatment of Men Hospitalized with Moderate to Severe COVID-19: A Randomized, Controlled Pilot Trial

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Abbreviations:
BMI: body mass index
COVID-19: Novel coronavirus disease 2019
DAIDS: Division of Acquired Immunodeficiency Syndrome
IBSA: Institut Biochimique SA
IL-1β: interleukin-1 beta
IL-4: interleukin-4
IL-5: interleukin-5
IL-6: interleukin-6
IL-10: interleukin-10
IL-12: interleukin-12
IND: Investigational New Drug
ECMO: extracorporeal membrane oxygenation
FDA: Food and Drug Administration
FiO2: fraction of inspired oxygen
HFNC: high-flow nasal cannula
IRB: Institutional Review Board
rRT-PCR: real-time reverse transcriptase polymerase chain reaction
SARS-CoV-2: Severe Acute Respiratory Distress Syndrome Coronavirus-2
SOC: standard of care
Th2: T-helper cell 2
TNFα: tumor necrosis factor alpha

Abstract

Background: Severity of illness in COVID-19 is consistently lower in women. Focus on sex as a biologic factor may suggest a potential therapeutic intervention for this disease. We assessed whether adding progesterone to standard of care would improve clinical outcomes of hospitalized men with moderate to severe COVID-19.

Research Question: Does short-term subcutaneous administration of progesterone safely improve clinical outcome in hypoxemic men hospitalized with COVID-19?

Study Design and Methods: We conducted a pilot, randomized, open-label, controlled trial of subcutaneous progesterone in men hospitalized with confirmed moderate to severe COVID-19. Patients were randomly assigned to receive standard of care (SOC) plus progesterone (100 mg subcutaneously twice daily for up to five days) or SOC alone. In addition to assessment of safety, the primary outcome was change in clinical status at day 7. Length of hospital stay and number of days on supplemental oxygen were key secondary outcomes.

Results: Forty-two patients were enrolled from April - August 2020; 22 were randomized to the control group and 20 to the progesterone group. Two patients from the progesterone group withdrew from the study prior to receiving progesterone. There was a 1.5-point overall improvement in median clinical status score on a seven-point ordinal scale from baseline to Day 7 in patients in the progesterone group as compared to controls (95%CI:0.0-2.0; P=0.024). There were no serious adverse events attributable to progesterone. Patients treated with progesterone

required 3 fewer days of supplemental oxygen (median of 4.5 vs 7.5 days) and were hospitalized for 2.5 fewer days (median of 7.0 vs 9.5 days) as compared to controls.

Interpretation: Progesterone at a dose of 100 mg, twice daily by subcutaneous injection in addition to SOC may represent a safe and effective approach for treatment in hypoxemic men with moderate to severe COVID-19.

Clinical Trial Registration: ClinicalTrials.gov, NCT04365127.

Key words: COVID-19, gender difference in COVID-19 outcomes, progesterone

As of January 2021, over 96 million cases of COVID-19 with 2 million deaths[1] have been reported; of these, men with severe illness appear to be disproportionately overrepresented, with some data suggesting that for every 10 women who are hospitalized, admitted to intensive care unit (ICU), or die of COVID-19, 12 men are hospitalized, 19 men are admitted to ICU, and 15 men die[2-7].

This sex disparity is attributable in part to higher prevalence of pre-existing co-morbidities associated with worse COVID-19 outcomes among men[8,9]. Men are more likely to engage in smoking and alcohol use, with greater reluctance to seek healthcare, which may promote poorly controlled chronic conditions[10]. At a biological level, differences in gene expression and hormonal influences may favor the female sex as it relates to the course of this disease[11,12]. Intriguingly, when women with COVID-19 were stratified by menstrual status, pre-menopausal women had lower rates of hospitalization, less requirement for respiratory support, and shorter duration of hospitalization compared to post-menopausal women[13].

In light of these observations, progesterone, a steroid hormone produced by the ovaries during reproductive cycles, is postulated to play a role in immunomodulation of COVID-19[11,12,14]. Progesterone receptors are expressed in both innate and adaptive immune cells, regulating local and systemic inflammation in pre-menopausal women[15]. These effects include inhibition of neutrophil degranulation and free radical generation, suppression of pro-inflammatory cytokine production, and skewing of T-cell signaling towards the production of anti-inflammatory cytokines[14-24]. With increased mortality in COVID-19 associated with the development of acute respiratory distress syndrome (ARDS), higher levels of endogenous progesterone in women may confer a protective factor by dampening the exaggerated inflammatory immune cascade, or "cytokine storm," that leads to severe lung injury[25-27]. In fact, in a mouse model of influenza A, exogenous progesterone administration has been shown to decrease pulmonary inflammation, reduce protein leakage into airways, and promote faster recovery by enhancing repair of pulmonary epithelial cells[28].

Given the immune-modulatory properties of progesterone, the purpose of this investigator-initiated randomized study was to assess clinical efficacy and safety of subcutaneous progesterone in hypoxemic men hospitalized with COVID-19. We hypothesized that the anti-inflammatory properties of progesterone could dampen the systemic cytokine response, reducing severity of illness, and shorten need for supplemental oxygen or hospitalization.

Method

Protocol was approved by Cedars-Sinai Institutional Review Board (IRB). Furthermore, the study was reviewed by the Food and Drug Administration (FDA) and was authorized to proceed under an Intermediate-size Expanded Access Investigational New Drug (IND 149534) protocol. **Supplement 1** outlines the trial protocol and statistical analysis plans. All patients or legally authorized representatives provided written informed consent. Study was registered at ClinicalTrials.gov (NCT04365127).

