CHEST Online Supplement

Progesterone in Addition to Standard of Care vs 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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e-Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Hospitalized adult (≥18 years old) genetic male patients with
2. Laboratory-confirmed COVID-19 as determined by PCR, or other commercial or public health assay, as documented by either of the following:

   a. in any specimen < 72 hours prior to randomization

   b. in any specimen collected ≥ 72 hours prior to randomization, with progressive disease suggestive of ongoing COVID-19 infection.
3. Patient (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
4. Patient understands and agrees to comply with planned study procedures.
5. Patient agrees to the collection of venous blood per protocol.
6. Illness of any duration and at least one of the following: Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), or clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air and/or requiring supplemental oxygen at no more than FiO2 50% by high flow nasal cannula.
7. Patient must agree to be placed on anticoagulation for prevention of deep venous thrombosis (DVT) while hospitalized.
8. Patient must agree to use suitable barrier method of contraception for the duration of the study.

Exclusion criteria:

1. ALT/AST >5 times the upper limit of normal.
2. History of thromboembolic disease.
3. History of breast cancer.
4. Allergy to progesterone or betacyclodextrin.
5. History of seizure disorder.
6. Use of supplemental oxygen prior to hospital admission.
7. Requiring higher than 50% supplemental oxygen by high flow nasal cannula or mechanical ventilation.
8. Enrolment in any other interventional clinical trials for COVID-19.

e-Table 2. Standard of Care Medications by Patient

Group	Order of Enrollment	Age (years)	Baseline Oxygen	Flow Rate	Hydroxy-chloroquine	Azithromycin	Convalescent Plasma	Tocilizumab	Remdesivir	Systemic Glucocorticoids
Control	01	55	Nasal cannula	4	•					
	02	70	Nasal cannula	5		•		•		•
	03	66	None	NA		•				•
	04	82	None	NA						
	05	63	Nasal cannula	6		•		•		•
	06	40	Nasal cannula	2		•				
	07	67	Nasal cannula	2		•			•	•
	08	75	Nasal cannula	2						
	09	67	Nasal cannula	3					•	
	10	48	Nasal cannula	2		•			•	
	11	28	Nasal cannula	2			•		•	•
	12	25	Nasal cannula	3					•	•
	13	70	Nasal cannula	2					•	•
	14	71	Nasal cannula	2		•	•	•	•	•
	15	35	Nasal cannula	2		•			•	•
	16	42	Nasal cannula	2					•	•
	17	56	Nasal cannula	4					•	•
	18	64	Nasal cannula	2					•	
	19	51	Nasal cannula	4		•		•	•	•
	20	43	Nasal cannula	6					•	•
	21	37	Nasal cannula	6					•	•
	22	47	Nasal cannula	3		•			•	•
Progesterone	01	46	None	NA		•				
	02	91	Nasal cannula	2						
	03	78	Nasal cannula	3					•	
	04	41	HFNC	20		•			•	
	05	33	Nasal cannula	2		•				•
	06	66	None	NA						
	07	47	HFNC	40		•			•	

Group	Order of Enrollment	Age (years)	Baseline Oxygen	Flow Rate	Hydroxy-chloroquine	Azithromycin	Convalescent Plasma	Tocilizumab	Remdesivir	Systemic Glucocorticoids
	08	65	Nasal cannula	4					•	•
	09	53	HFNC	25					•	•
	10	58	Nasal cannula	6		•				
	11	31	Nasal cannula	2						•
	12	33	None	NA		•				•
	13	68	Nasal cannula	1		•				
	14	73	Nasal cannula	4		•			•	•
	15	56	None	NA						
	16	50	Nasal cannula	2					•	•
	17	77	Nasal cannula	4		•		•	•	•
	18	42	Nasal cannula	3		•			•	•

