COVID-19 The Easter Trial

Outpatient prospective evaluation of H1R H2R Antagonist Synergy treatment to blunt the cytokine storm in early COVID-19 infections

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Estimated Start Date: within one week IRB approval

Estimated Completion: within 6 months of start date

Abbreviations: H1R – histamine 1 receptor
H2R – histamine 2 receptor
COVID-19 - Corona Virus Disease 2019

Purposes:

1. Proof of concept: To evaluate histamine receptor blockade effect in early COVID-19 infections. It is theorized that blunting the cytokine storm would slow the deterioration of pulmonary function, morbidity and prevent mortality. Additional points to study are length of the illness, need for hospitalization and when it happens, the length of hospital stay, time on ventilator and mortality rate. Histamine blockade is currently being evaluated at multiple sites

in the US. This is the only trial we are aware of that combines H1R and H2R antagonists in the same trial.

Brief Description of the study:

Those patients exhibiting COVID-19 related symptoms will be referred by St. Dominic affiliated clinics or other primary care clinics to one of the following St. Dominic's COVID testing centers" St. Dominic Family Medicine Gluckstadt and MEA North Primary Care Clinic. Those individuals who undergo COVI-19 testing at either of the two testing centers will be provided a handout containing information about the research study. The handout will instruct interested patinet's to contact GI Associates about the research study in the event they are provided a positive COVI-19 testing result. Once the interested patient has initiated contact with the GI Associates research team, patient names and contact information will be acquired. Upon receipt of information pertaining to the research study, interested patients will be prompted to read the informed consent online via GI Associates portal and be instructed to present in person to GI Associates Clinic.

Upon arrival to GI Associates Clinic, research personnel, certified in best practices and dressed in personal protective equipment, will explain in detail the study to the patient. If interested in proceeding, the research personnel will obtain informed consent and permission to review any testing center information and future outpatient and hospital records.

If the patient has interest after testing positive they will be instructed to contact the research coordinators at 601-718-1572 for full explanation of the research trial. Informed consent will be initiated after positive COVID testing results are in. Initial contact will be by phone or secure texting / email. Patients will be prompted to read the informed consent on line via portal connected to the GIA research division. This will facilitate informed consent on site if the patient wishes to proceed.

Following consent, the participant will be randomized to receive a 21 day supply, coded to 1:1 randomization, combination of cetirizine and famotidine or placebo. The 1st dose will be administered at the GI Associates Clinic. The medications will be in blister packaging, with patients assigned research number, packaged in linear AM-PM-AM-PM tear off packets. The study medications will be administered BID, AM and PM.

The testing center / research team associate will obtain current symptoms consistent with the CDC standards and give the participant a check list of symptoms to record on a weekly basis. A researcher / associate will be in contact with the participant by phone, text or email to collect clinical data. The expected target number of participants is 100-200. The end of the study is when all patients have either finished the 21 day treatment or the last participants tested either recover or die.

Patients will be provided a list of study logistics that they will be instructed to follow. Appendix E.

Data Entry / Documentation:
Data entry will be done under the direction of the PI and Study Coordinators. Utilization of the Research division employees as done with other studies will be used. May have a lead medical student / research intern assisting in this role. Anyone involved in data entry, discovery will be certified in our research department.
All study documentation will be in the research department at GI Associates.

Study devices / tests
No new tests or procedures expected

Study Medications
Cetirizine 10 mg & Famotidine 20 mg BID x up to 21 days, provided in 42 individual blister packs containing one pill of each medication, labeled am and pm, study medications (not compounded) provided as generics through The Transplant Pharmacy of Flowood Mississippi.

Inert Placebo provided by Garden Pharmacy and in similar blister packs, color coded packaging.

Study Location: Site for initiation of informed consent, randomization, follow-up: GI Associates, 2010 Lakeland Drive

Funding: This will be independently funded by GI Associates with support of ST Dominic if desired, but not asked for. A grant is being evaluated.

Confidentiality:
Patient/participant information will be kept private according to HIPPA regulations. At the end of the study period once statistical analysis has been performed, all documents/records will be kept by principle investigator for a period of 5 years in the research department at GI Associates. All researchers involved in patient HIPPA data are employees of either part of the study team at GI Associates or St. Dominic's and HIPPA trained in maintaining confidentiality.