Patients

Eligible patients were men at least 18 years of age, hospitalized with a single positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) real-time reverse transcriptase polymerase chain reaction (rRT-PCR) test from a nasopharyngeal swab sample obtained within 72 hours of randomization. Participants were included only if they had evidence of lower respiratory tract involvement based on imaging or presence of crackles on chest physical exam. Eligible patients had an oxygen saturation of ≤94% on room air, were receiving supplemental oxygen by regular nasal cannula, face make or high flow nasal cannula (HFNC) at a fraction of inspired oxygen (FiO2) of ≤50%. Patients were excluded if they were receiving invasive or noninvasive mechanical ventilation. All participants while hospitalized, were required to be on thromboembolism chemoprophylaxis (subcutaneous unfractionated heparin 5000 units twice daily or enoxaparin 40 mg daily). Contraindications to anticoagulants precluded study enrollment. Patients were excluded if they had a history of thromboembolic disease, breast cancer, or liver transaminases greater than five times the upper limit of normal. **e-Table 1** lists the full eligibility criteria.

Study Design

This was a pilot study to assess the feasibility, safety and potential efficacy of using progesterone in hypoxemic men with COVID-19. Patients were enrolled at a single center, a large academic hospital in Los Angeles, California between April 27 and August 5, 2020, and randomly assigned to receive institutional SOC with or without progesterone. Randomization was performed in an electronic case report form system (REDCap)[29,30], 1:1 with random block sizes of 4, 6, or 8 subjects using tables generated from STATA (v16.1). Block randomization was implemented in order to ensure that patients were equally assigned to each treatment group. Varying the block size reduced selection bias by keeping the investigator blinded to the size of the block, thus preventing predictability of the allocation of patients in a single-center study. Patients, investigators, and treating providers were not blinded to study drug assignment. The investigators were not involved in the decision of initiation of SOC treatment options, initiation or discontinuation of oxygen or mechanical ventilation, type or amount of supplemental oxygen, or discharge from the hospital. The clinical status assessment was made through chart review.

Patients randomized to the progesterone group received 100 mg of progesterone subcutaneously twice daily for five days while hospitalized. Patients who had sufficiently improved in the judgement of the treating providers, could be discharged from the hospital prior to completing their assigned courses of treatment. The protocol permitted use of other agents with presumptive activity against SARS-CoV-2 if such use was part of institutional SOC. With rapidly evolving therapeutic approaches for COVID-19 during the course of this trial, the SOC may have differed for patients enrolled at different timepoints into the trial; concomitant therapeutic interventions are outline in **Table 2** and **e-Table 2**.

Control patients with significant clinical deterioration (requiring higher supplemental oxygen through high flow devices or mechanical ventilation at any point during the study), or those at Day 7 without clinical improvement were permitted to cross over to receive progesterone therapy. These patients remained in their intention-to-treat group for purpose of analysis.

The protocol was amended on May 15, 2020, to include patients with chronic kidney disease based on an FDA general recommendation to COVID-19 clinical trials to consider inclusion of at-risk populations for severe illness. Study period was shortened to 15 days from the initially 29 days to allow enrolled patients with progressive illness to participate in other investigational trials without the need to withdraw from this study. Due to shortage in SARS-CoV-2 PCR testing supplies, an amendment was added to allow enrollment of patients with a positive PCR prior to 72 hours from the time of screening and clinical evidence of progressive disease. All subjects enrolled met the initial enrollment condition with a positive PCR within 72 hours of screening. Protocol amendments were authorized and approved by the IRB and FDA.

Study patients were assessed daily for 15 days or until discharge, whichever came first. Discharged patients participated in phone or video study visits on Days 7 and 15. Clinical assessment performed daily during hospitalization included evaluation of clinical status with daily vital signs, oxygen supplementation type and amount, need for mechanical ventilation, adverse events, and concomitant medications. White blood cells, hemoglobin, platelets, electrolytes, blood urea nitrogen, creatinine, liver transaminases, and inflammatory markers, if obtained as part of SOC, were monitored on Days 1-5, 7, and 15 while hospitalized. Serum free and total progesterone levels were also measured on Days 1-5. Self-reported race and ethnicity, obtained from medical records, were collected as demographic information to assess possible differences in disease severity or treatment response. Serious adverse events and Grade 3 and 4 adverse events as described in Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events were recorded.

Clinical status was assessed on a 7-point ordinal scale, similarly used by Goldman[31], as follows: 1. Death; 2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3. Hospitalized, on high flow oxygen devices; 4. Hospitalized, requiring supplemental oxygen; 5. Hospitalized, not requiring supplemental oxygen; 6. Not hospitalized, limitation on activities; 7. Not hospitalized, no limitations on activities. If the clinical status of a hospitalized patient changed on any given study day, the patient's worst clinical assessment score on the ordinal scale was documented.

Endpoint

In addition to safety and tolerability, the primary efficacy endpoint was change in patients' clinical status, assessed on a 7-point ordinal scale, from baseline to Day 7. Secondary endpoints were hospital LOS, days of supplemental oxygen use, and need for mechanical ventilation.

Statistical Analysis

Parameter estimates from this study will be used to power a definitive study. A sample size of 20 per group (total sample size of 40) was deemed adequate to provide this estimation.

