CLINICAL STUDY PROTOCOL

Open-Label, Non-Randomized Study to Evaluate Anti-Malarial/Anti-Infective Combination Therapies in Patients with Confirmed COVID-19 Infection

Protocol Number

HRI-COVID-19-Anti-Malarial-001

Sponsor

HonorHealth

10510 N. 92nd Street, Scottsdale, AZ, 85258, United States

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Study Personnel

Principal Investigator

Michael Gordon
Honor Health
Research
Email: mgordon@honorhealth.com

Investigator

Sunil Sharma
Email: ssharma@tgen.org

Synopsis

Primary Objective

The primary objective of this study is to evaluate the anti-viral activity of the drug combination of atovaquone (Mepron) and azithromycin (Zithromax) in patients with confirmed COVID-19 infection seen at any HonorHealth facility with regard to moderate or severe COVID-19 infection. The severity of the illness will be assessed by NEWS score (1). An online calculator which is available to rapidly calculate the NEWS Score (https://www.mdcalc.com/national-early-warning-score-news-2) for the participants.

Patients will be divided into two subgroups: Medium (5-6) or Severe (More than or equal to 7).

References

a. Authors: Liao X, Wang B & Kang Y. Title: Novel coronavirus infection during the 2019-2020 epidemic: preparing intensive care units-the experience in Sichuan Province, China. Publication: Intensive Care Medicine Publication date: 2020; Issue: 46: Page/Line: 357.

Secondary Objectives

The secondary objective of this trial is to study the effects of the combination of atovaquone and azithromycin in patients with confirmed COVID-19 infections which are being cared for at HonorHealth facilities with regard to:

1. Safety in this population of patients

Additionally, exploratory translational objectives will be studied.

Study Duration

6-12 months

Study Design

This is an open-label, non-randomized study. Patients seen at any HonorHealth facility presenting with a confirmed COVID-19 infection and deemed to be high risk or suffering from respiratory symptoms will be approached to participate.

Study Population

Male and Female participants 18 years of age or older and with a confirmed positive test COVID-19 infection.

Number of Participants

Up to twenty-eight (28) patients will be enrolled, and twenty-five (25) patients are anticipated to be evaluable. Assuming a drop-out rate of 10%.
Number of Study Sites This is single-institutional study conducted across all HonorHealth facilities caring for COVID-19 patients (SOMC, SSMC, and JCL).
Primary Outcome Variables The primary endpoint of this study is the virology cure rate of atovaquone/azithromycin combination therapy
Secondary and Exploratory Outcome Variables Secondary Endpoints: • Evaluate the safety and tolerability of the atovaquone/azithromycin combination therapy versus best supportive therapy related to cardiac toxicity (QTc), GI effects (Nausea, Vomiting, Diarrhea, and Constipation). Exploratory Endpoints: • Immune response as defined by changes in WBC with differentials, B cells, T cells, NK cells as a result of atovaquone/azithromycin combination therapy compared to best supportive therapy.

Abbreviations

Abbreviation	Explanation
Ab	Antibody
AE	Adverse Event
Ag	Antigen
AGEP	Acute generalised exanthematous pustulosis
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATQ	Atovaquone
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDAD	Clostridium difficile-associated diarrhea
CFR	Code of Federal Regulations
CITI	Collaborative Institutional Training Initiative
CK	Creatine Kinase
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRP	C-reactive protein

CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DRESS	Drug reaction with eosinophilia and systemic symptoms
ECG	Electrocardiogram
EDC	Electronic Data Capture
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HBV	Hepatitis B Virus
Hct	Hematocrit
HCV	Hepatitis C Virus
HGB	Hemoglobin
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
INR	International Normalized Ratio
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
MERS	Middle East Respiratory Syndrome

MG	Myasthenia Gravis
NK	Natural Killer
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QTcF	QT Interval corrected for heart rate using Fridericia's correction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SO	Schedule of Assessments
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper Limit of Normal
WBC	White Blood Cell
WNL	Within Normal Limit

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1 - Introduction

1.1 Introductory Statement

This protocol is for a human research trial. The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines, applicable United States (US) Code of Federal Regulations (CFR), and HonorHealth Institutional Policies.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol requires review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form must be IRB-approved: a determination shall be made by the IRB of record regarding whether a new consent needs to be obtained from participants who provided consent using a previously approved consent form.

2 - Background

2.1.1 Preclinical Experience

Atovaquone and Azithromycin

Atovaquone, a naphthoquinone antimalarial drug, is a ubiquinone (coenzyme Q) analog that inhibits mitochondrial transport by inhibiting the cytochrome complex III (bc1 complex). It also inhibits nucleic acid ad adenosine triphosphate (ATP) synthesis in susceptible cells. It also depleted trace cellular nucleotide pools by inhibiting dihydroorotate dehydrogenase, an enzyme for de novo pyrimidine synthesis. The drug has been able to inhibit a variety of viruses including CHIKV and ZIKV. Atovaquone was identified as a potential drug for COVID-19 based on analytical modeling performed by Sadek et al. (2) Azithromycin is a macrolide antibiotic with a broad range of anti-microbial activity. Gielen et al (3) have demonstrated that azithromycin has the ability to induce rhinovirus 1B- and rhinovirus 16-induced interferons and interferon stimulated gene mRNA expression and protein production. A combination of Atovaquone and Azithromycin has been approved for treatment of babesiosis which is a parasitic infection in humans.

