Acute Estradiol and Progesterone Therapy in Hospitalized Adults to Reduce COVID-19 Severity: A Randomized Control Trial

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1. Study aim, background, and design

Coronavirus SARS-CoV-2, causing COVID-19, has infected over 20 million people and killed over 700,000 as of August 2020. Although, the vaccination campaign is ramping up, vaccination hesitancy in the United States represents up to 25-30% of the population (1), and hospitalizations and deaths are still at the level of 2020. Apart from corticosteroids (2), most available therapeutic options are at best marginally efficient in reducing disease severity and mortality and extremely expensive (3-5). Therefore, the systematic investigation of clinically approved drugs is a priority in order to determine what does improve the disease and invest resources to go to full-scale production. Our current understanding of the disease is that COVID-19 deaths result from an inappropriate immune response with outpouring of pro-inflammatory chemokines leading to lung infiltration and hyperactivation of monocytes and macrophages producing pro-inflammatory cytokines (cytokine storm), resulting in lung edema, reduced gas exchange, and ultimately leading to acute respiratory distress syndrome and multiorgan failure (1-8). *Men with COVID-19 have a uniformly more severe outcome than women*. In series from China, Europe and the U.S., COVID-19 mortality was consistently 1.5 to 2-fold higher in men than in women, suggesting that female biological sex is protecting women from COVID-19 mortality (9-13). It is established that women exhibit heightened immune responses to viral infections compared to men (14), which is at least partially due to the genetic benefit of gene dosage in X-linked immune-response genes. Ovarian steroids, however, also play a protective role. In New York City, among 5700 hospitalized patients, the female protection from COVID-19 mortality was observed at all ages, but was more pronounced in subjects under 50 years of age (18% mortality in women) compared to patients > 50 years of age (40.5% mortality in women) (13), suggesting that ovarian steroids are involved in mitigating COVID-19 mortality in pre-menopausal women. Further, the analysis of electronic health records of over 68,000 COVID-19 patients revealed that estrogen therapy is associated with more than 50% reduction in mortality (15). The main female steroids, 17β-estradiol and progesterone exhibit potent immuno-modulatory and anti-inflammatory actions via estrogen and progesterone receptors expressed in all immune cells, including epithelial cells, macrophages, dendritic cells, CD4+ and CD8+ lymphocytes, and B cells (14,16). Progesterone also acts partially via the glucocorticoid receptor. Together estradiol and progesterone produce a state of *decreased innate immune cells production of proinflammatory cytokines, enhanced T cells anti-inflammatory responses and immune tolerance, and enhanced B-cell-mediated antibody production* (14,17,18). The National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel recommends the use of dexamethasone 6 mg per day for up to 10 days or until hospital Discharge (whichever comes first) as standard of care (SOC) for the treatment of hospitalized COVID-19 patients who require supplemental oxygen but who are not mechanically ventilated and for the treatment of hospitalized patients who are mechanically ventilated. Remdesivir is SOC at Tulane for COVID-19 patients who require supplemental oxygen but who are not mechanically ventilated. We believe that in hospitalized COVID-19 patients, a short treatment with the combination estradiol and progesterone, administered early and as a prevention in addition to SOC, will prevent or mitigate the cytokine storm while increasing antibody production and prevent severe outcomes, without side effects (18). Therefore, it will provide steroid immunomodulation without immunosuppression. The advantage of repurposing estradiol and progesterone compounds is the depth of knowledge regarding their clinical efficacy and toxicity that has accumulated from decades of clinical and basic studies. Estradiol and progesterone are widely available in hospitals, inexpensive, manufacturable to scale, and can be prescribed immediately. Please note there is no increased risk of blood clot following acute and systemic administration of natural hormones. The risk exists following chronic and orally administered synthetic hormones (as discussed below).

Study Objectives
The purpose of this study is to determine to what extent a short and preventive systemic steroid therapy with estradiol and progesterone, administered early to hospitalized and confirmed COVID-19 positive patients of both sexes in addition to standard of care (SOC) can reduce the severity of symptoms and outcomes compared to SOC alone. Note that premenopausal women will be included as acute illness can alter the function of the hypothalamo-pituitary gonadal axis, creating a functional hypogonadism leading to low estrogen levels.