Interaction for Informed consent:
Informed consent will be obtained at 2010 Lakeland drive. Informed consent will be obtained in a private setting by clinical research assistants, previously identified study RNs trained in HIPPA guidelines, or physicians who are part of this study team.

Study Population: Inclusion Criteria
Age: >/= 18 yo < 80 yo
Acute respiratory illness clinically suspected of being COVID-19. (Must have at least one: Fever >100.4, cough, myalgia, loss of sense of smell, headaches)
PCR swab test positive

Study Population: Exclusion Criteria
Allergy to study drugs

Patients with serious drug interactions.
Subjects who drink alcohol daily, more than 3 drinks per day for males, 2 drinks daily for females.
Patients currently on another investigational study for the treatment of COVID19
No way to do follow up (no phone or email)
Nursing mother
Incarcerated
Unable to sign own consent
Patients needing direct referral to hospital for admission evaluation
Unwilling to participate
Sensitivity to H1R or H2R antagonists
Patients already taking H1R or H2R antagonists

Randomization

1:1 non-stratified randomization Group A – study Rx
Group B – Placebo
Randomization will be sequential without stratifying. A-B-A-B-A-B…

Methodology:

Patients will be referred to St Dominic COVID testing centers by physicians' offices within the St Dominic health care system, or from other primary care systems. Immediately after standard Nasopharyngeal PCR Viral RNA detection has been obtained (turnaround time 1-3 days). Informed consent will not be done at this site, a simple flyer / handout about the research opportunity will be provided to the patient and if the patient has interest after testing positive they will be contacted for full explanation of the research trial. Informed consent will be initiated after positive COVID testing results are in.

At the research site, in a drive through setting at 2010 Lakeland Drive, research personnel, in personal protective equipment, will explain in detail the study to the patient, and if interested in proceeding the research personnel will obtain informed consent and permission to review any testing center information and future outpatient and hospital records. Demographics, History of symptom onset will be obtained by research team during the process of informed consent.

The participant will be randomized to receive a combination of cetirizine and famotidine or placebo.

Participant will be randomized to receive a combination of:

(1) cetirizine and famotidine, blister packs
(2) Placebo, 2 capsules blister pack.

1st dose will be administered at the time of randomization and informed consent

Participant will receive

(1) Check list, illness diary of CDC recognized symptoms to record
(2) CDC guidelines for sequestering at home.
(3) 21 day supply of study medications

Researcher / associate will be in contact with the participant by phone, text or email to collect clinical data. Expect weekly contact till symptoms resolved.

The expected target number of participants is 100-200. The end of the study is when all patients have either finished the 21 day treatment or the last participants tested either recover or die.

See Attachments: Initiation, randomization form, Excel Data spreadsheet

Length of therapy: 3 weeks or till patient feels free of disease.

Self-isolation until 2 weeks has passed and/or 7 days have passed with no fever, whichever is longer

Complete check list of symptoms daily, mail or fax to research center at end of study / resolution of symptoms. Electronic diary may be utilized if available.

If emergency warning signs, get medical attention immediately if:

a. Trouble breathing
b. Pain in chest
c. New confusion
d. Inability to arouse
e. Bluish lips or face

Patients will be instructed to consult medical adviser for any other symptoms that are severe or concerning.
Stay home except to get medical care
Rest and stay hydrated
Avoid any public transportation
Wear a cloth face covering over nose and mouth if you must be around other people

Dosing to be given at time of informed consent:

Treatment Group A: Treatment initiated with: Dual H1R H2R histamine blockade

1. **Initiate study medications**
   a. Famotidine 20 mg & Cetirizine 10 mg 1 Po Bid
   b. Subjects will remain on this dose of H1R & H2R blockers a total of 21 days or till free of symptoms

Treatment Group B: **Inert placebo**, will be provided for 21 days Bid

Treatment Groups A&B: **All COVID-19 patients** will be treated per current guidelines for mild – moderate disease. CDC guidelines: See attachment for handout: patients will be coached as per these guidelines.

