A5395

A Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy of Hydroxychloroquine and Azithromycin to Prevent Hospitalization or Death in Persons with COVID-19

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:
National Institute of Allergy and Infectious Diseases

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SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

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TABLE OF CONTENTS

Page

CONTENTS (Cont'd) Page

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STUDY MANAGEMENT

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Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5395 e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org.

Clinical Management:
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the Clinical Management Committee (CMC). Send an e-mail message to actg.cmcA5395@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to virologic or pharmacologic laboratory tests, contact the Protocol Virologist or Pharmacologist.

- Send an e-mail message to actg.teamA5395@fstrf.org (ATTENTION: Robert Coombs or Rada Savic).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the data manager. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP-119, and contact Sara Sieczkarski directly.
- For other questions, send an e-mail message to actg.teamA5395@fstrf.org (ATTENTION: Sara Sieczkarski).
- Include the protocol number, PID, and a detailed question.

Randomization/Participant Registration
For randomization/participant registration questions or problems and study identification number SID lists:

- Send an e-mail message to rando.support@fstrf.org or call the DMC Randomization Desk at 716-834-0900, extension 7301.

DMC Portal and Medidata Rave Problems
Contact DMC User Support.

- Send an e-mail message to actg.user.support@fstrf.org or call 716-834-0900 x7302.

Protocol Document Questions
For questions concerning the protocol document, contact the Clinical Trials Specialists.
- Send an e-mail message to actg.teamA5395@fstrf.org (ATTENTION: Christina Vernon and Chanelle Wimbish).

Copies of the Protocol
To request a hard copy of the protocol, send an e-mail message to ACTGNCC@dlhcorp.com. Electronic copies can be downloaded from the ACTG website at https://www.actgnetwork.org.

Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
For protocol registration questions, send an e-mail message to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation
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Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call Justine Beck or Shawn Chiambah, Protocol Pharmacists, at 301-496-8213.

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IND (Investigational New Drug) Number or Questions
For any questions related to the IND submission, contact the DAIDS RSC at Regulatory@tech-res.com or call 301-897-1706.

Expedited Adverse Event (EAE) Reporting/Questions
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- Send an e-mail message to actg.teamA5395@fstrf.org.

Protocol-Specific Web Page
Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

AE	adverse event
ARDS	acute respiratory distress syndrome
Azithro	azithromycin
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CQMP	Clinical Quality Management Plan
CrCl	creatinine clearance
CVD	cardiovascular disease
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
DRESS	drug reaction with eosinophilia and systemic symptoms
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
EKG	electrocardiogram
GCP	Good Clinical Practice
GI	gastrointestinal
HCQ	hydroxychloroquine
HTN	hypertension
IB	Investigator Brochure
ICF	informed consent form
ICU	intensive care unit
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	intravenous
MERS	Middle East Respiratory Syndrome
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections

PHI	Protected Health Information
PI	Principal Investigator
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
SDCC	Statistical and Data Coordinating Center
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TdP	torsades de pointes
WHO	World Health Organization

SCHEMA

A5395

A Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy of Hydroxychloroquine and Azithromycin to Prevent Hospitalization or Death in Persons with COVID-19

DESIGN	This is a phase IIB, double-blind, placebo-controlled, randomized trial, designed to compare the efficacy of hydroxychloroquine (HCQ) plus azithromycin (Azithro) versus placebo to prevent hospitalization and death in symptomatic adult outpatients with COVID-19 **caused by SARS-CoV-2 infection.**
DURATION	24 weeks. Treatment will be for 7 days with 23 weeks of follow-up.
SAMPLE SIZE	2000 participants who start study treatment; approximately 1000 participants in each of two treatment arms (A and B). Participants who are randomized but do not start study treatment will be replaced. A subset (200 participants who start treatment) will follow an additional sampling evaluation schedule.
POPULATION	Symptomatic, outpatient, adults (≥18 years) with SARS-CoV-2 infection
STRATIFICATION	Stratification will be by “high” versus “low” risk of progression to severe COVID-19, where “high risk” is defined as a person age ≥60 years or having at least one of several specified comorbidities.
REGIMEN	Participants will be randomized 1:1 to receive active/placebo study treatment as follows: HCQ/Placebo **400** mg **orally twice a day on Day 0** followed by 200 mg **orally twice a day for 6 days,** and Azithro/Placebo 500 mg on**ce on Day 0**, followed by 250 mg daily for **4** days.

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

1.1.1 Hydroxychloroquine (HCQ) and Azithromycin (Azithro) will prevent hospitalization and death in persons with symptomatic SARS-CoV-2 infection.

1.2 Primary Objective

1.2.1 To determine if HCQ and Azithro will prevent the composite endpoint of either hospitalization or death by 21 days after study entry. Hospitalization is defined as ≥24 hours of acute care.

1.3 Secondary Objectives

1.3.1 To determine safety of HCQ and Azithro including 1) adverse events (AEs) leading to early discontinuation of treatment with HCQ and Azithro and 2) cardiac AEs.

1.3.2 To determine if HCQ and Azithro reduce the frequency of detection and levels of SARS-CoV-2 RNA in site-collected nasopharyngeal (NP) swabs and self-collected nasal swabs in subset of participants.

1.3.3 To determine if HCQ and Azithro change the severity and duration of self-reported symptom experience of COVID-19.

1.3.4 To determine if HCQ and Azithro will prevent the composite endpoint of either hospitalization or death by 24 weeks after study entry. Hospitalization is defined as ≥24 hours of acute care.

1.4 Exploratory Objectives

1.4.1 To explore if outpatient HCQ and Azithro change the hospital course once a participant requires hospitalization.

1.4.2 To identify pretreatment hematology, chemistry, and inflammatory biomarkers that are associated with outcomes.

1.4.3 To explore differences in outcomes between HCQ and Azithro versus placebo treatment groups among subgroups of the population, notably by sex, race/ethnicity, and risk groups defined by age and comorbidities.

1.4.4 To explore possible predictors of outcomes across the study population, notably sex, race/ethnicity, and risk groups defined by age and comorbidities.

1.4.5 To determine the comparability between site-collected NP swabs and self-collected nasal swabs for the detection of SARS-CoV-2 shedding.

2.0 INTRODUCTION

2.1 Background

Threat

A novel pneumonia caused by a previously unknown betacoronavirus emerged in Wuhan, China, in December 2019. The virus is closely related to the severe acute respiratory syndrome coronavirus (SARS-CoV-1), which led to an outbreak in 2003, and has been named SARS-CoV-2. The human disease caused by SARS-CoV-2 is called COVID-19.

During the current SARS-CoV-2 outbreak, the incidence of known cases has rapidly increased such that, on January 5, 2020, there were 59 confirmed cases, 278 cases on January 20, 2118 cases on January 26, and more than 80,000 cases and 2700 deaths as of February 25, 2020, according to various international health reporting agencies. As a result, on January 30, 2020, the International Health Regulations Emergency Committee of the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern. On January 31, 2020, the US Department of Health and Human Services declared a public health emergency in the United States. As of **April 22, 2020,** there are **2,594,724** cases of COVID-19, including **826,248** cases in the United States (US), resulting in a total of **179,778** deaths globally. Despite quarantine measures, SARS-CoV-2 continues to spread [1]. Outbreak forecasting and modeling suggest that these numbers will continue to rise [2].

Global efforts to evaluate novel antivirals and therapeutic interventions to treat COVID-19 have intensified. There is currently no vaccine to prevent SARS-CoV-2 infection or therapeutic agent to treat COVID-19. Therefore, there is an urgent public health need for rapid development of novel interventions.

Virology

Coronaviruses (CoVs) are positive-sense, single-stranded, enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past two decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely, SARS-CoV-1 in 2002-2003 and Middle East Respiratory Syndrome coronavirus (MERS-CoV) in 2012.

Disease Course

Once infection occurs, the clinical course is variable. Best current data suggest that fewer than 2.5% of infected persons will show symptoms within “2.2 days (CI, 1.8 to 2.9 days) of exposure, and symptom onset will occur within 11.5 days (CI, 8.2 to 15.6 days) for 97.5% of infected persons” [3]. In most (~80%) cases, COVID-19 presents as a mild-to-moderately severe, self-limited acute respiratory illness with fever, cough, and shortness of breath. It remains unclear exactly what the rate of progression of COVID-19 is and what the predictors are for complications, including pneumonia, acute respiratory

distress syndrome (ARDS), kidney failure, and death. It is clear that older age, male sex, and comorbidities including diabetes and hypertension increase the risk for worse outcomes (Figure 2.1-1) [4-6]. In a recent meta-analysis, the main clinical symptoms were fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), and dyspnea (21.9%). Minor symptoms included headache or dizziness (12.1%), diarrhea (4.8%), and nausea and vomiting (3.9%) [7]. Laboratory examinations showed that lymphocytopenia (64.5%), increase of C-reactive protein (CRP) (44.3%), increase of lactate dehydrogenase (LDH) (28.3%), and leukocytopenia (29.4%) were more common in those with COVID-19 [4, 8].

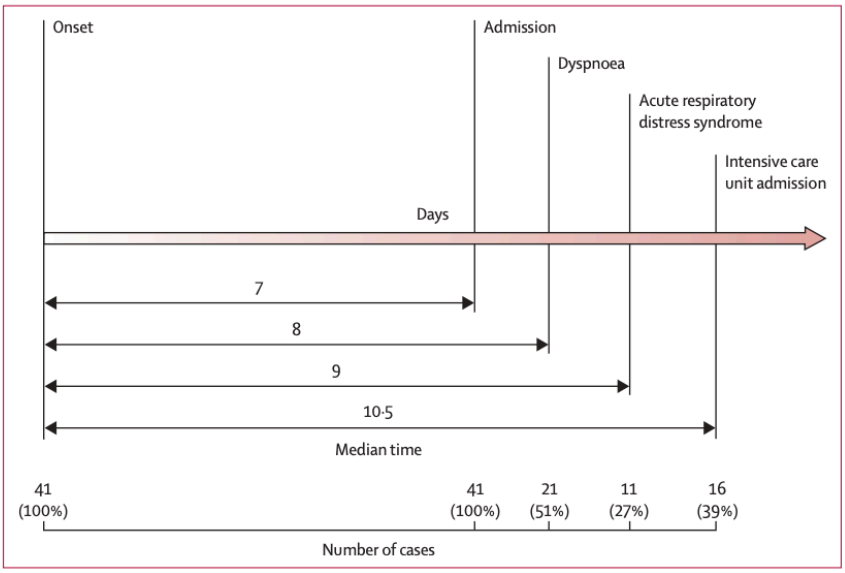

Figure 2.1-1: Timeline of COVID Disease Progression after Hospitalization. Onset refers to onset of symptoms.

Shedding

Viral infections jump from host to host through a variety of pathways. CoVs do this through respiratory droplets. Understanding this shedding is important to understanding epidemic spread and how shedding relates to disease progression. Best evidence available now suggests that viral shedding, especially in upper respiratory secretions, is detectable around 2 days before symptoms develop and continues throughout the symptomatic phase. This shedding can be quite high during active disease and can continue for up to 37 days, with a quarter of persons still shedding at 3 weeks, as detected by nasopharyngeal swabs [4].

Biomarkers

The literature also points to a systemic inflammatory response that predicts disease progression and death. Having a biomarker panel that can predict such progression early would be helpful in making clinical decisions and triaging clinical care [4]. In particular, patients requiring ICU admission had higher blood levels of interleukin (IL)2,

IL7, IL10, granulocyte colony stimulating factor (GCSF), interferon gamma-induced protein (IP)10, monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1-alpha (MIP1A), and tumor necrosis factor-alpha (TNFα) than hospitalized patients not requiring ICU admission [5]. Nothing is currently known about wh**ich** inflammatory biomarkers during early infection might predict increased risk for hospitalization.

Biomedical Interventions

There are no approved treatments for COVID-19. Some agents have shown activity against other betacoronaviruses, such as lopinavir/ritonavir, chlorpromazine, nitazoxanide, gemcitabine, and dasatinib [9], and two agents have shown *in vitro* activity against the virus, including chloroquine and the adenosine analog remdesivir [10]. There is no clinically proven antiviral treatment for SARS-CoV-2 infection, although a clinical trial of remdesivir [11] is underway in China [12], and the US for severe pulmonary disease, and anecdotal evidence has been published about HCQ and Azithro [13].

Chloroquine and its less toxic derivative HCQ (first FDA approved in 1955 for the treatment of malaria) have garnered substantial interest as off-label treatment for COVID-19. They are alkalinizing lysosomatropic drugs that accumulate in lysosomes [14]. 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 CoV, including SARS-CoV [15]. In vitro data in Vero E6 cells have demonstrated that chloroquine functions at both entry and at post-entry stages of the SARS-CoV-2 infection, unlike remdesivir [10]. Further in vitro data showed that there is an exposure-response relationship for HCQ (Figure 2.1-2). Both drugs also modulate the immune response, and have long been used to treat autoimmune diseases such as rheumatoid arthritis, porphyria cutanea tarda, and lupus [14]. Such immune modulation may also help in thwarting ARDS [16].

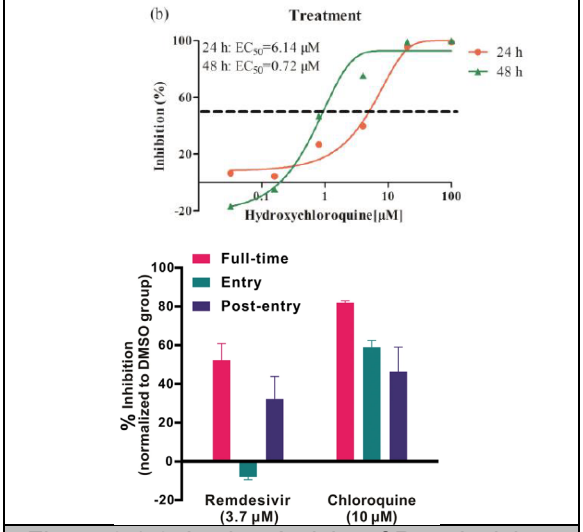

Figure 2.1-2: In vitro Activity of Remdesivir, Hydroxychloroquine, and Chloroquine [10]

HCQ Pharmacology

HCQ and chloroquine have similar pharmacokinetics, with 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 desethylhydroxy-chloroquine, desethylchloroquine, and bidesethylhydroxychloroquine by the liver and excreted by the kidneys, with desethylhydroxychloroquine being most common [17, 18a]. The absorption half-life is 3 to 4 hours and the terminal half-life ranges from 40 to 50 days. Based on modeling of HCQ pharmacokinetics and its antiviral effects, Dr. Rada Savic at UCSF found that higher doses of HCQ would be associated with progressive loss of detection

of SARS-CoV-2 in the nasopharynx over 6 days of dosing (**Figure 2.1-3**), in a dose-dependent manner [18b]. However, higher doses are also associated with longer QT interval prolongations; thus, **in order to balance the potential risks and benefits for treatment in the outpatient setting,** treatment in this trial will include a loading dose of **800 mg divided into two** 400 mg **doses taken 12 hours apart starting at enrollment, followed** by 200 mg **twice** daily **for 6 days** (12 doses), with a total dose of **32**00 mg of HCQ during the study.

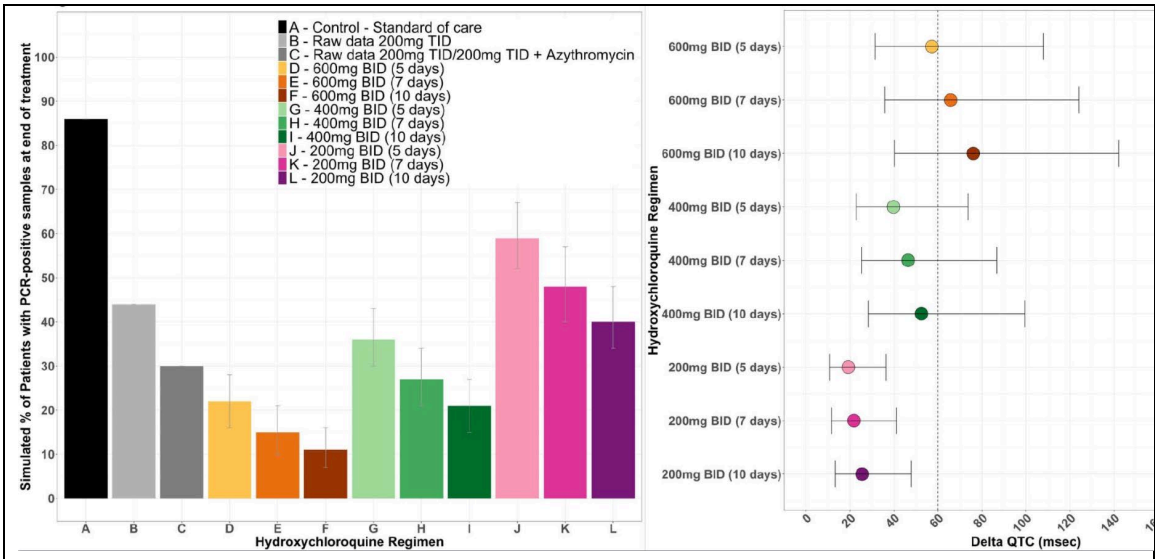

Figure 2.1-3: Estimated Efficacy (% of PCR-negative samples) and QTc Prolongation for Various Hydroxychloroquine Regimens

HCQ Interactions

HCQ does not have significant interactions with most other medications, but may enhance liver toxicity of select drugs, for example, aurothioglucose, cimetidine, or digoxin. It can also increase the blood plasma concentrations of penicillamine, which may contribute to the development of side effects from penicillamine, and decrease the levels of ampicillin and praziquantel. It can also enhance hypoglycemic effects of insulin and oral hypoglycemic agents.

Azithro Pharmacology

Azithro was first approved for clinical use in 1988 [19]. It is currently FDA approved for use in mild to moderate bacterial infections including sinusitis, community acquired pneumonia, urethritis/cervicitis, pharyngitis, and acute bacterial exacerbations of chronic obstructive pulmonary disease. It is the first of the azalide class of antimicrobials, which does not undergo significant metabolism and does not complex with or induce cytochromes P450 (CYPs), therefore decreasing the potential for drug interactions [19, 20]. Azithro has been found to have a long terminal half-life of 50 hours with 500 mg IV dosing and 79 hours with 500 mg oral dosing, making once a day or single dose treatments possible [21]. It is also known to have a large volume of distribution and achieves extensive tissue penetration compared to macrolides [20], **as well as** high

intracellular concentrations in immune cells [22]. The co-administration of meals along with Azithro has no impact on bioavailability [23].