Abbreviations: HFNC = High flow nasal cannula | NA = Not applicable

e-Table 3. Baseline Assessments

	All Subjects N=40	Progesterone N=18	Control N=22
Vital Signs, mean±SD			
Mean Arterial Pressure (mmHg)	94.8±11.2	94.1±9.2	95.3±12.7
Pulse Rate (beats/min)	87.7±13.2	87.1±10.6	88.2±15.3
Respiratory Rate (breaths/min)	20.0±2.3	19.7±2.2	20.2±2.3
Temperature (C)	37.2±0.7	37.2±0.8	37.2±0.6
Oxygen Saturation (%)	94.7±2.4	94.6±2.6	94.8±2.2
Laboratory, mean±SD			
WBC (x1000/UL)	8.3±4.3	8.9±5.0	7.9±3.7
Lymphocytes (x1000/UL)	1.2±0.7	1.3±0.6	1.2±0.8
Hemoglobin (g/dL)	13.2±2.0	13.7±2.0	12.9±1.9
Platelets (x1000/UL)	223.8±81.0	229.6±78.7	219.0±84.4
Alanine Aminotransferase (U/L)	57.2±40.6	57.8±41.3	56.6±41.0
Aspartate Aminotransferase (U/L)	52.8±22.2	52.3±23.7	53.2±21.3
Albumin (g/dL)	3.7±0.4	3.6±0.4	3.7±0.4
Bilirubin (mg/dL)	0.7±0.3	0.7±0.3	0.7±0.3
Creatinine (mg/dL)	1.5±2.8	0.9±0.3	2.0±3.7
NEWS, mean±SD	3.9±1.7	3.7±1.6	4.0±1.8

Abbreviations: WBC = White Blood Cells (Leukocytes) | NEWS = National Early Warning Score

e-Table 4. Sensitivity Analysis of Worst Clinical Outcome

	Progesterone N=18 n (%)	Control N=22 n (%)	P-value[b]
Worst Status Prior to Day 7[a], n (%)			
2 - Hospitalized; on invasive mechanical ventilation or ECMO	0 (0.0)	3 (13.6	
3 - Hospitalized; on high flow nasal cannula (HFNC)	5 (27.8)	4 (18.2)	
4 - Hospitalized; requiring supplemental oxygen (not HFNC)	10 (55.6)	13 (59.1)	
5 - Hospitalized; not requiring supplemental oxygen	3 (16.7)	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[a], n (%)			
+3	1 (5.6)	1 (4.5)	
+2	9 (50.0)	2 (9.1)	
+1	4 (22.2)	4 (18.2)	
0	3 (16.7)	15 (68.2)	
-4	1 (5.6)	0 (0.0)	
Change in Status at Day 7[a], median (IQR)	2.0 (1.0, 2.0)	0.0 (0.0, 1.0)	0.006

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

[a] Since several patients in both groups experienced clinical deterioration over Days 2-6, this sensitivity analysis is presented considering the patients' worst status prior to Day 7 as their baseline in order to capture the severity of illness.

[b] Exact Wilcoxon rank-sum test

e-Table 5. Sensitivity Analysis with Imputed Day 7 for Control Patients Who Received Progesterone

	Progesterone N=18 n (%)	Control N=22 n (%)	P-value[b]
Status at Baseline, n (%)			
3 - Hospitalized; on high flow nasal cannula (HFNC)	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[a], n (%)			
1 - Death	1 (5.6)	0 (0.0)	
2 - Hospitalized; on invasive mechanical ventilation or ECMO	0 (0.0)	2 (9.1)	
3 - Hospitalized; on high flow nasal cannula	2 (11.1)	5 (22.7)	
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)	3 (13.6)	
7 - Not hospitalized; no limitations on activities	2 (11.1)	0 (0.0)	
Change in Status at Day 7[a], n (%)			
+3	2 (11.1)	0 (0.0)	
+2	7 (38.9)	2 (9.1)	
+1	3 (16.7)	4 (18.2)	
0	3 (16.7)	9 (40.9)	
-1	2 (11.1)	5 (22.7)	
-2	0 (0.0)	2 (9.1)	
-3	1 (5.6)	0 (0.0)	
Change in Status at Day 7[a], median (IQR)	1.5 (0.0, 2.0)	0.0 (-1.0, 1.0)	0.010

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

[a] For control patients who received progesterone due to clinical deterioration prior to Day 7, this sensitivity analysis imputes the patient's last clinical assessment prior to receiving progesterone as their Day 7 outcome.