1. There is no treatment approved for this virus
2. Self-isolation for a period of 2 weeks or till 7 days have passed with no fever for 72 hours, and other symptoms have improved.
3. Keep track of symptoms, see diary
4. If emergency warning signs get medical attention immediately
    a. Trouble breathing
    b. Pain in chest
    c. New confusion
    d. Inability to arouse
    e. Bluish lips of face
5. Consult your medical adviser for any other symptoms that are severe or concerning.
6. Stay home except to get medical care,
7. Rest and stay hydrated
8. Avoid any public transportation
9. Wear a cloth face covering over nose and mouth if you must be around other people
10. Throw away used tissues
11. Immediately wash your hands after coughs and sneezes
12. Do not share dishes, avoid high-touch surfaces

Benefits to patients

The potential benefits to the participant with COVID-19 infection include possible faster healing due to successful treatment, the ability to take a low risk medication and help with the discovery of better treatment pathways and possible reduction of potential complications of COVID infections. Provider visits, follow up care are independent of this study and not covered financially.

Risks:

Both drugs in this study (cetirizine, famotidine) have long safety histories, are FDA approved, safe in infants and children, and are available over the counter. As with any medication, allergic reaction can occur, although these medicines are typically used to treat allergic reactions and allergy symptoms. Sleepiness, dry mouth, stomach pain, excessive tiredness, nausea, and diarrhea are rare but may occur. Individuals may experience other symptoms not listed. Time inconvenience is a potential issue due to waiting in line to receive testing. A risk to participation in this study is that the treatment may not work, and the illness would take its

natural course. There is a low risk, seemingly unlikely, that the study drugs might worsen the illness. The illness is variable in its expression from recovery to prolonged illness, or death.

Adverse Events:

Any adverse events associated with the medications or study will be recorded in the data file sheet, reviewed by the PI, and reported to the FDA through the research division at GI Associates by our normal reporting protocols.

Study Endpoints

Overall Endpoint:

1. Enrollment will stop when desired study group numbers have been reached.

Individual Endpoints:

1. Completion of 21 days of histamine blocker therapy for the individual patient, would consider continuation of therapy if prolonged disease but would require an adverse event evaluation, report, and out of protocol decisions.

2. Continued therapy if admission to the hospital, but it would be at the discretion of the admitting physician. There would be no researcher intervention of hospitalized patients. There would be only availability for questions and data collection.

3. Completion of follow-up at 2-4 weeks post completion of study medication by phone, email or text messaging.

4. Enrolled subjects will be asked to allow contact via phone call, text messaging or email after discharge to check on their status and residual pulmonary symptoms.

5. Adverse events of significant clinical nature.

Symptom Tracking Sheet (7 day check sheet)

Date
Name
Temperature Max for the day
Chills
Chest Pain
Cough: present, better, worse
Sore Throat
Nausea, Vomiting
Short of breath
Loss of smell / taste
Sore Muscles
Diarrhea
Miscellaneous Symptoms: Tolerability of study medications, blank lines
List medications taken on that day prescription and over the counter
Researcher Mailing address and fax for return

Analysis

All Data will be de-identified with all data collection sheets being DE identified when processed into the investigators possession.

Designated person (primary investigator or research coordinator) will review data in case of untoward results (patient safety issue)
Symptom onset/duration, Hospitalization (whether or not and date of admission), and outcomes will be compared
Comorbidity correlations for population
Tolerability of the study drugs will be assessed

Statistical analysis:
Professional statistician will be engaged for analysis. Expect evaluation with independent group t-test utilizing statistical WINKS program. This will be the most likely comparison method for the 2 groups. If there are unequal variances between groups of variables then a Welch's t-test may be needed. If the data for either test are not normally distributed, a nonparametric test, the Mann-Whitney test may be utilized.

Appendix A

COVID-19 The Easter Trial

Data collection points
4.11.20 revised

On admission to study: <u>labs if done at primary care provider, not to be obtained as a test within this study.</u>

1. **CBC**
2. **Ferritin**
3. **Lymphocyte count**
4. **COVID -19 test result**
5. **CRP**
6. **D dimer**
7. **MEDS specifically if on H1 or H2**