Azithro Interactions

In pre-clinical studies, Azithro has been shown to increase QT intervals, but without inducing torsades de pointes (TdP) [24]. Given QT prolongation may occur, concurrent Azithro administration is not recommended with high-risk QT-prolonging agents, such as fexinidazole and pimozide. Other QT-prolonging agents such as antipsychotics or class IC antiarrhythmics should be used with caution with monitoring of QT_c interval. In addition, Azithro as a P-glycoprotein (P-gp) inhibitor should be avoided in concurrent use of colchicine, topotecan, rimegepant, pazopanib, or vincristine, as it may increase the serum concentration of these drugs [25]. There is conflicting evidence on the effect of Azithro on warfarin drug metabolism. In general, it appears that there is a modest decrease in warfarin clearance and thus a possible increase in anticoagulant effect [26]. Patients should continue to have international normalized ratio monitored when Azithro is used with warfarin. In addition, there is potential risk of increased rhabdomyolysis with concurrent use of statins, and patients should be monitored on such therapy [27].

HCQ and Azithro Interactions

There are no pharmacologic drug-drug interactions between Azithro and chloroquine, and thus none are expected between Azithro and HCQ, including in pregnant women [28, 29].

Potential Risks of HCQ and Azithro

HCQ and Azithro have each been used widely for many years, for the independent indications described previously. Potential risks are described further in this section below.

HCQ

Common side effects of HCQ include headache, emesis, diarrhea, vision changes, and muscle weakness. Severe side effects are mainly limited to allergic reactions and eye toxicity, "chloroquine retinopathy" [30], and cardiac toxicity. "Chloroquine retinopathy" is a relatively serious toxicity associated with HCQ use among people taking HCQ for greater than 5 years [31]. Further, rapid-onset retinopathy has been reported in persons being treated with erlotinib and high-dose HCQ (1000 mg daily) for non-small cell lung cancer [32]. Generally, people taking **400** mg of HCQ or less per day or for short periods have a negligible risk of retinopathy, as macular toxicity is related to total cumulative dose [22]. The dose and durations proposed in this trial are unlikely to cause retinopathy [31].

HCQ can prolong the QT interval, and ventricular arrhythmias and TdP have been reported, but usually after prolonged administration [33], particularly in patients with lupus and other comorbidities such as end-stage renal disease [34-37]. **In general**, drug-induced TdP and life-threatening ventricular arrhythmias from HCQ are very rare and typically only observed when doses of 5 g or more are taken [14, 33, 38]. HCQ is a derivative of chloroquine, and the relationship between chloroquine and QT prolongation has been better defined. It is the same molecule that is associated with a prolonged QTc

interval. When chloroquine was administered to healthy adults (regimen 600 mg + 600 mg + 300 mg on Days 1, 2, and 3, respectively) the average increase in QTc interval was 28 ms (18-38 ms; 95% CI) with no cardiac AEs reported [39]. While chloroquine and HCQ are different compounds, animal toxicity studies indicate HCQ is two to three times less toxic across different species [40].

Further, the WHO states, "[d]rug-induced TdP and life-threatening ventricular tachy-arrhythmias are very rare events, and there are no simple screening tests to identify people at risk." Also from WHO, "[d]espite hundreds of millions of doses administered in the treatment of malaria, there have been no reports of sudden unexplained death associated with quinine, chloroquine or amodiaquine, although each drug causes QT/QTc interval prolongation" [38].

Azithro

Common side effects associated with both oral and IV administration of Azithro include nausea and vomiting, likely due to increased gastric motility [19]. Severe side effects include pseudomembranous colitis, exacerbation of myasthenia gravis, Stevens-Johnson syndrome/toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) [41, 42]. In addition, there is an increased rate of cancer relapse for hematopoietic stem cell transplant patients with acute lymphocytic leukemia (ALL), acute myelocytic leukemia or bronchiolitis obliterans who received long-term Azithro therapy (greater than 2 years) [43]. However, patients taking Azithro for short periods have a negligible risk of this complication. Azithro crosses the placenta and is found in low concentrations in breast milk, but is considered safe to use in pregnancy [44].

Prolongation of QT with Azithro treatment has been seen in pre-clinical studies, but clinical studies of long term treatment with Azithro have not observed this effect [45]. Additionally, in the preclinical studies that demonstrated QT prolongation with Azithro, the QT prolongation did not lead to TdP, the clinical outcome of concern [24]. Furthermore, in clinical studies of long-term treatment (median of 9 months) with Azithro in patients with non-tuberculous mycobacterial infection, no significant change in QTc intervals and no cardiovascular events were observed during the treatment period [45].

COVID-19

There are some concerning reports that COVID-19 is associated with cardiac disease. In particular, a recent study in China found that persons with underlying cardiovascular disease are at high risk for severe disease and death [46]. It is unclear if cardiac morbidity is worse in the setting of COVID-19 **with** other pneumonia-causing pathogens [47], and unknown if the risks of short course HCQ and Azithro differ in the context of COVID-19.

Assessment of Potential Risks and Benefits

Although there are limited clinical data of HCQ plus Azithro use, there are preclinical data on using chloroquine plus Azithro in a rapid-pacing model in an anesthetized guinea pig model, which has been shown to be predictive of concentration-dependent onset of TdP [48]. This study evaluated increasing doses of azithromycin dehydrate and chloroquine diphosphate given intravenously that achieved clinical use concentrations.

The investigators reported no biologically significant effect on mean alternans. In fact, when combined, Azithro reduced the magnitude of alternans observed with chloroquine alone. This preclinical data is supported by clinical studies using chloroquine with Azithro. The Kimani et al. study evaluated malaria prevention during pregnancy where 1445 women received 3 days of chloroquine plus Azithro that was repeated at 4-8 week intervals during the second and third trimesters of pregnancy. Although QT intervals were not assessed at baseline or throughout the study, there were no reported cardiac AEs [29]. Sagara et al. conducted two randomized, comparative, non-inferiority studies in Africa where patients with malaria received Azithro 1000 mg (n=227) or Azithro 500 mg (n=9) with chloroquine 600 mg, all once daily for 3 days [49]. While QT interval was not measured at the beginning or during the study, there were no cardiac AEs noted. While subjective adverse events of dizziness and palpitations were reported, they occurred no more frequently than seen in the mefloquine control arm. **The azithromycin label reports that, in comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF are 5 (10) ms, 7 (12) ms, and 9 (14) ms, with the co-administration of 500 mg, 1000 mg, and 1500 mg azithromycin, respectively.**

Given that the proposed study will exclude those taking **concomitant** medications with high risk of prolonging QT (section 5.4.1), we do not feel that electrocardiograms (EKGs) at study entry or during treatment are needed. **We believe that** exclusions on the basis of baseline QTc are unlikely to add significantly to **overall safety, above and beyond the planned exclusion** of participants with higher risk for drug-induced ventricular arrhythmias and cardiac events **based upon** relevant personal or family cardiac history, high risk clinical history including severe renal and liver disease, and those who are taking additional QTc prolonging agents. Further, in the midst of a global pandemic, the risk-benefit assessment must consider a wide range of participants, study staff and resource utilization-related issues. In this case, the condition of TdP is expected to be very rare and the performance of EKGs would require the use of personal protective equipment (PPE), for which supplies must be carefully preserved as the current pandemic escalates, and the risk of additional direct contact between staff and highly infectious study participants. As a result, we feel that the potential benefit of HCQ plus Azithro treatment for a disease with an overall case fatality rate of up to 3% (and based on preliminary estimates in the US, 3-11% among persons aged 65-84 years) outweighs the very small risk of a treatment-related cardiac AE, and therefore do not feel that EKGs at study screening or during treatment would be justified [50, 51].

2.2 Rationale

At present, there is no specific antiviral therapy for COVID-19. Few treatment studies have been conducted because most human CoV strains cause self-limited disease, and care is supportive. After SARS-CoV-1 was identified in 2002-2003 and caused a large global outbreak, there was an increased interest in the development of specific therapeutic agents. SARS-CoV-1 patients were treated with corticosteroids, type 1 IFN agents, convalescent plasma, ribavirin, and lopinavir or ritonavir; except for ribavirin, many of these agents have in vitro pre-clinical data that support their efficacy [52-67]. Since the SARS-CoV-1 outbreak in 2002-2003, new therapeutic agents targeting viral

entry proteins, proteases, polymerases, and methyltransferases have been tested; however, none of them has been shown to be efficacious in clinical trials [68-70].

Given the lack of specific antiviral therapy for SARS-CoV-2 infection, and the known safety profiles and ready availability of HCQ and Azithro as potential antiviral agents, **this regimen warranted further consideration. This, along with** some promise observed in pre-clinical and small clinical studies, **resulted in designing** this randomized, placebo-controlled trial **to** evaluate the efficacy and safety of HCQ and Azithro in persons who have active SARS-CoV-2 infection and mild to moderate COVID-19 symptoms.

Why HCQ and Azithro for COVID-19?

Mechanism: Since a putative antiviral mechanism for HCQ is alkalinizing of lysosomes [14, 15], there is good reasoning that Azithro can potentiate this activity because it also increases the pH of lysosomes, and has been documented to potentiate this effect with chloroquine. Given the extensive data from malaria studies, these drugs can be safely used together with no drug-drug interactions [29, 49] (see below).

French experience: There is a recent uncontrolled study by Gautret et al. that evaluated HCQ and Azithro for SARS-CoV-2 shedding. It was a 20-person single-arm study with SARS-CoV-2 infection in a hospital setting. The study evaluated 600 mg of HCQ daily, and Azithro 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 may be effective in reducing viral loads (Figure 2.2-1). Specifically, HCQ reduced the proportion of persons with SARS-CoV-2 infection with polymerase chain reaction (PCR)-positive samples by 75% in the 6-day period, and when it was combined with Azithro, it improved the treatment efficacy to 95% [13].

The same authors recently published on-line their experience with 80 patients, 6 of whom were in the original published cohort, admitted to their inpatient ward with documented SARS-CoV-2 infection [13, 71]. None of these individuals were originally admitted to **the** ICU, with 54% having evidence of lower respiratory tract infection and 5% being asymptomatic, and only 15% requiring supplemental oxygen at presentation. The **authors** reported that one died on their unit and one was transferred to **an** intensive care unit. **They** reported that 83% were nasopharyngeal swab PCR negative on Day 7 and 93% by Day 8. They further noted that 97.5% were culture negative by Day 5 of follow-up.

However, there are a number of limitations of the smaller study: 1) it was not randomized, 2) a therapeutic effect in the first 2 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 a death and 3 ICU admissions, 5) the reliance on clearance of SARS-CoV-2 detected by NP swab as the primary outcome given the natural history, even in severe disease, is clearance of virus from the upper respiratory tract, and 6) lower baseline viral load in

persons receiving HCQ and Azithro, compared to the persons receiving HCQ alone. A secondary analysis of the data from this non-randomized trial was conducted and concluded that the data “show modest to no impact of HCQ treatment, with more significant effects from the HCQ-AZ combination, potentially suggesting a role for co-infections in COVID-19 pathogenesis. The trial of Gautret and colleagues, with consideration of the effect sizes, and p-values from multiple models, does not provide sufficient evidence to support wide-scale rollout of HCQ monotherapy for the treatment of COVID-19; larger randomized studies should be considered. However, these data do suggest further study of HCQ-Azithro combination therapy should be prioritized “as rapidly as possible” [72].

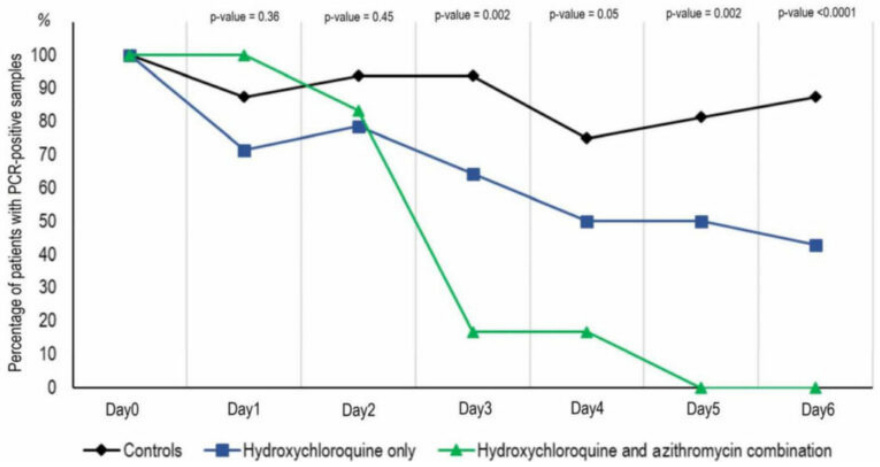

Figure 2.2-1: Clinical Course during HCQ and Azithromycin Treatment

The second larger study substantially increases the number of enrolled individuals, **but also** lacks a control group. It also enrolled a group with relatively mild disease, which is consistent with the population we plan to enroll and perhaps provides support for our strategy to use this regimen to prevent hospitalization in this subset of infected individuals.

Chinese experience: Reported clinical studies with these agents for COVID-19, apart from the Gautret studies, have been limited to chloroquine or HCQ and not Azithro or the combination. An initial report of clinical trials testing the safety and efficacy of chloroquine for the treatment of COVID-19 pneumonia across 10 hospitals in China noted that preliminary results from 100 patients suggested superiority of chloroquine phosphate to control treatment (control treatment unspecified), in outcomes including “inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course.” Further details are not available. Per this report, these initial findings have led to the recommendation that chloroquine phosphate be included in national Chinese guidelines for the management of COVID-19 [73].

An additional study of HCQ treatment in 30 “common” COVID-19 patients (reportedly with relatively mild disease) was published, with only the abstract available in English [74**a**]. In this study participants were randomized 1:1 to HCQ 400 mg po daily plus usual therapies vs usual therapies alone. All participants received inhaled interferon-alpha, and the majority in both arms (80% of the HCQ arm, 67% of the control arm) received umifenovir, and two participants in the control arm also received lopinavir and ritonavir. No difference in endpoints of PCR-negative Day 7 pharyngeal swabs, time to undetectable viral load, radiographic progression, and days to resolution of fever were observed. This small study was highly confounded by concomitant therapies and, thus the conclusions that can be made about the efficacy (or lack of efficacy) of HCQ are limited.

Future: Additional national and international trials of HCQ are underway or planned, largely in hospitalized patients, including a WHO trial (SOLIDARITY) comparing **five** treatment arms: chloroquine/HCQ, remdesivir, LPV/r, LPV/r plus interferon-beta, or standard of care; a European trial (DISCOVERY), with the same treatment arms as the WHO trial, but with HCQ only and not chloroquine or HCQ; a**n** RCT of LPV/r v**ersu**s HCQ in patients with mild disease (NCT04307693); a**n** RCT of HCQ v**ersu**s no HCQ in patients with mild or moderate disease, or asymptomatic (NCT04323631); HCQ v**ersu**s placebo for COVID-19-related ARDS (NCT04315896); an RCT of various combinations of HIV protease inhibitors, oseltamivir, favipiravir, and HCQ (NCT04303299); a non-randomized trial of LPV/r versus HCQ versus baricitinib (janus kinase inhibitor) v**ersu**s sarilumab (anti-IL-6 receptor antibody) (NCT04321993) for moderate to severe COVID-19 in hospitalized patients; a trial of remdesivir v**ersu**s HCQ v**ersu**s standard of care (NCT04321616); a randomized open-label trial of remdesivir, LPV/r, interferon beta, HCQ, or standard of care in hospitalized patients (NCT04315948); and multiple post-exposure prophylaxis trials of HCQ. Two unblinded studies of HCQ plus Azithro v**ersu**s HCQ for COVID-19 pneumonia and hospitalized patients are planned in Brazil (NCT04321278, NCT04322123). Both of these trials are planning doses of HCQ 400 mg po BID and Azithro 500 mg po daily, one given for 10 days and one for 7 days.

Summary: The combination of HCQ and Azithro deserves further evaluation in a rigorous clinical trial in the outpatient setting. If we evaluate HCQ alone and find that it is no better than Placebo, then we have not answered the question if HCQ and Azithro is effective for COVID-19. Given the biologic rationale of potentiating raising lysosome pH [14, 15], then we would be left without a clear answer. However, if the proposed study shows that HCQ and Azithro is not better than Placebo alone, then we can be relatively confident that neither had an effect.

Further, the use of HCQ and Azithro can be implemented at scale through one outpatient visit or remote non-face-to-face visit at study entry. This will minimize contact between study participants and study staff to reduce use of PPE and potential risk of SARS-CoV-2 transmission.

<u>Mitigation of Risk from HCQ and Azithro</u>
HCQ can prolong the QT interval, and ventricular arrhythmias and TdP have been reported, but usually after prolonged administration [33], particularly in patients with

lupus and other comorbidities such as end stage renal disease [34-37]. **In fact**, drug-induced TdP and other life-threatening ventricular arrhythmias from HCQ are very rare and typically only observed at high doses given for long periods of time [14, 33, 38]. HCQ is a derivative of chloroquine, and the same molecule in both drugs causes the QTc prolongation; therefore, the use of chloroquine in malaria studies helps guide our reasoning with HCQ. When chloroquine was administered to healthy adults (regimen 600 mg + 600 mg + 300 mg on Days 1, 2, and 3, respectively) the average increase in QTc interval was 28 ms (18-38 ms; 95% CI) with no cardiac AEs reported [39].

The combination of short-course chloroquine and Azithro has been observed to be well tolerated in malaria trials. In particular, Kimani et al studied malaria prevention during pregnancy where 1445 women received 3 days of chloroquine plus Azithro that was repeated at 4-8 week intervals during the second and third trimester of pregnancy. Although QT intervals were not assessed at baseline or throughout the study, there were no reported cardiac AEs [29], which would be the main danger signal for TdP in such a study. Further, Sagara et al. conducted two randomized, comparative, non-inferiority studies in Africa where patients with malaria received Azithro 1000 mg (n=227) or Azithro 500 mg (n=9) with chloroquine 600 mg base, all once daily for 3 days **and there were no treatment-related cardiac events** [49]. Given the extensive experience in malaria prophylaxis and treatment, it is clear that any QT prolongation by either drug is not likely to be clinically relevant. In fact, the WHO explicitly states “Despite hundreds of millions of doses administered in the treatment of malaria, there have been no reports of sudden unexplained death associated with quinine, chloroquine or amodiaquine, although each drug causes QT/QTc interval prolongation” [38].

Despite the low risk of clinically relevant QT prolongation, the proposed study design incorporates a number of measures to further reduce the risk. These include the exclusion of people who take other agents known to prolong QTc, have a personal or family history of Long QT syndrome, a history of ventricular arrhythmias, known structural or ischemic heart disease, or severe kidney or liver disease.