[b] Exact Wilcoxon rank-sum test

e-Table 6. Non-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 Non-Serious AE		9 (50.0)	16 (72.7)	5 (55.6)
Blood and lymphatic system disorders	Hemoglobin decreased	0 (0.0)	1 (4.5)	1 (11.1)
	Lymphocyte count decreased	2 (11.1)	7 (31.8)	2 (22.2)
	Thrombocytopenia	0 (0.0)	1 (4.5)	1 (11.1)
Cardiac disorders	Atrial fibrillation	0 (0.0)	1 (4.5)	1 (11.1)
	Heart rate increased	1 (5.6)	1 (4.5)	0 (0.0)
	Hypotension	1 (5.6)	1 (4.5)	0 (0.0)
	Sinus bradycardia	0 (0.0)	2 (9.1)	2 (22.2)
Infections and infestations	Urinary tract infection	0 (0.0)	1 (4.5)	1 (11.1)
Investigations	ALT increased	1 (5.6)	1 (4.5)	0 (0.0)
	AST increased	1 (5.6)	1 (4.5)	0 (0.0)
Metabolism and nutrition disorders	Blood calcium decreased	0 (0.0)	2 (9.1)	1 (11.1)
	Blood glucose increased	1 (5.6)	3 (13.6)	2 (22.2)
	Hyperkalemia	1 (5.6)	1 (4.5)	0 (0.0)
Renal and urinary disorders	Creatinine increased	0 (0.0)	1 (4.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Hypoxia	4 (22.2)	3 (13.6)	0 (0.0)

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

e-Appendix 1.

A Single Center, Randomized, Controlled Trial of the Safety and Efficacy of Progesterone for the Treatment of COVID-19 in Hospitalized Men

Protocol Number: STUDY00000611

FDA IND Number: 149534

Version 5.0, June 23, 2020

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Title	A Single Center, Randomized Controlled Trial of the Safety and Efficacy of Progesterone for the Treatment of COVID-19 in Hospitalized Men
Rationale	There are increasing reports that men are at higher risk of mortality from COVID-19 than women. Even pregnant women, who are generally considered relatively immunocompromised, have better outcomes than men.[12] This gender difference in mortality may suggest a female hormonal protection that reduces severity of illness. Progesterone levels are high during pregnancy and at varying levels during the ovulatory cycle. A recent comprehensive review article[1] discusses the diverse cell-based immune responses that impact the innate and classical immune responses to infection. In this study, we intend to evaluate the safety, tolerability and efficacy of subcutaneous progesterone administration to men with confirmed COVID-19 through a randomized controlled trial. We hypothesize that this product is safe and well tolerated, and that the documented anti-inflammatory properties of progesterone may dampen the systemic cytokine response, reduce the likelihood of acute respiratory distress syndrome (ARDS), and offer therapeutic benefit in this patient population.
Objectives	Primary Objective: Evaluate the safety and clinical efficacy of progesterone in comparison to standard of care (SOC) in hospitalized men with COVID-19. Exploratory Objective: Evaluate changes in a wide diverse group of inflammatory markers many of which would be expected to be elevated with COVID-19 and to show suppression patterns of these biomarkers following the treatment with subcutaneous progesterone.

