

## UC San Diego Health COVID-19 Interim Therapeutic Management Guideline

### **Purpose**

The intent of this guideline is to provide a framework for clinical management of individuals with COVID-19. Infection prevention instructions are outside the scope of this guideline.

Guidelines are intended to assist with clinical decision-making for common situations but cannot replace personalized evaluation and management decisions based on individual patient factors.

The document covers off-label use of medications based on the best evidence currently available.

Given the rapid evolution of the current COVID-19 pandemic, this will be a living document that is likely to change over time.

### **Guidance References**

National Institutes of Health: <https://covid19treatmentguidelines.nih.gov/>

IDSA: <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>

SCCM: <https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19>

CDC: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>

**Preliminary reports and manuscripts made widely-available pre-publication but that have not been peer-reviewed should not guide UCSD clinical decisions** in the treatment of SARS CoV-2 infection.

Insufficient information regarding efficacy of therapies in SARS-CoV-2 infection is currently available in the absence of clinical trials data.

### **UCSDH Resources**

[UC San Diego COVID-19 Pulse-Website](#)

[California Department of Public Health COVID-19 Guidance](#)

[Inpatient PCCSM Management Guidelines for Patients with Confirmed COVID-19 \(WD1217\)](#)

[Clinical Trials for SARS-CoV-2 at UC San Diego Health](#)

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Guidance document to be regularly reviewed and updated

## UC San Diego Health COVID-19 Interim Therapeutic Management Guideline

### General principles

During this unprecedented time, remember these principles:

- The practice of evidence-based medicine requires the utilization of rigorous clinical trials. When insufficient evidence is available with which to determine the utility of a therapeutic agent, if a clinical trial is available, in general, patients should be referred to these trials rather than treated off label. Clinical trials that are active or in planning for UC San Diego Patients can be found at this [link](#).
- Order diagnostic studies only when clinically indicated. Remember that each test may expose additional personnel to potential infection, remove exam rooms from circulation, and utilize additional personal protective equipment (PPE).
- Supply chain issues will impact every facet of clinical care, from lab testing to medications to blood products to personal protective equipment. Practice evidence-based medicine and order only testing and medications that are truly necessary.
- Clean your hands and utilize personal protective equipment as recommended by Infection Prevention and Clinical Epidemiology.

### PPE conservation

- Direct contact with the patient in the room should only occur if the provider will perform a direct physical exam or in-room procedure that will provide clinical information to impact patient assessment and clinical care in the next 24-48 hours.
- If deemed necessary, only one team member (the clinical decision maker) should perform the in-person encounter with suspected or confirmed COVID-19 patients. No other team members should enter the room unless needed to assist with a procedure.
- Telephone, E-consultation, and video consultations should be used if direct contact is not essential.
- Bundle care activities to limit the number of entries into the room.
- For aerosol-generating procedures, limit the number of individuals in the room to essential staff.
- The most experienced individuals should preferentially perform necessary procedures.
- Ensure all supplies needed for an exam or procedure are available prior to donning PPE and entering the room.

## Summary Table

Medication	Recommendation	Availability at UC San Diego Health
<a href="#">Remdesivir</a>	Clinical trials currently underway; insufficient data / EUA resources to provide use-recommendations at this time although EUA guidance suggests that remdesivir should be considered for hospitalized patients with symptomatic moderate to severe COVID-19 pneumonia and a SpO <sub>2</sub> of less than or equal to 94% on RA	Remdesivir vs. Placebo adaptive trial (ACTT-1) is now closed. <a href="#">ACTT-2</a> is activated and is now enrolling.  The FDA has granted EUA access for remdesivir. EUA supply is being distributed to UCSD Health by the Federal government through State Health Department and may be available mid-May.
<a href="#">Baricitinib</a>	Clinical trial is currently underway; insufficient data to provide use-recommendations at this time	Non-formulary at UC San Diego. A clinical trial ( <a href="#">DMID ACTT-2</a> ) is activated and is now enrolling comparing remdesivir alone to remdesivir plus baricitinib.
<a href="#">Hydroxychloroquine (HCQ)</a>	There is insufficient data to provide use-recommendations at this time	Supplies of HCQ are limited at UC San Diego. Currently available for treatment of persons with FDA-approved indications (i.e. rheumatoid arthritis, lupus, etc.).  A randomized placebo controlled clinical trial ( <a href="#">ACTG A5395</a> ) comparing HCQ plus azithromycin for mild to moderate COVID-19 disease in outpatients is now enrolling at the UCSD Antiviral Research Center (AVRC).  HCQ is available from the <a href="#">US Strategic National Stockpile</a> for patients who are “hospitalized with COVID-19 for whom a clinical trial is not available or participation is not feasible” ( <a href="#">FDA link</a> ). Currently, the mechanism for accessing the Strategic National Stockpile has not been clearly delineated.
<a href="#">Tocilizumab (TOCI)</a>	Clinical trials currently underway. Until more data are available, routine use of tocilizumab in the setting of severe or life-threatening COVID-19 is not recommended.	Currently stocked by UC San Diego pharmacy and available for treatment of persons with FDA-approved indications (i.e. chimeric antigen receptor (CAR) T-cell induced cytokine reactive syndrome (CRS), etc.) A clinical trial is available to UC San Diego Inpatients. Entry & exclusion criteria can be found <a href="#">here</a> .
<a href="#">Sarilumab</a>	Insufficient data to provide use-recommendations at this time	Non-formulary at UC San Diego. Not currently part of a clinical trial at UC San Diego.
<a href="#">ACE Inhibitors and ACE Receptor Blocking Agents</a>	Observational studies consistently showing no increased risk of COVID infection nor risk of increased severity of infection.	A ramipril study ( <a href="#">RAMIC</a> ) for hospitalized or emergency department patients is activated.  Currently stocked by UC San Diego pharmacy and available for treatment of persons with hypertension, coronary artery disease, and/or heart failure.
<a href="#">Convalescent Plasma</a>	Insufficient data to provide use-recommendations at this time	A clinical trial will start soon.