Differences between groups in primary endpoints were tested with an exact Wilcoxon rank-sum test with exact Hodges-Lehmann confidence limits calculated for the median shift between groups. The cumulative probability of improvement in clinical status (an increase of at least 1 point on a seven-point scale or live discharge) over the first 7 days was estimated by the Kaplan-

Meier method and differences across the study groups were assessed by a log-rank test. To compare LOS and duration of supplemental oxygen between groups, separate competing-risk analysis was performed with death as a competing outcome, and data were censored when time exceeded the study endpoint at 15 days[32,33]. Other measures were tested with Student's t-test (parametric data) or Fisher's exact test (categorical data) where appropriate. Inferential tests were considered significant when the two-tailed P-value was <0.05; although adjustments for multiplicity were not made due to the exploratory nature of this pilot study. Analysis was performed on an intent-to-treat basis using SAS v9.4 software.

Post Hoc Analyses

Since several patients in both groups experienced clinical deterioration over Days 2-6, a sensitivity analysis was performed considering the patients' worst status prior to Day 7 as their baseline to capture the illness severity while assessing the change in clinical status score between the two groups. In another sensitivity analysis, for control patients who crossed over prior to Day 7, their last clinical assessment prior to receiving progesterone was imputed as the Day 7 assessment.

Results

Between April 27 and August 5, 2020, 136 patients were screened and assessed for eligibility, 94 were deemed ineligible for the study. Of the 42 enrolled patients, 20 were randomized to the progesterone group and 22 to the control group. The trial completed enrollment and final follow-up for the last enrollee was on August 20, 2020. Two patients in the progesterone group withdrew from the study prior to receiving progesterone and were excluded from analysis (**Figure 1**). Nine control patients were treated with progesterone due to clinical deterioration prior to Day 7 (n=6, 27%) or absence of clinical improvement by Day 7 (n=3, 14%). One patient assigned to the progesterone group had repeated protocol noncompliance and was transferred to another hospital at Day 5 for insurance coverage reasons. For the purpose of safety evaluation, follow up revealed that this patient died on Day 7 due to complications of disseminated cryptococcal infection in setting of untreated human immunodeficiency virus (HIV) infection. All available data on this patient as obtained on Days 1-5 of study and clinical status at Day 7 have been included in the analysis.

Because of faster than anticipated enrollment, the trial terminated recruitment soon after the interim safety analysis. After discussion with the data safety monitoring committee, further interim analyses were deemed unnecessary.

Demographics and baseline characteristics of the study population were balanced in the two study groups (**Table 1 and e-Table 3**). The patient population had an overall mean age of 55.3±16.4 years and a mean body mass index (BMI) of a 31.6±9.5 kg/m^2. Self-reported race and ethnicity indicated that most were of white race (78%) and Hispanic ethnicity (60%). Most patients had comorbid conditions including hypertension, diabetes, obesity, or a combination of these. At baseline, there was no statistical difference in clinical status between the two groups with 85% of all patients requiring supplemental oxygen.

Primary Endpoint

The primary outcome, ascertained as the overall change in clinical score status from baseline to Day 7 on a seven-point ordinal scale, was a median of 1.5-points better for the progesterone group than the control group (95%CI:0.0-2.0; P=0.024) (**Table 2**). During the first seven study days, the cumulative probability of clinical improvement (an increase of at least 1 point on a seven-point scale or live discharge) was significantly higher in the progesterone group, 0.76 (95%CI:0.55-0.93) versus 0.55 (95%CI:0.28-0.68) in the control group (log-rank P=0.014), by Kaplan-Meier estimation. One patient in the progesterone group showed improvement at Day 2 but was subsequently non-compliant with study protocols and was transferred to another facility. For the purpose of this Kaplan-Meier estimation, this subject was excluded (**Figure 2**).

Post Hoc Analyses:

In a sensitivity analysis comparing worst clinical status prior to Day 7 to the clinical status at Day 7, the progesterone group improved a median of 2-points more than the control group (95%CI:0.0-2.0; P=0.006) (**e-Table 4**). This analysis captures the illness severity while assessing the change in clinical status score between the two groups; again favoring the progesterone group.

In a sensitivity analysis in which the last clinical assessment on the seven-point ordinal scale prior to crossing over was imputed as the Day 7 score, overall change in score from baseline to Day 7 was a median of 1.5-points better for the progesterone group than the control group (95%CI:1.0-2.0; P=0.010) (**e-Table 5**).

Secondary Endpoints and Adverse Events

Among patients assigned to the progesterone group, the median number of days on supplemental oxygen was 4.5 (IQR:2.0,6.0) compared to 7.5 (IQR:6.0,11.0) in the control group for a median difference of 3 days. By Day 7, nine of 18 (50%) patients in the progesterone group remained hospitalized, compared to 19 of 22 (86%) of patients in the control group. Patients in the progesterone group had a median LOS of 7.0 days (IQR:4.0,9.0) while the control group had a median LOS of 9.5 days (IQR:7.0,14.0). At study completion, one patient in the progesterone group remained hospitalized compared to five in the control group. Mechanical ventilation was initiated in four of 22 (18%) control patients, three prior to Day 7, compared to none in the progesterone group. Although we see evidence of improved clinical outcomes in patients receiving progesterone, with fewer days of hospitalization, and lower need for supplemental oxygen or mechanical ventilation, differences between groups did not meet conventional levels of statistical significance.

Although the patients were analyzed on an intent-to-treat basis, notably half of the six control patients who crossed over due to clinical deterioration prior to Day 7 progressed to require mechanical ventilation. Of those, one was successfully liberated from the ventilator prior to completion of the study. The remaining half of crossed over patients (n=3), despite clear

trajectory of decline, did not require mechanical ventilation and improved to discharge prior to completion of study.