Endpoints	Primary Endpoint: Change in clinical status of subjects at Day 7 based on the following 7-point ordinal scale: 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 Secondary Endpoints: • Change in ordinal outcome assessed daily while hospitalized and on Day 15 • National Early Warning Score (NEWS) assessed daily while hospitalized and on Day 7 and 15 • Duration of supplemental oxygen (if applicable) • Duration of mechanical ventilation (if applicable) • Duration of hospitalization • Date and cause of death (if applicable) • Grade 3 and 4 adverse events (AEs) • Serious adverse events (SAEs) • White cell count (WBC), hemoglobin, platelets, creatinine, glucose, total bilirubin, alanine transaminase (ALT), and aspartate transaminase (AST) on Days 1-5, (while hospitalized); and Day 15 (if able to return to clinic or still hospitalized) Exploratory Endpoints: • Evaluate changes in a wide diverse group of inflammatory markers many of which would be expected to be elevated with COVID-19 and to show suppression patterns following the treatment with subcutaneous progesterone

Subject Population	Inclusion Criteria: 1. Hospitalized adult (≥18 years old) genetic male patients with 2. Laboratory-confirmed COVID-19 as determined by PCR, or other commercial or public health assay, as documented by either of the following: a. in any specimen < 72 hours prior to randomization b. in any specimen collected ≥ 72 hours prior to randomization, with progressive disease suggestive of ongoing COVID-19 infection. 3. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures 4. Understands and agrees to comply with planned study procedures 5. Agrees to the collection of venous blood per protocol 6. Illness of any duration and at least one of the following: Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), or clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air and/or requiring supplemental oxygen no more than 50% high flow nasal cannula <50% High flow nasal cannula 7. Must agree to be placed on anticoagulation for prevention of deep venous thrombosis (DVT) while hospitalized 8. Must agree to use suitable barrier method of contraception for the duration of the study Exclusion criteria: 1. ALT/AST >5 times the upper limit of normal 2. History of thromboembolic disease 3. History of breast cancer 4. Allergy to progesterone or betacyclodextrin 5. History of seizure disorder 6. Use of supplemental oxygen prior to hospital admission 7. Requiring higher than 50% supplemental oxygen by high flow nasal cannula or mechanical ventilation 8. Enrolled in any other interventional clinical trials for COVID-19

Phase	1b Pilot Study
Investigational Site	Cedars-Sinai Medical Center
Participants	Approximately 40 hospitalized men with COVID-19
Description of Study Intervention	Progesterone administered subcutaneously at 100 mg twice daily for five days in addition to standard of care (SOC).
Safety	Given the severity of illness in COVID-19, there are no pre-specified study stopping rules. As the study is non-blinded, investigators will review AE / SAE data every 2 weeks. If there are a significant number of unexpected AEs, the an independent reviewer will be asked to review safety data in an ad hoc meeting. There will be temporary or permanent cessation of enrollment based on recommendation of this safety review.
Study Duration	Approximately 12 months
Participant Duration	Approximately 15 days, from screening at Day -1 or 1 to follow-up on Day 15 ±1 days

CSMC Co-Investigators	Samuel Pepkowitz, M.D., co-investigator Michael Lewis, MD, co-investigator Victor Tapson, MD, co-investigator Yuri Matusov, M.D, co-investigator Robert Goodman, M.D., co-investigator Tamana Kaderi, M.D., co-investigator Josephine Hwang, M.D., co-investigator Divya Narayanan, M.D., co-investigator
Sponsor/Funder	Cedars-Sinai Partial Support: Investigator initiated study funded by Institut Biochimique SA (IBSA), a pharmaceutical company
Collaborating Institutions Involved in the Research	None

1. BACKGROUND, RATIONALE

There are increasing reports that men are at higher risk of mortality from COVID-19 than woman. Even pregnant women, who are generally considered relatively immunocompromised, have better outcomes than men.[12] This sex difference in mortality may suggest a hormonal protection that perhaps reduces severity of illness. Progesterone levels are at high levels during pregnancy and at varying levels during ovulatory cycle. A recent comprehensive review article[1] discusses the diverse cellularly-based immune responses that impact the innate and classical immune responses to infection. For example, progesterone (P4) can inhibit innate immune response by several pathways that includes gene transcription of the NF-KB pathway as well as the cyclooxygenase 2 pathway to decrease TNF, INFϒ, IL-1β, and other inflammatory cytokines as well as to augment IL-10 (an anti-inflammatory cytokine). Further impact on the immune response to infection include modulation of macrophage phenotype to an anti-inflammatory M2 state, downregulation of macrophage nitric oxide production, skew TH1 responses to TH2, reduce NK cells, and increase T regs.