Medication	Recommendation	Availability at UC San Diego Health
<a href="#">Corticosteroids</a>	Interim <a href="#">guidance</a> recommends that corticosteroids be avoided unless indicated for reasons other than COVID-19. Until more data are available, routine use of corticosteroids in the setting of severe or life-threatening COVID-19 is not recommended outside of a clinical trial setting.	Currently stocked by UC San Diego pharmacy and available for treatment of persons with various allergic and inflammatory conditions
<a href="#">Antipyretics Including NSAIDs and APAPs</a>	NSAIDs and APAPs are not generally contraindicated in the setting of SARS-CoV-2 infection; acetaminophen should not be used in conjunction with remdesivir	Currently stocked by UC San Diego pharmacy and available for treatment of persons with fever and inflammatory conditions
<a href="#">Empiric Antibiotics</a>	Empiric antibiotics should not be used unless bacterial superinfection is clinically suspected or proven	Currently stocked by UC San Diego pharmacy and available for treatment of persons with suspected or proven bacterial infection
<a href="#">Zinc sulfate</a>	Zinc sulfate is not recommended for the prevention or treatment of SARS-CoV-2 infection	Currently stocked by UC San Diego pharmacy and available for treatment of persons with FDA-approved indications (i.e. need for nutrition supplementation, in zinc deficiency, etc.)
<a href="#">Ritonavir / Lopinavir (Kaletra)</a>	Not recommended for the treatment of patients with SARS-CoV-2 infection	Supplies of Ritonavir/Lopinavir are currently limited but stocked by UC San Diego pharmacy and available for treatment of persons with HIV infection
Ivermectin	Not recommended for the treatment of patients with SARS-CoV-2 infection	Currently stocked by UC San Diego pharmacy for the treatment of specific parasitic infections (ie. scabies, strongyloidiasis, onchocerciasis)

## **Medication Mechanisms of Use and Recommendations**

### **Remdesivir**

#### **Background and Mechanism:**

Remdesivir is an experimental agent that is under investigation for the intravenous treatment of SARS CoV-2 infection. The drug is a nucleoside analog that inhibits the RNA polymerase of all known coronaviruses as well as Ebola virus. The drug blocks viral replication by serving as a chain terminator in the RNA polymerization process. Remdesivir inhibits SARS CoV-2 replication at concentrations of ~0.5  $\mu\text{M}$  (1,2). The drug is beneficial clinically and inhibits viral replication when given prior to or shortly after viral challenge in animal models of the related coronavirus, MERS virus (the Middle Eastern Respiratory Syndrome Virus) (3). Remdesivir was administered to patients in a recent outbreak of Ebola virus infection in the Democratic Republic of the Congo in a three-arm trial in which it was compared to two different monoclonal antibody preparations (4). The drug did not perform as well as the monoclonal antibodies but since there was no placebo group, clinical benefit could not be excluded. The drug has been used under compassionate use in a number of cases in the US and elsewhere (5). The compassionate use program has been stopped except for pregnant women and children under the age of 19. As of March 27, Gilead transitioned to an "expanded access" program for Remdesivir. Under the guidance from FDA, Gilead is no longer offering participation in the expanded access program pending provision of remdesivir through the Emergency Use Authorization.

#### **Efficacy, Safety and Emergency Use Authorization (EUA):**

On May 1, 2020 the U.S. Food and Drug Administration granted Emergency Use Authorization (6) for remdesivir on the basis of data from two randomized clinical trials and compassionate use in patients with COVID-19 (5,7-8). Preliminary data from the National Institute for Allergy and Immunology (NIAID) placebo-controlled Phase 3 ACCT-1 Adaptive COVID-19 Treatment Trial (NCT04280705) (7) involving 1063 patients was reviewed by an independent data safety monitoring board (DSMB). Interim analysis of preliminary results from 606 recovered patients indicated those who received remdesivir recovered 31% more quickly compared to placebo (11 days versus 15 days, respectively ( $p < 0.001$ )) (9,10). Initial results also suggest a survival benefit (8.0% vs. 11.6% mortality in the remdesivir versus placebo groups, respectively) (9,10). A multi-center, randomized, open-label, no-placebo control trial (8) assessing clinical improvement and comparing 5-day and 10-day treatment durations is ongoing. Preliminary results (unpublished) suggest similar improvement in clinical status at Day 14 (10-11). A randomized, double-blind, remdesivir versus placebo-controlled trial in China was recently published (12). The study did not complete enrollment, did not meet criteria for statistical significance and did not have statistical power for comparisons between treatment arms. Of note, despite not reaching statistical significance, there was a trend toward faster time to clinical improvement for remdesivir versus placebo (12). The drug was generally well tolerated although reversible hepatocellular enzyme elevations have been noted in some trial participants (5,8,12).

#### **Availability at UC San Diego:**

Stage 1 of the NIAID-sponsored Remdesivir versus placebo-controlled trial (ACTT-1) closed to enrollment 4/19/2020. Stage 2 of the NIAID-sponsored adaptive trial ([ACTT-2](#)) began enrolling nationally on May 8 and at UCSD on May 13, and includes the combination of remdesivir and the JAK1/2 inhibitor baricitinib compared to remdesivir therapy alone. Physicians wishing to refer patients to the [adaptive DMID clinical trial](#) should contact Dr. Dan Sweeney ([dasweeney@ucsd.edu](mailto:dasweeney@ucsd.edu)) or Dr. Constance Benson ([cbenson@ucsd.edu](mailto:cbenson@ucsd.edu)).

As of May 14, 2020, UC San Diego Health had not been selected to receive EUA Remdesivir and does not have any supply for EUA use. Additional information pending supply and allocation is currently being determined by the California Department of Health (13,14).

#### **Recommendations and Additional Resources:**

Clinical trials of remdesivir are underway. The Therapeutics Committee will continue to evaluate status in regards to EUA access and make updates to recommendations, as applicable.

- EUA Website (Gilead Sciences, Inc.): <https://prodremds02.azurewebsites.net/us/>
- EUA Fact Sheet for Health Care Providers (May 1, 2020): <https://www.fda.gov/media/137566/download>

- EUA Fact Sheet for Patients and Caregivers (May 1, 2020): <https://www.fda.gov/media/137565/download>
- California Department of Public Health Remdesivir Distribution Fact Sheet 5/11/2020: <https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/COVID-19/CaliforniaRemdesivirDistributionFactSheet.pdf>

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3. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proceedings of the National Academy of Sciences of the United States of America*; 2020. pii: 201922083. <https://doi.org/10.1073/pnas.1922083117>.
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9. NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19, 29 April 2020. <https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19> (Accessed April 29, 2020).
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11. Gilead Sciences. Gilead Announces Results From Phase 3 Trial of Investigational Antiviral Remdesivir in Patients with Severe COVID-19: Study Demonstrates Similar Efficacy with 5- and 10-Day Dosing Durations of Remdesivir. 29 Apr 2020. <https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19> (Accessed April 29, 2020).
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14. California Department of Public Health Remdesivir Distribution Fact Sheet 5/11/2020: <https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/COVID-19/CaliforniaRemdesivirDistributionFactSheet.pdf>



## **Baricitinib**

### **Background and Mechanism:**

Baricitinib is a selective Janus kinase (JAK1 and JAK2) inhibitor with anti-inflammatory activity, FDA approved for the treatment of adults with moderate to severe rheumatoid arthritis (1). An artificial intelligence query identified baricitinib as a potential treatment for SARS-CoV-2 with possible antiviral and immunomodulatory effects (2-4) hypothesizing that it may impair SARS-CoV-2 endocytosis and/or inhibit signaling of cytokines implicated in viral pneumonia pathogenesis (5).