The use of mobile devices that can perform ECG and measure vital signs has been discussed extensively by the study team and team leads have discussed the capabilities of select devices with their manufacturers or researchers who have used them. Based on these discussions, we have chosen to not include such monitoring for safety purposes for several reasons. Foremost, real-time monitoring for the large number of participants who will be enrolled at any one time will likely be unmanageable, and our older participants may have a harder time with such devices. Therefore, such monitoring is unlikely to lead to an immediate intervention. In addition, given the short duration of treatment and the long half-life of HCQ and Azithro, discontinuation of these drugs following detection of QTc prolongation, even if feasible, may have limited impact.

To help mitigate the risk of HCQ and Azithro causing TdP, we have followed the guidance from Simpson et al. [74b], which states, “minimizing exposure/contact: It may be reasonable to forego ECG screening to allow patients to remain in quarantine if no high-risk features exist (history of long QT syndrome, concomitant QT prolonging medications, structural or ischemic heart disease,

history of prolonged QTc on any ECG, history of abnormal renal function and/or electrolytes)." Therefore, we will exclude potential participants with underlying conditions associated with TdP, including: history of ventricular arrhythmia or on antiarrhythmics, personal or family history of long QT syndrome, history of hypomagnesemia or hypokalemia, history of structural or ischemic cardiac disease, use of antiepileptic or loop diuretic drugs, or use of drugs that can also prolong the QT interval. We will also have the close monitoring by the DSMB that can assist in quickly identifying safety issues with HCQ.

Overall, HCQ and Azithro are FDA-approved drugs that have the potential to decrease disease progression in early COVID-19 illness. HCQ shown anti-SARS-CoV-2 activity in vitro and there is a clear mechanistic pathway for Azithro to enhance HCQ activity. The combination has preliminary, though limited, non-randomized in vivo studies, as described above, to suggest candidacy as treatment for COVID-19. Rigorous clinical trials must be conducted to ascertain effectiveness and safety. These agents may be more likely to have an effect early in the course of SARS-CoV-2 infection and an intervention that decreases or prevent hospitalization would have substantial clinical, public health and economic impact. The proposed study is a multicenter, randomized, placebo-controlled study. As designed, it will be able to acquire rigorous data about the safety and efficacy of HCQ and Azithro compared to placebo for COVID-19 that will lead to generalizable evidence.

Justification for Dose

Doses of HCQ and Azithro are based on the pharmacokinetics of each drug, historical population pharmacokinetics models' PK-QTc relationship, in vitro concentration-response relationship for HCQ, clinical PKPD model from persons treated for COVID-19 in the Gautret et al. study, the natural course of viral infection in humans and, finally, clinical trial simulations for efficacy and safety using all available pharmacological data [10, 71, 75-77]. **Further, this trial has been designed to approximate outpatient clinical practice. For outpatients with mild-to-moderate COVID-19 receiving HCQ and Azithro, an EKG would not be standard (nor would blood work). This, again, reflects a balance between the value of assessment and the risk of infection to healthcare workers (and study staff) in the setting of active and acute COVID-19. Thus, we have opted for a "no touch" research protocol for outpatient participants, and, in close discussions with the FDA and heeding their guidance, we have chosen doses of HCQ and Azithro that are commonly used in the outpatient setting with no laboratory or EKG monitoring.**

Justification for the Control Arm

In light of the heterogeneity of disease progression in those with COVID-19, it is extremely important that this study include a control group. To this end, this trial will have a double-blinded placebo control arm to best determine the efficacy and safety of HCQ and Azithro in the outpatient setting for persons with COVID-19.

Justification for Placebo Controlled Design

There is public interest in several putative therapeutic agents for COVID-19. However, the available data on efficacy and safety for each remains preliminary and limited. The

above-mentioned non-randomized trial of HCQ with and without Azithro signals a possible benefit of the combination but is far from conclusive, as highlighted by a recently performed secondary analysis of the study data. Further, as described, these medications are not without potential side effects. Given the absence of high-quality efficacy data and the potential risks, there is clear equipoise regarding the use of HCQ and Azithro for patients with COVID-19. A well-powered placebo-controlled trial will provide the best opportunity to recruit outpatients with COVID-19 and rigorously evaluate the safety and efficacy of these medications.

Justification for Age Restriction
Children and adolescents will not be included in this trial. 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 regarding SARS-CoV-2 infection 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.

Justification for Comorbidities
Individuals with comorbidities, such as diabetes and HIV, will be included, as they may have a higher risk of hospitalization and life-threatening COVID-19.

Justification for Pregnancy and Breastfeeding
The proposed doses of HCQ and Azithro have been used safely in pregnant women and women who are breastfeeding [29]; therefore, these persons will be eligible for the study.

3.0 STUDY DESIGN

This is a phase IIB, double-blind, placebo-controlled randomized trial, designed to compare the efficacy of HCQ and Azithro versus placebo to prevent hospitalization and death in symptomatic adult outpatients with COVID-19**, caused by SARS-CoV-2 infection.** The study is a multicenter trial that will be conducted in the United States.

A total of 2000 participants who start study treatment (approximately 1000 in each treatment arm) will be followed on study for 7 days on treatment and an additional 23 weeks off treatment. Participants who do not start study treatment will be replaced. Participants will be randomized 1:1 to receive either **400** mg **orally twice a day on Day 0** followed by 200 mg **orally twice a day for 6 days,** and Azithro/Placebo 500 mg on**ce on Day 0**, followed by 250 mg daily for four days (Figure 3-1).

Randomization will be stratified by “high” versus “low” risk of severe disease, where “high” risk is defined by any of the following:

- Persons aged 60 years and older
- Persons having at least one of the following conditions:
  - Chronic lung disease or moderate to severe asthma
  - Immunocompromised status due to disease (for example, those living with HIV with a CD4+ T-cell count of <200/mm^3)

- Immunocompromised status due to medication (for example, persons taking 20 mg or more of prednisone equivalents a day, anti-inflammatory monoclonal antibody therapies, or cancer therapies)
- Severe obesity (body mass index [BMI] >40; may be based on self-report of height and weight)
- Hypertension
- Cardiovascular disease
- Diabetes
- Chronic kidney disease
- Chronic liver disease

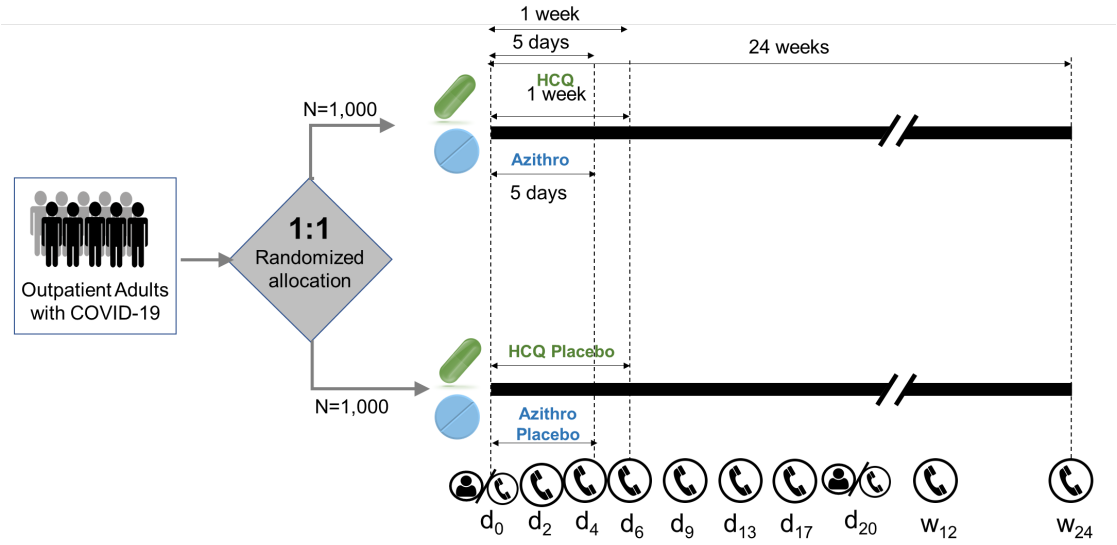

Figure 3-1: Study Design

Recruitment

Participants can be recruited by sites in several ways, which will be enhanced because many clinical research sites (CRSs) are participating in COVID-19 screening activities. Thus, sites may work with local SARS-CoV-2 testing sites through outreach staff and recruitment materials placed at this location. It is also expected that participants will be referred to the study immediately upon SARS-CoV-2 diagnosis from partnering testing sites or ordering providers who receive test results. Symptomatic persons receiving a positive SARS-CoV-2 result by molecular test can be informed about the study opportunity and be provided with study site contact information.

Study Visits

The study is designed to minimize in-person contact between participants and study staff or other persons at the CRS. The informed consent process, screening, and randomization may be performed remotely, in compliance with institutional and regulatory requirements.

At study entry, all participants will have either a remote visit or an in-person study visit at a secure location of the CRS, such as an isolation room, a room with a separate

entrance, or while in their car in a parking lot/parking garage. Participants will be given study treatment, a study symptom and adherence diary (i.e., Study Diary), and contact numbers for the study staff. Participants will provide medical and medication histories, and contact information for themselves, including their home address, **a list of local hospitals where they are likely to seek medical services if needed,** and for persons who will know about their study participation, in case study staff cannot reach the participant. Further, participants will be provided contact information for research staff in the event they require hospitalization. Participants will then complete **the Pre-Treatment page** of the Study Diary prior to starting study treatment.

The participant's first symptom(s) associated with COVID-19 and when it/they occurred will be recorded. Participants will also be observed taking their first dose of study treatment if it is an in-person visit.

Participants will record their symptoms, temperature (if participant is able to provide), medication adherence, and major events such as hospital visits and hospitalization in the Study Diary daily on Days 0-20**, in the evening** (section 6.3.10). Study staff will contact participants per the Schedule of Evaluations (SOE) to review study diaries. If participants cannot be reached after two attempts 24 hours apart, then their alternative contact person(s) will be called.

At Day 20, **for non-sampling subset participants,** an in-person **or remote** visit will occur for assessment of the primary outcome and collection of the Study Diary. At this time the participants are expected to no longer be infectious, if they remain un-hospitalized. For participants that cannot **be reached,** the study staff will contact the alternative contacts the **participant** provided to collect information on these outcome measures. **If the participant is symptomatic on Day 20 and an in-person study visit was planned, the in-person study visit may be delayed (refer to section 6.2.3) or converted to a remote visit. If a remote Day 20 visit is conducted, arrangements should be made for future transfer of Study Diary from the participant to the study staff (i.e., mailing the Study Diary or sending images) and provision of compensation for study participation.**

At weeks 12 and 24, remote visits will be performed to review longer term disease course. At these visits, study staff will record any hospitalizations or deaths that occurred since the Day 20 visit. Additional approaches (such as querying death registries) may be used as feasible at the sites.

Participants will be instructed to contact study staff immediately if they seek medical help at any time during the study.

Additional Evaluation Subset
Some sites will be selected to conduct more in-person visits, depending on availability of staff, PPE, and isolation rooms.

At pre-selected sites, **at study entry [Day 0] and Days 6 and 20**, a subset of participants who agree will undergo self-collected nasal swabs, staff-collected NP swab,

and blood collection on site under appropriate infection control conditions, as described below. Single sparse pharmacokinetics (PK) sampling will be collected at Days 6 and 20 (refer to section 11.0 for details).

Isolation Procedures
Given that SARS-CoV-2 is spread through respiratory droplets, each site must develop procedures to protect study staff and participants of other trials from infectious exposure. Each site will have a plan for maximal protection by providing PPE, setting up isolation rooms or outside areas, providing special access points or contact with study participants. Each site will develop their own set of procedures for such participant contact.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Participant (or legally authorized representative) provides informed consent prior to initiation of any study procedures.

4.1.2 Individual ≥18 years of age.

4.1.3 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 **from when the first dose of study treatment is expected to be taken.**

4.1.4 Experiencing at least one of the following SARS-CoV-2 infection symptoms **within 24 hours of screening:** fever (can be subjective) OR cough OR shortness of breath.

4.1.5 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.

4.1.6 Agrees to not obtain study medications outside of the A5395 study.

4.2 Exclusion Criteria

(Medical history can be by self-report. Refer to the A5395 MOPS.)

4.2.1 Need for hospitalization or immediate medical attention in the clinical opinion of the study investigator.

4.2.2 History of or current hospitalization for COVID-19.

NOTE: Individuals hospitalized and then discharged, even if only hospitalized for 1 day, are excluded.

4.2.3 History of ventricular arrhythmia or **using antiarrhythmics within the past 30 days**.

4.2.4 Personal or family history of Long QT syndrome.

4.2.5 History of kidney disease.

NOTE A: If the individual responds “yes” but can provide a creatinine clearance (**CrCl)** value **of** ≥45 mL/min by Cockcroft-Gault equation **from** within 1 year **of** study entry, the individual may participate.

NOTE B: Please refer to the A5395 PSWP for the website link to the Cockcroft-Gault calculator.

4.2.6 History of ischemic or structural heart disease.

4.2.7 History of hypokalemia or hypomagnesemia or taking potassium supplementation or magnesium supplementation.

4.2.8 Personal medical history of porphyria, retinopathy, severe hepatic impairment, or G6PD deficiency.

4.2.9 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.

4.2.10 Requirement or expected requirement for a medication that significantly prolongs QT **intervals or increases risk for QT prolongation** (medications summarized in section 5.4), from 96 hours prior to study entry through 4 weeks after discontinuation of study treatment **except for escitalopram, citalopram, maprotiline, SC/IM risperidone, carbamazepine, ethosuximine, and zonisamide, which should not be used within 7 days prior to study entry.**

4.2.11 Loop diuretics are exceptions to exclusion criterion 4.2.10 but these cannot be used within 30 days prior to study entry.

4.2.12 Participating in a study where co-enrollment is not allowed.

4.2.13 Receipt of a SARS-CoV-2 vaccination prior to study entry.

4.2.14 Known allergy/sensitivity or any hypersensitivity to components of HCQ, azithromycin, or their formulation.

4.2.15 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements

4.3 Study Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by the institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE) responsible for oversight of the study. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific ICF(s) WILL NOT be reviewed or approved by the DAIDS PRO. Sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The participant will be asked to read and sign the approved protocol consent form.

Participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify. An ACTG Screening Checklist must be entered through the DMC Participant Enrollment System.

4.3.1 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.3.2 Randomization/Participant Registration

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database. Participants who meet the enrollment criteria will be registered to the study according to standard ACTG DMC procedures.

4.4 Co-enrollment Guidelines

For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the protocol team via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

5.1 Regimens, Administration, and Duration

Participants will be randomized to receive one of the following two regimens:

ARM A:
HCQ 400 mg (administered as **two** 200 mg capsules) orally **twice daily for 2 doses starting** on Day 0, **followed by** 200 mg (administered as one 200 mg capsule) **orally twice** daily for **12 doses (6 days), *PLUS:***

Azithro 500 mg (administered as two 250 mg capsules) orally as a single dose on Day 0, followed by 250 mg (administered as one 250 mg capsule) orally once daily for 4 doses (4 days).

ARM B:
Placebo for **HCQ** (administered as **two** matching placebo capsules) **orally twice daily for 2 doses starting** on Day 0, **followed by Placebo for HCQ** (administered as one 200 mg capsule) **orally twice daily for 12 doses (6 days), *PLUS:***

Placebo for Azithro (administered as two matching placebo capsules) orally as a single dose on Day 0, followed by Placebo for Azithro (administered as one matching placebo capsule) orally once daily for 4 doses (4 days).

HCQ or Placebo for **HCQ** should be taken with food or a glass of milk. **Doses of HCQ or Placebo for HCQ should be separated by at least 6 hours.** Azithro or Placebo for Azithro capsules can be taken with or without food. **HCQ** or Placebo for **HCQ** and Azithro or Placebo for Azithro may be taken at the same time.

5.2 Study Product Formulation and Preparation

5.2.1 HCQ 200 mg: Supplied as over-encapsulated 200 mg tablets. Store at controlled room temperature 20-25°C.

5.2.2 Azithro 250 mg: Supplied as over-encapsulated 250 mg tablets. Store at controlled room temperature 20-25°C.

5.2.3 Placebo for HCQ: Supplied as matching placebo capsules to visually match the over-encapsulated HCQ. Store at controlled room temperature 20-25°C.

5.2.4 Placebo for Azithro: Supplied as matching placebo capsules to visually match the over-encapsulated Azithro. Store at controlled room temperature 20-25°C.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

HCQ tablets are manufactured by Watson Pharma, distributed by Actavis Pharma, and supplied by Teva Pharmaceuticals.

Azithro tablets are manufactured by Pliva Hrvatska and supplied by Teva Pharmaceuticals.

Over-encapsulated HCQ, over-encapsulated Azithro, Placebo for HCQ and Placebo for Azithro capsules are manufactured by Eminent Services Corporation and supplied by NIAID/DAIT Clinical Product Center (CPC) as matching active and placebo capsules.

All study products are available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study product(s) for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. All unused study products in US CRSs must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

Refer to the A5395 MOPS for additional protocol-specific instructions regarding study product management considerations.

5.4 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the ACTG Precautionary and Prohibited Medications Database located at http://tprc.pharm.buffalo.edu/home/di_search/.