In a mouse mode of influenza A, a model closest to the human situation with COVID-19, Hall OJ et al[6] conclude that exogenous progesterone administration conferred protection from both lethal and sublethal infections, decreased inflammation and promoted faster recovery by promoting increased production of and epidermal growth factor (amphiregulin) by enhancing repair of pulmonary epithelial cells.

Further, there is in-vitro data, that administration of progesterone present in high amount in cord blood impacts the macrophage inflammatory response, favoring repair.[2] There are data to support that progesterone may benefit wound healing and repair.[7] Progesterone is widely used for a variety of indications in the form of oral and intramuscular preparations. In a few clinical trials, intravenous (IV) progesterone has been used in severe traumatic brain injury. While the results were mixed on therapeutic benefit in this setting, IV progesterone was found to have a favorable safety profile.[5,8] Frequency of adverse events including thromboembolic events were similar in IV progesterone group compared to placebo.

In this study we intend to evaluate the clinical safety and efficacy of progesterone administration to men with confirmed COVID-19 through a randomized controlled trial. We hypothesize that the anti-inflammatory properties of progesterone may dampen the systemic cytokine response and offer therapeutic benefit in this patient population. This in turn will lead to reducing severity of illness, length of hospital stays, need for intubation and mechanical ventilation, as well as death. You should consider using an adaptive design trial so you can stop when there are signs of clear benefit and then assign controls to the treatment groups as needed.

2. STUDY OBJECTIVES

Primary Objective: Evaluate the safety and clinical efficacy of progesterone in comparison to and standard of care (SOC) in hospitalized men with COVID-19 disease.

Exploratory Objective: Evaluate changes in a wide diverse group of inflammatory markers many of which would be expected to be elevated with COVID-19 and to show suppression patterns following the treatment with subcutaneous progesterone.

3.0 STUDY POPULATION

3.1 SELECTION OF THE STUDY POPULATION

Adult (≥18 years old) genetic male patients with laboratory-confirmed COVID-19 hospitalized at Cedars-Sinai Medical Center

3.2 INCLUSION CRITERIA

1. Hospitalized adult (≥18 years old) genetic male patients
2. Laboratory-confirmed COVID-19 as determined by PCR, or other commercial or public health assay, as documented by either of the following:
   a. in any specimen < 72 hours prior to randomization
   b. in any specimen collected ≥ 72 hours prior to randomization, with progressive disease suggestive of ongoing COVID-19 infection.
3. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures
4. Understands and agrees to comply with planned study procedures
5. Agrees to the collection of venous blood per protocol
6. Illness of any duration and at least one of the following: Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), or clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air or requiring supplemental oxygen
7. Must agree to be placed on anticoagulation for prevention of deep venous thrombosis (DVT) while hospitalized
8. Must agree to use suitable barrier method of contraception for the duration of the study

3.3 EXCLUSION CRITERIA

1. ALT/AST > 5 times the upper limit of normal
2. History of thromboembolic disease
3. History of breast cancer
4. Allergy to progesterone and betcyclodextrin
5. History of seizure disorder
6. Use of supplemental oxygen prior to hospital admission
7. Requiring higher than 50% supplemental oxygen by high flow nasal cannula or mechanical ventilation
8. Enrolled in any other interventional clinical trials for COVID-19

3.4 SUBJECT SCREENING AND ENROLLMENT

Because COVID-19 is a reportable disease, hospital epidemiology knows about every patient under investigation and confirmed case that occurs in Cedars-Sinai Medical Center. Screening will be conducted by any study team member who has access to the hospital epidemiology COVID-19 case list. They study team, will then screen the patients based on the stated inclusion and exclusion criteria and potential participants will be identified.

3.5 Subject Recruitment

They study team, will then screen the patients based on the stated inclusion and exclusion criteria and potential participants will be identified.