This study has two study arms. One arm will receive standard of care (SOC) with administration of placebo-equivalent with similar frequency, volume and method of administration as for the drug below. The other arm will receive SOC along with the study drugs, a single IM injection of long-acting estradiol cypionate (Depo-Estradiol) 5mg upon admission and a daily oral administration of progesterone 200mg (Progesterone generic 200mg) for 5 days. Clinical status will be assessed at day 14 and day 28 and 60 days.

Study Design

Study Type:	Interventional (Clinical Trial)
Estimated Enrollment:	120 participants
Allocation:	Randomized, placebo-equivalent controlled
Masking:	Double-blinded
Primary Purpose:	Treatment
Setting:	Inpatient hospitalization

2. Subject population
Up to 120 participants hospitalized in the Department of General Internal Medicine and Geriatrics at the Medical Center with mild to severe COVID-19 (WHO ordinal scale score 3-5, Fig.2) confirmed by SARS-CoV-2 PCR test will be recruited for this study. Participants will be recruited at admission by the medical staff of the Department of General Internal Medicine and Geriatrics under the leadership of Dr. Bateman (Co-I) who will identify participants that meet study eligibility criteria from their admission list.

2.1. Sample Size Considerations
Sample size calculations are based on 80% Power, using a two-sided Pearson's Chi-square Test for Proportion Differences at the 5% significance level. It is estimated that between 60% and 70% of hospitalized patients with mild or severe disease will improve clinically and become ambulatory after standard treatment (WHO ordinal scale score 1-2 Fig.2)). Table 1 presents the sample sizes that are required in each treatment group to detect a significant difference in the percent of hospitalized patient leading to an ambulatory disease (shift from category 5-8 to category1-2 in 20%, 25%, 30% or 35% of hospitalized patients after treatment with estradiol (E2) and progesterone (P4)). Efforts will be made to recruit 60 patients in each treatment group in order to stratify by disease severity, age and gender.

Table 1.		
Treatment	Percent leading to a scale 1-2	Sample Size
SOC	60%	32
SOC + E2 + P4	90%	32
SOC	60%	22
SOC + E2 + P4	95%	22
SOC	70%	62
SOC + E2 + P4	90%	62
SOC	70%	36
SOC + E2 + P4	95%	36

An interim analysis will be performed at 50% enrollment to determine to what extent a strong treatment efficacy warrants stopping the trial early. Table 2 presents interim sample sizes and required Z test statistics for comparing two proportions at each of stage of a O'Brien-Fleming alpha-spending sequential design (24). Based on 80% power and an overall 5% significance level, if the interim analysis for the first 60 enrolled patients results in differences that are more than 2.96 standard deviations from 0, the trial will end, and treatment efficacy will be concluded. Otherwise, the trial will enroll the total 120 patients.

Table 2.			
	Treatment	Sample Size	Standardized Z test Statistic
Stage 1	SOC	30	2.96
	SOC + E2 + P4	30	
Stage 2	SOC	60	1.96
	SOC + E2 + P4	60	

2.2 Inclusion Criteria:

1. Hospitalization at the Medical Center in the Department of General Internal Medicine and Geriatrics with COVID-19 (WHO Ordinal scale score 3-5, Fig.2) and confirmed by SARS-CoV-2 PCR.
2. Respiratory symptoms (fever, shortness of breath or cough) or abnormal lung exam or chest imaging characteristic of mild to severe COVID-19 pneumonia*.
3. Patient and/or legally authorized representative (LAR) agrees to comply with study procedures and the collection of blood samples per protocol
4. Patient and/or LAR agrees to be placed on prophylactic dose of anticoagulation for prevention of deep venous thrombosis (DVT) (if necessary).

5. Patient or legally authorized representative has signed informed consent
6. Women of childbearing age with a negative pregnancy test on admission

*Severity of COVID-19 defined by FDA guidance document “COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry” (https://www.fda.gov/media/137926/download).