### **Adverse effects:**

JAK inhibitors have broad immunosuppressive activities and can potentially predispose patients to a number of infections, including, but not limited to tuberculosis and herpesvirus infection. Baricitinib may induce a number of adverse effects, including upper respiratory infection, hepatotoxicity and thrombocytosis.

### **Availability at UC San Diego:**

Baricitinib is non-formulary at UC San Diego Health.

Stage 2 of the NIAID-sponsored adaptive trial ([ACTT-2](#)) began enrolling at UC San Diego Health on May 13 and includes a combination of remdesivir and baricitinib compared to remdesivir therapy alone. Physicians wishing to refer patients to the [adaptive DMID clinical trial](#) should contact Dr. Dan Sweeney ([dasweeney@ucsd.edu](mailto:dasweeney@ucsd.edu)) or Dr. Constance Benson ([cbenson@ucsd.edu](mailto:cbenson@ucsd.edu)).

### **Recommendations:**

Insufficient information regarding its efficacy in SARS CoV 2 infection is available to recommend use outside of clinical trials.

### **References:**

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## Hydroxychloroquine (HCQ)

### Background and Mechanism:

Chloroquine and HCQ are alkalinizing lysosomotropic drugs that accumulate in lysosomes (1). Both drugs block viral infection by increasing endosomal pH, which is required for viral particles to fuse with a cell. Chloroquine also interferes with glycosylation of cellular receptors of coronaviruses, including SARS-CoV (2). *In vitro* data in Vero E6 cells has demonstrated that chloroquine functions at both entry, and at post-entry stages of the SARS-CoV-2 infection, unlike Remdesivir (3). Both drugs also modulate the immune response. HCQ has long been used to treat autoimmune diseases, like rheumatoid arthritis, porphyria cutanea tarda, and lupus (1). Such immune modulation may also help in thwarting ARDS (4).

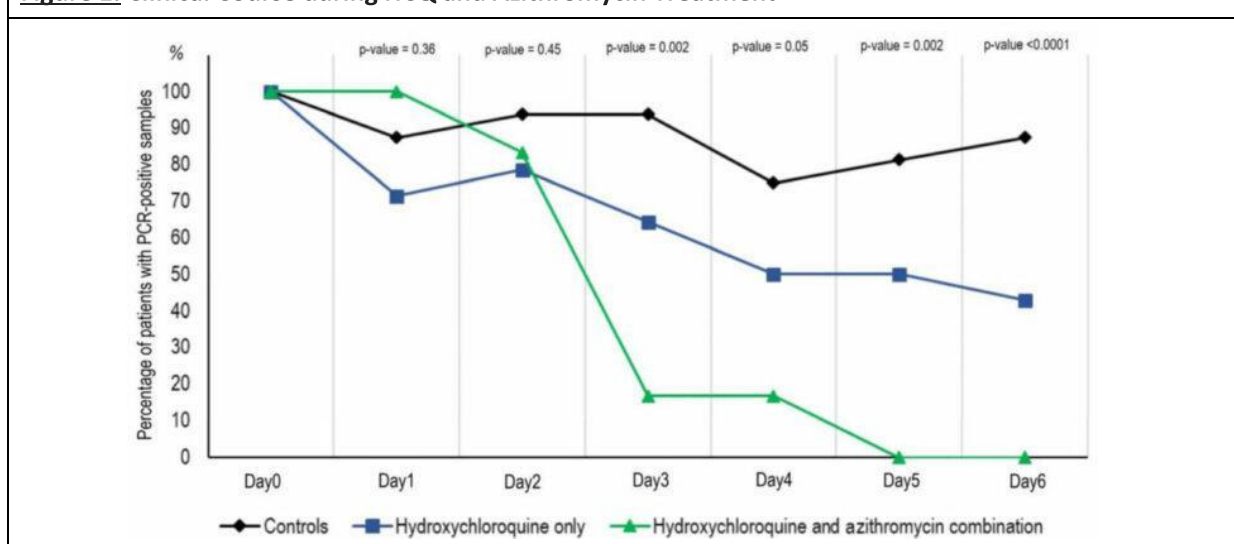
### In Vivo Activity:

In a recent study, 20 patients with SARS-CoV-2 infection were included in a single arm protocol to receive 600mg of HCQ daily. The outcome of the study was viral load from daily nasopharyngeal swabs. All participants were in a hospital setting. Further, azithromycin was added to the HCQ treatment based on clinical status. Untreated patients from another center and cases refusing the protocol were included as negative controls. Presence and absence of virus at Day 6-post inclusion was the study end point. The authors showed that HCQ was effective in reducing viral loads (Figure 1). Specifically, HCQ reduced the proportion of persons with SARS-CoV-2 infection with PCR-positive samples by 75% in the 6-day period, and when it was combined with azithromycin, it improved the treatment efficacy to 95% (5).

There are a number of limitations of this study:

- 1) It was not randomized.
- 2) A therapeutic effect in the first two days of treatment is unusual, as drug levels are unlikely to have achieved therapeutic levels.
- 3) The small number of participants
- 4) The dropout rate in the treatment arm and exclusion from the analysis of death
- 5) The primary outcome was clearance of SARS-CoV-2 as detected by nasopharyngeal swab, however the current understanding of the natural history of infection is that virus is eventually cleared from the upper respiratory tract, even in severe disease
- 6) Lower baseline viral load in persons receiving HCQ and azithromycin, compared to the patients receiving HCQ alone

**Figure 1. Clinical Course during HCQ and Azithromycin Treatment**



### Pharmacology:

HCQ has rapid gastrointestinal absorption and elimination by the kidneys. Both are also metabolized by the cytochrome P450 enzymes (CYP2D6, 2C8, 3A4 and 3A5). HCQ is metabolized to desethylhydroxychloroquine,



desethylchloroquine, and bidesethylhydroxychloroquine by the liver and excreted by the kidneys, with desethylhydroxychloroquine being most common (6, 7). HCQ distributes widely into body tissues and given its large volume of distribution, it takes a long time to reach steady-state levels (8,9). The absorption half-life is 3 to 4 hours and the terminal half-life ranges from 40 to 50 days.