References

a. Authors: Farag A, Wang P, Ahmed M, Sadek H. Title: Identification of FDA Approved Drugs Targeting COVID-19 Virus by Structure-Based Drug Repositioning. Publication: ChemRxiv Publication date: 2020; doi: 10.26434/chemrxiv.12003930.v.

b. Authors: Gielen V, Johnston, SL, Edwards, MR. Title: Azithromycin induces anti-viral responses in bronchial epithelial cells. Publication: European Respiratory Journal Publication date: 2010; Issue: 36: Page/Line: 646.

2.1.2 Clinical Experience

Gautret et al (4) initially reported a small study in patients with COVID-19 infection, **HCQ** 200 mg orally three times daily showed a significant reduction in viral load at D6-post inclusion compared to best supportive therapy controls. Azithromycin added to HCQ was significantly more efficient in virus elimination. At Day 6 post-study inclusion, 70% of patients treated with HCQ were virologically cured compared with 12.5% of patients in the control group (best supportive care) (p=0.001). Between HCQ monotherapy and HCQ/AZI combination therapy, 100% of patients in the combination therapy were virologically cured at Day 6 post-study inclusion versus 57.1% in the monotherapy group (p<0.001). In a subsequent publication, 80 patients with COVID-19 infection were treated with the combination of HCQ/AZI with an associated rapid decline in nasopharyngeal viral load tested by qPCR. 83% of patients were negative at Day 7 and 93% at Day 8. The number of patients presumably contagious steadily decreased over time and reached zero by Day 12.

The combination of **atovaquone** and **azithromycin** has been extensively studied in the setting of systemic babesiosis where patients were treated with ATQ 750 mg PO Q12H and azithromycin (500 mg PO day 1 and 250 mg PO QD thru day 7). The most common side effects of the ATQ/AZI combination were diarrhea and rash (each 8 percent of the subjects).

The ATQ/AZI combination was successful in clearing babesiosis infection in 65% of the patients studied. In a subsequent trial, Krause et al (5) achieved successful results in 98% of patients treated with the same regimen with similar safety and tolerability.

References

a. Authors: Gautret P, Lagier JC, Parola P et al. Title: Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Publication: International Journal of Antimicrobial Agents

b. Authors: Krause PJ, Lepore T, Sikand VK et al. Title: Atovaquone and Azithromycin for the Treatment of Babesiosis. Publication: New England Journal of Medicine Publication date: 2000; Issue: 343: Page/Line: 1454.

2.2 Background/prevalence of research topic

Corona viruses are a large family of viruses that can cause illnesses ranging widely in severity. The first known severe illness caused by a coronavirus emerged with the 2003 Severe Acute Respiratory Syndrome (SARS) epidemic in China. A second outbreak of severe illness began in 2012 in Saudi Arabia with the Middle East Respiratory Syndrome (MERS).

On December 31, 2019, Chinese authorities alerted the World Health Organization of an outbreak of a novel strain of coronavirus causing severe illness, which was subsequently names SARS-CoV-2. As of March 23, 2020, nearly 368,000 COVID-19 cases have been confirmed, although many more mild cases have likely gone undiagnosed. The virus has killed over 69,000 people worldwide as of March 23, 2020.

There are no known cures/treatment for COVID-19.

This study will evaluate anti-malarial/anti-infective combinations and single agents as more information becomes available. The first combination therapy to be evaluated is that of atovaquone/azithromycin in COVID-19 confirmed positive infections. Other agents will be evaluated in future amendments. In addition, the participants will be asked to participate in an add-on repository study HRI-COVID-19-002 collecting peripheral blood to evaluate immune function and for future research.

3 - Rationale/Significance

3.1 Problem Statement

COVID-19 infection, caused by the Severe Acute Respiratory syndrome, coronavirus-2 (SARS-CoV-2), has reached pandemic proportions. Up to 20% of symptomatic patients have severe disease involving the lungs, with 6.1% of these having critical disease. Among confirmed cases of infection, mortality across countries has been reported to vary between 0.8% to 8%. Respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality. Currently there are no proven treatments/cures for COVID-19 infection.

3.2 Purpose of Study/Potential Impact

This study shall evaluate the combination of atovaquone and azithromycin in patients with COVID-19 confirmed positive infection requiring therapy as determined by risk factors for complications (e.g. age, comorbid illnesses, or the presence of respiratory compromise).

3.3.1 Potential Risks

Atovaquone risks include:

- Hepatotoxicity - cases of cholestatic hepatitis, elevated liver enzymes, and fatal liver failure have been reported in patients treated with atovaquone. Patients with severe hepatic impairment must be closely monitored.
- Diarrhea
- Rash
- Headache
- Nausea
- Vomiting
- Rhinitis
- Fever
- Insomnia

Azithromycin potential risks:

- Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. Fatalities have been reported. Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the

long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is presently unknown. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that allergic symptoms may reappear when symptomatic therapy has been discontinued.