It is anticipated that patients with COVID-19 will present to participating hospitals, and that no external recruitment efforts towards potential subjects are needed. Recruitment efforts may also include dissemination of information about this trial to other medical professionals / hospitals.

Patients that are confirmed to have SARS-CoV-2 will be assessed for eligibility.

Screening will begin with a brief discussion with study staff. Some will be excluded based on demographic data and medical history, < 18 years of age, renal failure, etc. Information about the study will be presented to potential subjects (or legally authorized representative) and questions will be asked to determine potential eligibility. Screening procedures can begin only after informed consent is obtained.

4.0 STUDY DESIGN AND METHODS

This study is a phase 1b, pilot, randomized control trial to evaluate safety and clinical efficacy of progesterone in comparison to standard of care (SOC) in hospitalized men with COVID-19.

We hypothesize that progesterone confers protection to women by reducing the inflammatory surge that leads to lung injury in COVID-19. Neither the oral nor intramuscular (IM) progesterone administration achieve serum progesterone levels that are sufficient to reduce the inflammatory cascade triggered by the virus. However, there is a subcutaneous formulation of progesterone which allows for higher and more predictable serum concentration. This formulation is currently commercially available outside of United States for use in fertility treatment. There is an active Investigational New Drug (IND) application with the Food and Drug Administration for fertility treatments using this proprietary formulation

In our trial, 40 subjects will be randomized, 20 will receive institutional standard of care (SOC) and 20 will receive progesterone 100 mg subcutaneously twice daily for five days in addition to SOC.

Subjects will be assessed daily while hospitalized. In the event of clinical deterioration or at Day 7 and absence of clinical improvement, subjects in the control group may receive treatment with study product.

Subjects may be withdrawn from active participation at day 7 or clinical deterioration requiring mechanical ventilation whichever comes first. This is to allow subjects to enroll in other trials should their condition not improve. Follow-up is for approximately 15 days. Withdrawn subjects will also be assessed at day 15. Discharged patients will be asked to participate in a phone or video study visits on Days 7 and 15.

All subjects will undergo a series of efficacy, safety, and laboratory assessments. Research Blood samples will be obtained on Day 1-5. Routine care and safety monitoring labs including White cell count (WBC), hemoglobin, platelets, creatinine, glucose, total bilirubin, alanine transaminase (ALT), and aspartate transaminase (AST) will be collected on Days 1-5, 7 and 15 (only while hospitalized) if they are performed as part of standard of care. In the control subjects who deteriorate and receive treatment with study drug, research labs (progesterone level and cytokine sample) will be obtained for 5 days. The standard of care safety labs will be collected during the five days of treatment if drawn as part of standard of care.

The change in clinical status of subjects at Day 7 will be assessed based on the following 7-point ordinal scale:

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

Secondary endpoints will include change in ordinal outcome assessed daily while hospitalized and on Day 15, National Early Warning Score (NEWS) assessed daily while hospitalized and on Days 7 and 15, if available . Also, duration of supplemental oxygen, mechanical ventilation, and hospitalization are included in secondary endpoints.

Death, serious adverse events (SAE's), and grade 3 and 4 adverse events (AEs) are will be assessed and reported throughout the study.

Routine care and safety monitoring labs will include White blood cell count (WBC), hemoglobin, platelets, creatinine, glucose, total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST). These lab will be collected on Days 1-5, 7 or 15 (while hospitalized) only if obtained as part of standard of care. Any inflammatory markers such as D-dimer, C-reactive protein, ferritin level or IL-6 levels that are obtained as part of standard of care during the study will also be collected.

Standard of care safety labs that are obtained on control subjects who deteriorate and receive treatment with study drug will also be collected during the five days of treatment. Research labs will again get collected on these patients.

Specimen collection:

- Blood will be collected in conjunction with scheduled blood draws required for medical necessity and delivered to the biobank for processing and storage.

Specimen processing

- Plasma and serum will be aliquoted into 500 ul Eppendorf tubes.
- All specimens will be labeled with labeled with a unique subject number that is generated after entering the patient information into a REDCap database.
- Blood specimens will be stored in a -80° freezer in (SSB110).