#### **Risks:**

Retinopathy, anemias, cardiac toxicity, arrhythmias and hypoglycemia events are potentially serious risks with use of HCQ. However, only arrhythmias and G6PD-related hemolysis are real risks with the limited dosing proposed for treatments for COVID-19. Given the low prevalence of G6PD Deficiency in San Diego, only arrhythmias remain as a main risk during the proposed short treatment courses. However, these risks are real in older patients and those taking medications that already prolong the QT interval. Further, as with all serious respiratory illnesses, cardiovascular events remain common, and a number of anecdotal heart attacks and ventricular arrhythmias have been documented. Without rigorous, controlled trials, we will not know the true risk of these events during treatment with HCQ. Given heightened risk for toxicities, the NIH COVID-19 Treatment Guidelines now recommend against the use of high-dose chloroquine for the treatment of COVID-19 (10,11). The FDA warns against use of chloroquine or HCQ for COVID-19 outside of a clinical trial or hospital setting (12).

#### **Availability at UC San Diego:**

Supplies of HCQ are limited at UC San Diego.

HCQ or chloroquine are available from the [US Strategic National Stockpile](#) for patients who are “hospitalized with COVID-19 for whom a clinical trial is not available or participation is not feasible” ([FDA link](#)) (13). Currently, the mechanism for accessing the Strategic National Stockpile has not been clearly delineated.

#### **Recommendations:**

Clinical trials of HCQ are being developed for UC San Diego inpatients, outpatients and for post-exposure prophylaxis. A randomized placebo-controlled trial is available from the University of Minnesota for those with exposure to or mild symptoms from SARS CoV-2 infection. Details about the study can be found at <http://trialcovid.com>.

A randomized placebo controlled [trial of HCQ plus azithromycin vs. placebo](#) for treatment of mild to moderate COVID-19 disease in outpatients began enrolling at UC San Diego Health at the Antiviral Research Center on the Hillcrest campus on May 13. Physicians wishing to refer patients to [this trial](#) should contact Dr. Constance Benson ([cbenson@ucsd.edu](mailto:cbenson@ucsd.edu)) or Dr. Davey Smith ([d13smith@ucsd.edu](mailto:d13smith@ucsd.edu)).

Insufficient information regarding its efficacy in SARS-CoV-2 infection is available to recommend its use in the absence of clinical trials data.

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## **Tocilizumab**

### **Background and Mechanism:**

Tocilizumab is an FDA approved recombinant humanized monoclonal antibody against IL-6 receptor used in rheumatoid arthritis. Experience more recently comes from use in the treatment of life-threatening cytokine release syndrome (CRS) after CAR-T cell therapy. There is some increased risk for developing serious infections reported, especially in individuals being treated with immunosuppressants, such as methotrexate or steroids. Limited data about potential benefit exist from uncontrolled studies in patients with COVID-19. There are randomized controlled clinical trials in China and the U.S. using tocilizumab in this context, including an international trial that is sponsored by Genentech: (EudraCT Number: 2020-001110-38) entitled: "Multicenter study on the efficacy and tolerability of tocilizumab in the treatment of patients with COVID-19 pneumonia".

### **Evidence on specific use to date:**

In an open-label experience from China (21 patients) with documented COVID-19 and severe O<sub>2</sub> impairment, including RR≥30, SpO<sub>2</sub>≤93% on room air, PaO<sub>2</sub>/FiO<sub>2</sub>≤300mmHg or need for mechanical ventilation, shock, or combined organ failure Tocilizumab use was associated with reduced O<sub>2</sub> requirement, normalization of the CRP level, and increasing the lymphocyte count to normal. Nineteen of the 21 patients were discharged (1). Further guidelines on determining timing of administration are being developed.

### **Risks:**

- LFT abnormalities
- Local injection site reactions
- Increased risk of serious infections, including TB, invasive fungal infections; albeit a distinct population in terms of risks in typical CAR-T cell patients, so possibly better able to tolerate therapy from the immunocompromise standpoint.

### **Dosing:**

- Tocilizumab 8 mg/kg (max 800 mg) iv. Can repeat again x 1 in 8-12 hours. Can consider 2 additional doses (max 4) with same dosing interval.
- Check IL-6 and inflammatory markers (IL-6, CRP, Ferritin, LDH, fibrinogen, D-dimer) prior to administration and consider daily monitoring.

### **Rationale for use:**

Cytokine release syndrome (CRS) (2) is a key component of critical illness associated with COVID-19. However, it has not been rigorously studied in the setting of such viral infection. The role of cytokines and a secondary HLH-analogy syndrome is highlighted as well (3).

### **Recommendations:**

Until more data are available, routine use of tocilizumab in the setting of severe or life-threatening COVID-19 is not recommended.

Experimental use is recommended only under a randomized clinical trial. Physicians wishing to refer patients to this [trial](#) should contact Dr. Atul Malhotra ([amalhotra@health.ucsd.edu](mailto:amalhotra@health.ucsd.edu)) or Dr. Aaron Carlin ([acarlin@health.ucsd.edu](mailto:acarlin@health.ucsd.edu)). Inclusion and exclusion criteria can be found [here](#).

The UCSD COVID Therapeutics Committee is currently discussing an approach for off-label use in certain patients that will be excluded from the randomized clinical trial, such as those who *"have received oral anti-rejection or immunomodulatory drugs within the past 6 months."*

### **References:**

1. Xu X, Han M, Li T, et. al. Effective treatment of severe COVID-19 patients with Tocilizumab. PNAS, first published April 29, 2020 <https://doi.org/10.1073/pnas.2005615117>. First available (pre-peer-review) on ChinaXiv website (Accessed March 27, 2020).