5.4.1 Prohibited Medications

- Non-study HCQ and Azithro
- Cardiac medications
  - Antiarrhythmic drugs: Class Ia (quinidine, procainamide, disopyramide); Class III (dofetilide, ibutilide, sotalol)
  - **Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid)**
- Non-cardiac medications
  - Diphenhydramine
  - **Antiepileptic medications (carbamazepine, eslicarazepine, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcabazepine, phenobarbital, phenytoin, piracetam, pregabalin, Rufinamide, stiripentol, tiagabine, topiramate, sodium valproate, valproic acid, zonisamide)**
  - Antipsychotic and antidepressant agents: Neuroleptic (haloperidol, droperidol, thioridazine, chlorpromazine); Atypical antipsychotics (ziprasidone, risperidone, zimeldine, citalopram); Antidepressants (amitriptyline, desipramine, imipramine, maprotiline, doxepin, fluoxetine, escitalopram, citalopram)
  - Antibiotics: quinolone (levofloxacin, moxifloxacin); Macrolide (erythromycin, clarithromycin)
  - Antimalarials (quinine, halofantrine**, chloroquine**)
  - Antiprotozoal (pentamidine)
  - Antifungal (azole group)
  - Antimotility Agents
  - Methadone

5.4.2 Precautionary Medications

A list of precautionary medications can be generated using the ACTG Precautionary and Prohibited Medications Database located at http://tprc.pharm.buffalo.edu/home/di_search/

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations (SOE)

EVALUATION	Screening	Entry/ Day 0	Post-Entry Evaluations									Premature Study Discontinuation[1]
			Day 2	**Day 4**	Day 6	Day 9	Day 13	Day 17	Day 20	Week 12	Week 24	
Visit Windows (days)			+/-1				+/-2		0/+7	0/+30		0/+7
Informed Consent	X											
Documentation **of** SARS-CoV-2 **Result**	X											
COVID-19 Symptom Screen	X											
Medical History	X	X										
Medication History	X	X										
Clinical Assessments		X	X	**X**	X	X	X	X	X	X	X	X
Collect Secondary Contacts Information		X										
Study Kit Dispensed		X										
Dispensing of Study Drug, Confirmation of First Dose, and Counseling		X										
Distribution of Study Diary		X										
Review of Study Diary		X	X	**X**	X	X	X	X	X			X
Review of Treatment Adherence			X	**X**	X	X						X
Collection of Study Diary									X			X
Remote Contact		**X²**	X	**X**	X	X	X	X	X²	X	X	
Study Endpoint Determination			X	**X**	X	X	X	X	X	X	X	X
Vital Status Follow-up			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
Household Linkage									X^			
In-person visits at pre-selected sites (optional for participants); additional to the above evaluations												

EVALUATION	Screening	Entry/ Day 0	Post-Entry Evaluations									Premature Study Discontinuation[1]
			Day 2	**Day 4**	Day 6	Day 9	Day 13	Day 17	Day 20	Week 12	Week 24	
Visit Windows (days)			+/-1				+/-2		0/+7	0/+30		0/+7
Self-collected Nasal Swab		X			X				X			X
Nasopharyngeal (NP) Swab		X			X				X			X
Hematology		X			X				X			X
Chemistry		X			X				X			X
Inflammatory Markers		X			X				X			X
Stored Plasma		X			X				X			X
Stored Sera		X			X				X			X
Pharmacokinetics (Sparse)					X				X			X

[1]See Section 6.2.4 for specific instructions on evaluations to be performed at the Premature Study Discontinuation visit. Some or all of the evaluations will be performed, depending on the timing of study discontinuation.

[2]Entry/Day 0 and 20 visits may be in-person or remote for non-sampling subset participants

^Household linkage should be assessed after all participants at the site have been enrolled and by the last enrolled participant's Day 20 visit.

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant starting any study medications, treatments, or interventions.

Screening
Screening evaluations to determine eligibility must be completed prior to study entry unless otherwise specified and may be completed remotely or in-person. Screening and entry visit may occur on the same day.

At sites that are performing additional NP swab, self-collected nasal swabs, and blood collection, those participants that agree to the additional sample collection will indicate consent at the screening visit.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

6.2.2 Entry Evaluations

Screening and entry visits may be combined. The study entry visit **can be** either a remote or in-person visit. **Participants must begin study treatment within 96 hours of the collection time of the respiratory specimen that was positive for SARS-CoV-2 and qualified them for the study**. The first dose of study treatment must be directly observed at the in-person visit or confirmed remotely (by video or telephone) **for those with remote study entry visit**. **The day of the first dose is considered Day 0.**

Depending on how the screening and study entry/Day 0 visits are conducted, randomization must occur after screening but may occur prior to the study entry/Day 0 visit, or at the study entry/Day 0 visit.

Those participants that agree to the additional sample collection must have the NP swab, self-collected nasal swab, and blood collected prior to receiving the first treatment dose.

6.2.3 Post-Entry Evaluations

On-Treatment Evaluations
Participants will undergo remote evaluations as outlined in the SOE, section 6.1.

Those participants undergoing additional NP swab, self-collected nasal swab, and blood collection **will be required** to have in-person visits at Day**s** 6 **and 20**.

Post-Treatment Evaluations
Participants will undergo remote evaluations as outlined in the SOE, Section 6.1. **Participants** not participating in the sampling subset will undergo **an** in-person **or remote** study visit on Day 20, as outlined in the SOE, Section 6.1. **Subset participants will have an in-person study visit at Day 20.** The Day 20 visit may occur anytime during the window outlined in the SOE, Section 6.1. For non-subset participants, Day 20 in-person visits should be performed only if the participant has been afebrile for at least 72 hours and other symptoms have improved. If these criteria are not met, the visit should be conducted remotely. **If a remote Day 20 visit is conducted,** arrangements should be made for future transfer of diary **from the participant to the study staff** and provision of compensation for study participation.

Study Completion Evaluations
Participants will undergo a remote evaluation at Week 24.

6.2.4 Discontinuation Evaluations

Evaluations for Participants Who Do Not Start Study Treatment
Participants who are randomized but do not take the first (confirmed) dose of study treatment do not need to be followed. A study discontinuation eCRF must be completed and any evaluations completed for these participants should also be recorded on the Day 0 eCRFs.

Premature Treatment Discontinuation Evaluations
Participants who discontinue study treatment early should remain on study and all evaluations should be performed as outlined in the SOE.

For participants consenting to the optional intensive sampling study, if the Day 0 CrCl result is <45 mL/min, as calculated by the Cockcroft-Gault equation (see Cockcroft-Gault calculator on the A5395 PSWP), the participant will be prematurely discontinued from study treatment.

Premature Study Discontinuation Evaluations
Participants who discontinue study participation should undergo premature study discontinuation evaluations, as outlined in the SOE within 7 days of study discontinuation. If study discontinuation occurs on or prior to Day 7, all procedures should be performed as described in the SOE for premature study discontinuation evaluations. If study discontinuation occurs on or between Day 8 and Day 20, all evaluations EXCEPT treatment adherence should be performed. If study discontinuation occurs after Day 20, all evaluations EXCEPT treatment adherence, site-collected NP swab, self-collected nasal swab, and blood collection should be performed.

For participants who prematurely discontinue from the study for reasons other than withdrawal of consent, sites will attempt to obtain information regarding vital status and endpoints per the SOE (see section 6.3.13).

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document: https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the DAIDS AE Grading Table and requirements for reporting of AEs.

6.3.1 Informed Consent

Participants will review and provide informed consent to participate in the study either over the telephone, by video, or in person. For more information about the consent process, please refer to the A5395 MOPS.

6.3.2 Documentation of SARS-CoV-2 Result

Documentation of **infection with SARS CoV-2 by a molecular test with a positive result from any respiratory specimen collected within 96 hours prior to first study product dose.**

Section 4.1.3 specifies assay requirements for SARS CoV-2 infection documentation. **See MOPS for documentation requirements.** Active SARS CoV-2 infection documentation is recorded on the eCRF.

6.3.3 COVID-19 Symptom Screen

Participants will be asked about their first symptoms related to COVID-19 and their current symptoms, to document eligibility. This will include when and what symptoms the participant noticed having. A screening questionnaire is posted on the DMC Portal in the Forms Management Utility.

6.3.4 Medical History

The medical history must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within the past 14 days. In addition, the following diagnoses should be recorded regardless of when the diagnosis was made **(verbal history is acceptable):**

- Hypertension
- Chronic obstructive pulmonary disease
- “Severe Obesity” (BMI > 40)
- Epilepsy requiring medications

- **Kidney disease**
- **Liver disease**
- Immunosuppressive conditions
- Reactive airway disease, Asthma
- Autoimmune disease
- Inflammatory bowel disease
- AIDS-defining conditions
- HIV infection
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Heart failure
- Myocarditis
- Arrhythmias
- Valvular heart disease
- Stroke
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B
- Pregnancy history
- If known by participant if they have been diagnosed with an acute viral respiratory infection (influenza, parainfluenza, respiratory syncytial virus, rhinovirus) within the previous 14 days.

A Smoking Status questionnaire will be completed at the **entry** visit as part of medical history and recorded on the eCRF. The questionnaire is posted on the DMC Portal in the Forms Management Utility.

Any allergies to any medications and their formulations must also be documented.

6.3.5 Medication History

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history at screening **and updated at entry.**

Table 6.3.5-1: Medication History

Medication Category	Complete History or Timeframe
All prescription drugs	Last 7 days
Prescription drugs for high blood pressure	Last 3 months
Prescription drugs for diabetes and pre-diabetes	Last 3 months

Medication Category	Complete History or Timeframe
Prescription drugs for lung disease	Last 3 months
Prescription drugs for heart disease	Last 3 months
Prescription drugs for autoimmune disease	Last 3 months
Cancer chemotherapy	Complete history
Antiretroviral therapy	Last 3 months
Immune-based therapy	Last 3 months
Blinded study treatment	Last 12 months
CoV-related vaccines	Complete history
Alternative therapies	Last 3 months
Dietary supplements	Last 3 months

6.3.6 Clinical Assessments

No physical exams will be conducted.

Site clinical investigators will perform a clinical assessment at enrollment **for all participants**. In their clinical judgment, they may identify some participants who are ill enough to warrant further clinical evaluation, which may result in hospitalization. They will then refer these participants for such evaluation. These participants will not start study treatment, and not be included in the analyses. While clinical judgement may not be standard across sites, the process should balance site variation.

Post entry, see section 8.4 for collection requirements for pregnancy.

Refer to section 7.2 for AE collection requirements.

Concomitant Medications

Post-entry, the following new and discontinued concomitant medications must be recorded:

- High blood pressure medications
- Steroids or other immunosuppressive or immunomodulatory medication
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Chemotherapy
- Antibiotics, antifungals and antivirals (including antiretrovirals)
- HCQ or chloroquine or any agent felt to have potential COVID-19 activity
- Inhalers
- Agents with QTc prolongation potential and antiarrhythmics listed in section 5.4.1.

Study Treatment (Intervention) Modifications

Record any modification to treatment, treatment interruption, and permanent discontinuation of treatment, and the reason for the modification, interruption, or discontinuation.

6.3.7 Secondary Contact

Sites will capture secondary contact information for two individuals that the site can contact if the participant cannot be reached (e.g., spouse, friend, neighbor, etc.). Sites will also request their health care provider contact information and a few hospitals that the participant is likely to go to if they get sick. Contact information for secondary contacts or health care provider will not be recorded on any eCRF. If participants cannot be reached after two attempts 24 hours apart, then their listed secondary contact person(s) or health care provider will be called. At study entry only, sites will record the participant's home address in site records (it will not be reported on the eCRF).

6.3.8 Study Kit Dispensed

The kit will include:

- Copy of informed consent
- Information about the study
- Instructions on study procedures
- Study Diary
- Study medications
- Pocket/wallet card with site staff contact information
- Instructions on what to do if they have worsening symptoms/become hospitalized
- **Self-addressed stamped envelope for participant to return Study Diary at end of study in case Day 20 is remote**

6.3.9 Dispensing of Study **Product**, Confirmation of First Dose, and Counseling

Study **product** will be dispensed at study entry. Study staff will confirm **(via video or verbal report)** the first dose **is taken** by the participant **with food or a glass of milk** and record this confirmation on an eCRF. **The participant and the study staff will record the date and time of the first dose in the Study Diary and in site records. Day 0 is the day the participant self-administers the first dose of study product.** Participants who do not start study treatment will be discontinued from the study.

Intensive counseling must be performed at the time the first dose of study treatment is observed or confirmed remotely. This counseling should include review of the timing of the first dose and the timing for the two subsequent doses.

6.3.10 Study Diary

Distribution of Study Diary
Participants will be provided a Study Diary at study entry. The Study Diary is posted on the DMC Portal in the Forms Management Utility.

Participants will be asked to keep a log of symptoms, temperature (if possible), medications they are taking, and major events such as urgent visit to an emergency room or clinic and hospitalization in their Study Diary on Days 0-20. At study entry, participants will complete the Study Diary prior to study treatment initiation. Depending on timing of each participant's dosing, some may complete HCQ/Placebo study treatment on Day 7 instead of Day 6 and need to report a Day 7 dose. Participants will be asked to complete the diary each evening.

Review of Study Diary
The Study Diary will be reviewed by study staff with each participant at the remote and in-person visits described in the SOE and the participant's answers recorded in the Participant Study Diary eCRF. If feasible, prior to or during the remote study visits, sites will request that the participant send images of each of their study diary entries to be reviewed at the next study contact.

Participants who report worsening illness from any cause during the trial may be referred to their health care provider or closest emergency room. Such instances will be recorded at the time of the notification, and during follow-up to assess study endpoints, i.e., hospitalization or death.

Review of Treatment Adherence
The treatment adherence portion of the Study Diary will be reviewed by study staff with each participant at the remote and in-person visits (if applicable), as described in the SOE. The participant's answers of timing of doses taken will be recorded in the Adherence Assessment eCRF. If any doses are missed, the reason for the missed dose will be recorded.

Collection of Study Diary
The Study Diary will be collected per the SOE. **If Day 20 is conducted remotely, arrangements should be made for future transfer of study diary from the participant to the study staff (i.e., mailing the study diary or sending images).**

6.3.11 Remote Contact

Sites will contact participants per the SOE. Participants in the pre-selected site subset will have an in-person visit, instead of a remote visit on Days 0, 6, **and 20**, but will be contacted by telephone for that visit if they fail to attend the in-person visit. Refer to the A5395 MOPS for the remote contact script. Remote contact **attempts** will be recorded on the eCRF.

6.3.12 Study Endpoint Determination

Study endpoints will be collected per the SOE and outlined in section 10.2. These will be recorded on the eCRF. Information about AEs, hospitalizations or death should be keyed on the eCRF within 72 hours of a site becoming aware of an AE, hospitalization or death.

6.3.13 Vital Status Follow-up

Site personnel should attempt to obtain information regarding vital status (including date last seen alive, hospitalization, date of death, and primary cause of death) **from the participant or other sources (such as family members, other designated contacts, hospital the participant stated they would most likely go to, clinic/hospital/medical records, and local or national databases),** per the SOE. Please see MOPS for additional information. Information about hospitalizations and deaths should be keyed on the eCRF within 72 hours of a site becoming aware of a hospitalization or death.

6.3.14 Household Linkage

At each site, at completion of the Day 20 visit for the last participant enrolled in the study at the site, the site will review all home addresses of A5395 participants to identify participants who live at the same address. The Household Linkage eCRF will be completed, and “linked” participant IDs recorded.

6.3.15 Virologic Studies

Self-Collected Dry Swabs
At pre-selected sites, a subset of participants may opt to self-collect Dry Swabs (nasal swabs) per the SOE. Participants will be instructed by study staff and will obtain the swab while observed by study personnel. Additional information can be found in the MOPS and the LPC. At study entry (Day 0), the sample should be collected prior to the first dose of study treatment.

Nasopharyngeal (NP) Swab
At pre-selected sites, a subset of participants may opt to have an NP swab per the SOE. Additional information can be found in the MOPS and the LPC. At study entry (Day 0), the sample should be collected prior to the first dose of study treatment.

Samples collected for viral assessment may be evaluated for the emergence of antiviral resistance at a future date.

6.3.15 Laboratory Evaluations

Laboratory evaluations will be performed on some participants at pre-selected sites. At study entry (Day 0), blood samples should be collected prior to the first dose of study treatment.

Hematology
Per the SOE, participants will have the option to have a blood draw for complete blood cell count (CBC) with automated differential and platelet count. These tests will be performed in real-time at the local clinic laboratory.

Chemistry
Per the SOE, participants will have the option to have a blood draw for liver function tests (ALT, ALP, AST, Total Bilirubin, Direct Bilirubin, and Total Protein) and renal function tests (BUN, Creatinine, Potassium, Glucose, and Sodium). A **CrCl** will be calculated and recorded by Cockcroft-Gault equation (**see Cockcroft-Gault calculator on the A5395 PSWP**). These tests will be performed in real-time at the local clinic laboratory.

Inflammatory Markers
Per the SOE, participants will have the option to have a blood draw for lactate dehydrogenase, C-reactive protein, ferritin and D-dimer. These tests will be performed in real-time at the local clinic laboratory.

Stored Plasma
Per the SOE, blood plasma will be collected and stored for future testing for immune responses and drug levels.

Stored Sera
Per the SOE, blood sera will be collected and stored for future testing for immune responses and to compare antibody levels between treatment and control samples.

6.3.16 Pharmacokinetics

Per the SOE, single sparse PK sampling will be collected. This will be done on a subset of participants who opt to have their blood drawn. Days 6 and 20 blood collection may be used to measure drug levels to assess drug adherence or surreptitious use of HCQ or Azithro.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Collection Requirements for This Protocol

Post-entry, all AEs must be recorded on the eCRFs within 72 hours if any of the following criteria have been met:

- All Grade ≥3 AEs
- All cardiac AEs regardless of grade
- All AEs that led to a change in study treatment/intervention regardless of grade
- All AEs meeting SAE definition or EAE reporting requirement

NOTE: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System (DAERS), an Internet-based reporting system.

All AEs that are reported must have their severity graded. To grade AEs, sites must refer to the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Serious Adverse Events (SAEs)
An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening illness
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

Ventricular arrhythmias, cardiac events requiring intervention or hospitalization, and deaths should be reported as soon as possible but no later than 24 hours to the A5395 Clinical Management Committee (CMC; e-mail: actg.cmcA5395@fstrf.org). If known, sites should indicate if the death was a sudden cardiac death. Sudden cardiac death is defined in this study as unexpected death from a cardiac cause within 1 hour of onset of symptoms OR found dead without clear explanation.

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

The DAIDS Adverse Experience Reporting System (DAERS), an Internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

7.3.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting are required are:
    - HCQ or Placebo for HCQ
    - Azithro or Placebo for Azithro
- In addition to SAEs, other AEs that must be reported in an expedited manner are: all ventricular arrhythmias, and cardiac events requiring hospitalization or intervention

7.3.3 Grading Severity of Events

The DAIDS AE Grading Table, corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is Day 0 (post first dose of study treatment, not including entry pre-treatment assessments) to Day 20.
- After the protocol-defined EAE reporting period (i.e., after Day 20, such as at remote visits at Weeks 12 and 24), unless otherwise noted, only suspected, *unexpected* serious adverse reactions (SUSARs), as defined in Version 2.0 of the DAIDS EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).
- Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases to severity level 3 or 4 after starting study treatment, it should be recorded as an AE.

7.4 Study Monitoring

7.4.1 Adverse Events

The DAIDS Clinical Representative will review and assess select EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs as applicable. The A5395 protocol chair, vice chairs, and DAIDS Clinical Representative will review all deaths on a weekly basis in a blinded fashion.

7.4.2 Interim Review

The protocol team will monitor the conduct of the study via regular summaries of screening, accrual, study and study treatment discontinuation, and data and specimen completeness. An independent Data and Safety Monitoring Board (DSMB) will monitor safety regularly (see section 10.5 for details.)

Detailed plans for study monitoring are outlined in a Study Progress, Data, and Safety Monitoring Plan (SPDSMP) developed by the Statistical and Data Management Center (SDMC) prior to enrollment of the first participant.