- Hepatotoxicity: Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.
- QT Prolongation: Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsade's de pointes, have been seen with treatment with macrolides, including azithromycin. Cases of torsade's de pointes have been spontaneously reported during post marketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:
    - patients with known prolongation of the QT interval, a history of torsade's de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure;
    - patients on drugs known to prolong the QT interval;
    - patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia,
    - and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.
    - elderly patients may be more susceptible to drug-associated effects on the QT interval.
- Clostridium difficile-Associated Diarrhea (CDAD): Clostridium difficile-associated diarrhea has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

- Exacerbation of Myasthenia Gravis: Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.

Other risks include those associated with venipuncture (small risk of bleeding, bruising and/or infection) and hypersensitivity to ECG machine electrodes.

As a result of the COVID-19 current situation, it is possible that participants may misunderstand the purpose of the study, or may feel anxious or about participating in a study in general. There is a potential risk of Privacy and/or Confidentiality breaches. There may be psychological risks involved in participating in this study. Participants may be referred to counseling when appropriate.

3.3.2 Potential Benefits

Anticipated benefits include successful virological control/cure of patients with COVID-19 infection and potentially a better understanding of the immunological response to COVID-19 infection.

4 - Study Objectives

4.1 Hypothesis

The combination of atovaquone/azithromycin will demonstrate favorable results with regard to control/cure of COVID-19 systemic infection.

4.2 Primary Objective

The primary objective of this study is to evaluate the anti-viral activity of the drug combination of atovaquone (Mepron) and azithromycin (Zithromax) in patients with confirmed COVID-19 infection seen at any HonorHealth facility with regard to moderate or severe COVID-19 infection. The severity of the illness will be assessed by NEWS score (1). An online calculator which is available to rapidly calculate the NEWS Score https://www.mdcalc.com/national-early-warning-score-news-2) for the participants.

Patients will be divided into two subgroups: Medium (5-6) or Severe (More than or equal to 7).

References

a. Authors: Liao X, Wang B & Kang Y. Title: Novel coronavirus infection during the 2019-2020 epidemic: preparing intensive care units-the experience in Sichuan Province, China. Publication: Intensive Care Medicine Publication date: 2020; Issue: 46: Page/Line: 357.

4.3 Secondary Objectives

The secondary objective of this trial is to study the effects of the combination of atovaquone and azithromycin in patients with confirmed COVID-19 infections which are being cared for at HonorHealth facilities with regard to:

1. Safety in this population of patients

Additionally, exploratory translational objectives will be studied.

5 - Study Design

5.1 General Design Description

This an open-label, non-randomized clinical study. Participants who consent, but do not fit eligibility criteria to receive atovaquone/ azithromycin therapy will be offered best supportive care/ best standard of care.

5.1.1 Study Date Range and Duration

The study shall enroll patients for up to 6-months with an additional 6-months for data analysis. The study will require 12-months to complete. A total of up to 30 patients will be enrolled. As the landscape for COVID-19 therapy is rapidly changing, the study may be terminated early, or extended beyond the enrollment period.

5.1.2 Number of Study Sites

This is single-institutional study conducted across all HonorHealth facilities caring for COVID-19 patients (SOMC, SSMC, and JCL).

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

The primary endpoints will be dependent on NEWS score.

1. Medium NEWS score (5-6), i) an aggressive clinical course requiring transfer to the ICU after at least three days of treatment, ii) contagiousness as assessed by PCR and/or culture, and iii) length of stay in the hospital

2. Severe NEWS score (More than or equal to 7): i) contagiousness as assessed by PCR and/or culture, and ii) length of stay in the hospital

5.2.2 Secondary and Exploratory Outcome Variables

Secondary Endpoints:

- Evaluate the safety and tolerability of the atovaquone/azithromycin combination therapy related to cardiac toxicity (QTc), GI effects (Nausea, Vomiting, Diarrhea, Constipation)

Exploratory Endpoints:

- Immune response as defined by changes in WBC with differentials, B cells, T cells, NK cells and cytokine levels as a result of atovaquone/azithromycin combination therapy

- Blood collection for whole exome/ RNA or whole genome analysis for detecting sensitivity to COVID-19 infection and/or sensitivity to response

5.3 Study Population

Male and Female participants 18 years of age or older with a confirmed positive COVID-19 test, with either Medium or High NEWS scores.

The severity of the illness will be assessed by NEWS score (6). An online calculator is available to rapidly calculate the NEWS score for the participants (National Early Warning Score (NEWS) (https://www.mdcalc.com/national-early-warning-score-news-2).

Patients will be divided into two subgroups: Medium (5-6) or Severe (More than or equal to 7).

References

a. Authors: Liao X, Wang B & Kang Y. Title: Novel coronavirus infection during the 2019-2020 epidemic: preparing intensive care units-the experience in Sichuan Province, China. Publication: Intensive Care Medicine Publication date: 2020; Issue: 46: Page/Line: 357.