Administration of expanded use access and other medications was allowed for both the control and intervention groups (**Table 3 and e-Table 2**). A larger percentage of the control group received remdesivir, systemic glucocorticoids, tocilizumab, and convalescent plasma, but these differences were not significant. A greater proportion but equal number of patients in the intervention arm received azithromycin, though this was also not significant.

There were no serious adverse events, including life-threatening events, attributable to progesterone. There were two thromboembolic events in one patient (5.6%) in the progesterone group and two thromboembolic events in two patients (9.1%) in the control group (**Table 4**). Overall, there was no meaningful difference in the incidence of serious adverse events between the two groups. There were two deaths, one in each group, during the total 15-day surveillance period, neither attributable to progesterone administration. There were no events requiring discontinuation of progesterone. For the control patients who crossed over, significant adverse events post progesterone administration are also listed in **Table 4**. Non-serious Grade 3 and 4 adverse events are listed in **e-Table 6**.

Serum progesterone levels were obtained at baseline and as anticipated, were less than 1 ng/ml in all patients. After administration of two doses of subcutaneous progesterone, goal serum levels were achieved and maintained between 11.1 – 288 ng/ml on subsequent samples. Levels as high as 288 ng/ml, which can be seen during the third trimester of pregnancy[34], were tolerated well and not associated with any adverse events.

Discussion

The current pilot study results suggest that the use of progesterone, in addition to SOC treatment measures in hospitalized men with COVID-19 who are hypoxemic, could lead to improved clinical outcomes with minimal safety concerns. We noted that addition of progesterone to SOC treatment was associated with improved clinical status assessed on a seven-point ordinal scale, a trend towards fewer days on supplemental oxygen, lower need for mechanical ventilation, and reduced length of hospital stay.

The sex difference in illness severity and mortality outcomes in COVID-19, as well as in prior coronavirus outbreaks, has been demonstrated in multiple populations[2-7]. The concept of a less effective immune response to viral infections as a consequence of differences in sex hormones between men and women has been described previously and may be related to unequal endogenous progesterone levels, a steroid hormone with well described anti-inflammatory properties[11,17,19,21-24]. The corpus luteum produces progesterone in women with peak levels (10-20 ng/ml) during the luteal phase of the menstrual cycle[35]. Adrenal glands and testes produce progesterone in men, but in much lower concentrations (0.13-0.97 ng/ml), similar to those of post-menopausal women[35-37]. The role of progesterone extends beyond fertility and menstruation. It binds to glucocorticoid receptors, and indeed most immune cells express progesterone receptors[17]. It is possible that higher endogenous levels of progesterone protect women from progressing to severe illness in COVID-19.

A major driver of morbidity and mortality in COVID-19 is the exuberant inflammatory response sometimes termed "cytokine storm," mediated by production of proinflammatory cytokines (IL-6, IL-1β, TNFα), and macrophage hyperactivation[25,26]. Previous preclinical and clinical studies have demonstrated that the elevated concentrations of estrogen and progesterone in women are associated with inflammatory response attenuation through IL-1β and IL-12 inhibition, decreased T cell IL-6 receptors expression, and bias toward Th2 cell production, which secrete IL-4, IL-5, IL-10, and other anti-inflammatory cytokines [24,38-40]. Exogenous progesterone administration in mice infected with influenza A showed enhanced repair of pulmonary epithelial cells, supporting the role of this steroid hormone in reducing inflammation and promoting faster recovery[28]. While direct evidence of specific cytokine modulation is lacking in our study, the potential utility of progesterone in treatment of early COVID-19 in men is compelling.

The progesterone dose of 100 mg injected subcutaneously was based on the previously-demonstrated observation that a subcutaneous formulation, commercially available for use in fertility treatment outside of the United States (FDA IND 102771), achieves rapid, reliable progesterone serum concentrations[41,42] approximating the luteal phase of the menstrual cycle. We aimed to target a progesterone level between that of the luteal phase and pregnancy, the latter of which can be as high as 290 ng/ml[34]. While data on outcomes of pregnant women with COVID-19 remain inconclusive, some reports have suggested that the pulmonary disease in pregnant women may be milder than in age-matched nonpregnant female controls[43]. This may be partly due to a decreased production of pro-inflammatory factors inherent in pregnancy[44]. To maintain our target progesterone level, the dose was administered twice daily for up to five days. Daily serum measurements confirm the rapid increase and sustained levels of progesterone; as expected, ranged between levels seen in the luteal phase of menstrual cycle and the third trimester of pregnancy.

A major concern about exogenous sex hormone administration is the development of thrombotic disease; particularly when coupled with a disease already known for its coagulopathic effects[45]. This risk is most prominent in women who receive estrogen-containing contraceptives and appears to be most related to estrogen dose. In fact, progesterone-only contraceptives do not confer an increased risk of venous thromboembolic disease[46]. Even intravenous progesterone as used in phase 3 clinical trials of traumatic brain injury, was not associated with increased risk of thromboembolic disease[47]. Nonetheless, all patients in our study received prophylactic-dose anticoagulation, as is recommended for hospitalized patients with COVID-19[48]. We similarly observed that use of progesterone was overall safe and not associated with any significant increase in the risk of thromboembolism.

Limitations

This study was conducted at a large academic quaternary care medical center in the racially and ethnically diverse city of Los Angeles. Our study population was predominantly white, Hispanic, and obese, with a moderate burden of comorbidities associated with worse outcomes in COVID-19[2]. Thus, the patients included in this analysis may represent those at higher risk for worse outcomes from COVID-19, which may limit the generalizability of this trial to other populations. Other limitations include the relatively small study population size, that the study was unblinded,

and it was performed at a single site. Finally, with the rapidly changing climate of COVID-19 treatment approaches, patients' receipt of other medications for COVID-19 varied somewhat over the course of the study **(Table 3 and e-Table 2)**. These variations were similar in both groups and were not statistically significant; however, as progesterone is a steroid hormone, discerning its beneficial effect on immune modulation over systemic glucocorticoids is limited in this study. A further study will need to delineate the mechanism of action of progesterone and compare its efficacy to that of glucocorticoids in COVID-19.