2.3 Exclusion Criteria:

1. Patient under 18 years of age
2. Critical COVID-19 (respiratory failure requiring intubation and mechanical ventilation, shock, multi-organ failure)
3. Pregnant women confirmed by pregnancy test
4. Women who are within six weeks of postpartum
5. Patient is not hospitalized at the Medical Center with confirmed COVID-19
6. Patient included in another COVID-19 trial (excluding hydroxychloroquine and dexamethasone)
7. Women already treated by estrogen and or progestogen therapy two weeks prior to admission
8. Men already treated by testosterone therapy prior to admission
9. History of breast or endometrial cancer
10. Abnormal genital bleeding
11. Active or recent (e.g., within the past year) stroke or myocardial infarction
12. History of blood clots including deep vein thrombosis related to clotting disease, or pulmonary emboli (prior to hospitalization).
13. History of liver dysfunction or disease.
14. Patients with end-stage renal disease
15. Patients taking inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, and ritonavir.
16. Patients taking St. John’s Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin.
17. Patients within 6 weeks of major orthopedic surgery

3. Procedure

The study will begin after the study team obtains IND from the FDA and IRB approval from Tulane University Biomedical IRB. The study will utilize the Medical Center Research Pharmacy for randomization, the accountability, storage, dispensing, handling, and disposal of drugs. The Clinical Translational Unit (CTU) will also participate in the implementation of the study. We estimate that the study will be complete within 12 months.

3.1 Collection of blood samples

The collection of routine blood samples and patient monitoring will be conducted as part of the standard of care procedures that are utilized at the hospital for COVID-19 patients. The collection of blood samples (CBC with differential, blood chemistry, inflammation markers) is to monitor disease severity and is independent from this protocol, but we will use the data in our analysis as explained in section 3.5. Women of childbearing age will have a pregnancy test on admission

An additional blood sample will be collected for our study at admission and after 5 days of treatment. We will collect about 1-5 teaspoons of blood at these two time points. This blood sample will be stored in Dr. Mauvais-Jarvis lab for 1) isolation of peripheral blood mononuclear cells (PBMC) to assess the effect of treatment on immune cells populations by flow cytometry and PBMC gene expression by RNA-Seq 2) and metabolomics profiling to determine metabolic and molecular signatures of the efficacy of treatment. De-identified serum and PBMC frozen samples will be transferred to the University of Michigan Metabolomics Core to perform untargeted metabolomic analyses. University of Michigan will not receive identifiable information nor a link to identifiers related to the samples.

Additionally, we propose to use the serum and PBMC from our collected blood samples to perform multi-dimensional analysis in the Center for Translational Research in Infection and Inflammation (Collaboration with Dr. Jay Kolls), and the laboratories of Dr. James McLachlan and Dr. Mauvais-Jarvis at Tulane University School of Medicine. Blood samples will be stored for up to 3 years.

3.2 Treatment arms and interventions

Treatment Arm: Standard of Care* along with Estradiol Cypionate 5mg intramuscular injection at admission and Progesterone 200mg by mouth daily for 5 days starting at admission.
Control Arm: Standard of Care along with placebo-equivalent injection of normal saline at admission and placebo-equivalent pill folic acid 400 mg pill daily for 5 days starting at admission. The dose of folic acid (400 mg daily for 5 days) is safe. Participants will be able to take additional folic acid (e.g., over the counter vitamins, or through food) should they choose, as there is no safety concern for overdose over 5 day period of folic acid. Folic acid is not expected to have a treatment or preventive effect for SARS-CoV-19 and is considered a placebo-equivalent product for this study.

*Standard of Care at the Medical Center is consistent with the National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel and consists of *dexamethasone 6 mg per day* for up to 10 days or until hospital Discharge (whichever comes first) for the treatment of hospitalized COVID-19 patients who require supplemental oxygen but who are not mechanically ventilated and in hospitalized patients who are mechanically ventilated. Remdesivir is SOC at Tulane for COVID-19 patients who require supplemental oxygen but who are not mechanically ventilated.

Blinding:
This is a blinded study. However, the medications are not identical-appearing. The dosing is also different for the oral study drug and placebo (folic acid) so blinding will operate in different ways across those involved in the study to preserve blinding for the participants, those who directly interact with them, and measurement of the study endpoints:

- Participants will be blinded. The injection syringe for Estradiol Cypionate or normal saline will be covered with blinding tape to mask the difference in color. The bottles of oral medications will not identify the treatment allocation. Medication bottles will be labeled to say “Progesterone 200mg or folic acid 400 mg).
- Treating clinicians and study team will be blinded
- Study pharmacy staff will be unblinded, as they will prepare and blind the study medications.

Dosing Instructions:

Estradiol cypionate 5 mg (1mL) or normal saline (1 mL) will be administered intramuscularly. One pill of oral progesterone 200 mg or Folic acid 400 mg will be administered orally at bedtime with a glass of water.