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## **ACE Inhibitors and ACE Receptor Blocking Agents**

Patients with underlying cardiovascular disease appear to have an increased risk for adverse outcomes when infected with the SARS-CoV2 virus (1,2). Angiotensin converting enzyme 2 (ACE2) receptors, that are present in the lung and other organs have been shown to be the entry point into human cells for SARS-CoV-2 virus (3). Furthermore, in a few experimental studies with animal models, both angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown to upregulate ACE2 expression in the heart (4). As a result, there has been speculation that this potential upregulation of ACE2 receptors by ACE inhibitors or ARBs will increase the risk or severity of COVID-19 infection in patients who are on these drugs (5,6).

At this time, the Heart Failure Society of America, the American College of Cardiology (ACC) and the American Heart Association, do not recommend stopping ACE inhibitors, ARB's or any renin angiotensin aldosterone system (RAAS) antagonists in patients taking these drugs for cardiovascular indications (7). The rationale includes:

1. Upregulation of ACE2 receptors with ACE or ARB have not been shown in human studies, nor in the setting of COVID-19, and to date there are no clinical data demonstrating beneficial or adverse outcomes of these drugs in COVID-19 patients.
2. Experimental studies have also shown both ACE inhibitors and ARBs reduce severe lung injury in certain viral pneumonias and as a result these agents could potentially be beneficial in COVID-19 infection (8).
3. ACE inhibitors and ARBs have clear beneficial effects in patients with kidney disease, heart failure, hypertension and ischemic heart disease and stopping them has been shown to worsen outcomes.

Three recent observational studies published in the *New England Journal of Medicine* found no positive association between ACE inhibitors or ARBs for either a positive COVID test result or severe illness or death among those infected (10-12). Although these studies are subject to the limitations inherent in observational studies, taken together, these studies make it unlikely that ACE inhibitors or ARBs are harmful in patients with COVID-19.

### **Availability at UC San Diego:**

A randomized, double-blinded, placebo-controlled [clinical trial](#) to examine the efficacy of ramipril 2.5 mg capsule versus placebo orally once daily for 14 days to improve outcomes in patients with documented COVID-19 infection has been activated. In this study, approximately 560 subjects  $\geq 18$  years with confirmed SARS-CoV-2 infection currently hospitalized, in an emergency department, or urgent care with SpO<sub>2</sub>  $\geq 93\%$  on room air will be randomized in a 2:1 ratio to treatment or placebo. Physicians wishing to refer patients to [this trial](#) should contact Dr. Rohit Loomba ([roloomba@health.ucsd.edu](mailto:roloomba@health.ucsd.edu)) and Dr. Veeral Ajmera ([v1ajmera@health.ucsd.edu](mailto:v1ajmera@health.ucsd.edu)).

### **References:**

1. Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020. Feb 28. <https://doi.org/10.1056/NEJMoa2002032>. [Epub ahead of print]
2. Peng YD, Meng K, Guan HQ, et al. Clinical Characteristics and outcomes of 112 cardiovascular patients infected by 2019-nCoV. *Zhonghua Xin Xue Guan Bing Za Zhi* Mar 2;48(0):E004. <https://doi.org/10.3760/cma.j.cn112148-20200220-00105>. [Epub ahead of print]
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5. Diaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19, *Journal of Travel Medicine*. taaa041, 2020. <https://doi.org/10.1093/jtm/taaa041>
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11. Mancia G, Rea F, Ludergnani M, et al. Renin-Aldosterone System Blockers and the Risk of Covid-19. *N Engl J Med*. 2020 May 1. <https://doi.org/10.1056/NEJMoa2006923> [Epub ahead of print].
12. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med*. 2020 May 1. <https://doi.org/10.1056/NEJMoa2008975> [Epub ahead of print].



## **Convalescent Plasma**

Convalescent plasma collected from individuals who have recovered from COVID-19 infection and who have developed pathogen-specific neutralizing antibodies against SARS-CoV-2 is being studied for administration in patients with or at risk for COVID-19 (1-3). Use of passive antibody therapy has been utilized historically to treat certain infectious diseases and has been studied in other recent viral outbreaks, including against SARS-CoV-1 (2003), H1N1 influenza pandemic (2009-2010) and against MERS-CoV (2012)) (1-3). In a few initial reports, convalescent plasma showed improved outcomes in critically-ill patients with severe COVID-19, however, these results should be cautiously reviewed due to the absence of control groups (4-6). The FDA has approved the investigational use of convalescent plasma via an investigational new drug (IND) application (7-9).

### **Recommendations:**

At UCSD, a clinical trial led by Dr. Edward Cachay will start soon. The study focuses on stemming COVID-19 among people or health-care workers who had a high-risk exposure to someone with COVID-19 but have not developed the disease yet. Physicians wishing to refer patients to this trial should contact the Study research coordinator at the UCSD CTRI Ms. Donna Brusch ([dbrusch@health.ucsd.edu](mailto:dbrusch@health.ucsd.edu)) with the email title "COVID-19 Referral."

### **Information Regarding Donation of Convalescent Plasma:**

COVID-19 donors can register at:

- <https://redcrossblood.org/plasma4covid>
- <https://www.redcrossblood.org/donate-blood/dlp/plasma-donations-from-recovered-covid-19-patients.html>
- <https://www.redcrossblood.org/donate-blood/how-to-donate/eligibility-requirements.html>

For San Diego Blood Bank, donors need to register at:

- <https://www.sandiegobloodbank.org/covid-19-and-convalescent-plasma-donation>

COVID-19 Convalescent Plasma Project (CCPP19): <https://ccpp19.org/index.html>

### **References:**

1. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest*. 2020;130(4):1545-1548. <https://doi.org/10.1172/JCI138003>, PMID 32167489.
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11. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest*. 2020; pii: 138745. <https://doi.org/10.1172/JCI138745>, [Epub ahead of print]. PMID 32254064.

## **Corticosteroids**

### **Rationale:**

Because COVID-19 has been associated with a hyperinflammatory state characterized by multiorgan failure and cytokine release there is an interest in the use of corticosteroids as an immunomodulatory agent. There is interest in use of corticosteroids specifically to suppress lung inflammation in the setting of ARDS related to COVID-19.

### **Evidence to date on use of steroids in COVID19:**

A retrospective cohort of 201 patients with COVID-19 in China was examined to determine clinical characteristics of patients and outcomes of patients who developed ARDS or died. Methylprednisolone appeared to reduce risk of death in patients with ARDS (1).

Steroids have not proven beneficial in prior SARS or MERS epidemics and have been associated with delayed coronavirus RNA clearance (2,3). In influenza, corticosteroid treatment is associated with increased mortality and hospital acquired infections (4). Current clinical evidence is lacking to support use of corticosteroids in treatment of viral pneumonia (5). More data would also be needed to assess any combinations with which corticosteroids could have greater efficacy in the setting of COVID-19 (e.g., interferon plus corticosteroids, as tested in SARS-CoV) than either steroids alone or no steroids in specific groups during the course of illness.