Interpretation

This proof of concept pilot trial showed very encouraging outcome data, suggesting that administration of progesterone at a dose of 100 mg twice daily by subcutaneous injection may represent a safe and effective approach to treatment of COVID-19 by improving clinical status among men with moderate to severe illness. Further research is necessary in larger, more heterogeneous populations, including post-menopausal women and at other treatment centers, to establish the degree of clinical efficacy and assess any other potential safety concerns of this treatment approach.

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Take home points:

- **Study Question:** Does the addition of subcutaneous progesterone in hypoxemic men with COVID-19 improve clinical outcomes?
- **Results:** This study demonstrates that in men with COVID-19, the addition of progesterone for 5 days improves clinical status at day 7, reduces the need for supplemental oxygen, and reduces hospital length of stay with no significant adverse effects.
- **Interpretation:** Addition of subcutaneous progesterone may represent a safe and novel approach to treatment of hypoxemic men hospitalized with COVID-19.

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Data Sharing Statement: Request for de-identified patient data should be sent to sara.ghandehari@cshs.org beginning 08-20-2021. Depending on the nature of the request, the merit of the research proposed, and the intended use of the data, and only with a signed data access agreement, will data sharing be considered.

Table 1. Baseline Characteristics

	All Subjects N=40	Progesterone N=18	Control N=22
Age (years), mean±SD	55.3±16.4	56.0±17.3	54.6±16.0
Baseline BMI (kg/m²), mean±SD	31.6±9.5	31.9±11.1	31.4±8.3
Race, n (%)			
White	31 (77.5)	12 (66.7)	19 (86.4)
Black/African American	4 (10.0)	2 (11.1)	2 (9.1)
Asian/Pacific Islander	2 (5.0)	1 (5.6)	1 (4.5)
Other	3 (7.5)	3 (16.7)	0 (0.0)
Ethnicities, n (%)			
Hispanic or Latino	24 (60.0)	10 (55.6)	14 (63.6)
Not Hispanic or Latino	16 (40.0)	8 (44.4)	8 (36.4)
Comorbidities, n (%)			
Hypertension	19 (47.5)	7 (38.9)	12 (54.5)
Diabetes	10 (25.0)	4 (22.2)	6 (27.3)
Obesity	18 (45.0)	6 (33.3)	12 (54.5)

Table 2. Clinical Status Based on 7-Point Ordinal Scale

	Progesterone N=18 n (%)	Control N=22 n (%)	P-value[a]
Status at Baseline, n (%)			
3 - Hospitalized; on high flow nasal cannula	3 (16.7)	0 (0.0)	
4 - Hospitalized; requiring supplemental oxygen (not HFNC)	11 (61.1)	20 (90.9)	
5 - Hospitalized; not requiring supplemental oxygen	4 (22.2)	2 (9.1)	
Status at Day 7, n (%)			
1 - Death	1 (5.6)	0 (0.0)	
2 - Hospitalized; on invasive mechanical ventilation or ECMO	0 (0.0)	3 (13.6)	
3 - Hospitalized; on high flow nasal cannula	2 (11.1)	3 (13.6)	
4 - Hospitalized; requiring supplemental oxygen (not HFNC)	2 (11.1)	8 (36.4)	
5 - Hospitalized; not requiring supplemental oxygen	4 (22.2)	4 (18.2)	
6 - Not hospitalized; limitations on activities	7 (38.9)	4 (18.2)	
7 - Not hospitalized; no limitations on activities	2 (11.1)	0 (0.0)	
Change in Status at Day 7, n (%)			
+3	2 (11.1)	0 (0.0)	
+2	7 (38.9)	3 (13.6)	
+1	3 (16.7)	4 (18.2)	
0	3 (16.7)	9 (40.9)	
-1	2 (11.1)	3 (13.6)	
-2	0 (0.0)	3 (13.6)	
-3	1 (5.6)	0 (0.0)	
Change in Status at Day 7, median (IQR)	1.5 (0.0, 2.0)	0.0 (-1.0, 1.0)	0.024
Status at Day 15, n (%)			
1 - Death	1 (5.6)	1 (4.5)	
2 - Hospitalized; on invasive mechanical ventilation or ECMO	0 (0.0)	2 (9.1)	
3 - Hospitalized; on high flow nasal cannula	0 (0.0)	2 (9.1)	
4 - Hospitalized; requiring supplemental oxygen (not HFNC)	1 (5.6)	0 (0.0)	
5 - Hospitalized; not requiring supplemental oxygen	1 (5.6)	1 (4.5)	
6 - Not hospitalized; limitations on activities	8 (44.4)	12 (54.5)	
7 - Not hospitalized; no limitations on activities	7 (38.9)	4 (18.2)	
Change Status at Day 15, n (%)			
+4	1 (5.6)	0 (0.0)	
+3	7 (38.9)	2 (9.1)	
+2	4 (22.2)	14 (63.6)	
+1	4 (22.2)	1 (4.5)	
0	1 (5.6)	0 (0.0)	
-1	0 (0.0)	2 (9.1)	
-2	0 (0.0)	2 (9.1)	
-3	1 (5.6)	1 (4.5)	
Change in Status at Day 15, median (IQR)	2.0 (1.0, 3.0)	2.0 (1.0, 2.0)	0.150