Hazardous Drugs Handling Considerations
Estradiol Cypioante and progesterone are hazardous agents (NIOSH 2016 [group 2]). NIOSH recommends single gloving for administration of intact tablets or capsules. For IM preparation, NIOSH recommends double gloving, a protective gown, and ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator). Double gloving and a gown are required during IM administration.

3.3 Outcome Measures
For all randomized patients according to section 2.2, demographic and clinical variables, including sex, age, race/ethnicity, BMI, symptoms, vital signs blood pressure, respiratory rate, temperature, oxygen saturation), chronic comorbidities through diagnosis codes, medications, clinical course during hospitalization (described in primary outcome below) will be reviewed in the patients' medical charts. Laboratory measurements including when available CBC, blood chemistry, liver function test, creatinine, BUN, lactate, troponin, ferritin, CRP, procalcitinin, Brain-type natriuretic peptide, D-dimer, interleukin-6, G6PD. We will review the participants' medical records for up to 6 months after hospital discharge.

Primary outcome:
For all randomized patients with baseline inclusion criteria, WHO ordinal scale score 3-5, the primary efficacy end point will be the proportion of patients who achieve scores 1 or 2 on the 9-point World Health Organization (WHO) ordinal scale (Fig. 2) through day 28.

Secondary outcomes:
For all randomized patients, the following secondary end points will be assessed at day 14, 28 and 60

1. Length of hospital stay
2. Duration of mechanical ventilation
3. Cause of death and number of days death occurred after admission
4. Readmission
5. Change in biological markers below between admission and occurrence of primary endpoint (2 values at least 2 days apart)
6. Grade 3 and 4 adverse events
7. Serious adverse events

Biological markers
Obtained from Standard Of Care: *Inflammation:* neutrophil:lymphocyte ratio, C-reactive protein, ferritin, procalcitonin.
Hypercoagulability: D-dimers, fibrinogen
Tissue injury: troponin, ALAT, ASAT, LDH

Metabolome, Proteome, PBMC

Safety measures and monitoring.
This study is considered greater than minimal risks. In all randomized patients according to section 2.2, we will monitor adverse events described in section 4 on a daily basis (Fig.1). Thus, we will perform daily examination of injection sites with documentation and measurement of any erythema, swelling, tenderness or induration; legs will be examined daily for evidence of deep vein thrombosis. Note that daily monitoring of clinical status (including symptoms, examination, laboratory assessments, oxygen saturation) is already part of COVID-19 SOC. We will carefully monitor patients with renal impairment for potential fluid retention.

We have formed an independent Data Safety and Monitoring Board (DSMB) to monitor study safety. The DSMB will consists of four board members who are MDs clinicians and researchers with the experience necessary to interpret the data and ensure patient safety. Specifically, the board members are knowledgeable about COVID-19 and the treatment involved in this study. The DSMB includes, an Infectious disease specialist, an endocrinologist, hematologists-oncologists, women's health specialist and a biostatistician. The initial DSMB meeting occured before the start of the trial to discuss the protocol and guidelines for monitoring the study. At this meeting, guidelines were defined for stopping the study for safety concerns (Study stopping rules) and where relevant, for efficacy based on plans specified in the protocol. The DSMB will meet on a quarterly basis. It will provide the Principal Investigator a letter after each meeting with the results of their review and their recommendations for the continuation of the study. The DSMB includes the following 5 members outside of the Tulane University School of Medicine faculty who were identified by Dr Mauvais-Jarvis prior to the start of the study:

1. Frank Greenway, MD, Chair of DSMB (Endocrinology) - The Pennington Biomedical Research Center
2. Erin Brewer, MD, MPH (Women's Health) - Southeast Louisiana Veterans Health Care System (SLVHCS)
3. Phillip Yeon, MD, MPHTM (Infectious Diseases)- SLVHCS
4. Nancy Vander Velde, MD (Hematology and Oncology)- SLVHCS
5. Donald E. Mercante, PhD (Biostatistics)- Louisiana State University