### **Consensus Statements:**

- Interim guidance from WHO recommends that corticosteroids be avoided unless indicated for reasons other than COVID-19 (6).
- Society of Critical Care Medicine recommends against the use of corticosteroids in mechanically ventilated patients with COVID-19 without ARDS. In patients with ARDS, SCCM is recommending use of corticosteroids over not using corticosteroids (7).

### **Recommendations:**

- Until more data are available, routine use of corticosteroids in the setting of severe or life-threatening COVID-19 is not recommended outside of a clinical trial setting.
- Corticosteroid use should be considered in patients with COVID-19 and refractory shock.
- Corticosteroid use should be considered in patients with COVID-19 and chronic steroid use.
- Corticosteroid use should be considered in patients with COVID-19 infection associated with severe ARDS.
- Corticosteroid use should be considered in patients with COVID-19 infection and significant underlying lung disease such as asthma or COPD.

### **References:**

1. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020; <https://doi.org/10.1001/jamainternmed.2020.0994>.
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7. Alhazzani W, Moller MH, Arabi YM, et. al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med.* 2020, <https://doi.org/10.1097/CCM.0000000000004363>.

## **Antipyretics: Non-Steroidal Anti-inflammatory Drugs (NSAIDs) vs Acetaminophen (APAP)**

### **Background and Rationale:**

Concerns have been raised about the use of non-steroidal anti-inflammatory drugs (NSAIDs) because of the potential that they might blunt the pro-inflammatory immune response and, thus, exacerbate SARS CoV 2 replication. In addition, the potential for aggravating renal injury has been raised (1).

### **Availability at UC San Diego:**

Multiple NSAIDs and other antipyretics including acetaminophen and aspirin are stocked in the UC San Diego pharmacy.

### **Recommendation:**

No clinical evidence presently exists showing a clear connection between worse outcomes and NSAID use in COVID-19 patients. Acetaminophen carries a lower risk and should be used first line as an anti-pyretic agent (limited to 4g daily or less depending on hepatic function) until further evidence emerges. For additional supportive management (e.g., persistent fever despite maximum APAP, insensible volume loss), providers may decide on a case-by-case basis whether isolated doses of NSAIDs may be appropriate. Use of meperidine to treat symptomatic fever or rigors in COVID-19 patients has not been adequately studied.

Note: Patients potentially considered for enrollment in tocilizumab or remdesivir clinical trials are excluded if transaminases exceed 5x upper limit of normal and may need to discontinue antipyretics prior to enrollment; please see corresponding inclusion/exclusion criteria.

### **Reference:**

1. EMA COVID 19 Treatment Guidelines <https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19> (accessed 3/18/2020).

## **Empiric Antibiotics**

### **Background and Rationale:**

Secondary bacterial infection was documented in 15% of hospitalized patients in one Chinese study (1). Bacterial superinfection is generally not the initial cause of respiratory deterioration in patients with SARS-CoV-2 infection but it can occur in patients after intubation. In critically ill patients with MERS, rates of 18% bacterial and 5% viral co-infections have been documented. COVID-19 does not appear to increase procalcitonin alone, but does appear to increase CRP (2).

### **Recommendation:**

Non-ventilated patients should not be treated with empiric antibiotics without evidence of bacterial infection. Empiric antimicrobials may be considered when the clinical suspicion of bacterial superinfection is high (especially following intubation) while clarifying evidence is gathered (2). Some institutions advise using procalcitonin levels to guide decision making (3).

### **References:**

1. Zhou F, Yu T Du R, et. al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*; 2020;395(10229):1054-1062. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3).
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## **Zinc Sulfate**

### **Rationale:**

Zn<sup>2+</sup> Inhibits SARS-CoV2 RNA polymerase activity *in vitro* (1). Used in combination with zinc ionophores including chloroquine and hydroxychloroquine, *in vitro* viral replication is further disrupted. [2] Zinc sulfate has not been demonstrated to have any beneficial clinical effect alone or in combination with hydroxychloroquine or chloroquine.

### **Recommendation:**

The use of Zinc sulfate is not recommended alone or in combination with hydroxychloroquine or chloroquine for the prevention or treatment of persons with or at risk for SARS-Co-V-2 infection.

### **References:**

1. Velthuis AJ, et al. Zn<sup>2+</sup> Inhibits Coronavirus and Arterivirus RNA Polymerase Activity In Vitro and Zinc Ionophores Block the Replication of These Viruses in Cell Culture. *PLOS pathogens*, 2010;6(11):e1001176. <https://doi.org/10.1371/journal.ppat.1001176>.
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## **Lopinavir/ritonavir (Kaletra)**

### **Background and Mechanism:**

Lopinavir is an HIV-1 protease inhibitor that is administered orally in conjunction with ritonavir in order to assure adequate systemic exposure of lopinavir on the basis of CYP 3A4 inhibition. There is a vast experience with this combination agent in the treatment of HIV infection. It is generally well tolerated but the ritonavir-driven CYP 3A4 inhibition leads to significant interactions with a number of other pharmacological agents. At the time of the original SARS outbreak, it was demonstrated to have *in vitro* activity against SARS-CoV. It was administered to 41 SARS-CoV patients in combination with high dose ribavirin and corticosteroids in an uncontrolled experience during that outbreak. When compared to historical controls who received ribavirin and corticosteroids, a lower fraction of patients experienced adult respiratory distress syndrome or death. It has also been shown to have *in vitro* activity against the MERS CoV agent and this drug or interferon beta 1-b were each associated with histologic, virologic and clinical improvement.

It has been studied in a well-performed randomized, controlled study of patients with SARS-CoV-2 in a 199 patient study that was recently reported in the *New England Journal of Medicine* (2). The drug did not significantly reduce either the time to clinical improvement or 28-day mortality in this trial.

A phase 2 randomized, open-label study was recently published in *The Lancet* and assessed triple-drug combination ribavirin, interferon 1-beta and lopinavir-ritonavir compared to a lopinavir-ritonavir control (3). In this small trial of 127 participants, randomized 2:1, those that received triple-drug combination therapy had a shorter time to the primary end-point of negative nasopharyngeal swab (7 days versus 12 days) compared to the control group (3). Notably, this study had numerous limitations, including, but not limited to, the chosen primary end-point, absence of a placebo group, absence of additional one or two drug treatment arm comparisons and a study population largely composed of subjects with mild disease.