5.3.1 Number of Participants

Twenty-five (25) evaluable patients with up to Thirty (30) patients enrolled.

Evaluable patients for safety are all patients who received at least 1 dose of Atovaquone/Azithromycin combination therapy.

Evaluable patients for efficacy are all patients who received at least five (5) days of combination therapy and completed efficacy evaluations within this period.

Enrolled non-evaluable patients may be replaced.

5.3.2 Eligibility Criteria/Vulnerable Populations

Inclusion Criteria:

- Male and Female patients age 18 years or older
- COVID-19 confirmed positive test results
- High risk for complications including with Medium (5-6) or High (More than or equal to 7) NEWS score
- Hematology criteria: ANC >500 cells/mcl, HGB >9 g/dl, Platelet count >75,000/mcl
- Metabolic criteria: Serum creatinine $\leq$2.0 mg/dl or calculated creatinine clearance (using Cockcroft-Gault) $\geq$30 ml/min, AST/ALT $\leq$5x ULN AND Total Bilirubin WNL (for patients with Gilbert's disease, direct bilirubin $\leq$ULN)

Exclusion Criteria:

- COVID-19 negative test result
- Inability to adhere to study protocol requirements

- Other acute or chronic medical or psychiatric condition that in the judgment of the investigator would make the participant inappropriate to take part in the study
- Pregnant or lactating women who are breast feeding should not participate
- Patient under treatment with experimental therapies
- QTc interval greater than 470 msecs at baseline
- History of hypersensitivity to atovaquone and/or azithromycin
- History of known intolerance to atovaquone and/or azithromycin

6 - Methods

6.1 Treatment - Drug

6.1.1 Identity of Investigational Product/New Drug

Atovaquone - Please refer to Mepron Prescribing Information (https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Mepron/pdf/MEPRON.PDF)

Azithromycin - Please refer to Zithromax Prescribing Information (http://labeling.pfizer.com/ShowLabeling.aspx?id=511#section-5)

6.1.2 Dosage, Admin, Schedule

Atovaquone 750 mg, PO, Q12 hours for up to 10 days. Each dose of atovaquone should be administered at the same time each day with a meal or a milky drink. If patient is on enteral nutrition (tube feeding), atovaquone should be given after enteral feeding unless this is not possible.

Azithromycin 500 mg, PO, will receive a loading dose on Day 1, followed by 250 mg, PO, Daily for up to 10 days (Days 2-10). Azithromycin tablets can be taken with or without food. **A**zithromycin should not be administered at the same time as antacids that contain aluminum or magnesium. In patients who are intubated, the equivalent azithromycin dose can be administered intravenously per prescribing information.

6.1.3 Method of Assignment/Randomization

Not applicable. This is a non-randomized study. All patients enrolled under this protocol will receive Atovaquone/ Azithromycin.

6.1.4 Blinding and Procedures for Unblinding

Not applicable

6.1.5 Packaging/Labelling

Atovaquone - Please refer to Mepron Prescribing Information (https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Mepron/pdf/MEPRON.PDF)

Azithromycin - Please refer to Zithromax Prescribing Information (http://labeling.pfizer.com/ShowLabeling.aspx?id=511#section-5)

6.1.6 Storage Conditions

Atovaquone - Please refer to Mepron Prescribing Information (https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Mepron/pdf/MEPRON.PDF)

Azithromycin - Please refer to Zithromax Prescribing Information (http://labeling.pfizer.com/ShowLabeling.aspx?id=511#section-5)

6.1.7 Concomitant therapy

Necessary supportive measures for optimal medical care including anti-viral therapy may be given throughout the study, including but not limited to anti-infectives, blood components, pain medication, hydration, bronchodilators and antiemetics. Additional care will be administered as indicated by the treating physician and the patient's medical need. No other investigational therapy will be allowed during this study. All concomitant medications and supportive therapy must be recorded on the appropriate case report form (CRF). Azithromycin should not be administered with calcium or magnesium antacids.

6.1.8 Restrictions

Atovaquone should be administered with a meal or milky drink unless this is not possible

Azithromycin capsules or liquid should be administered on an empty stomach. Azithromycin tablets can be taken with or without food.

Pregnant or lactating women who are breast feeding should not participate

6.2 Assessments

Details on procedures and timing of assessments can be found in Section 6.3.

6.2.1 Efficacy

The primary efficacy endpoints will be dependent on NEWS score.

1. Medium NEWS score (5-6) i) an aggressive clinical course requiring transfer to the ICU after at least three days of treatment (median), ii) contagiousness as assessed by PCR and/or culture (Median), and iii) length of stay in the hospital (Median) after starting the trial treatment

2. Severe NEWS score (More than or equal to 7): i) contagiousness (Median duration) as assessed by PCR and/or culture, and iii) length of stay in the hospital (Median) after starting the trial treatment.

6.2.2 Safety/Pregnancy-related policy

All females of child-bearing potential shall be evaluated for pregnancy prior to entry into the study. Study participants must use at least one method of highly effective contraception for

3 months after the final administration of study drug. Periodic abstinence with a female partner using calendar, symptothermal, post-ovulation methods, etc. is not true abstinence; participants practicing these methods shall be considered sexually active.