Comorbidities

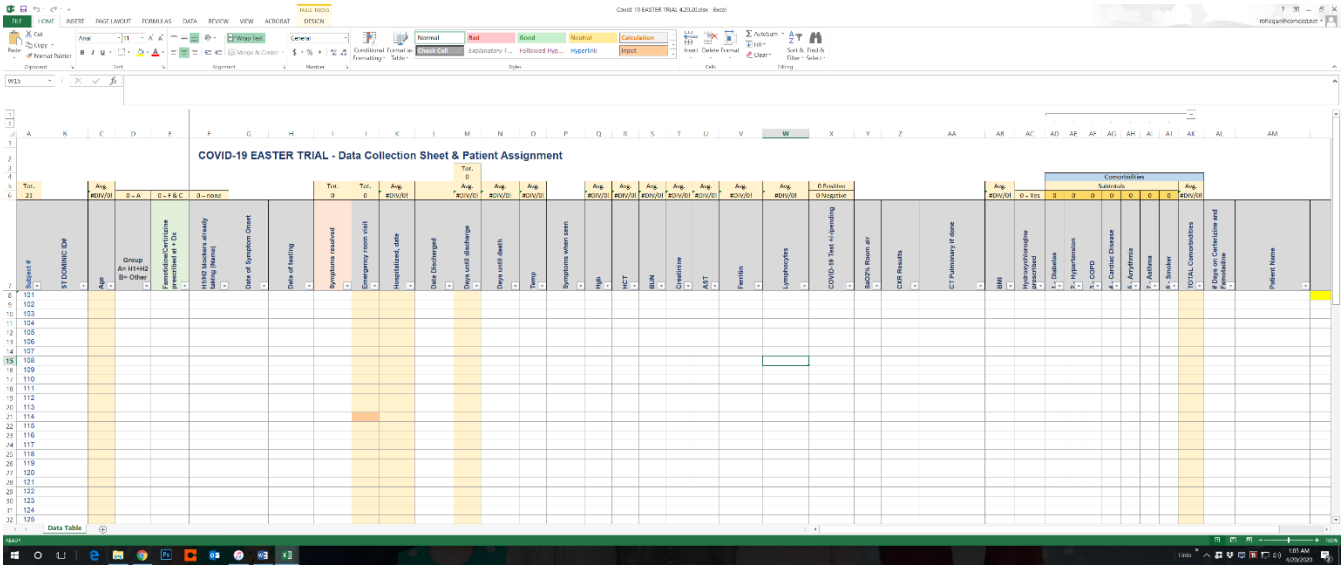
1. **Diabetes**
2. **Hypertenstion**
3. **Cardiac disease**
4. **Diarrhea**
5. **Hyperlipidemia**
6. **COPD**
7. **Asthma**
8. **Smoker**
9. **Obesity**

Other data points of study

1. **Onset of symptoms days prior to testing**
2. **Resolution of fever, days**
3. **Resolution of cough, days**
4. **Admitted to hospital or ICU, days**
5. **Intubation**
6. **Days till death**
7. **Stratify by variables for data analysis**

No expected procedures for study except as ordered per provider in COVID like illness evaluation. This study evaluates a new method of care through data collection and outcomes.

Appendix B



Screen shot of excel database sheet

Appendix C

Patient questionnaire – mail or fax back at end of study

COVID-19 EASTER TRIAL

Please help us track your symptoms and fill these forms out until you are back to normal. If you develop any of the following emergency warning signs, seek medical attention immediately: significant trouble breathing, chest pain, new confusion, inability to arouse, or bluish lips or face.

Name:_____ **DOB:**_____ **Cell #:**_____ **Med. Record #:**_____

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date:							
Symptoms:	(check each box to indicate positive symptoms)						
Fever							
Chills							
Fatigue							
Cough							
Congestion							
Shortness of Breath							
Chest Pain							
Loss of Taste/Smell							
Sore Muscles							
Return to Normal							

Consult your medical adviser for any other symptoms that are severe or concerning. Stay home except to get medical care. Rest and stay hydrated. Avoid any public transportation. Wear a cloth face covering over nose and mouth if you must be around other people.

Please return this form by email, fax, or US postage:

COVID-19 Easter Study
2510 Lakeland Drive
Flowood, MS 39232

Phone: (601) 355-1234
Fax: (601) 352-4882
email: info@gi.md

Appendix D Handout for screening clinic at time of COVID testing

The Easter COVID-19 Trial
Treatment Trial for Coronavirus – COVID-19 Patients

If you have a positive test for COVID-19: There is a research study available aimed at decreasing the severity of the disease process.
The purpose of this study is to offer a safe alternative treatment option to COVID-19 positive participants and to find out whether the participants who take the study drugs will experience better outcomes than those participants who do not take the study drugs. The study drugs have long safety histories, are FDA approved, and are available over the counter in adult, pediatric and infant doses. Researchers with experience in this area of inflammatory diseases suggest that our approach, with very safe medications, may provide a path to lessen the disease process you will experience with your CO"VID-19 infection.
Our goal is to prevent you from requiring hospitalization and possible ventilator use.