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

Criteria for participant management, dose adjustments and discontinuation, or changes in treatment will be described only for toxicities attributable to the study drugs (HCQ and Azithro). The grading system for drug toxicities is located in the DAIDS AE Grading Table (see section 7.2).

NOTE: The team must be notified via e-mail within 72 hours regarding toxicities that result in a change in study regimen (actg.cmca5395@fstrf.org).

It is possible that some participants will experience transient or prolonged AEs during the study. However, it is important to note that, in this trial, the majority of visits will be conducted remotely and hence, AEs will be assessed remotely and unplanned study visits scheduled if deemed necessary by the site investigator. For any concerning AEs that are felt to require clinical intervention, participants should be instructed to contact their health care provider or seek urgent or emergent care, or 911 should be called, as appropriate.

Treatment may be discontinued without contacting the CMC in advance, but the study team should be notified via email within 72 hours of treatment discontinuation, as described above.

8.2 Management of Side Effects of HCQ [78]

Gastrointestinal effects
Gastrointestinal (GI) symptoms including nausea, vomiting, and diarrhea are common with HCQ. HCQ should be administered with food or milk. In the event of GI symptoms, the study staff should review with the participant if HCQ is being taken with food, as administration of HCQ with food may reduce GI effects. GI side effects do not require treatment discontinuation and participants may be referred to their health care provider for symptomatic treatment (e.g., antiemetics). However, in the event of any treatment-related toxicity (GI or other), the site investigator has the option to discontinue study treatment if the side effect is intolerable or at their discretion.

Rash
A range of dermatologic reactions may be observed with HCQ. For pruritus, emollients may be used. For other more significant reactions, such as potential allergic skin reactions, HCQ should be discontinued immediately, and the participant referred to their health care provider or for urgent evaluation and management as appropriate, as determined by the site investigator. Over-the-counter topical agents may be recommended by the site clinical investigator, if the investigator feels able to make such a recommendation.

Hypoglycemia
Severe hypoglycemia (i.e., hypoglycemia that requires intervention) may occur with HCQ. HCQ should be discontinued immediately in participants who develop severe hypoglycemia.

Cardiovascular effects
Cardiomyopathy, QT prolongation, and ventricular arrhythmias have been reported with HCQ use. HCQ should be discontinued immediately in participants who experience a cardiovascular event, and additional evaluation and management pursued as appropriate for the clinical condition, as determined by the site investigator.

In the event of any treatment-related toxicity, the site investigator has the option to discontinue study treatment if treatment is intolerable or at the investigator's discretion. Treatment may be discontinued without contacting the A5395 clinical management committee (CMC) in advance, but the study team should be notified via email within 72 hours of treatment discontinuation, as described above.

Dose modification of HCQ will not be allowed in the study. If HCQ/Placebo is discontinued for toxicity reasons, all study medications should be discontinued and not be restarted.

NOTE: Grades 1 and 2 AEs associated with HCQ require no change in study treatment.

8.3 Management of Side Effects of Azithro [79]

Hypersensitivity reactions
Allergic reactions such as angioedema, anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS have been reported rarely with azithromycin

administration. Azithromycin should be discontinued immediately in the event of a hypersensitivity reaction.

Cardiovascular events and altered cardiac conduction
Macrolides have been associated with rare QT prolongation and ventricular arrhythmias but not Azithro in clinical studies (see Rationale above). Some studies, but not all, have described an association between azithromycin and cardiovascular events and mortality [41]. Therefore, to be conservative, Azithro should be discontinued immediately in the event of a cardiovascular event and additional evaluation and management pursued as appropriate for the clinical condition, as determined by the site investigator.

GI symptoms including diarrhea, nausea, and vomiting occur frequently (>10%) in azithromycin recipients. Azithro may be administered with food to reduce GI side effects. GI side effects do not require treatment discontinuation and participants may be referred to their health care provider for symptomatic treatment (e.g., antiemetics). However, in the event of any treatment-related toxicity (GI or other), the site investigator has the option to discontinue study treatment if the side effect is intolerable or at their discretion.

Dose modification of Azithro will not be allowed in the study. If Azithro/Placebo is discontinued for toxicity reasons, all study medications should be discontinued and not be restarted.

NOTE: Grades 1 and 2 AEs associated with Azithro require no change in study treatment.

8.4 Pregnancy

The study products may be given in pregnancy. To maximize study staff safety, the proposed study will be primarily remote visit based, thus we will not get weights, ultrasounds, vitals, physical exams, etc. during study treatment. However, pregnancy information and outcomes will be captured on an eCRF, including: gestational age during study treatment, and pregnancy outcomes.

8.5 Breastfeeding

The study products may be given to women who are breastfeeding.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Drug-related toxicity (see section 8.0 Clinical Management Issues).
- Participant experiencing an SAE that is considered at least possibly related to study drug.
- Requirement for prohibited concomitant medications (see section 5.4).
- Request by participant to terminate treatment.

NOTE: The reason for treatment discontinuation should be documented (e.g., concern for AE, lack of efficacy, or other reason).

- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.
- **Day 0 CrCl <45 mL/min, for participants in optional intensive sampling study (see section 6.2.4).**

9.2 Premature Study Discontinuation

- Failure to take the first (directly observed/confirmed) dose of study treatment at the study entry visit.
- Request by the participant to withdraw consent.
- Request of the health care provider if she or he thinks the study is no longer in the best interest of the participant.
- At the discretion of the IRB/EC, FDA, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

In the event that a participant prematurely discontinues from the study, unless they have withdrawn consent, sites will attempt to obtain information regarding vital status (including date last seen alive, hospitalization, date of death, and primary cause of death) from other sources (such as family members, other designated contacts, or clinic records) per section 6.2.4.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

This is a double-blind placebo-controlled randomized trial, designed to compare the efficacy of HCQ and Azithro for the treatment of COVID-19 in adults compared to adults receiving placebo to decrease hospitalization and death during SARS-CoV-2 infection.

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the study's primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript and results reporting to ClinicalTrials.gov.

10.2.1 Primary Outcome Measure

Death from any cause or hospitalization during the 21-day period from and including the day of the first (confirmed) dose of study treatment. Hospitalization is defined as requiring at least 24 hours of acute care in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted

to address needs during the COVID-19 pandemic. Evaluation at a hospital or similar facility with less than 24 hours of acute care is not considered a hospitalization.

10.2.2 Secondary Outcome Measures

10.2.2.1 Death from any cause during the 21-day period from and including the day of the first (confirmed) dose of study treatment.

10.2.2.2 Death from any cause or hospitalization or urgent visit to an emergency room or clinic during the 21-day period from and including the day of the first (confirmed) dose of study treatment.

10.2.2.3 Death from any cause or hospitalization during the 24-week period from and including the day of the first (confirmed) dose of study treatment. Hospitalization is defined as requiring at least 24 hours of acute care in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address needs during the COVID-19 pandemic. Evaluation at a hospital or similar facility with less than 24 hours of acute care is not considered a hospitalization.

10.2.2.4 Premature discontinuation of study treatment due to an adverse event.

10.2.2.5 Occurrence of any cardiac adverse events from start of study treatment through Day 20.

10.2.2.6. Duration of fever defined as the last day in the participant's daily diary card on which a temperature greater than 100.4°F was recorded or a potentially antipyretic drug, such as acetaminophen or ibuprofen, was taken.

10.2.2.7 Duration of symptoms associated with COVID-19 disease defined as the last day in the participant's daily diary card on which a moderate or worse symptom was recorded. The set of targeted symptoms are the same ones that are used in many influenza studies, with the addition of the symptoms of loss of smell and loss of taste, which have been associated with COVID-19 infection. The symptoms from influenza studies are: cough, shortness of breath, feeling feverish, fatigue, muscle aches, diarrhea, vomiting, nausea, headache, sore throat, nasal obstruction (stuffy nose), and nasal discharge (runny nose). These symptoms are listed individually on the Study Diary that each participant will complete each day. The scoring is that used in influenza studies, whereby participants grade each symptom as absent (score 0), mild (1), moderate (2), or severe (3).

10.2.2.8 **Participant-specific area under the curve (AUC) of the s**ymptom

score associated with COVID-19 disease **over time (through Day 20)** defined as the sum of scores for the targeted symptoms (defined above) in the participant's daily diary record (each individual symptom is scored from 0 to 3).

10.2.2.9 Time to self-reported return to usual (pre-COVID) health.

10.2.2.10 Level (detectable versus not detectable, and continuous) of SARS-CoV-2 RNA from self-collected nasal and site-collected NP swabs at entry and Days 6 and 20 among subset.

10.2.3 Other Outcomes

10.2.3.1 Worst clinical status assessed using ordinal scale among participants who become hospitalized. Ordinal scale defined as:

- Death
- Hospitalized, on invasive mechanical ventilation or ECMO;
- Hospitalized, on non-invasive ventilation or high flow oxygen devices;
- Hospitalized, requiring supplemental oxygen;
- Hospitalized, not requiring supplemental oxygen (COVID-19 related or otherwise)

10.2.3.2 Duration of hospital stay among participants who become hospitalized.

10.2.3.3 ICU admission (yes vs no) among participants who become hospitalized.

10.2.3.4 Duration of ICU admission among participants who get admitted to the ICU.

10.3 Randomization and Stratification

Eligible participants will be randomized using a 1:1 ratio to each of the study arms using permuted blocks with dynamic institutional balancing to minimize imbalances at any clinical site.

Randomization will be stratified by "high" vs "low" risk of severe disease, where "high" risk is defined by any of the following: age ≥60 years, or having any of the following conditions: hypertension, cardiovascular disease, diabetes, chronic kidney disease, chronic liver disease, chronic lung disease or moderate to severe asthma, severe obesity (BMI >40 based on self-report of height and weight), or immunocompromised due to disease or medication.

The study aims to enroll at least 50% of participants in the high-risk stratum. Initially, there will be no restriction on sites to enroll participants in the low-risk stratum. However,

after at least 200 participants have been enrolled, if fewer than 40% of enrolled participants are in the high-risk stratum, then sites may be asked to restrict enrollment to the low-risk stratum, such that, for every five participants they enroll in the low-risk stratum, at least five participants are enrolled to the high-risk stratum.

10.4 Sample Size and Accrual

The proposed sample size is 2000 participants who take the first (confirmed) dose of study treatment (approximately 1000 per arm). Participants who are randomized but do not take the first (confirmed) dose of study treatment will not be followed and will be replaced.

The study accrual rate will depend on the status of the epidemics at each site, but based on a survey of possible sites is believed to be 100 to 400 participants per week.

- With 100 participants per week the study should fully accrue in 20 weeks
- With 200 participants per week the study should fully accrue in 10 weeks
- With 400 participants per week the study should fully accrue in 5 weeks

The study is designed to evaluate the efficacy of HCQ and Azithro to prevent hospitalizations and death in outpatient adults diagnosed with COVID-19 compared to those receiving placebo. The primary analysis will include testing the null hypothesis of equality of proportions hospitalized/dying in the two randomized arms, and construction of 95% confidence intervals (CIs) for the ratio of proportions between the study arms. The primary analysis will focus on comparing the ratio of proportions because of the uncertainty in knowing what the hospitalization/death rate will be.

With 2000 participants, the study has 90% power to detect a relative reduction of 33.3% in the proportion of participants hospitalized/dying between the study arms (HCQ and Azithro vs. placebo), using the following assumptions:

- Proportion hospitalized/dying in the placebo arm is 15%
- Two-sided test of two proportions with 5% Type I error rate
- Three interim analyses and one final analysis, equally spaced, with stopping guideline determined using the Lan-DeMets spending function approach with an O'Brien and Fleming boundary.
- Allowance for 5% of participants to be lost-to-follow-up prior to being hospitalized or dying.

Using this sample size, the following Figure 10.4-1 shows the power to detect effects of different sizes (expressed as the ratio of true proportions hospitalized/dying in the HCQ and Azithro arm vs placebo arm), for a range of true proportions in the placebo arm. The large star indicates the choice of parameters used to design the study: power of 0.9 (i.e., 90%) to detect a true effect size of 33.3% (i.e., 0.667 ratio of proportions) when the true proportion hospitalized/dying in the control arm is 0.15 (i.e., 15%). The power of the study to detect an effect of HCQ and Azithro is reduced if the true ratio of proportions gets closer to 1.0 and/or if the true proportion hospitalized/dying is lower than 0.15.

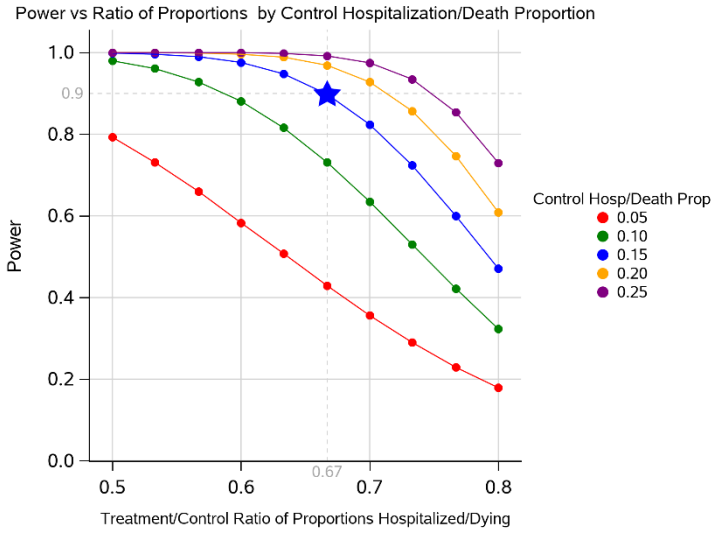

Figure 10.4-1: Treatment/Control Ratio of Proportions Hospitalized/Dying

The following Table 10.4-2 shows the power to detect an effect of the HCQ and Azithro arm accounting for treatment crossover in the placebo arm (i.e., those on the placebo arm who take HCQ and/or Azithro obtained from a source outside the study) for a range of crossover proportions assuming that these participants then experience a 10% hospitalization/death rate. The power is reduced to less than 80% when there is 15% or more crossover in the control arm.

Table 10.4-2: Power to Detect an Effect of the HCQ and Azithro Arm Accounting for Treatment Crossover in the Placebo Arm

Assumed Crossover Proportion In Control Arm	Assumed Hosp/Death Proportion in Control Arm Accounting for Crossover	Power Accounting for Crossover
5%	14.7%	86.4%
10%	14.5%	83.6%
12.5%	14.4%	82.1%
15%	14.2%	78.8%
20%	14%	75.1%

10.5 Data and Safety Monitoring

A NIAID-appointed Data and Safety Monitoring Board (DSMB) will undertake reviews of interim data from the study to help ensure the safety of participants in the study, and to recommend changes to the study including termination or modification for safety reasons

or if there is persuasive evidence of efficacy or lack of efficacy of HCQ and Azithro versus placebo in preventing hospitalizations and deaths. The DSMB may also recommend termination or modification of the study if it appears futile on operational grounds to continue the study as designed. The operation of the DSMB is governed by the NIAID DSMB Charter.

To monitor for potential cardiac safety issues, the DSMB will be notified of cases of TdP, ventricular arrhythmias and sudden deaths (with treatment assignment), as the study team becomes aware of them.

At each interim review, the DSMB will review summaries of data by randomized treatment arm for the primary outcome of hospitalization/death, losses to follow-up, adverse events, self-report of treatment cross-over, and the secondary outcomes of death, study treatment discontinuations and associated reasons, duration of symptoms of COVID-19 disease and duration of fever. By-stratum summaries will also be reviewed.

There will be a review of safety data by the DSMB when 250 participants have completed Day 20 of follow-up. Unless otherwise recommended by the DSMB, interim analyses of both safety and efficacy data will occur weekly from when approximately 500 participants have been followed for the primary outcome assessed at Day 20. To allow for the possibility that the proportion of hospitalizations or death is higher than anticipated, the first review of efficacy and safety data may occur earlier, when approximately 62 participants in the two arms combined have been hospitalized or have died (62 is the expected number based on 15% hospitalizations/deaths in the placebo arm and 10% in the HCQ and Azithro arm, with an interim sample size of 500 participants).

As a stopping guideline for greater efficacy of HCQ and Azithro compared with placebo, the O'Brien and Fleming boundary will be used. Because this spending function is particularly extreme at early interim analyses, a nominal two-sided p-value of <0.001 will instead be used to evaluate early efficacy when a more extreme nominal p-value would be suggested by the O'Brien and Fleming boundary; this has minimal effect on the overall Type I error rate. The stopping guideline will be implemented using the Lan-DeMets spending function approach to allow for the possibility of changes in the timing of interim analyses and/or additional (or fewer) interim analyses if recommended by the DSMB.

In considering possible modifications to the study or termination of the study, the DSMB may consider other outcome measures besides the primary composite hospitalization/death outcome measure, or differences within subgroups. For example, the DSMB might make recommendations based on a high level of evidence for a difference between randomized arms in the proportion dying. Also, for example, recognizing that there may be more hospitalizations/deaths in the higher risk stratum of the study, recommendations might be based on a high level of evidence for a difference in that stratum in the proportion hospitalized/dying or in the proportion dying. In these contexts, a "high level of evidence" might be based on application of the O'Brien and Fleming stopping guideline to the death outcome or the high risk stratum. There is the

possibility that differences between the treatment arms may be observed at an early study time point (for example cumulative proportion at Day 6), however the overall goal of the study is to prevent hospitalization and deaths regardless of the timing, and therefore the focus of the treatment arm comparisons will be at Day 20.

In the absence of a significant difference between randomized arms that leads to termination of the randomized comparison, the study team believes that there is value in continuing the randomized comparison of HCQ and Azithro versus placebo to full enrollment (i.e., 2000 participants) in order to obtain as much precision as possible and to provide maximal information to inform the field.

The DSMB will also monitor operational futility. With respect to operational futility, the DSMB may recommend modification or termination of the study if the proportion hospitalized/dying in the control arm is low. In particular, the DSMB might recommend restricting or closing enrollment to the low risk stratum in favor of increasing enrollment to the high-risk stratum. In addition, the DSMB will monitor the loss to follow-up (LTFU) rate. As a benchmark, an overall LTFU rate of more than 10% would be cause for concern. The DSMB should also monitor the treatment cross-over in the placebo arm by participant self-report and, if available, by PK levels of HCQ and Azithro. As a benchmark, a crossover rate of more than 10% in the placebo arm would be a cause for concern.

10.6 Analyses

A Statistical Analysis Plan will be developed that describes, in detail, the analyses to address the study's primary and secondary objectives. The following provides an outline of the methods for the main comparisons between randomized arms, particularly for the primary outcome measure.