6.2.2.1 Adverse Events Definition and Reporting

An adverse event (AE) is an event that occurs any time during the research study and causes undesirable and unintended results which may or may not have a causal relationship with the treatment.

All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the CRF. Each AE is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors. (AE -Adverse Event)(CRF: Case Report Form)

A serious adverse event (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Life-threatening is defined as an event with immediate risk of death from the event as it occurred. It does not include an event that might have caused death if it occurred with a greater severity
- In-patient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events 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 listed outcomes above

6.2.3 Pharmacokinetics

Not Applicable

6.2.4 Biomarkers

1. Collection of Plasma for Cytokine levels and antibody serology: Screening, Day 3, Day 10 and 2 weeks after finishing the trial treatment. Two tubes of plasma will be collected (See Lab Manual for Details)

2. Collection of Whole Blood for Genomic Sequencing: At Screening

3. Throat swabs for COVID-19 PCR and/or culture: Screening, Day 3, Day 10 and 2 weeks after finishing the trial treatment.

6.3 Study Procedures

Eligibility Screening

Eligibility screening will include serology to confirm SARS-CoV-2 (COVID-19) infection, physical examination, ECG or telemetry, vital signs, safety laboratories, review of medical history and pregnancy testing in women of child-bearing potential.

Medical history, Demographics and Other Baseline Information

Medical history includes general medical history, medication history and any other relevant history as per the investigator's discretion.

The following demographic information will be recorded: Age, Ethnic origin, Race, Height and Weight

Adverse event reporting will begin for each subject from the date the informed consent is signed and will continue for 30 +/- 7 days after the final dose of study drug.

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6.3.1 Study Schedule

Table 1. Schedule of Assessments (SOA)

	Prior to first study drug administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	FU 1 (14 days + 3 days after last dose administered)	FU 2 (30 days ± 7 days after last dose administered)
Informed Consent	X												
Eligibility	X												
Medical History	X												
Demographic data	X												
Vital signs	X	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG[1]	X		X	X	X	X	X	X	X	X	X		
Chest X-Ray[2]	X	X											
Physical Examination[3]	X			X							X		
Safety Laboratory Assessments[4]	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy[5]	X												
Urinalysis[6]	X												
D-Dimer, LDH[7]	X	X	X	X	X	X	X	X	X	X	X		
Troponin[8]	X		X	X	X	X	X	X	X	X	X		
Procalcitonin[9]	X												
HBV, HCV, HIV1/2 testing	X												
SARS-CoV-2	X										X		
CD4/CD8[10]	X	X											
Plasma for Cytokines	X			X							X	X	
Whole blood	X												
Throat swabs	X			X							X	X	
Respiratory Status	X	X	X	X	X	X	X	X	X		X		
Blood and Sputum Cultures[9]	X												
Atovaquone Administration[11]		X	X	X	X	X	X	X	X	X	X		
Azithromycin Administratio[12]		X	X	X	X	X	X	X	X	X	X		
Concomitant Medications[13]	X												
Adverse Events[14]		X											

[1]If starting QTc prolonging drug, can repeat ECG in 24-48 hours to monitor QTc. If baseline QTc > 500, repeat within 24 hours and consider stopping other QTc prolonging drugs. Continue monitoring every 1-2 days if on two or more QTC prolonging drugs.
[2]Chest X-ray at screening within 48 hours of start of study therapy. Chest X-ray during study as per investigator discretion.
[3]Physical Exam at screening within 24 hours of start of study therapy and to be repeated between days 3-4, day 7 and more frequent as per investigator discretion.
[4]Safety laboratories are listed in Table 2.
[5]Only for women of child-bearing potential. Urine or serum pregnancy test as per investigator discretion.
[6]For acute kidney injury (i.e. serum creatinine >0.3 above baseline), send urinalysis and spot urine protein:creatinine
[7]Repeat daily only if elevated and as per investigator discretion.
[8]Repeat every 2-3 days if elevated or with clinical deterioration as per investigator discretion.
[9]As per participant clinical presentation and investigator discretion.
[10]At screening and as per investigator discretion
[11]Atovaquone dose: 750 mg orally every 12 hours for up to 10 days. Daily dose should be separated by approximately 12 hours at the same times each day, whenever possible, with a meal or a milky drink.
[12]Azithromycin dose: 500 mg orally once on Day 1, followed by 250 mg orally once daily for up to 10 days (Days 2-10). Daily dose should be approximately at the same time each day, whenever possible. Tablet dosage forms may be crushed after eating. Tablet dosage forms can be administered regardless of meals and should not be administered at the same time as aluminum or magnesium-containing antacids.
[13]Concomitant medications to be documented from after informed consent is obtained to completion of study medication therapy.
[14]Adverse Event assessment for FU visit may be completed by telephone call.