No member of the DSMB will have direct involvement in the conduct of the study. The DSMB will review and evaluate the accumulated study data for participant safety, adverse events, study conduct, progress, adherence to the protocol and efficacy. The DSMB will consider study-specific data as well as relevant background knowledge about COVID-19, estrogen and progesterone therapy, and the patient population under study. The data will remain blinded. The frequency of DSMB meetings will depend on the rate of enrollment but will roughly occur quarterly. The DSMB meetings will be private and closed meetings. Dr. Mauvais-Jarvis will be responsible for convening meetings by conference calls or Zoom videoconferences or as face-to-face meetings, and coordinating the distribution of meeting materials to DSMB members. The written open session reports from DSMB meetings will be submitted to the Tulane IRB.
We will implement a group sequential trial framework with the option for stopping for safety or harm with an early interim look once 30 patients finish the Day 28 assessment. This will allow the DSMB to evaluate trial safety data. A decision about study continuation will be made based on the independent DSMB recommendations. The DSMB will convene if study participants experience a higher rate than the background rate of thromboembolic disease. The DSMB will also convene when ≥ Grade 3 AE are observed and considered related to drug or not.

We will follow-up in person or by telephone for all subjects in your trial for any adverse events/serious adverse events (AEs/SAEs) and mortality at Day 60.

Adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version5 and taken care with the corresponding specialized clinical management of the SAE.
Grade 1 adverse events (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated) or Grade 2 adverse events (moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living): such as breast tenderness, nausea, vomiting, bloating, stomach cramps, headaches, vaginal itching, abnormal uterine bleeding will not require discontinuation of treatment.
Grade 3 (severe) like DVT and 4 (life-threatening) serious adverse events such as MI, stroke, POME, anaphylaxis will be managed by treatment discontinuation (except SOC) and appropriate specialized clinical management of the SAE.

A schedule of risk assessment is shown on Fig.1

3.4 Statistical Analysis
For all randomized patients according to section 2.2, clinical outcomes and demographic characteristics will be summarized and presented separately for the treatment group and the control group, as well as overall for all patients. Categorical variables such as the primary outcome, readmission, as well as race and sex will be summarized with counts and percentages. Quantitative outcomes, such as length of stay, change in biological markers, age and BMI will be summarized with means, medians, standard deviations, and interquartile ranges. Univariate analyses will be performed as the primary method to assess the unadjusted effect of treatment on the primary outcome and on readmission rate using the Pearson Chi-square test. Differences in average length of stay and in change in biological markers will be assessed with either a two-sample t test or the Mann-Whitney nonparametric test. Multivariate analyses will be performed to compare treatment to control responses while adjusting for various co-factors. Multiple logistic regression will be used as supportive method to test for significant differences in the proportion with the primary outcome, between the active treatment and placebo-equivalent groups, while adjusting for age, race, sex, bmi and other potential co-factors. For the secondary outcomes. multiple logistic regression will also be used to test for significant differences in the proportion readmits, between the active treatment and placebo-equivalent groups, and multiple linear regression will be used to test for significant differences in average length of stay and changes in biological markers, between the treatment and SOC groups, while adjusting for potential influencing co factors.

3.5 Data Storage
All data and research files will be de-identified and stored using the secure web application Research Electronic Data Capture (REDCap). REDCap is protected by a login as well as encryption. There is also an audit trail, which tracks all logins and activities in the database. All data for this study will be electronic; there will be no paper records. Enrolled subjects will be assigned a sequential study ID (i.e. 001, 002, etc) that is linked to their medical record number. A link between the study ID numbers and medical record number will be kept in a separate file from the de-identified database and stored securely in REDCap. Only the IRB-approved study investigators will have access to the data and link. The password-protected study log will be destroyed three years after the study is complete.

4. Risks

This is a greater than minimal risk study due to the new investigational use of an FDA-approved drug in this study. IM injection may cause some swelling and tenderness at the injection site. The side effects of estradiol includes breast tenderness. The side effects of progesterone include vaginal bleeding. In

addition, drawing blood from a vein may cause local pain, bruising, occasional lightheadedness, dizziness, fainting, and very rarely, infection at the site of the blood draw. To reduce risk of anxiety or pain related to the blood draw, experienced nurses or phlebotomists will draw blood.