The PI will be responsible for the storage and care of the specimens. The specimens will be kept indefinitely until all the material is used up.

Revisions from May 4, 2020 protocol: Remove day 29 from the procedure chart, day 7 replaces day 15, day 15 replaces day 29.

Procedures	**Screening Visit**	**Day 1[b]**	**Daily, until hospital discharge**	**Day 7[e]** (±1 days) **In-hospital, phone visit, or outpatient visit**	**Day 15[e]** (±1 days) **In-hospital, phone visit, or outpatient visit**	**Early Termination**
Informed Consent	X					
Inclusion & exclusion criteria	X	X				
Randomization to receive study drug or no study drug [g]	X					
Data collection: Demographics	X					
Data collection: Medical history	X					
Data collection: Current and prior procedures/medications	X	X				
Targeted Physical Examination[f]	X					
Height, Weight	X					
Vital signs		X	X (Daily)	X	X	X
SpO2 (estimate of oxygen in the blood)		X	X (Daily)	X	X	X
Clinical and safety laboratory sampling[c]		X	X (Days 2-5 while hospitalized)	X (while hospitalized)	X (while hospitalized)	X(while hospitalized)
Data collection: Assessment of supplemental oxygen and mechanical ventilation requirements		X	X (Daily)	X	X	X

Clinical status assessment		X	X (Daily)	X	X	X
NEWS (National Early Warning Score) assessment of degree of illness		X	X (Daily)	X	X	X
Study drug (if randomized to receive study drug)		X	X			
Administration of study drug		X	X (Days 2-5, while hospitalized)			
Adverse events (AEs) assessment and data collection concomitant procedures/therapies/medications		X	X (Daily)	X	X	X
Progesterone and cytokine blood samples		X	RX (Days 2-5, while hospitalized)			

[a] Screening Visit to occur on the day of or one day before first administration of study drug (Day -1 or 1)
[b] All procedures should be performed prior to study drug administration with the exception of AEs and concomitant procedures/therapies/medications data. Lab results within 48 hours of Screening or Day 1 is acceptable
[c] Clinical laboratory sampling includes chemistry and hematology panels will be collected only if drawn as part of standard of care.
[d] Study drug to be administered twice daily
e May be a phone visit(for discharged patients); Procedures will be performed if patient available for clinic visit; If patient is in-house, information will be collected via chart review.
f. Physical exam obtained between admission and Day 1 is acceptable.
g. In the event of clinical deterioration or at Day 7 and absence of clinical improvement, subjects in the control group may receive treatment with study product. These subjects will have progesterone and cytokine samples again collected.

5.0 DATA COLLECTION AND MANAGEMENT

5.1 DATA PROCUREMENT

- The study team, including the PI, Dr. Ghandehari, MD, and study coordinators/nurse, will be responsible for data procurement from the medical chart. After the patient has provided informed consent to join the study, study staff will create a subject profile within a REDCap database, which will generate a subject identifier. The study team members will be the only ones that will have access to this information that is stored in a password protected file on a secure server behind a CSMC firewall. Chart review throughout hospitalization will be conducted and periodic chart review up to a year will be performed to determine the patient status.

5.2 TIME PERIOD OF DATA UNDER REVIEW

- Data will be collected daily during admission to monitor laboratory and clinical status as well as safety. Follow-up data will be collected as available.
- Information will be kept for an indefinite amount of time.

5.3 VARIABLES COLLECTED

- The following data points/variables will be collected:
  - Demographics
  - Medical history
  - Vital signs
  - Imaging
  - Progress information
  - Lab results
  - Hospital/ICU assessments
  - Hospital course and discharge location
  - Collection of data from patient charts to evaluate overall outcome.

5.4 SOURCE DOCUMENTS

- CS-link will be the source of all the data. The information will be directly entered into the REDCap database for long-term storage.