Table 2. Clinical Laboratory Assessments

Hematology	Serum Chemistry	Coagulation	Urinalysis
Red Blood Cell Count Hemoglobin Hematocrit Platelets White Blood Cells Count with Differential (absolute cell counts)	Sodium Potassium Chloride Creatinine Blood Urea Nitrogen (BUN) Total Bilirubin Direct Bilirubin, if abnormal total bilirubin Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Alkaline Phosphatase (ALP) Ferritin C-Reactive Protein Erythrocyte Sedimentation Rate Creatine Kinase	Prothrombin Time/International Normalized Ration (PT/INR) Partial Thromboplastin Time (PTT)	For acute kidney injury (i.e. serum creatinine >0.3 above baseline), send urinalysis and spot urine protein:creatinine

6.3.2 Informed Consent

Informed consent of the patient or legally authorized representative to participate in the study must be obtained and documented by the Investigator in accordance with the FDA regulations set forth in (21 CFR 50) as well as the applicable regulatory bodies in all other participating countries outside the United States.

Due to the risk for contamination and infection from COVID-19, the patient/legally authorized representative will be consented by explaining the study verbally. The patient/legally authorized representative will be given an IRB written consent and have the opportunity to review and to ask questions. The investigator/designee must document the verbal partisan consent in the patient's medical record. Once the patient is given the written informed consent, the document must remain in the patient's isolation area for their reference. Once it is determined that the patient is no longer infectious, the contaminated informed consent document must be disposed with all contaminated items and a new document must be provided for the patient to review and sign. At that time and before the patient is discharged from the hospital, the Investigator/designee must provide the patient with a copy of the signed informed consent form and a copy must be retained in the Investigator's study records. Verbal consent must be obtained before any protocol-required procedures are performed, including any procedure not part of normal patient care.

6.3.3 Screening

Screening shall be initiated within 24 hours of the patient/legally authorized representative providing consent to participate.

6.3.4 Recruitment, Enrollment and Retention

Patients for this study will be recruited from any HonorHealth facilities admitted patients with COVID-19 suspected/confirmed infection.

6.3.5 On Study Visits

Screening: After obtaining informed consent from the patient or legally authorized representative the following assessments shall be completed:

- Review Eligibility
- Obtain Medical History
- Obtain Demographic Data
- Vital Signs - Temperature, Blood Pressure, Respiratory Rate, Heart Rate
- 12-Lead ECG
- Chest X-Ray
- Physical Examination
- Hematology
- Chemistry
- Coagulation
- Urinalysis
- Pregnancy test for WOCBP
- D-Dimer, LDH
- Troponin
- CD4/CD8
- Procalcitonin, if clinically indicated
- HBV, HCV, HIV1/2 and COVID-19 serology
- Plasma for cytokines
- Whole blood
- Throat swabs
- Respiratory Status
- Blood and Sputum cultures, if clinically indicated
- Prior and Concomitant Medications

Day 1

- Vital signs
- Hematology
- Chemistry
- Coagulation

- Urinalysis, if serum creatinine > 0.3 above baseline
- D-Dimer, LDH
- Respiratory Status
- Atovaquone administration - twice daily
- Azithromycin administration - daily
- Blood and Sputum cultures, if clinically indicated
- Procalcitonin, if clinically indicated
- CD4/CD8, if clinically indicated
- Chest X-Ray, if clinically indicated
- Prior and Concomitant Medications
- Adverse event assessment

Day 2

- Vital Signs
- 12-Lead ECG
- Hematology
- Chemistry
- Coagulation
- Urinalysis, if serum creatinine > 0.3 above baseline
- D-Dimer, LDH
- Troponin, if clinically indicated
- Respiratory Status
- Atovaquone administration - twice daily
- Azithromycin administration - daily
- Blood and Sputum cultures, if clinically indicated
- Procalcitonin, if clinically indicated
- CD4/CD8, if clinically indicated
- Chest X-Ray, if clinically indicated
- Prior and Concomitant Medications
- Adverse event assessment

Day 3

- Vital Signs
- 12-Lead ECG, if clinically indicated (QTc >500 msec)
- Physical Exam - either day 3 or day 4
- Hematology
- Chemistry
- Coagulation
- Urinalysis, if serum creatinine > 0.3 above baseline
- D-Dimer, LDH
- Troponin, if clinically indicated
- Plasma for cytokines
- Throat swabs
- Respiratory Status
- Atovaquone administration - twice daily
- Azithromycin administration - daily
- Blood and Sputum cultures, if clinically indicated
- Procalcitonin, if clinically indicated
- CD4/CD8, if clinically indicated
- Chest X-Ray, if clinically indicated
- Prior and Concomitant Medications
- Adverse event assessment

Day 4

- Vital Signs
- 12-Lead ECG, if clinically indicated (QTc >500 msec)
- Physical Exam - either day 3 or day 4
- Hematology
- Chemistry
- Coagulation
- Urinalysis, if serum creatinine > 0.3 above baseline
- D-Dimer, LDH
- Troponin, if clinically indicated

- Respiratory Status
- Atovaquone administration - twice daily
- Azithromycin administration - daily
- Blood and Sputum cultures, if clinically indicated
- Procalcitonin, if clinically indicated
- CD4/CD8, if clinically indicated
- Chest X-Ray, if clinically indicated
- Prior and Concomitant Medications
- Adverse event assessment