All analyses involving randomized comparisons will include all randomized participants who received the first (confirmed) dose of study treatment, according to a modified intention-to-treat approach. This is motivated by the fact that consent/eligibility confirmation and randomization may occur remotely, prior to the study entry visit. For those who opt to have an in-person entry visit, it is possible that some randomized individuals will not show up. Additionally, it is possible (though unlikely) that some participants show up for the in-person study entry visit, but then decline study treatment. For participants who have a remote entry visit, confirmation of the first dose of study treatment is required.

10.6.1 Primary Outcome Measure

The cumulative proportion of participants hospitalized or dying during the first 21 days of follow-up will be estimated for each randomized arm, in each risk stratum, using Kaplan-Meier methods to take account of losses to follow-up. For each stratum, the difference between randomized arms in the estimated log cumulative proportion will be calculated and the variance for this difference will be obtained using Greenwood's formula. To compare the outcome in the overall study

population, the stratum-specific estimated differences in log proportion will be combined across strata, weighted by the inverse of the stratum-specific variance of the difference. Two-sided 95% confidence intervals (adjusted for multiple interim analyses), based on this weighted estimator, and associated p-value for the test of no difference between arms will then be obtained.

Participants who prematurely discontinue the study, who are not able to be contacted by the site to ascertain outcomes after discontinuation, will have follow up censored at the date of last known status.

The above analysis assumes that losses to follow-up are non-informative. As a sensitivity analysis of this assumption, causal inference methods, specifically inverse probability of censoring, may be used. These methods may also be used to evaluate the sensitivity of results to crossover of treatment in the placebo arm (i.e., participants taking HCQ and/or Azithro from sources outside of the study).

To evaluate the potential impact of multiple participants enrolling from the same household on the primary inference an additional sensitivity, analysis will restrict to the first person enrolled form each household. If differences are observed, additional considerations will be given to analyses that account for clustering, for example, bootstrap methods to estimate the variance of difference in the primary outcome between randomized arms.

10.6.2 Secondary Outcomes

The cumulative proportion of participants dying during the first 21 days of follow-up, and through to 24 weeks, and the cumulative proportion hospitalized/dying through to 24 weeks will be analyzed in a similar manner to the primary outcome.

Tolerability (occurrence of premature discontinuation of study treatment due to an adverse event) will be evaluated by estimating the proportion of participants who discontinue study treatment, and will be compared between arms using binary regression with adjustment for a participant's risk stratum. The proportion of participants who experience cardiac adverse events will be analyzed in a similar manner.

Duration of fever, duration of symptoms and duration of time to self-reported return to usual health will be summarized with descriptive statistics. Participant-specific durations of fever and symptoms will be compared between study arms using a two-sided stratified Wilcoxon test with a 5% Type I error rate. Total symptom score will be calculated on each day and the participant-specific area under the curve (AUC) over time will also be compared using a two-sided stratified Wilcoxon test. Participants who do not have complete diary cards due to hospitalization or death will be ranked in these analyses as having poorer outcomes than participants who survived without hospitalization.

The comparison of the proportion of participants with detectable SARS-CoV-2 RNA will use binary regression, with adjustment for risk stratum and pre-treatment SARS-CoV-2 RNA level. The model will be fitted using generalized estimating equations (GEE) to handle the repeated measurements, where the comparison between randomized arms will use a two-sided Wald test. Levels of SARS-CoV2 RNA levels will be compared between arms using non-parametric Wilcoxon rank-sum tests, separately at Day 6 and Day 20, considering results below assay limit as the lowest rank.

Descriptive summaries of clinical outcomes among those hospitalized will be provided by arm, recognizing that this would not be a randomized comparison, if restricted to participants who were hospitalized.

10.7 Unblinding

For unblinding requests, including emergency unblinding, refer to ACTG Standard Operating Procedure (SOP)-123, Unblinding Participants, (https://member.mis.s-3.net/cms/dl/10466/ACTG-123+Unblinding+Participants-V7+011719).

In the event that emergency disclosure of treatment assignment is thought to be required, the site investigator must follow ACTG SOP-123, Unblinding Participants.

Planned Unblinding
Participants will be unblinded at completion of the study. Please refer to ACTG SOP-123 Unblinding Participants for details.

(1) Sudden/Unplanned Unblinding: The decision to unblind one or more arms, or treatment specific to an individual participant, of an ongoing study is made by the team in conjunction with the relevant Scientific Committee and the Executive Committee. This can occur based on a recommendation from the DSMB or the results of another trial (also see the DAIDS SOP “Termination of a Trial or a Single Treatment Arm”).

(2) Participant contact: If the decision is made to unblind, participants should be unblinded as soon as possible. Unblinding is conducted through the DMC, which sends treatment assignments to the sites soon after the unblinding decision. Every effort should be made by the sites to contact participants who have completed follow-up in order to explain the study results.

(3) Implications of unblinding on study data: When a treatment comparison is unblinded based on an interim analysis, the results of that interim analysis must be reported in publications. Data from visits that occurred before the interim review but that were not in the database at the data cutoff date have little potential for bias and may be reported with a comment. Data from visits that occurred after unblinding are potentially biased and must not be used if the intent is to claim that all the data are from a blinded study. In unblinding due to both “interim analysis” and the “other trial results” situations, if analyses are reported on clinical data or samples taken after the unblinding date, the conditions under which these data were gathered must be made clear in any publication.

Unblinding will not occur to allow replacement of participants (see section 6.2.4). Failure to initiate study treatment would result in an increase in the applicable limit for enrollment into the active or placebo arm (as appropriate) for the designated cohort by the ACTG randomization department.

In general, participants who become hospitalized at any time during the study period of 24 weeks can have their individual study treatment unblinded if essential for their future treatment management or if necessary for enrollment into a COVID-19 treatment clinical trial. This determination should be made by the Investigator of Record at the ACTG site and documented on the eCRF.

If treatment assignment is unblinded, this information should only be shared with the physicians responsible for the management of the participant on a need-to-know basis. Treatment assignment should not be shared with others. This includes not sharing treatment assignment with the study team.

All site e-mails to the team should be carefully worded to prevent unblinding the team.

Unblinding of all study participants will take place after the last participant has completed the study, all data have been entered into the database and cleaned for primary and secondary outcome measures. For details, please refer to ACTG SOP-123 Unblinding Participants.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

The pharmacology objectives are: 1) to characterize pharmacokinetics of HCQ and Azithro in patients with COVID-19 following administration of study regimen; 2) to characterize relationship between HCQ and Azithro pharmacokinetics and rate of viral clearance.

11.2 Pharmacology Study Design

11.2.1 Overview

Single sparse sample collected at Days 6 and 20 from a subset of participants will be analyzed using population pharmacokinetic approach using Bayesian methodology, with priors informed by historical controls. The model will be supported by 1) sparse sampling corresponding to Days 6 and 20 trough, collected in subset of participants (n=200); 2) historical data from healthy volunteers and participants treated for COVID 19 in other studies (as Bayesian priors).

Population PK modelling will be used to estimate potential difference in HCQ clearance and exposure in patients treated for COVID-19 from historical

controls. A PK-PD model will be developed to examine the relationship between HCQ and Azithro PK, rate of viral clearance and potential clinical outcomes.

PK analysis may also be undertaken to evaluate whether HCQ and/or Azithro might have been used by participants in the placebo arm.

11.2.2 Methods and Timing for Assessing, Recording, and Analyzing PK Outcome Measures

Sparse PK sampling: Sparse sampling will be conducted at Days 6 and 20, approximately 0-1 hour prior to last or second-to-last dose taken. The exact time of 3 doses preceding the PK sampling and the exact time of the PK sample collection should be noted.

11.2.3 PK: Blood Collection and Processing

Detailed blood collection, processing, handling, and storage procedures can be found in the A5395 Laboratory Processing Chart (LPC).

11.2.4 Laboratory Performing the Assays

Plasma HCQ and Azithro concentrations will be determined by a validated procedure performed according to written standard operating procedures. The intraday accuracy and intraday precision will be obtained with quality control samples, which will be analyzed concurrently with each set of participant samples. Quality control procedures will be in place to ensure stability of sample materials. Plasma assays for HCQ and Azithro are being developed in the analytical laboratory at University of California at San Francisco (UCSF).

11.3 Pharmacological Data Analysis and Modeling Plan

The drug concentration-time data will be analyzed using nonlinear mixed-effects (NLME) modeling using the software NONMEM merged with historical control data. We anticipate that we will utilize historical model structures to fit the data. The main focus will be to estimate potential difference in HCQ and Azithro oral clearance (CL/F) in participant treated for COVID-19 and historical controls. Graphical and statistical diagnostic tools will be used during model development for model selection and data tracking. PK/PD models will be developed to explore the relationship between drug concentrations and rate of viral clearance.

11.4 Anticipated Outcomes

HCQ plasma levels will be associated with increased rate of viral clearance. Baseline viral load will also be an important determinant of viral clearance.

12.0 DATA COLLECTION AND MONITORING

12.1 Reporting Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Important protocol deviations are a subset of protocol deviations that may significantly impact the accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being (ICH E3). The site principal investigator and personnel are responsible for identifying and reporting important deviations. Once important protocol deviations are identified, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be sent to the IRB/EC per their guidelines.

For A5395, all protocol deviations that meet the definition of important, as defined in the MOPS, relating to participant safety and confidentiality must be recorded on the study protocol deviation eCRF. Since the ACTG has in place its SOP-153, Appendix II, "Critical Event and Key Protocol Violation Reporting Form," please also review the A5395 MOPS to determine when to use the Critical Event and Key Protocol Violation Reporting Form in ACTG 5395.

12.2 Records to Be Kept

Electronic case report form screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization.

12.3 Role of Data Management

12.3.1 Instructions concerning entering study data on eCRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

12.3.2 It is the responsibility of the ACTG DMC to ensure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

12.4 Clinical Site Monitoring and Record Availability

12.4.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent records, eCRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

12.4.2 The site investigator will make study documents (e.g., consent records, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, the NIAID, the OHRP, the industry supporters or designee, other local, US, and international regulatory entities for confirmation of the study data.

12.4.3 Given the epidemic spread of SARS-CoV-2 and the risk for visiting personnel, the study can be monitored remotely by clinical trial monitors. This will be decided based on the risk environment at the time of monitoring.

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. Informed consent will be obtained from the participant either through a signed consent form or through appropriate remote consenting procedures. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant and this fact will be documented in the participant's record.

13.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, the FDA, NIAID, OHRP, other local, US, and international regulatory entities as part of their duties.

13.3 Study Discontinuation

The study may be discontinued at any time by the FDA, ACTG, IRB/EC, NIAID, or OHRP as part of their duties to ensure that research participants are protected, or the industry supporters.

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporters prior to submission.

15.0 BIOHAZARD CONTAINMENT

As the transmission of SARS-CoV-2 and other droplet-borne pathogens can occur through contact with persons with active SARS-CoV-2 and infection-contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the clinical research setting and in drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

16.0 REFERENCES

1. ESRI StoryMaps Team. Mapping the Wuhan coronavirus outbreak. [Available from: https://storymaps.arcgis.com/stories/4fdc0d03d3a34aa485de1fb0d2650ee0].
2. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. Lancet 2020;395(10225):689-97.
3. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 2020 Mar 16. pii: ciaa272. doi: 10.1093/cid/ciaa272. [Epub ahead of print].
4. 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):1054-62.
5. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020 Feb 24. pii: S2213-2600(20)30079-5. doi: 10.1016/S2213-2600(20)30079-5. [Epub ahead of print].
6. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507-13.
7. Li LQ, Huang T, Wang YQ, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol 2020 Mar 12. doi: 10.1002/jmv.25757. [Epub ahead of print].
8. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.
9. Andersen PI, Ianevski A, Lysvand H, et al. Discovery and development of safe-in-man broad-spectrum antiviral agents. Int J Infect Dis. 2020;93(02/16/2020):268-76.
10. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30(3):269-71.
11. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017;9(396). pii: eaal3653. doi: 10.1126/scitranslmed.aal3653.
12. Capital Medical University, China [Sponsor]. NCT04257656. Severe 2019-nCoV Remdesivir RCT. [A phase 3 randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of remdesivir in hospitalized adult patients with severe 2019-nCoV respiratory disease]. February 6, 2020. ClinicalTrials.gov.
13. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020; March 20:105949. doi: 10.1016/j.ijantimicag.2020.105949. [Epub ahead of print].
14. Ponticelli C, Moroni G. Hydroxychloroquine in systemic lupus erythematosus (SLE). Expert Opin Drug Saf 2017;16:411-9.

15. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005;2:69.
16. Xu L, Wang Z. Chloroquine rescues A549 cells from paraquat-induced death. Drug Chem Toxicol 2016;39:167-73.
17. Kalia S, Dutz JP. New concepts in antimalarial use and mode of action in dermatology. Dermatol Ther 2007;20:160-74.
18a. Drugs.com. Hydroxychloroquine sulfate 2020 [02/16/2020]. Available from: https://www.drugs.com/pro/plaquenil.html.
18b. Garcia-Cremades M, Solans BP, Hughes E, Ernest JP, Wallender E, Aweeka F, Luetkemeyer AL, Savic RM. Optimizing hydroxychloroquine dosing for patients with COVID-19: an integrative modeling approach for effective drug repurposing. Clin Pharmacol Ther [Accepted for publication April 13, 2020]. **doi:10.1002/cpt.1856.**
19. Ballow CH, Amsden GW. Azithromycin: the first azalide antibiotic. Ann Pharmacother 1992;26:1253-61.
20. Amsden GW. Macrolides versus azalides: a drug interaction update. Ann Pharmacother 1995;29:906-17.
21. Luke DR, Foulds G. Disposition of oral azithromycin in humans. Clin Pharmacol Ther 1997;61:641-8.
22. Flach AJ. Improving the risk-benefit relationship and informed consent for patients treated with hydroxychloroquine. Trans Am Ophthalmol Soc. 2007;105:191-4; discussion 5-7.
23. Foulds G, Luke DR, Teng R, Willavize SA, Friedman H, Curatolo WJ. The absence of an effect of food on the bioavailability of azithromycin administered as tablets, sachet or suspension. J Antimicrob Chemother 1996;37 Suppl C:37-44.
24. Milberg P, Eckardt L, Bruns HJ, Biertz J, Ramtin S, Reinsch N, et al. Divergent proarrhythmic potential of macrolide antibiotics despite similar QT prolongation: fast phase 3 repolarization prevents early afterdepolarizations and torsade de pointes. J Pharmacol Exp Ther 2002;303:218-25.
25. Lexicomp Drug Interactions [Internet]. Wolters Kluwer Clinical Drug Information, Inc. 2013 [cited March 22, 2020]. Available from: https://www.wolterskluwercdi.com/lexicomp-online/.
26. Bachmann K, Schwartz JI, Forney R, Jr., Frogameni A, Jauregui LE. The effect of erythromycin on the disposition kinetics of warfarin. Pharmacology 1984;28:171-6.
27. Strandell J, Bate A, Hagg S, Edwards IR. Rhabdomyolysis a result of azithromycin and statins: an unrecognized interaction. Br J Clin Pharmacol 2009;68:427-34.
28. Cook JA, Randinitis EJ, Bramson CR, Wesche DL. Lack of a pharmacokinetic interaction between azithromycin and chloroquine. Am J Trop Med Hyg 2006;74:407-12.
29. Kimani J, Phiri K, Kamiza S, et al. Efficacy and safety of azithromycin-chloroquine versus sulfadoxine-pyrimethamine for intermittent preventive treatment of plasmodium falciparum malaria infection in pregnant women in Africa: an open-label, randomized trial. PLoS One 2016;11:e0157045.
30. Ganne P, Srinivasan R. Chloroquine retinopathy. JAMA Ophthalmol 2015;133:603-4.

31. Yusuf IH, Sharma S, Luqmani R, Downes SM. Hydroxychloroquine retinopathy. Eye (Lond) 2017;31:828-45.
32. Leung LS, Neal JW, Wakelee HA, Sequist LV, Marmor MF. Rapid onset of retinal toxicity from high-dose hydroxychloroquine given for cancer therapy. Am J Ophthalmol 2015;160:799-805 e1.
33. Chen CY, Wang FL, Lin CC. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. Clin Toxicol (Phila) 2006;44:173-5.
34. O'Laughlin JP, Mehta PH, Wong BC. Life threatening severe QTc prolongation in patient with systemic lupus erythematosus due to hydroxychloroquine. Case Rep Cardiol 2016;2016:4626279.
35. Ten Broeke R, Mestrom E, Woo L, Kreeftenberg H. Early treatment with intravenous lipid emulsion in a potentially lethal hydroxychloroquine intoxication. Neth J Med 2016;74:210-4.
36. Gunja N, Roberts D, McCoubrie D, et al. Survival after massive hydroxychloroquine overdose. Anaesth Intensive Care 2009;37:130-3.
37. Jordan P, Brookes JG, Nikolic G, Le Couteur DG. Hydroxychloroquine overdose: toxicokinetics and management. J Toxicol Clin Toxicol 1999;37:861-4.
38. WHO Evidence Review Group. The cardiotoxicity of antimalarials. Geneva, Switzerland: World Health Organization; 2017. p. 49.
39. Mzayek F, Deng H, Mather FJ, Wasilevich EC, Liu H, Hadi CM, et al. Randomized dose-ranging controlled trial of AQ-13, a candidate antimalarial, and chloroquine in healthy volunteers. PLoS Clin Trials 2007;2:e6.
40. McChesney EW. Animal toxicity and pharmacokinetics of hydroxychloroquine sulfate. Am J Med 1983;75:11-8.
41. Administration USFD. Azithromycin 2013 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050710s039,050711s036,050784s023lbl.pdf.
42. Bizjak ED, Haug MT, 3rd, Schilz RJ, Sarodia BD, Dresing JM. Intravenous azithromycin-induced ototoxicity. Pharmacotherapy 1999;19:245-8.
43. Patel B, Sheshadri A, Saliba RM, et al. Azithromycin exposure following hematopoietic stem cell transplantation is associated with an increased risk of cancer relapse in acute leukemia. Biol Blood Marrow Transpl 2019;25:S231-S2.
44. Ramsey PS, Vaules MB, Vasdev GM, Andrews WW, Ramin KD. Maternal and transplacental pharmacokinetics of azithromycin. Am J Obstet Gynecol 2003;188:714-8.
45. Shin B, Park HY, Koh WJ. Changes in QT intervals after azithromycin-containing antibiotic therapy in patients with NTM lung disease. Int J Tuberc Lung Dis 2014;18:1385-6.
46. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. Prog Cardiovasc Dis 2020; Mar 10. pii: S0033-0620(20)30055-4. doi: 10.1016/j.pcad.2020.03.001. [Epub ahead of print].