The current NIH COVID-19 Therapeutic Guidelines currently recommend against the use of lopinavir/ritonavir outside of a clinical trial due to “unfavorable pharmacodynamics and negative clinical trial data”(4).

### **Availability at UC San Diego:**

The drug is stocked by the UC San Diego pharmacy and is available for the treatment of persons with HIV infection.

### **Recommendations:**

Lopinavir/ritonavir is not recommended for the treatment of patients with SARS CoV-2 infection.

### **References:**

1. Arabi YM, Allothman A, Balkhy HH, et. al., Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-beta1b (MIRACLE trial): study protocol for a randomized controlled trial. *Trials* 2018;19(1):81. <https://doi.org/10.1186/s13063-017-2427-0>.
2. Cao B, Wang Y, Wen D, et. al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *New Engl J Med* 2020 Mar 18. <https://doi.org/10.1056/NEJMoa2001282>. [Epub ahead of print]
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## **UC San Diego Health COVID-19 Therapeutics Committee**

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## **Overview of Clinical Trial Inclusion/Exclusion Criteria**

- [ACTT-2 \(Adaptive COVID-19 Treatment Trial: Remdesivir and Baricitinib/placebo\)](#)
- [ACTG A5395 Phase 2b RCT to Compare Efficacy of Hydroxychloroquine + Azithromycin vs SOC for Mild COVID-19](#)
- [Tocilizumab vs. Placebo Trial](#)
- [Ramipril for the Treatment of COVID-19 \(RAMIC\) Trial](#)

**For a full list of current Clinical Trial information, please visit:**

<https://medschool.ucsd.edu/som/medicine/divisions/idgph/research/Pages/sars-cov-2.aspx#clinical-trials>

## **ACTT-2 Adaptive COVID-19 Treatment Trial (DMID/NIAID Supported Trial)**

Title/#: DMID 20-0006, Phase 3 Adaptive Clinical Trial Comparing Safety and Efficacy of Remdesivir vs. Placebo  
IRB 20-0388

Treatment arms: Remdesivir and Placebo versus Remdesivir and Baricitinib

Contact: Dr. Daniel Sweeney ([dasweeney@ucsd.edu](mailto:dasweeney@ucsd.edu)) and Dr. Constance Benson ([cbenson@ucsd.edu](mailto:cbenson@ucsd.edu))

### **5.1 Inclusion Criteria**

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

1. Admitted to a hospital with symptoms suggestive of COVID-19 infection.
2. Subject (or legally authorized representative) provides informed consent prior to initiation of any study procedures.
3. Subject (or legally authorized representative) understands and agrees to comply with planned study procedures.
4. Male or non-pregnant female adult  $\geq 18$  years of age at time of enrollment.
5. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, as documented by either of the following:
  - PCR positive in sample collected  $< 72$  hours prior to randomization;  
OR
  - PCR positive in sample collected  $\geq 72$  hours prior to randomization, documented inability to obtain a repeat sample (e.g. due to lack of testing supplies, limited testing capacity, results taking  $> 24$  hours, etc.). AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
6. Illness of any duration, and at least one of the following:
  - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
  - $SpO_2 \leq 94\%$  on room air, OR
  - Requiring supplemental oxygen, OR
  - Requiring mechanical ventilation.
7. Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 29.
8. Agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 through Day 29.

### **5.2 Exclusion Criteria**

An individual who meets any of the following criteria will be excluded from participation in this study:

1. ALT or AST  $> 5$  times the upper limit of normal.
2. Estimated glomerular filtration rate (eGFR)  $< 30$  ml/min (including patients receiving hemodialysis or hemofiltration).
3. Pregnancy or breast feeding.
4. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
5. Allergy to any study medication.

### **Exclusion of Specific Populations**

Children and adolescents will not be included in this trial. Remdesivir has only been used in a small number of pediatric patients. Initial information about the epidemiology of COVID-19 indicates that the overwhelming

burden of severe disease occurs among older adults, especially those with comorbidities. Given significant gaps in knowledge in this population, and a low incidence of severe morbidity/mortality in children, the risk/benefits do not warrant inclusion of this population into this trial at this time. In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals. Embryonic toxicity was seen when remdesivir was initiated in female animals prior to mating and conception, but only at a systemically toxic dose. Remdesivir has not been studied in pregnant women. Because the effects on the fetus and the pregnant woman are not fully known, pregnant women will not be eligible for the trial. In animal studies, remdesivir metabolites have been detected in the nursing pups of mothers given remdesivir. It is not known whether remdesivir is secreted in human milk. Because the effects of remdesivir on the breastfeeding infant is not known, women who are breast feeding will not be eligible for the trial.

### **5.3 Inclusion of Vulnerable Subjects**

Certain human subjects are categorized as vulnerable populations and require special treatment with respect to safeguards of their well-being. For this clinical trial, examples include cognitively impaired or mentally disabled persons and intubated individuals who are sedated. When it is determined that a potential research subject is cognitively impaired, federal and institutional regulations permit researchers to obtain consent from a legally authorized representative (LAR). The study team will obtain consent from these vulnerable subjects using an IRB-approved protocol- specific process for consent using a LAR. For subjects for whom a LAR gave consent, during the course of the study, if the subject regains the capacity to consent, informed consent must be obtained from the subject and the subject offered the ability to leave the study if desired.

### **5.4 Lifestyle Considerations**

During this study, subjects are asked to:

- Refrain from drinking alcohol through Day 15.
- Avoid getting pregnant during the study from Day 1 through Day 29.
- Avoid participation in another clinical trial for the treatment of COVID-19 or SARS-CoV-2. Co-enrollment for natural history studies of COVID-19 or SARS-CoV-2 is permitted; however, participation in both ACTT and natural history studies can only occur if the recommended blood collection volumes are not exceeded.