There is no cost to participate in this study.

If you have a positive test for COVID-19, and wish to consider participating in this study:

Contact the Research coordinators for this study at:
601-718-1572 and ask for the coronavirus study
or the Easter trial coordinator

Appendix E: Handout at informed consent initiation of trial

The Easter COVID-19 Trial
Treatment Trial for Coronavirus – COVID-19 Patients

You have TESTED POSITIVE for COVID-19:

The purpose of this study is to offer a safe alternative treatment option to COVID-19 positive participants and to find out whether the participants who take the study drugs will experience better outcomes than those participants who do not take the study drugs. The study drugs have long safety histories, are FDA approved, and are available over the counter in adult, pediatric and infant doses.

To Participate: you must:

- Be COVID-19 Positive
- Review and agree to the informed consent process
- Agree to allow the study coordinators to obtain history, symptoms, changes in your health status during your illness
- Agree to reporting your symptoms weekly or more often if needed by phone, text, email or by agreeable manner
- Take study medications as required, twice daily
- Report any possible significant side effects of medications
- Notify study coordinators when symptoms resolved or hospitalized

If issues arise during the course of this study
Contact the Research coordinators at:
601-718-1572 and ask for the coronavirus study
or the Easter trial coordinator

Study Background for Hypothesis of Therapy

The proposed therapy is a synergistic combination of cetirizine (antihistamine-1) and famotidine (antihistamine-2) currently being studied to treat diarrhea illnesses at GI Associates (Flowood, MS). Rodent models demonstrate a synergistic effect of dual histamine blockade by showing that both histamines are required and that a therapeutic window exists in which the synergistic effect is maximized (1). Phase 2a study designs have been approved by the FDA and are pending. The use of dual histamine blockade for the treatment of diarrhea is a novel concept developed by Dr. Reed Hogan and his team who began investigating this therapy in 2008. Previously, neither of these drug categories were used in the treatment of diarrhea. Both drugs have a pristine safety profile and have been approved by the FDA for OTC use. This team has extensively studied the histamine pathways with both animal studies and clinical studies over the past decade. These studies have shown incredible efficacy (2) which continues to be seen routinely in clinical practice. This experience and research has led to the consideration that dual-histamine blockade may play a therapeutic role in fighting COVID19

COVID-19 and the Cytokine Storm:

COVID-19 has a reactive immune response that results in a cytokine release which is similar to other well defined viral infections including SARS, MERS, and influenza. Studies from Wuhan China have defined the COVID-19 cytokine profile (3) and identified risk factors that increase mortality (4). These retrospective studies suggests mortality may be linked to inflammatory processes caused by viral infection and the "cytokine storm" which was very common in patients with severe COVID-19 infection (5).

COVID-19 Pulmonary Disease:

Pulmonary pathology in early-phase COVID-19 pneumonia has shown exudative and proliferative phases of acute lung injury (edema, inflammatory infiltrates, pneumocyte hyperplasia) even prior to the development of any respiratory symptoms (6). In the later stage of disease, patients can develop Acute Respiratory Distress Syndrome (ARDS) and multi-organ failure. The main causes of death are thought to be massive alveolar damage and progressive respiratory failure (7). The initial autopsy report from novel coronavirus pneumonia patient in China showed an inflammatory response with deep airway and alveolar damage and a large amount of viscous secretions (8). The reason for the wide range in severity of disease for COVID-19 patients remains unclear. Some patients are completely asymptomatic, while others progress rapidly to respiratory failure and death. While the triggers remain unclear, ARDS has taken center stage with the "cytokine storm" emerging as a key mechanism leading to patient deterioration and death. Because of this, efforts are being made to find immunotherapies that resist or blunt the cytokine storm (9, 10, 11).