Day 5

- Vital Signs
- 12-Lead ECG, if clinically indicated (QTc >500 msec)
- Hematology
- Chemistry
- Coagulation
- Urinalysis, if serum creatinine > 0.3 above baseline
- D-Dimer, LDH
- Troponin, if clinically indicated
- Respiratory Status
- Atovaquone administration - twice daily
- Azithromycin administration - daily
- Blood and Sputum cultures, if clinically indicated
- Procalcitonin, if clinically indicated
- CD4/CD8, if clinically indicated
- Chest X-Ray, if clinically indicated
- Prior and Concomitant Medications
- Adverse event assessment

Day 6

- Vital Signs
- 12-Lead ECG, if clinically indicated (QTc >500 msec)

- Hematology
- Chemistry
- Coagulation
- Urinalysis, if serum creatinine > 0.3 above baseline
- D-Dimer, LDH
- Troponin, if clinically indicated
- Respiratory Status
- Atovaquone administration - twice daily
- Azithromycin administration - daily
- Blood and Sputum cultures, if clinically indicated
- Procalcitonin, if clinically indicated
- CD4/CD8, if clinically indicated
- Chest X-Ray, if clinically indicated
- Prior and Concomitant Medications
- Adverse event assessment

Day 7

- Vital Signs
- 12-Lead ECG, if clinically indicated (QTc >500 msec)
- Hematology
- Chemistry
- Coagulation
- Urinalysis, if serum creatinine > 0.3 above baseline
- D-Dimer, LDH
- Troponin, if clinically indicated
- Respiratory Status
- Atovaquone administration - twice daily
- Azithromycin administration - daily
- Blood and Sputum cultures, if clinically indicated
- Procalcitonin, if clinically indicated
- CD4/CD8, if clinically indicated

- Chest X-Ray, if clinically indicated
- Prior and Concomitant Medications
- Adverse event assessment

Day 8

- Vital Signs
- 12-Lead ECG, if clinically indicated (QTc >500 msec)
- Hematology
- Chemistry
- Coagulation
- Urinalysis, if serum creatinine > 0.3 above baseline
- D-Dimer, LDH
- Troponin, if clinically indicated
- Respiratory Status
- Atovaquone administration - twice daily
- Azithromycin administration - daily
- Blood and Sputum cultures, if clinically indicated
- Procalcitonin, if clinically indicated
- CD4/CD8, if clinically indicated
- Chest X-Ray, if clinically indicated
- Prior and Concomitant Medications
- Adverse event assessment

Day 9

- Vital Signs
- 12-Lead ECG, if clinically indicated (QTc >500 msec)
- Hematology
- Chemistry
- Coagulation
- Urinalysis, if serum creatinine > 0.3 above baseline
- D-Dimer, LDH
- Troponin, if clinically indicated

- Respiratory Status
- Atovaquone administration - twice daily
- Azithromycin administration - daily
- Blood and Sputum cultures, if clinically indicated
- Procalcitonin, if clinically indicated
- CD4/CD8, if clinically indicated
- Chest X-Ray, if clinically indicated
- Prior and Concomitant Medications
- Adverse event assessment

Day 10

- Vital Signs
- 12-Lead ECG, if clinically indicated (QTc >500 msec)
- Physical Exam
- Hematology
- Chemistry
- Coagulation
- Urinalysis, if serum creatinine > 0.3 above baseline
- D-Dimer, LDH
- Troponin, if clinically indicated
- Respiratory Status
- Atovaquone administration - twice daily
- Azithromycin administration - daily
- Blood and Sputum cultures, if clinically indicated
- Procalcitonin, if clinically indicated
- CD4/CD8, if clinically indicated
- Chest X-Ray, if clinically indicated
- Prior and Concomitant Medications
- Adverse event assessment

6.3.6 End of Study and Follow-up

Follow-Up Visit 1: 14 days +/- 3 days after last dose of study drug

- Plasma for cytokines

- Throat swabs
- Concomitant medications - may take place by telephone contact
- Adverse Event Assessment - may take place by telephone contact

Follow-Up Visit 2: 30 days +/- 7 days after last dose of study drug

- Adverse Events - Telephone Contact

6.3.7 Removal of subjects

Patients may be removed from the study under the following circumstances:

- Deterioration of patient clinical state
- Improvement of patient clinical state
- Patient's physician considers a change of therapy would be in the best interest of the patient
- Patient requests discontinuation/withdrawal from study
- Continued unacceptable toxicities despite optimal treatment or dose reduction
- Patient becomes pregnant or fails to use adequate birth control (for those patients who are fertile)
- Need for any treatment not allowed by the protocol
- Non-compliance
- Critical protocol violation that may invalidate the data, at the discretion of the investigator

Participants who withdraw or are withdrawn prior to completing Day 3 visit assessments may be replaced, except those withdrawn due to AEs or for safety reasons at the discretion of the investigator.

6.4 Statistical Method

6.4.1 Statistical Design

All data will be entered an analyzed using IBM SPSS v. 26. Data will be screened for parametric statistical test assumptions. Non-parametric tests will be employed should parametric assumptions not be met. The a priori alpha level for all tests will be set at .05. The Bonferroni correction will be applied for multiple tests on the same sample to adjust for inflation of the alphawise error rate.