The risk of deep vein thrombosis (DVT) or pulmonary embolism associated with estradiol and progesterone treatment exists but is minimal. First, the risk of DVT is associated with chronic hormone therapy, over months, not acute hormone therapy of several days. Most importantly, the risk is minimal because of parenteral estradiol administration, which does not alter clotting factors. DVT risk occurs mainly following orally administered estrogens and synthetic progestin because of first-pass liver metabolism leading to high liver exposures to hormones that increase hepatic production of clotting and inflammatory factors (19). Additionally, the DVT risks are usually associated with the use of conjugated equine estrogens (Premarin) alone or associated with a synthetic progestin like medroxyprogesterone acetate (Prempro) (19). There is no documented risk with natural hormones estradiol given systemically (IM, SC) and no documented risk with the use of progesterone. Additionally, most COVID-19 patients are at risk of DVT and will be placed on prophylactic anticoagulants at admission as Tulane SOC.

There is a risk of breach of confidentiality. In order to minimize this risk, all data will be de-identified and minimal PHI will be gathered (i.e., medical record number). Maintaining a link between the study ID number and medical record number is important to prevent a given chart being entered twice in the database. PHI will be stored securely in REDCap and separately from the study dataset.

A schedule of risk assessment is shown on Fig.1

Subjects withdrawal criteria

- when a subject's safety may be compromised such as when a subject is experiencing related adverse events requiring discontinuation of treatment,
- when the study is being closed by the PI related to increased risk to participants
- when the subject is non-compliant with required study regimens or procedures
- when the subject desires to voluntary withdraw for the study

5. Benefits

There is immediate benefit for individual subjects in this study as we expect the hormonal treatment to prevent mortality and to decrease the severity of COVID-19 disease. Additionally, the knowledge gained by this study may provide important insights into the pathogenesis of the disease. Overall this study will benefit society as it will address the question of whether hormones partially explain the female protection from COVID-19 and if we can use hormone therapy for life saving off-label therapeutic applications.

6. Remuneration

Subjects will be compensated for participation in this research study. Compensation will be in form of clin card which is a specially designed debit card for clinical research onto which your funds will be loaded as appropriate. As each scheduled visit is completed, funds will be approved and added to your card. The funds will be available within 1 business day and often times immediately after being loaded and can be used at your discretion. You will be issued one card for the duration of your participation in the study. If your card is lost or stolen, ask a study team member for a replacement ClinCard .Subjects will be given $25 for each completed visit 1-6 (screening visit and each day of treatment (maximum of 5 days)) and $50 for the end of study visit 7 (via telephone).

7. Academic or Extra Credit
NA

8. Costs
Patient and/or their insurance will be responsible for the entire standard of care costs associated with hospitalization. The patient will not need to pay for anything related to the study drugs.

9. Alternatives
NA

10. Consent process and documentation
The consent process will be administered to the patient (or legally authorized representative (LAR) in the case that the patient is unable to consent) using the Adobe Sign feature on an iPad or smartphone in order to minimize the safety concerns for study personnel conducting the consent procedures. Adobe Sign minimizes the exposure of research team members to the COVID-19 virus by minimizing the need for them to go into the room to obtain the signature from the patient. Adobe Sign also protects patient privacy by signing the informed consent form securely and electronically. Adobe Sign also provides a secure way for the LAR to sign the informed consent form in situations where they cannot be physically present in the hospital due to Stay at Home Order or for being out of state. The patient or LAR have the option to keep the password-protected signed electronic copy of the informed consent form by entering their Email address and choosing a password while signing through Adobe Sign. That way, the patient or LAR do not face the risk of losing the written informed consent form after the patient is discharged.

The consent interview will take place in a private setting. If the patient does not have a personal smartphone device that they would like to use for the consent process, the study team member will hand an iPad which can be encased in a plastic case to the clinical care team member, who will go into the patient's room when they have to for clinical care and hand out the iPad to the patient. The study team member will go over and discuss the informed consent with the patient over the phone and answer any questions the patient might have. Patients who wish to proceed with consenting will be provided with time to ask questions and discuss the consent and the study to demonstrate that they have a clear understanding of the study. Only then will the consent process be finalized with signatures and initials as appropriate and described below, using a pen, stylus, or finger.