5.5 DATA COLLECTION AND STORAGE

- All data are collected and stored electronically behind a password and firewall-protected CSMC server. No hardcopies will be recorded. Only the PI, Sara Ghandehari, MD, and study staff will have access to the data and link to PHI. The PHI will be removed from the database 1 year after enrollment. However, the HIPAA-limited data will be kept indefinitely in the REDCap database and maintained by the PI.

5.6 CONFIDENTIALITY AND SECURITY OF DATA

- To minimize the potential for risks related to a breach of confidentiality or research data:
  - Only the PI and delegated study staff will have access to PHI.
  - All samples will be labeled with a unique subject identifier. All data provided to collaborators will be labeled with the subject identifier with no reference to PHI.
  - Electronic research records will not be stored on a researcher's private computer, laptop or portable device unless these devices are encrypted and approved by the EIS. Research data and patient information may not leave Cedars-Sinai except for legitimate work-related purposes and in accordance with rules for off-campus transport of such information.

6. DATA AND SAFETY MONITORING

6.1 DATA AND SAFETY MONITORING PLAN

- A Data Monitoring Committee (DMC) will be assembled to assess safety endpoints. The committee will be comprised of the study biostatistician and 1 non-study personnel who is an expert in the field of Pulmonary Medicine. The DMC will not have competing or any financial interests.
- The committee will meet for an interim analysis after the first 10 patients, 5 in each arm, complete Day 15 of the study.

- A rigorous screening process will be utilized to verify eligibility.
- During study drug treatment period, the subject will be monitored, and treatment will be discontinued at the PI's discretion.
- At the PI or treating provider's discretion, subjects may be removed from active participation if their condition deteriorates requiring mechanical intubation to allow them to participate in other studies or receive other courses of treatment.
- During the follow-up period, changes in health status will be evaluated by the study doctor and reported as deemed appropriate.

6.2 QUALITY CONTROL AND QUALITY ASSURANCE

- Through the combination of our use of REDCap with its electronic error detection, QA/QC plan, and regular site monitoring, we will ensure the quality and completeness of data in this trial.

7.0 STATISTICAL CONSIDERATIONS

7.1 STUDY OUTCOME MEASURES

The primary outcome measure is change (Delta) in clinical status (from baseline) at Day 7 on the following 7-point ordinal scale:
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

In the event that a subject assigned to SOC is given study product due to clinical deterioration, the primary outcome will be imputed at Day & as the subject's last clinical assessment prior to receiving study product.

The above Delta will be condensed into the following 3-point ordinal scale, Delta3:
1 = Patient status worsened (for example went from level 4 to level 3 on the 7-point scale)
2 = Patient stayed the same
3 = Patient improved (for example went from level 2 to level 5 on the 7-point scale)
The above Delta3 will be further condensed into a binary outcome variable: Worsened versus {Stayed the same or Improved}.
Delta, Delta3, and the binary Worsened variable will be summarized by frequency and percent in each group (SOC + Progesterone and SOC).
Promising/Favorable Study Result: A shift in the Delta or Delta3 or Worsened group distribution towards more improvement in the SOC + Progesterone group will be viewed as a promising/favorable study result.

Delta and Delta3 will be compared across the groups by the Wilcoxon rank sum test. Worsened will be compared across the groups by the Fisher exact test.
Continuous variables will be summarized by mean, standard deviation (SD), median, and range, and will be compared across groups by the independent samples t test and the Wilcoxon rank sum test, as appropriate. Categorical variables will be summarized by frequency and percentage and will be compared across groups by the Fisher exact test. Within group change on numerical variables will be assessed by the paired t test and the Wilcoxon signed rank test, as appropriate. Within group change on ordinal variables will be assessed by the Wilcoxon signed rank test. Within group change on binary variables will be assessed by McNemar's test for related proportions.

7.2 SAMPLE SIZE CONSIDERATIONS

The study is a pilot study. If the result is favorable/promising, we plan to do a larger, definitive study. Parameter estimates from this pilot study will be used to power the definitive study. A sample size of 20 per group (total sample size = 40) will provide estimates that are adequate for powering the definitive study.

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