Abbreviations: ECMO = extracorporeal membrane oxygenation | IQR = interquartile range

[a] Exact Wilcoxon rank-sum test

Table 3. Concomitant Therapeutic Interventions

	Progesterone N=18 n (%)	**Control N=22 n (%)**
Azithromycin	10 (55.6)	10 (45.5)
Remdesivir	9 (50.0)	15 (68.2)
System Glucocorticoids	9 (50.0)	15 (68.2)
Dexamethasone	7 (38.9)	10 (45.5)
Tocilizumab	1 (5.6)	4 (18.2)
Convalescent Plasma	0 (0.0)	2 (9.1)
Hydroxychloroquine	0 (0.0)	1 (4.5)

Table 4. Serious Adverse Events by System Organ Class and Preferred Term

		Progesterone N=18 n (%)	Control N=22 n (%)	Control After Progesterone[a] N=9 n (%)
Any SAE or death		2 (11.1)	5 (22.7)	3 (33.3)
Blood and lymphatic system disorders	Lymphocyte count decreased	0 (0.0)	1 (4.5)	0 (0.0)
Cardiac disorders	Cardiac arrest	0 (0.0)	1 (4.5)	0 (0.0)
	Hypoperfusion	0 (0.0)	3 (13.6)	2 (22.2)
Renal and urinary disorders	Creatinine increased	0 (0.0)	1 (4.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Hypoxia	0 (0.0)	4 (18.2)	3 (33.3)
Vascular disorders	Deep vein thrombosis	1 (5.6)	2 (9.1)	1 (11.1)
	Pulmonary embolism	1 (5.6)	0 (0.0)	0 (0.0)
Death		1 (5.6)	1 (4.5)	0 (0.0)

[a] For control patients who received progesterone due to clinical deterioration, this column represents SAEs that occurred after receiving progesterone.

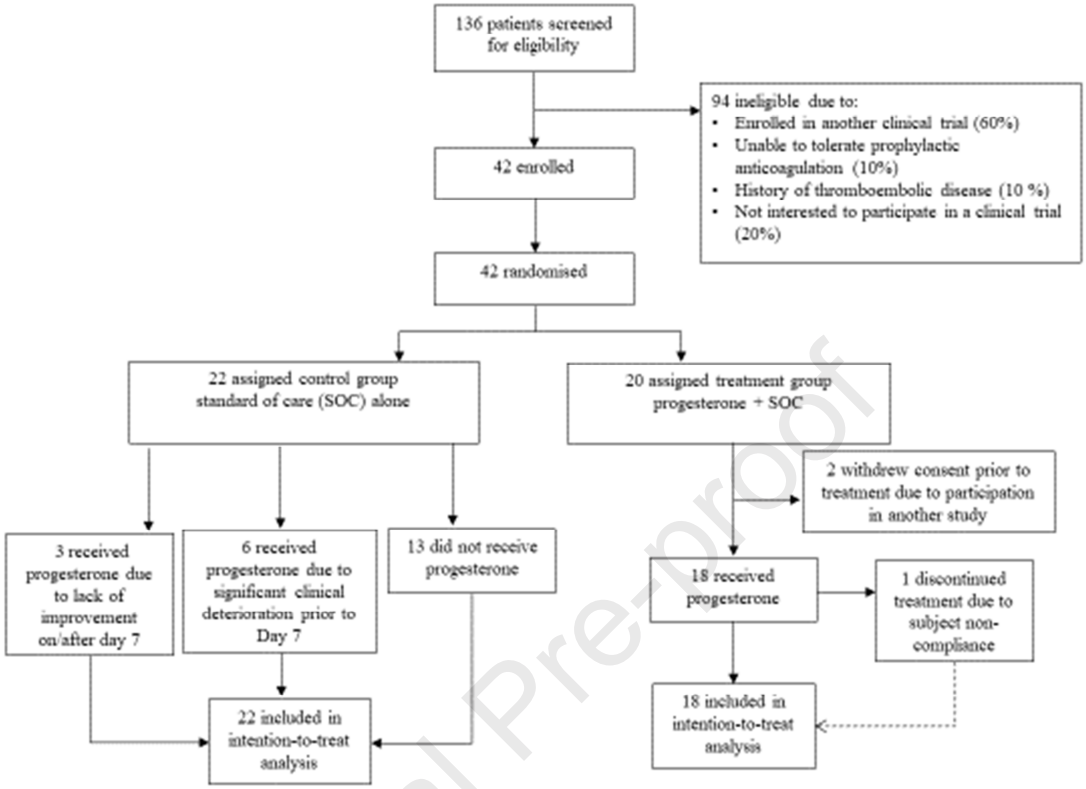


Figure 1: Participant Flow in a Randomized Clinical Trial of Progesterone vs Standard of Care in Men with Moderate to Severe Coronavirus Disease 2019