To complete the informed consent form, the patient will log into Adobe Sign for TUMG and follow the instructions given to them over the phone from the research team member to sign the informed consent document. There will be two signature requirements: 1) the patient or LAR, and 2) the witness/clinical care team member obtaining the signature. The patient/LAR and witness/clinical care team member will enter their email address and get an electronic copy of the informed consent signature page where they will sign. After the patient/LAR sign the informed consent, an Email will be sent to the witness/clinical care team member to sign as well. Then, an email from Adobe Sign will be sent to the patient and the research team member to have an electronic copy of the signed informed consent. There is a password option available for the patient or LAR to use so the electronic copy sent to their email can be locked and seen only by them using the password. If the patient/LAR used the iPad (not personal smartphone device) for this process, then the clinical care team will bring out the iPad from the patient's room and give it back to the research team member, where either the plastic case can be disposed of or the iPad can be disinfected. For the LAR who couldn't be present physically (e.g., out of state, Stay at Home Order, etc), the research team member will send an electronic copy of the informed consent to the LAR's email to read. They will talk over the phone with the LAR to explain and discuss the informed consent in detail. The LAR and another witness from LAR's side will sign the informed consent using

the same steps mentioned above using Adobe Sign on their mobile or tablet devices by using the link sent from the research team member to the LAR's email after the informed consent was discussed. The LAR and research team member will receive an electronic copy of the signed informed consent sent to their emails.

The HIPAA authorization form will also be signed using AdobeSign, as detailed above. The HIPAA authorization form will thus be documented using an electronic signature.

11. Qualifications of the investigators

PI: Franck Mauvais-Jarvis, MD, PhD, Professor of Medicine, Division of Endocrinology
Dr. Mauvais-Jarvis is a physician-scientist and Endocrinologist and expert in diabetes and obesity and the role of sex hormones in biology and disease. Dr. Mauvais-Jarvis has extensive experience in investigator-initiated clinical trials

Co-I: Dragana Lovre, MD, Assistant Professor, Section of Endocrinology Dept of Medicine.
Dr. Lovre is an attending physician in the Section of Endocrinology and has several years of experience in conducting clinical trials at Tulane University.
She will lead all of the clinical trial activities along with Dr. Mauvais-Jarvis and Dr. Bateman.
Dr. Lovre will also be involved in data management, statistical analysis, visualization and publication of data.

Co-I: Kristin Bateman, MD, Assistant Professor, Section of General Internal Medicine and Geriatrics Associate Program Director, Internal Medicine. Dr. Bateman is an attending physician in the Section of General Internal Medicine and Geriatrics and will be the primary physician involve in recruiting patients.

Co-I: Manika Bhondeley, PhD, Staff scientist. Dr. Bhondeley has experience in handling and processing blood samples, cellular and molecular biology techniques, cell culture techniques, and Bioinformatics tools. She will be responsible for the processing of blood samples and isolation of PBMC.

Co-I: Vivian Fonseca, MD, Department of Medicine - Section of Endocrinology and Metabolism. Dr. Fonseca is the Assistant Dean for Clinical Research at Tulane University School of Medicine. He is also a Professor of Medicine, the Tullis–Tulane Alumni Chair in Diabetes, and Chief of the Section of Endocrinology.

Co-I: John Lefante, PhD, Biostatistics and Data Science. Dr. Lefante is a Professor and Chair in Biostatistics and Data Science in the Tulane University School of Public Health and Tropical Medicine. He received his PhD from University of Alabama in Birmingham, and his MS and BA from University of New Orleans. Dr. Lefante will be the statistician for this study.

Co-I: James McLachlan, PhD, Department of Microbiology and Immunology. Dr. McLachlan is an Associate Professor in Microbiology and Immunology in the Tulane University School of Medicine.

Co-I: Jay Kolls, MD, Medicine & Pediatrics. Dr. Kolls is a Professor of Medicine & Pediatrics and the John W. Deming Endowed Chair in Internal Medicine in the Tulane University School of Medicine.

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Figure 1. Schedule of safety assessments

Surveillance	Days following initiation of treatment								
	0	1	2	3	4	5	7	28	60
Pregnancy test*	X								
Injection site		X	X	X	X	X	X		
E2 side effects		X	X	X	X	X	X	X	
P4 side effects		X	X	X	X	X	X		
DVT symptoms		X	X	X	X	X	X	X	X
MI symptoms		X	X	X	X	X	X	X	X
Stroke symptoms		X	X	X	X	X	X	X	X
Fluid retention**		X	X	X	X	X	X	X	X

* Women in reproductive age
** Patients with renal impairment

Figure 2. Adapted from WHO R&D Blueprint Feb 18, 2020, Geneva, Switzerland

Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8