Histamines Role in Cytokine Storm, Lung Disease, T-Cells:

The histamine-cytokine network has been studied extensively and is well defined in literature. Histamine modulates the release of cytokines, has well established pro-inflammatory effects, and influences local immune responses in the lung that can lead to pulmonary tissue damage (12). Coronavirus infected mice have shown that T-cell responses are required for protection from clinical disease and for virus clearance in severe acute respiratory syndrome (13). The immunomodulation of histamine depends mostly on its influence of T-cells (14).

Histamine Blockade for ARDS and Pneumonia Treatment:

Multiple remote studies have shown successful treatment of ARDS with therapies that include dual histamine blockade. When a combination of histamine-1 blocker + histamine-2 blocker + cyclooxygenase inhibitor + IV steroids + anti-hypertensives were studied in ARDS models, it was the dual-histamine blockade that proved to be the most beneficial. This study concluded that dual-histamine blockade + ibuprofen was essential in the treatment of hypoxemia, pulmonary hypertension, and pulmonary microvascular injury in this fulminant ARDS model (15). A more recent study evaluating H1N1 influenza models also showed that histamine blockade decreased inflammatory cytokines and decreased severe pneumonia (16).

Histamine Blockade with Famotidine alone to decrease Viral Replication

Famotidine is currently being tried in combination trials with Hydroxychloroquine to decrease viral replication. There is a papain like protease which helps the pathogen replicate. Gene sequences of the COVID 19 virus were studied and famotidine was one of three compounds potentially able to interact with the new protease. Trials are underway.

Hypothesis / Considerations

Histamines play a key role in modulating the immune response, inflammation, and cytokine release. Blocking Histamine-1 and Histamine-2 (Dual-histamine blockade) is a very safe therapy that has shown significant efficacy in several clinical applications and peer-reviewed studies. These studies have shown positive results of dual-histamine blockade in both ARDS models and H1N1 influenza models. COVID-19 is known to cause pulmonary disease with a wide range of severity. Patients have shown significant pulmonary disease on radiographic imaging and pathology specimens even before exhibiting any pulmonary symptoms. The "cytokine storm" is thought to be a key mechanism of action that results in patient deterioration.

We believe it is very reasonable to consider the use of dual-histamine blockade to retard the histamine-cytokine network and blunt the cytokine storm. The incredible safety profile of dual-histamine blockade makes this an appealing consideration for all patients who test positive for COVID-19. If dual-histamine blockade is able to blunt the cytokine system, the risk of progressing to severe disease would lessen. Successful studies of dual-histamine blockade

on ARDS models and H1N1 influenza models support this possibility. If true, this could save many lives, dramatically reduce the need for ventilators, and have a tremendous positive impact on our healthcare system during this pandemic.

The incredible safety profile of dual-histamine blockade makes this an appealing consideration for all patients who test positive for COVID-19. If able to blunt the Cytokine Storm, it is hypothesized that the severity of disease would lessen, decrease admissions, and ventilator use would decrease. Reducing severity of disease and reducing the need for ventilators would have a tremendous impact on our healthcare infrastructure and would save many lives during this pandemic.

We have initiated clinical studies on COVID19 hospitalized patients to evaluate the effect of aggressive dual-histamine blockade in this population: Primary Investigator: Reed B Hogan II, MD. Chairman Research Division GI Associates. Co-Investigators: Reed B Hogan III MD, Mike Byers MD, Tim Cannon MD, Maria Rappai MD.

Ready to proceed

We have an action ready plan to proceed with a quick trial. The tip of the COVID spear is in Jackson, MS, expected to peak shortly. We can implement, in an outpatient setting, rapidly expand to other locals, but need to start fast.

Unique opportunity to have impact and follow the epidemiology of blunting the curve of this pandemic for the US. A **5-10% reduction would be a game changer**. In our prior work in the GI inflammatory cascade, our combination's efficacy is 65% compared to the best analog in market less than 20%. Consultants from around the country encourage this study with high hopes that we can help find a solution in Jackson MS. Similar studies are ongoing around the US with different antihistamine protocols. Preliminary data on in patient population of COVID patients suggest a definite synergistic benefit of the H1R H2R combination of antagonists.

The H1R H2R blockade is an amazingly complex pathway, an remarkably safe therapy, low cost, and easy to implement. Just need data, we have the potential to be a game changer if we can blunt the storm early enough. Our Infectious disease and ICU intensivists are on board, we have no other good options to medically slow this pandemic. Thank you for consideration of this study.

References

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