47. Corrales-Medina VF, Suh KN, Rose G, et al. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. PLoS Med 2011;8:e1001048.
48. Fossa AA, Wisialowski T, Duncan JN, Deng S, Dunne M. Azithromycin/chloroquine combination does not increase cardiac instability despite an increase in monophasic action potential duration in the anesthetized guinea pig. Am J Trop Med Hyg 2007;77:929-38.
49. Sagara I, Oduro AR, Mulenga M, et al. Efficacy and safety of a combination of azithromycin and chloroquine for the treatment of uncomplicated Plasmodium falciparum malaria in two multi-country randomised clinical trials in African adults. Malar J 2014;13:458.
50. Bialek S, Boundy E, Bowen V, et al. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep 2020;69(12):343-6. doi: 10.15585/mmwr.mm6912e2.
51. Wilson N, Kvalsvig A, Barnard LT, Baker MG. Case-fatality risk estimates for COVID-19 calculated by using a lag time for fatality. Emerg Infect Dis 2020;26(6). doi: 10.3201/eid2606.200320. [Epub ahead of print].
52. Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J 2003;9:399-406.
53. Loutfy MR, Blatt LM, Siminovitch KA, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. JAMA 2003;290:3222-8.
54. Wong VW, Dai D, Wu AK, Sung JJ. Treatment of severe acute respiratory syndrome with convalescent plasma. Hong Kong Med J 2003;9:199-201.
55. Barnard DL, Hubbard VD, Burton J, et al. Inhibition of severe acute respiratory syndrome-associated coronavirus (SARSCoV) by calpain inhibitors and beta-D-N4-hydroxycytidine. Antivir Chem Chemother 2004;15:15-22.
56. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59:252-6.
57. Cinatl J, Jr., Michaelis M, Scholz M, Doerr HW. Role of interferons in the treatment of severe acute respiratory syndrome. Expert Opin Biol Ther 2004;4:827-36.
58. Haagmans BL, Kuiken T, Martina BE, et al. Pegylated interferon-alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques. Nat Med 2004;10:290-3.
59. Hensley LE, Fritz LE, Jahrling PB, Karp CL, Huggins JW, Geisbert TW. Interferon-beta 1a and SARS coronavirus replication. Emerg Infect Dis 2004;10:317-9.
60. Stroher U, DiCaro A, Li Y, et al. Severe acute respiratory syndrome-related coronavirus is inhibited by interferon-alpha. J Infect Dis 2004;189:1164-7.
61. Tan EL, Ooi EE, Lin CY, et al. Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs. Emerg Infect Dis 2004;10:581-6.
62. Yamamoto N, Yang R, Yoshinaka Y, et al. HIV protease inhibitor nelfinavir inhibits replication of SARS-associated coronavirus. Biochem Biophys Res Commun 2004;318:719-25.

63. Zheng B, He ML, Wong KL, et al. Potent inhibition of SARS-associated coronavirus (SCOV) infection and replication by type I interferons (IFN-alpha/beta) but not by type II interferon (IFN-gamma). J Interferon Cytokine Res 2004;24:388-90.
64. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 2003;361:2045-6.
65. Groneberg DA, Poutanen SM, Low DE, Lode H, Welte T, Zabel P. Treatment and vaccines for severe acute respiratory syndrome. Lancet Infect Dis 2005;5:147-55.
66. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211:80-90.
67. Public Health England. Treatment of MERS-CoV: information for clinicians. Clinical decision-making support for treatment of MERS-CoV patients. England: UK Government; 2015.
68. Chan JF, Chan KH, Kao RY, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect 2013;67:606-16.
69. Cheng KW, Cheng SC, Chen WY, et al. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. Antiviral Res 2015;115:9-16.
70. Wang Y, Sun Y, Wu A, et al. Coronavirus nsp10/nsp16 methyltransferase can be targeted by nsp10-derived peptide in vitro and in vivo to reduce replication and pathogenesis. J Virol 2015;89:8416-27.
71. Gautret P, Lagier J-C, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. Pan American Health Organization (PAHO)/World Health Organization (WHO) 2020. Available at: https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf.
72. Lover AA. Quantifying treatment effects of hydroxychloroquine and azithromycin for COVID-19: a secondary analysis of an open label non-randomized clinical trial (Gautret et al., 2020). medRxiv. 2020:2020.03.22.20040949.
73. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14(1):72-3.
74**a**. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci) 2020;49(1):0-0. doi: 10.3785/j.issn.1008-9292.2020.03.03.
74b. Simpson TF, Kovacs RJ, Stecker EC. Ventricular arrhythmia risk due to hydroxychloroquine-azithromycin treatment for COVID-19. Cardiology Magazine 2020;March 29.

75. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020. Mar 9. pii: ciaa237. doi: 10.1093/cid/ciaa237. [Epub ahead of print].
76. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020. Mar 18. doi: 10.1056/NEJMoa2001282. [Epub ahead of print].
77. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med 2020;382:1177-9.
78. LABEL: HYDROXYCHLOROQUINE SULFATE tablet, film coated [Internet]. National Institutes of Health. 2020 [cited March 28, 2020]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5f5f1dee-854a-41f6-b304-d7fdf8dd3ea0.
79. LABEL: AZITHROMYCIN DIHYDRATE tablet, film coated [Internet]. National Institutes of Health. 2019 [cited March 28, 2020]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9f0501bf-d1c4-46a5-b253-3b9e61015e82.

APPENDIX I: SAMPLE INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)

SAMPLE INFORMED CONSENT

For protocol: A5395

A Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy of Hydroxychloroquine and Azithromycin to Prevent Hospitalization or Death in Persons with COVID-19

FINAL Version **2**.0, 4/24/20

SHORT TITLE FOR THE STUDY: HCQ and Azithro for Non-hospitalized Persons with COVID-19

SUMMARY

PURPOSE	This is a research study and your participation in this study is voluntary. The purpose of this study is to evaluate the ability **of** hydroxychloroquine (HCQ) and azithromycin (Azithro) compared to placebo **to** prevent hospitalization or death in persons with COVID-19.
STUDY TREATMENT	There will be study treatment provided and required in this study. It is not known whether this study treatment will help your COVID-19 or not. You will be randomized to either Group A or Group B. Randomized means that your assignment will be random, like rolling dice. In this study, you will have a 50/50 chance of receiving either **hydroxychloroquine** and Azithro or Placebos. You and the study doctor will not know what group you are in, and therefore, will not know which study treatment you are taking (this is also referred to as “double-blinded”). You will take **hydroxychloroquine**/Placebo **two** (**2**00 mg each) capsules by mouth **twice a day on the first day, followed by one 200 mg capsule twice a day for 6 days. Hydroxychloroquine**/Placebo should be taken with food or milk. You will also take Azithro/Placebo two (250 mg each) capsules by mouth **once on** the first day and then **one** capsule (250 mg) every day for 4 additional days.
NUMBER OF PARTICIPANTS	There will be 2 treatment groups of 1000 people, for a total of 2000 participants.

LENGTH OF STUDY

The study will last for about 6 months (7 days on study treatment)

REQUIRED ACTIVITIES

Sample collections

For US sites that are pre-selected include this: At the start of the study you may have some blood collected from a vein in your arm, perform a self-collect nose swab, and, in addition, have study staff do a nasopharyngeal swab of your nose. You will have both types of nose swabs at Day 6 and 20 and blood collected again at Days 6 and 20. All blood will be stored.

You will have the option to self-collect a nose swab three times during the study. Swabs are used to detect viruses. You will place a swab in each nostril and rotate the swab several times. You may also have the option of having study staff do three nasopharyngeal swabs (intensive nose swabs), if the site is able to do these swabs.

You will report your symptoms and temperature (if you have a thermometer at home) and how often you took medication and at what time throughout the study.

RISKS

The following are possible:

- **Hydroxychloroquine** side effects
  - Nausea
  - Diarrhea
  - Vomiting
  - Headache
  - Tiredness
  - Stomach (abdominal) pain
  - Muscle weakness

- Possible **hydroxychloroquine** side effects that are uncommon but potentially serious:
  - Serious (including fatal) allergic and skin reaction
  - Fast heart rate or pulse
  - Prolongation of QT interval (heart takes longer than normal to recharge between beats) and cases of “torsades de pointes” (dangerous fast heart beats)
  - Ventricular tachycardia or fibrillation, a condition of the heart that can cause a fast heart rate and increase the risk of stroke and heart attack
  - Hypoglycemia (blood sugar is low)
  - Blurry vision

- Muscle pain
- Death

- Azithro side effects
  - Diarrhea
  - Nausea
  - Abdominal pain
  - Vomiting

- Possible Azithro side effects that are uncommon but potentially serious:
  - Serious (including fatal) allergic and skin reaction
  - Pseudomembranous colitis (swelling or inflammation of the large intestine due to overgrowth of *Clostridium difficile*)
  - New onset of myasthenia gravis (long-term neuromuscular disease that leads to skeletal muscle weakness)
  - Exacerbation of myasthenia gravis (weakness in skeletal muscles)
  - Ventricular arrhythmias (occurs more frequently in people with heart disease)
  - Severe, and sometimes fatal, hepatotoxicity (liver damage)
  - Prolongation of QT interval (heart takes longer than normal to recharge between beats) and cases of “torsades de pointes” (heart beats faster than usual)
  - *Clostridium difficile* (bacteria)-associated diarrhea
  - Death

For US sites that are able to do blood draws, self-collect nasal swabs, and perform nasopharyngeal swabs, include the following:

Risks associated with blood draws
-Pain and bruising at the site of blood draw
-Infection (rare)
-Hypotension (lowering of blood pressure) (rare)

Other blood draw risks
-Anemia (low red blood cell count) (rare)
-Feeling lightheaded or fainting

Risks associated with nose swabs
- Stimulating a gag reflex
- Sneezing
- Discomfort

BENEFITS If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have SARS-CoV-2 infection.

OTHER CHOICES Instead of being in this study, you have the option of:

- Treatment with prescription drugs available to you by your medical provider.
- Treatment with experimental drugs, if you qualify, treatment with "off-label" treatment with hydroxychloroquine and/or azithromycin if prescribed by your medical provider.
- No treatment.

INTRODUCTION

You are being asked to take part in this research study because you have been diagnosed with SARS-CoV-2 (a new virus that can cause severe pneumonia and death) and have symptoms of this infection, commonly known as COVID-19. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

SARS-CoV-2 is a new virus that has caused a widespread outbreak of an illness called COVID-19. In most people it causes a mild to moderate upper respiratory infection, like a "cold". In others, this virus can cause a pneumonia, which can be serious and life-threatening. There is no proven therapy for COVID-19.

The investigators of this study would like to know if the medication hydroxychloroquine (HCQ) combined with azithromycin (Azithro) can protect people from becoming sick enough from SARS-CoV-2 infection to require hospitalization or from dying. This study will gather data on the effectiveness of **hydroxychloroquine** and Azithro to prevent hospitalization and death in adults with SARS-CoV-2 infection when compared to Placebo (sugar capsule). Another purpose of this study is to see if **hydroxychloroquine** and Azithro is safe for people who are infected with SARS-CoV-2 and have symptoms consistent with COVID-19.

Hydroxychloroquine is currently approved by the Food and Drug Administration (FDA) for prevention and treatment of malaria infection and treatment of disease in individuals with rheumatoid arthritis, porphyria cutanea tarda (blood disorder that affects the skin), and lupus (an

autoimmune disease). Azithromycin is currently FDA approved for treating bacterial infections. **Hydroxychloroquine** and Azithro have not previously been tested in a randomized controlled trial (people are assigned randomly to study treatment and compared to people not taking study treatment) in people to see if they can prevent severe disease from SARS-CoV-2 infection.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Information Collected at Screening
If you decide to take part in this study, you will be screened to determine if you qualify for the study.

There is some information that we collect on everyone who is screened for an **AIDS Clinical Trials Group (ACTG)** study. As part of the screening, some demographic (such as, age, sex/gender, race), clinical (such as disease condition, diagnosis), and laboratory (such as, inflammation and SARS-CoV-2 levels) information will be collected from you. We also collect information on whether you use (or have used) IV drugs or smoke marijuana or have smoked tobacco or other nicotine products.

We will collect this information even if you do not enroll in this study. This information is collected so that researchers can determine whether there are patterns and/or common reasons why people do not join a study.

Study Visits
The schedule of visits and study procedures are explained in Attachment B.

You will most likely be screened over the phone, but you also could be screened in person. If you qualify for the study, you will have an in-person entry visit to get your study treatment for the duration of the study, or a remote (i.e., by telephone or video) visit in which your study treatment for the duration of the study will be mailed or delivered to you. The screening and entry visit may occur on the same day. You will be randomized to receive either **hydroxychloroquine** and Azithro (Group A) or Placebos (Group B). Randomized means that your assignment will be random, like rolling dice. In this study, you will have a 50/50 chance of receiving either **hydroxychloroquine** and Azithro or Placebos. You and the study doctor will not know what study **group you are in**.

If you are in Group A, you will take **hydroxychloroquine two (200 mg each) capsules by mouth twice a day on the first day**, **followed by one 200 mg capsule twice a day for 6 days**. **Hydroxychloroquine** should be taken with food or milk. You will also take two Azithro capsules (250 mg each) by mouth **once on** the first day and then **one** capsule (250 mg) every day for 4 additional days.

If you are in Group B, you will take Placebo **hydroxychloroquine two (200 mg each) capsules by mouth twice a day on the first day**, **followed by one 200 mg capsule twice a day for 6 days**. Placebo **hydroxychloroquine** should be taken with food or milk. You will also take two Placebo Azithro capsules **(250 mg each)** by mouth **once on** the first day and then **one** capsule **(250 mg each)** every day for 4 additional days. Study staff will counsel you on how to take

these study medications. Both study groups are important to the study to answer the study questions.

After entry, you will be followed-up by telephone or video a few times. These phone calls will take between 30 and 60 minutes to complete. During the study, you will take your temperature if you have a thermometer at home and complete a symptom diary.

For US sites that are pre-selected, include the following: You may choose to have blood collected and stored at entry and on Days 6 and 20. Blood will be collected by venipuncture (puncture of the vein). You may choose to self-collect nose swabs and have an intensive nose swab at entry and Day 6 and Day 20.

If you need medical help at any time during the study, please contact the study staff right away.

Screening Visit (in-person or remote)
You will be asked for your medical and medication history. You will be asked about your symptoms.

Study Entry (in-person or remote)
Following the screening visit **(if not combined with the entry visit)**, if you qualify for the study, you will be asked for your medical and medication history again, be given your study treatment and be given a Study Diary packet and complete the Study Diary for that day (if remote visit, these items will be mailed or delivered to you). You will be asked to provide contact information for people close to you in case study staff cannot reach you during the study. We would like you to tell these contacts that you are in the study, so they know they may receive a call from study staff. You will also be asked to provide your health care provider's contact information along with the name(s) of the hospital you would likely go to if you get really sick (see consent below under "WHAT IF THE SITE CAN NO LONGER REACH ME DURING THE STUDY?"). You will also be asked to provide your home address. You will take your study treatment on this day. If you have an in-person visit, study staff will observe you taking the study treatment. If you have a remote visit, you will need to tell study staff when you have taken the study drug.

For US sites that are pre-selected, include the following: You may have blood collected and stored, self-collect a nose swab, and have a deeper nose swab. Up to 37 mL of blood will be collected at entry.

Follow-up Visits
You will be contacted by phone by study staff on Days 2, **4,** 6, 9, 13, and 17, and at 3 and 6 months after you enter the study. During the study, you will complete a symptom diary. You will also be asked questions about how you are taking the study treatment and health care that you have accessed. Site staff will also ask you to update your secondary contact information. These visits will take between 30 and 60 minutes.

You will have an in-person visit **or remote visit** on Day 20 to see how you are feeling and for you to turn in your Study Diary. If you**r** Day 20 visit **is not done** in person, you will be called by

study staff to do the visit over the phone or by video. Arrangements will be made for you to send the symptom diary to the clinic. This visit will take between 30 and 60 minutes.

For US sites that are pre-selected, include the following: You will have the option of study staff doing a blood draw, self-collect a nose swab, and have an intensive nose swab done by study staff at Days 6 and 20. Up to 41 mL of blood will be collected at Day 6 and at Day 20. Blood will be stored. You will receive study reimbursement at study entry, and Days 6 and 20.

If you cannot be reached, the study staff will contact your alternative contacts or your health care provider. If you become hospitalized, the study staff will ask your contacts for information about you being in the hospital. The study staff will also ask your contacts about death, should that occur (see consent below under "WHAT IF THE SITE CAN NO LONGER REACH ME DURING THE STUDY?").

Early discontinuation

If at any point in the study you want to stop study treatment or stop participating in the study, you must contact the site immediately **and will be asked to come to the clinic for an extra visit**.

1. *Stopping the study treatment early*
   You or your doctor may decide to stop the study treatment that you began at entry.

   If you must stop taking the study treatment early, you will continue the study and complete the study visits as described in this form.

2. *Leaving the study early*
   You or your doctor may decide that you will no longer stay in the study or you are notified the study is stopped early. You will be asked to complete some evaluations before being taken off the study.

For US sites that are pre-selected, include the following: If you agree to participate in the optional procedures, you will have a blood draw, self-collect a nose swab, and have an intensive nose swab by study staff if you end the study early. Up to 41 mL of blood will be collected and stored.

For US sites that are pre-selected, include the following:

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your blood and nose secretions (samples) will be stored and used for testing of inflammation, pharmacokinetics (to test how the study drug works in your body), and the presence of SARS-CoV-2 that is required for this study.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

The tests described in this consent are required by this study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 2000 people will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 6 months (7 days on treatment).

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- The study is stopped or cancelled.
- Continuing the study treatment may be harmful to you.
- Your primary care provider requests that you stop participating in the study.
- You do not take your first dose of study treatment when you start the study.

The study doctor may also need to take you off the study medication without your permission if:
- You are taking other medications that should not be taken with the study drug.

If you must stop taking the study treatments before the study is over, the study doctor will ask you to continue to be part of the study and return for study visits and procedures.

WHAT HAPPENS IF I DECIDE TO PERMANENTLY STOP TAKING STUDY-PROVIDED MEDICATIONS?

If you must permanently stop taking study-provided **hydroxychloroquine** and Azithro or Placebo before your study participation is over, the study staff will discuss other options that may be of benefit to you.

WHAT HAPPENS WHEN I FINISH THE ONE WEEK STUDY-PROVIDED MEDICATIONS?

After you have completed your study participation, the study will not be able to continue to provide you with the **hydroxychloroquine** and Azithro you received on the study. If continuing to take these or similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

There are risks to taking part in any research study. The effectiveness of the study treatments is not known. One risk is that the study treatments may not stop you from becoming sicker, being hospitalized or dying from SARS-CoV-2. Another risk is that the study treatments used in this study may have side effects, some of which are listed below. Additionally, the study drugs tested in the study may have unknown side-effects in persons with SARS-CoV-2 infection. In a research study, all of the risks or side effects may not be known before you start the study. You need to tell your doctor or a member of the study team immediately if you experience any side effects.