## **Outpatient Hydroxychloroquine + Azithromycin versus Standard of Care for Mild COVID-19**

Title/#: ACTG A5395 Phase 2b RCT to Compare Efficacy of HCQ + Azithromycin vs SOC for Mild COVID-19  
IRB 20-0590

Treatment arms: Hydroxychloroquine + Azithromycin versus Standard of Care

Contact: Dr. Daniel Sweeney ([dasweeney@ucsd.edu](mailto:dasweeney@ucsd.edu)) and Dr. Constance Benson ([cbenson@ucsd.edu](mailto:cbenson@ucsd.edu))

### **Inclusion Criteria:**

- Participant (or legally authorized representative) provides informed consent prior to initiation of any study procedures.
- Individual  $\geq 18$  years of age.
- Documentation of confirmed active SARS-CoV-2 infection, as determined by a molecular test conducted at any US clinic or laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent from any respiratory specimen collected  $< 96$  hours prior to study entry.  
NOTE: If  $\geq 96$  hours since the collection date of the positive SARS-CoV-2 test result, then a repeat SARS-CoV-2 test may be performed to re-screen for eligibility outside of the study, and must be collected  $< 96$  hours prior to study entry.
- Experiencing at least one of the following SARS-CoV-2 infection symptoms: fever (can be subjective) OR cough OR shortness of breath.
- Agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 during the study period up until reaching hospitalization or 21 days, whichever is earliest.
- Agrees to not obtain study medications outside of the A5395 study.

### **Exclusion Criteria:**

- Need for hospitalization or immediate medical attention in the clinical opinion of the study investigator.
- History of or current hospitalization for COVID-19.  
NOTE: Individuals hospitalized and then discharged, even if only hospitalized for 1 day, are excluded.
- History of ventricular arrhythmia or on antiarrhythmics.
- Personal or family history of Long QT syndrome.
- History of kidney disease.  
NOTE A: If the individual responds “yes” but can provide a creatinine clearance value  $\geq 45$  mL/min by Cockcroft-Gault equation within 1 year prior to study entry, the individual may participate.  
NOTE B: Please refer to the A5395 PSWP for the website link to the Cockcroft-Gault calculator.
- History of ischemic or structural heart disease.
- Personal medical history of porphyria, retinopathy, severe hepatic impairment, or G6PD deficiency.
- Use of drugs with possible anti-SARS-CoV-2 activity within 30 days prior to study entry, e.g., remdesivir, lopinavir/ritonavir fixed dose combination, ribavirin, chloroquine, hydroxychloroquine, and azithromycin, or participation in a clinical trial involving any of these drugs whether for treatment or prophylaxis.
- Use of antiepileptic drugs.
- Requirement or expected requirement for a medication that significantly prolongs QT (medications summarized in section 5.4), from 96 hours prior to study entry through 4 weeks after discontinuation of study treatment.
- Participating in a study where co-enrollment is not allowed.
- Receipt of a SARS-CoV-2 vaccination prior to study entry.
- Known allergy/sensitivity or any hypersensitivity to components of HCQ, azithromycin, or their formulation.
- Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements

## **Tocilizumab vs. Placebo Trial**

Title/#: WA42380, Multicenter RCT to Evaluate Safety and Efficacy of Tocilizumab vs. Placebo  
IRB 20-0491

Treatment arms: Tocilizumab IV x 1 (with up to 1 additional dose within 8 – 24 hours from initial dose may be given if clinical symptoms worsen or show no improvement) versus placebo.

Contact: Dr. Atul Malhotra ([amalhotra@health.ucsd.edu](mailto:amalhotra@health.ucsd.edu)) or Dr. Aaron Carlin ([acarlin@health.ucsd.edu](mailto:acarlin@health.ucsd.edu))

### **Inclusion Criteria:**

- Hospitalized with COVID-19 pneumonia confirmed per WHO criteria (including a positive PCR of any specimen; e.g., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan
- SPO<sub>2</sub>  $\leq$  93% or PaO<sub>2</sub>/FiO<sub>2</sub>  $<$  300 mmHg - \*If a patient is on supplemental oxygen with SpO<sub>2</sub>  $>$  93%, but desaturation to  $\leq$  93% on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met

### **Exclusion Criteria:**

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $>$  10 x upper limit of normal (ULN) detected within 24 hours at screening or at baseline (per local lab)
- Absolute neutrophil count (ANC)  $<$  1000/mL at screening and baseline (per local lab)
- Platelet count  $<$  50,000/mL at screening and baseline (per local lab)
- Known severe allergic reactions to TCZ or other monoclonal antibodies
- Active tuberculosis (TB) infection
- Suspected active bacterial, fungal, viral, or other infection (besides COVID-19)
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Have received oral anti-rejection or immunomodulatory drugs (including TCZ) within the past 6 months
- Participating in other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if approved by Medical Monitor)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted if approved by Medical Monitor)
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

### **Ramipril for the Treatment of COVID-19 (RAMIC) Trial**

Title/#: RAMIC: Phase 3 RCT Safety and Efficacy of Ramipril versus Placebo

IRB 20-0624

Treatment arms: Ramipril 2.5 mg oral capsule versus placebo oral capsule

Contact: Dr. Rohit Loomba ([roloomba@health.ucsd.edu](mailto:roloomba@health.ucsd.edu)) and Dr. Veeral Ajmera ([v1ajmera@health.ucsd.edu](mailto:v1ajmera@health.ucsd.edu)).

#### **Inclusion Criteria:**

- Age  $\geq$  18 years
- Willing and able to provide written informed consent prior to performing study procedures
- Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test  $\leq$  5 days before randomization

*OR*

- Clinical presentation consistent with COVID-19 infection (fever or cough or shortness of breath) with positive IgM serology
- Currently hospitalized or in an emergency department or urgent care
- Peripheral capillary oxygen saturation (SpO<sub>2</sub>)  $\geq$  93% on room air at screening

#### **Exclusion Criteria:**

- Participation in any other clinical trial of an experimental treatment for COVID-19 (use of hydroxychloroquine or compassionate use of chloroquine or azithromycin is allowed)
- Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 is prohibited  $<$  24 hours prior to study drug/placebo dosing
- Requiring mechanical ventilation at screening
- Requiring ICU care at admission
- NSAID use within 12 hours of randomization or requiring continued NSAID use during this trial
- Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST)  $>$  5 X upper limit of normal (ULN)
- Estimated GFR  $<$  40 mL/min
- History of serum creatinine  $\geq$  2 mg/dl in the previous 28 days
- Systolic BP  $<$  100 mm hg or diastolic BP  $<$  65 mm hg
- Hypersensitivity to ACEI
- History of angioedema
- Outpatient use of ACE inhibitor or Angiotensin II receptor blocker in the last 7 days
- History of renal artery stenosis
- Serum potassium  $\geq$  5.1 mEq/L
- Pregnancy or breastfeeding
- Use of aliskiren, amifostine, lithium, sacubitril, within 7 days