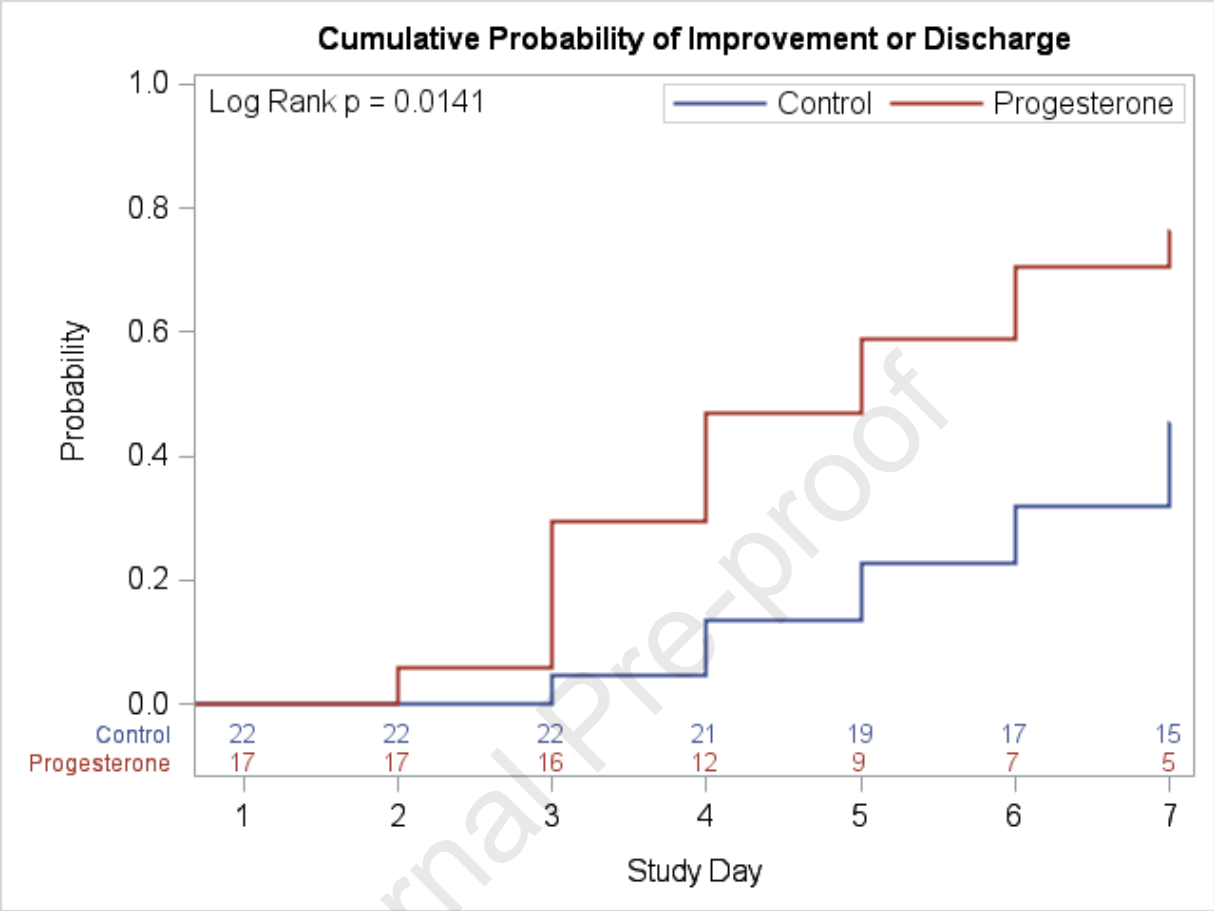
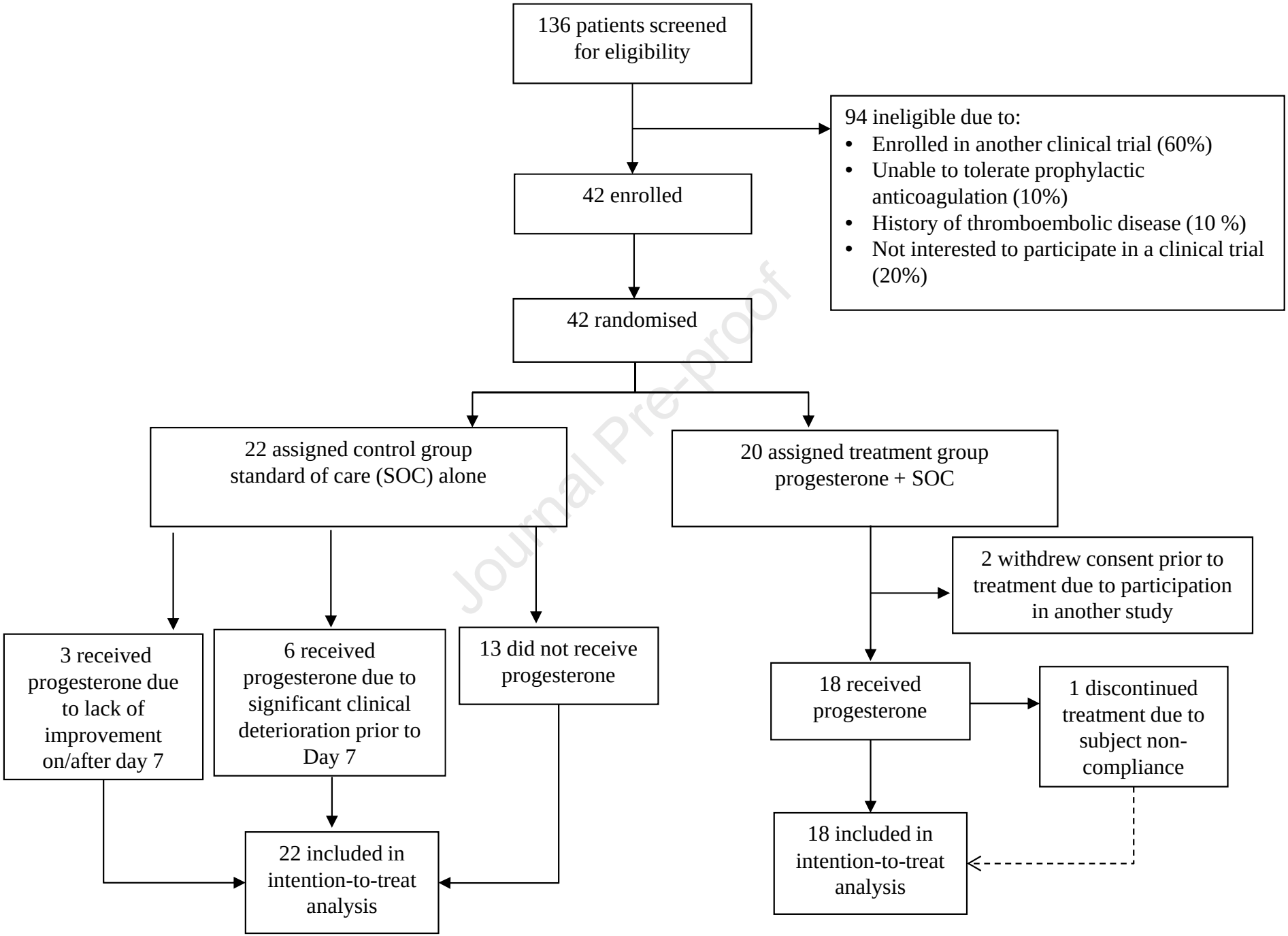
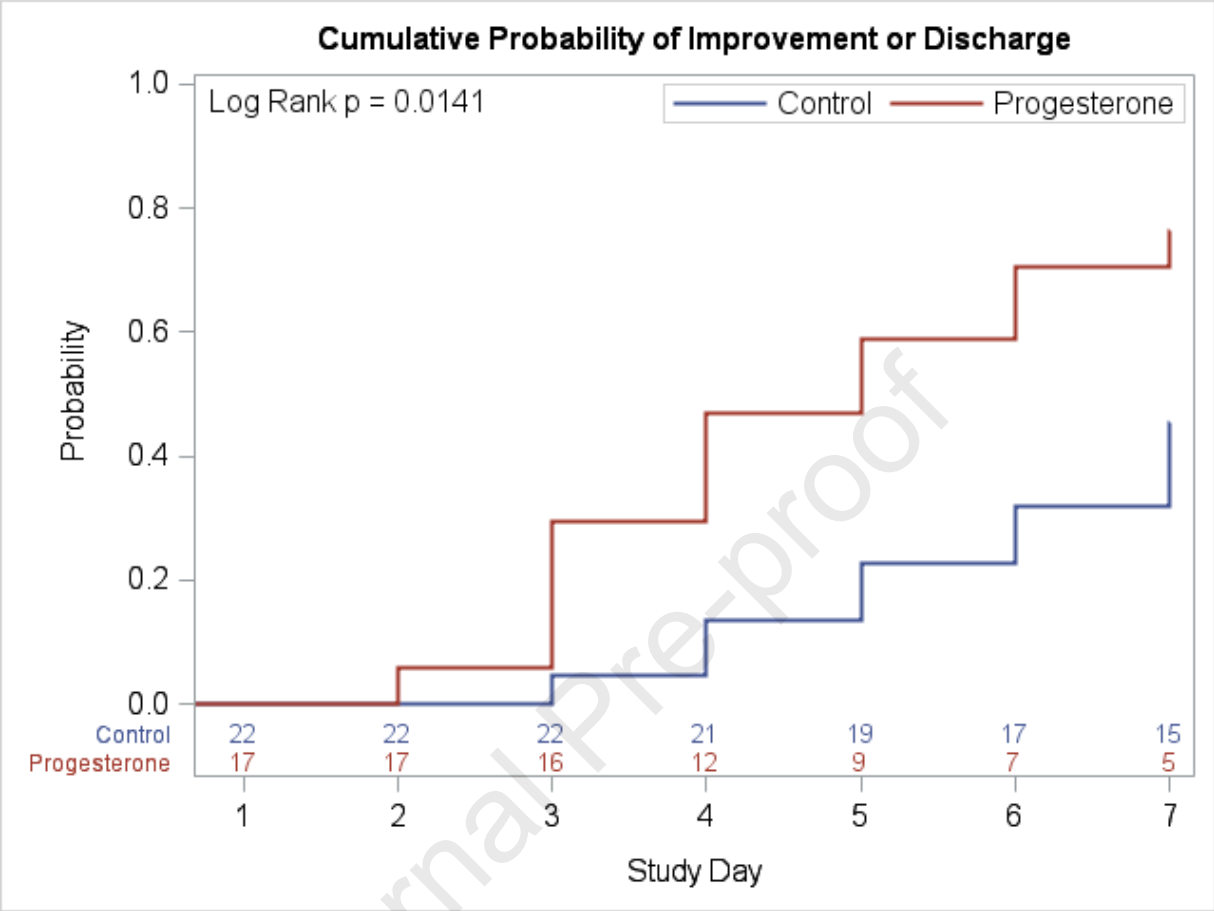


Figure 2: Cumulative probability of improvement or discharge at Day 7
During the first 7 study days, the cumulative probability of clinical improvement (an increase of at least 1 point on the seven-point scale or live discharge) was significantly higher in the Progesterone group, 0.76 (95% confidence interval [CI] 0.55-0.93) versus 0.55 (95% CI 0.28-0.68) in the Control group (Log Rank p = 0.014), by Kaplan-Meier estimation. One patient in the progesterone group showed improvement at day 2 but was subsequently non-compliant with study protocols and was transferred to another facility. For the purpose of this analysis, this patient was excluded.





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