Please note that these lists do not include all the side effects seen with these medications. These lists include the more serious or common side effects with a known or possible relationship to the study drugs. If you have questions concerning the additional side effects, please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are given with the study treatment. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study. Medications that are high risk are:

- "Off-label" prescription for hydroxychloroquine, **chloroquine**, and/or azithromycin
- Cardiac medications
  - Antiarrhythmic drugs: Class Ia (quinidine [Quinidex Extentabs, Quinaglute, Quinalan, Cardioquin], procainamide [Pronestyl], disopyramide [Norpace, Norpace CR]); Class III (dofetilide [Tikosyn], ibutilide [Corvert], sotalol [Betapace, Betapace AF, Sorine, Sotylize])
  - **Loop diuretics (furosemide [Furocot, Lasix], bumetanide [Bumex], torsemide [Demadex], ethacrynic acid [Edecrin])**
- Non-cardiac medications
  - Diphenhydramine (Benadryl, Banophen, Allermax, Genahist, Sominex, Unisom, ZzzQuil)

- **Antiepileptic medications: Carbamazepine (Tegretol, Carbegen), Eslicarazepine (Aptiom), Ethosuximide, Felbamate (Felbatol), Gabapentin (Neurontin), Lamotrigine (Lamitcal), Levetiracetam (Desitrend, Keppra), Oxcabazepine (Trileptal), Phenobarbital, Phenytoin (Dilantin, Epanutin), Piracetam (Nootropil), Pregabalin (Alzain, Axalid, Lyrica, Rewisca), Rufinamide (Inovelon), Stiripentol (Diacomit), Tiagabine (Gabitril), Topiramate (Topamax), Sodium Valproate (Epilim, Episenta, Epival), Valproic Acid (Convulex, Depakote, Depakene), Zonisamide (Zonegran)**
- Antipsychotic and antidepressant agents: Neuroleptic (haloperidol [Haldol], droperidol [Inapsine], thioridazine [Mellaril, Mellaril-S], chlorpromazine [Thorazine, Ormazine]); Atypical antipsychotics (ziprasidone [Geodon], risperidone [Risperdal M-Tab, RisperiDONE M-Tab], zimeldine [Normud, Zelmid], citalopram [CeleXA]); Antidepressants (amitriptyline [Elavil, Vanatrip], desipramine [Norpramin], imipramine [Tofranil and Tofranil-PM], maprotiline [Ludiomil], doxepin [Silenor, SINEquan], fluoxetine [PROzac, PROzac Weekly, Rapiflux, Sarafem, Selfemra], escitalopram [Lexapro], citalopram [CeleXA])
- Antibiotics: Quinolone (levofloxacin [Levaquin], moxifloxacin [Moxeza, Vigamox]); Macrolide (erythromycin [EES 200, EES 400, EES Granules, Eryc, Eryped, Eyrped 200, Eyrped 400, Ery-Tab, Erythrocin, Erythrocin Stearate, IIosone, PCE, PCE Dispertab], clarithromycin [Biaxin, Biaxin Filmtab, Biaxin XL])
- Antimalarials (quinine [Qualaquin, Quinamm, Quiphile], halofantrine [Halfan])
- Antiprotozoal (pentamidine [Pentam])
- Antifungal (azole group [Vfend, Sporanox, Noxafil, Diflucan, Nizoral, Mycelex Troche, Cresemba, Onmel, Oravig, Tolsura])
- Antimotility agents (antidiarrheals)
- Methadone [Diskets Dispersible, Dolophine, Methadone HCl Intensol, Methadose]

Please contact the study doctor or nurse before starting any of these medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

If you enroll in this trial and are randomized to receive active hydroxychloroquine and azithromycin drugs, and you also receive “off-label” prescription for hydroxychloroquine, **chloroquine,** and/or azithromycin, then there is a risk of over-dosing. It is possible to have serious side effects with risk for death. It is important that you do not take **hydroxychloroquine** or Azithro from sources outside of the study, like from your primary doctor. If you do take one or both of these drugs from sources outside the study, please let the study staff know right away.

There is also a risk that these drugs have no benefit for COVID-19, and thus drug exposure would carry more risk than placebo.

Commonly reported side effects of **hydroxychloroquine** are:
- Nausea
- Diarrhea
- Vomiting
- Headache
- Tiredness
- Stomach (abdominal) pain
- Muscle weakness

Less common, but potentially severe and potentially life-threatening side effects of **hydroxychloroquine** in volunteers were:
- Allergic reactions and rash
- Tachycardia (fast heart rate or pulse)
- Prolongation of QT interval (heart takes longer than normal to recharge between beats) and cases of "torsades de pointes" (dangerously fast heart beats)
- Ventricular tachycardia or fibrillation, a condition of the heart that can cause a fast heart rate and increase the risk of stroke and heart attack
- Hypoglycemia (blood sugar is low)
- Blurry vision
- Muscle pain
- Death

If you have psoriasis and are randomized to receive **hydroxychloroquine**, you may experience a psoriasis flare.

Side Effects of Azithro
- Diarrhea
- Nausea
- Abdominal pain
- Vomiting
- Pseudomembranous colitis (swelling or inflammation of the large intestine due to overgrowth of *Clostridium difficile*)
- New onset of myasthenia gravis (long-term neuromuscular disease that leads to skeletal muscle weakness)
- Exacerbation of myasthenia gravis (weakness in skeletal muscles)
- Ventricular arrhythmias (occurs more frequently in people with heart disease)

The following severe and potentially life-threatening side effects have been reported:
- Serious (including fatal) allergic and skin reaction
- Severe, and sometimes fatal, hepatotoxicity (liver damage)
- Prolongation of QT interval (heart takes longer than normal to recharge between beats) and cases of "torsades de pointes" (dangerously fast heart beats)
- *Clostridium difficile* (bacteria)-associated diarrhea
- Death

As with all drugs, you could have an allergic reaction such as a rash or hives. Allergic reactions can be dangerous; if you develop an allergic reaction, you will be given medication (similar to Benadryl) to counter the reaction and be taken off study drug.

For US sites that are pre-selected, include the following:

Risks Associated with Blood Draw
Blood draws may cause pain and bruising, and rarely, infection at the site of the blood draw. There is also a risk of anemia (low red blood cell count) or hypotension (low blood pressure). Sometimes, having blood drawn will cause people to feel lightheaded or even to faint.

Risks Associated with Collection of Nasopharyngeal Swabs and Self-collected Nose Swabs
- *You may experience mild discomfort related to the insertion of the nasopharyngeal swab (intensive nose swab).*
- *Occasionally there can be a tingling feeling, or slight stinging.*
- *You may have a gag reflux or sneeze*

ARE THERE RISKS RELATED TO PREGNANCY AND BREASTFEEDING?

Pregnancy
The safety of **hydroxychloroquine** during pregnancy is not fully established. However, pregnant women with lupus and arthritis are recommended to continue **hydroxychloroquine** throughout pregnancy. Studies have shown that taking **hydroxychloroquine** during pregnancy does not harm the fetus. It should be noted that **hydroxychloroquine** at the dose used in this study has not been used before during pregnancy and may involve risks.

In animal studies, no evidence of harm to the fetus due to Azithro was found. When given as malaria prevention during pregnancy, Azithro was not shown to harm the fetus.

The study treatment may involve risks to you (or to the embryo or fetus, if you or your partner become pregnant), which are currently unforeseen. Let your doctor know immediately if you become pregnant. If you become pregnant while on the study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends).

If you are pregnant, please discuss study participation with your OB/GYN provider.

Breastfeeding
Hydroxychloroquine is excreted in human breast milk. When given at the dose used in this study the relative amount of **hydroxychloroquine** in breast milk is considered safe for infants. Azithro is excreted in human milk, but considered safe to use during breastfeeding.

It is unknown if SARS-CoV-2 is excreted in human breast milk. If you would like to breastfeed during this study, please talk to your OB/GYN provider.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

No direct benefits should be expected from participating in this study. If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have SARS-CoV-2 infection.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- Treatment with prescription drugs available to you by your medical provider.
- Treatment with experimental drugs, if you qualify, treatment with “off-label” treatment with hydroxychloroquine and/or azithromycin if prescribed by your medical provider.
- No treatment.

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties, (insert name of site) institutional review board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT IF THE SITE CAN NO LONGER REACH ME DURING THE STUDY?

In the event you cannot be reached after multiple attempts to contact you, study staff may try to contact you through alternate phone numbers of family, friends, case manager, or acquaintances obtained **from you** at screening and updated at each visit. If you are still unable to be reached, we will attempt to obtain information about you from your designated contacts, clinic records, or by contacting your health care providers (if you agree).

Contacting Your Health Care Providers
[Sites to modify per local requirements for obtaining health care records.]
With your permission, for which you would need to sign a waiver, study staff may contact your health care providers or hospitals where you might receive care to determine if you have been hospitalized or died while in the study, and the cause of death. Will you allow us to contact your health care provider(s) or hospitals to obtain this information?

_____ YES _____ NO _____Initials

If you said Yes, please list the names of your health care provider and the hospitals you would likely be admitted to, below:

WHAT ARE THE COSTS TO ME?

There will be no cost to you for study-related visits *[add the following only if at pre-selected US site: laboratory tests,]* or procedures. If you require medical care as a result of taking study medications, it is possible that your insurance company will not pay for these costs because you are taking part in a research study. You are more likely to require medical care as a result of having COVID-19. Costs related to acute care/hospitalization will not be covered by the study.

WILL I RECEIVE ANY PAYMENT?

[Insert site-specific information on compensation to study participants.]

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

For US sites that are pre-selected, include the following:

In the subset of participants from the pre-selected sites, results from the in-study SARS-CoV-2 testing and blood work (CBC and chemistries) will be provided to you. These results will also be provided to your primary/health care provider if requested by you.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- Name of the investigator or other study staff
- Telephone number of above

For questions about your rights as a research participant, contact:

- Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- Telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)	Participant's Signature and Date
Participant's Legally Authorized Representative (print) (As appropriate)	Legally Authorized Representative Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date

ATTACHMENT A: CONSENT TO PARTICIPATE IN OPTIONAL INTENSIVE SAMPLING STUDY

[Attachment A Consent is only for US sites that are pre-selected to participate in the intensive sampling study.]

The optional intensive sampling study includes three different procedures (as described below) and will advance the scientific goals of this study but will offer no direct benefit to participants. Neither you nor your doctor will receive any results from these procedures because these tests are for research purposes only. If you agree to participate in the optional intensive sampling study, you must agree to have all three procedures described below done. If you choose not to participate in the optional intensive sampling study, it will not affect your ability to take part in the main study.

Self-collected nose swabs
The self-collected nose swabs will be performed by you at *[insert site-specific details]*. The procedure will take about *[insert site-specific details]*.

Self-collected nose swabs are used to detect respiratory viruses. You will place a swab in each nostril and rotate the swab several times.

[Note to sites: Insert details regarding how this procedure is performed in your institution].

Nasopharyngeal swabs
The nasopharyngeal swabs will be performed by study staff at *[insert site-specific details]*. The procedure will take about *[insert site-specific details]*.

Nasopharyngeal swabs are used to detect respiratory viruses. Study staff will tell you how this procedure is performed. A swab will be inserted into your nostril. The swab will be placed in deep towards the back of your throat. The swab will be in place for several seconds. The swab will be slowly removed. This is an uncomfortable procedure.

[Note to sites: Insert details regarding how this procedure is performed in your institution].

Blood draws and blood storage
Blood draws will be performed by study staff at *[insert site-specific details]*. The procedure will take about *[insert site-specific details]*.

[Note to sites: Insert details regarding how this procedure is performed in your institution].

Please indicate below if you agree to participate in this optional intensive sampling study and have all three of these procedures done. No matter what you decide, it will not affect your participation in the main study.

Self-collected nose swabs, nasopharyngeal swabs, blood draws and blood storage:

_____ (initials) YES, I agree _____ (initials) NO, I do not agree

ATTACHMENT B: EXPLANATION OF STUDY VISITS AND EVALUATIONS

Section A: Study Visits

Table 1: Schedule for Participants

Procedure	Screen-ing	Entry (in-person or remote)	On study visits									End Study Early
			Days							Months		
		Day 0	2	**4**	6	9	13	17	20	3	6	
Consent	✓											
Confirm SARS-CoV-2 Infection	✓											
Questions about symptoms	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Questions about your health	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Questions about the medications you are taking	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Secondary contact request		✓										
Study kit received		✓										
Remote contact			✓	✓	✓	✓	✓	✓	✓	✓	✓	
Adherence assessment			✓	✓	✓	✓						✓
Review Study Diary		✓	✓	✓	✓	✓	✓	✓	✓			✓
Return of Study Diary **to Study Staff**									✓			✓
Optional Sampling Study Procedures												
In person visit[1]		✓			✓				✓			✓
Self-collect nose swab[1]		✓			✓				✓			✓
Intensive nose swab[1]		✓			✓				✓			✓
Blood collected and stored[1]		✓			✓				✓			✓

[1] *[Remove if site cannot administer blood draws, self-collect nasal swab, and perform NP swab]*

Section B: Explanation of Visit Schedule

Screening: This visit may be done in-person or over the phone. **It is possible that the screening and entry visits are combined.**

Entry: This in-person or remote visit will take place after the screening visit. This visit may be done at the same time as screening. You will be required to take the first dose of study treatment in front of someone from the study staff. If this visit is done remotely, you will tell the site that you have taken or are taking the first study dose **and record the time of your first dose.** Study staff will counsel you on how to take these study medications. **This visit will take place and you should start study treatment within 96 hours of the time your positive COVID-19 test was performed (when the specimen was collected).**

On-study: You will be contacted by phone on Days 2, **4,** 6, 9, 13, and 17, and at 3 (week 12) and 6 months (week 24) after you enter the study.

For US sites that are pre-selected to do blood draws, self-collect nasal swabs, and perform NP swabs, include the following: If you choose, *you may have an in-person visit on Days 0 and 6 for a blood draw, an intensive nose swab, and/or a self-collected nose swab.*

Day 20: You **will** have an in-person **or remote** visit**.** If you are not feeling well and you cannot do the Day 20 visit in-person, you will be called by study staff to conduct the visit by phone or video. Arrangements will be made to send you study payment and for you to send the symptom diary to the clinic.

For US sites that are pre-selected to do blood draws, self-collect nasal swabs, and perform nasopharyngeal swabs, include the following: You may choose to have blood collected and stored, have study staff perform an intensive nose swab, and self-collect a nose swab on Day 20.

At months 3 (week 12) and 6 (week 24), you will be contacted by telephone/video.

End study early: if you leave the study after Day 6, all procedures will be done indicated in the table except treatment adherence.

For US sites that are pre-selected to do blood draws, self-collect nasal swabs, and perform nasopharyngeal swabs, include the following:

End study early: if you end the study after Day 6, all procedures will be done except treatment adherence. Up to 41 mL of blood will be collected.

Section C: Explanation of Procedures

Confirm SARS-CoV-2 infection: Study staff will confirm that you have SARS CoV-2.

Questions about symptoms: You will be asked about symptoms you are experiencing.

Questions about your health: Study staff will ask you about any health conditions you have and questions about your health in general.

Questions about medications you are taking: Study staff will ask you about medication history and medications you are taking while on study.

Secondary contact request: You will be asked to provide contacts close to you (like a family member or a neighbor) in case study staff cannot reach you. We ask that you tell these contacts about your being in the study, and that they may receive a call from study staff if study staff cannot reach you. You will also be asked to provide your health care provider contact information. If study staff cannot reach you, they will call your secondary contacts. You will also be asked to provide your home address at study entry only.

Study kit received: You will receive a kit that includes information about the study, instructions on study procedures, the symptom diary, study treatment (you will take the first dose of study treatment at the entry visit), instructions on what to do if you have worsening symptoms and go to the hospital, and contact information for the study staff. **You may also receive a self-addressed stamped envelope to mail your symptom diary back to the clinic in case your Day 20 study visit is remote.**

Remote contact: Study staff will call you on the phone, or by video. If study staff cannot reach you, they will call your secondary contacts.

Adherence assessment: You will be asked to keep track of how you are taking study treatment in the symptom diary (**hydroxychloroquine** and Azithro or Placebo**s**). Study staff will ask you how you are taking your study treatment when they review the symptom diary with you.

Review symptom diary: At study entry, you will review the symptom diary in person or remotely with study staff. You will complete the first day of the diary with the study staff **prior to taking your first dose of study medication**. You will then fill out the diary every day in the evening for 21 days. You will review the diary over the phone with study staff at the scheduled visits. They will ask you the questions that are on the diary. The questions are about how you are feeling related to COVID-19, other medications you are taking, and if you have received any urgent medical care during the study. You will also take your temperature, if you have a thermometer at home.

Return of symptom diary **to study staff**: You will **return** the symptom diary packet back to **study staff**.

For US sites that are pre-selected, include the following:

In-person visit: Some study visits will be in-person only if you choose to have study staff conduct an intensive nose swab, self-collect nose swab, or have blood collected and stored.

Blood collected and stored: Blood may be collected from a vein in your arm for research tests that may include SARS-CoV-2. Your blood will be stored.

Self-collect nose swab: Swabs are used to detect viruses. You will place a swab in each nostril and rotate the swab several times. Study staff will provide you with further instructions about the nose swabs. You will not receive results of these tests.

Intensive nose swab: You will have the option of having study staff do nasopharyngeal swabs. They are used to detect respiratory viruses. Study staff will tell you how this procedure is performed. A swab will be inserted into your nostril. The swab will be placed in deep towards to the back of your throat. The swab will be in place for several seconds and then slowly removed. This is an uncomfortable procedure. You will not receive results of these tests.

ATTACHMENT C: CONSENT FOR USE OF EXTRA SAMPLES

[Attachment C Consent is only for US sites that are pre-selected]

When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called “extra samples.” The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the ACTG repository located in the United States.

There is no limit on how long your extra samples will be stored. *[Site: Revise the previous sentence to insert limits if your regulatory authority imposes them.]*

When a researcher wants to use your samples and information, his or her research plan must be approved by the ACTG. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review the plan. *[Site: If review by your institution’s IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher’s location. This means that researchers who are not part of the protocol team may use your samples without asking you again for your consent.

You will not be paid for your samples. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you.

You may withdraw your consent for research on your extra samples at any time and the specimens will be discarded.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selection.

Research without Human Genetic Testing
If you agree, your extra samples may be stored (with usual protection of your identity) and used for ACTG-approved research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my samples.

OR
____ (initials) I understand but I do not agree to this storage and possible use of my samples.

Research with Human Genetic Testing
Your extra samples will not be used for human genetic testing.