6.4.2 Sample Size Considerations

This investigation will utilize a convenience sample and therefor the sample size determination was not statistically based. With 25 evaluable patients, an alpha of .05, and using a hypothesized median difference of time to viral cure rate of 7 days (from 14 days), there is a 75% probability of correctly assessing a true difference.

6.4.3 Planned Analyses

6.4.3.1 Primary Analyses

The primary endpoint is the virology cure rate of atovaquone/azithromycin combination therapy. Time-to-event tests will be conducted to assess median time to viral cure for patients receiving atovaquone/azithromycin combination therapy compared to those receiving best supportive therapy.

6.4.3.2 Secondary Objectives Analyses

The secondary endpoint is to evaluate the safety and tolerability of the atovaquone/azithromycin combination therapy versus best supportive therapy related to cardiac toxicity (QTc), GI effects (Nausea, Vomiting, Diarrhea, and Constipation). Frequencies of adverse and severe adverse events (AE and SAE) will be reported and descriptive statistics on severity for each AE (scaled from 1-4) will be reported for each documented AE and SAE.

Exploratory endpoints include immune response as defined by changes in WBC with differentials, B cells, T cells, NK cells as a result of atovaquone/azithromycin combination therapy compared to best supportive therapy. Repeated-measures analysis of variance (RM-ANOVA) and multiple analysis of variance tests (RM-MANOVA) will be conducted to evaluate changes in WBC with differentials, B cells, T cells, NK cells in patients receiving atovaquone/azithromycin combination therapy compared to those receiving best supportive therapy at baseline, day 7, day 14, and end of treatment.

6.4.3.3 Safety/Pregnancy-related policy

Refer to Section 6.2.2

6.4.3.4 Analysis of Subject Characteristics

Descriptive and clinical characteristics will be reported using means and standard deviations for continuous variables and frequencies for categorical variables. Initial group comparisons using t-tests (for continuous) and $\chi 2$ (for frequencies) will be conducted to assess initial group differences. If differences are found, variables will be treated as covariates.

6.4.3.5 Interim Analysis

Not applicable

6.4.3.6 Health economic evaluation

Not applicable

6.4.4 Subsets and Covariates

Not applicable

6.4.5 Handling of Missing Data

When there is missing data for any particular assessment/ time point, the patient will not be evaluable at that specific assessment/timepoint.

7 - Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each study procedure/assessment. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by providing verbal consent, and/or signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that informed consent was obtained using the updated/revised Consent Forms for continued participation in the study. A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by regulatory agency inspectors at any time. Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996.

Due to the risk for contamination and infection from COVID-19, the patient/legally authorized representative will be consented by explaining the study verbally, over the phone, if necessary, using the written IRB-approved informed consent document. The patient/legally authorized representative will have the opportunity to review the written consent document and to ask questions. The investigator/designee must document the verbal consent in the patient's medical record. Once the patient is given consent, the document must remain with the patient for their reference. Once the patient is discharged, the contaminated informed consent document must be disposed with all contaminated items and a new document must be provided for the patient. The informed consent document may be provided to the patient in person, via e-mail or via mail. Verbal consent must be obtained and documented before any protocol-required procedures are performed, including any procedure not part of normal patient care.

7.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required.

The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year.

A study closure report will be submitted to the IRB after all research activities have been completed.

Other study events (e.g. data breaches, protocol deviations) will be submitted per Honor Health IRB's policies.

7.3 Subject Confidentiality

Subject confidentiality is held in strict trust by the research team. Subject medical record review will be limited to the just the elements needed to complete the study. Only authorized HIPAA and CITI trained study team members will be allowed to extract research data from medical records and enter it into RedCap electronic data capture (EDC). No direct subject identifiers will be entered into RedCap.

Each subject will be assigned a unique study number. A master list linking the unique study number to the human subject will be maintained the Clinical Trial Management System.

7.4 Deviations/Unanticipated Problems

If the study team becomes aware of an anticipated problem (e.g. data breach, protocol deviation), the event will be reported to the IRB according to institutional policies and procedures.

7.5 Data Collection

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the patient medical records. In these cases, data collected on the CRFs must match the data in those charts. In some cases, the CRF may also serve as the source document. In these cases, a note to file document should be available at the investigator site that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

7.6 Data Quality Assurance

The Sponsor will oversee the study conduct to ensure that the protocol and Good Clinical Practices (GCP) are being followed. The sponsor representative may review the source documents to confirm that the data recorded on the CRFs are accurate.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Honor Health, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Sponsor immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor to prepare the investigator site for the inspection. The investigator site and investigator will promptly

resolve any discrepancies that are identified between the study data and the patient's medical records.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

7.7 Study Records

The investigator shall comply with all applicable Federal regulatory requirements, ICH-GCP and Clinical Trials Registration (42 CFR Part 11).

7.8 Access to Source

Source documentation may be maintained electronically and in paper form. Sponsor and regulatory agencies shall have access to all study source documentation upon request. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to Institutional Policies and Procedures. Once study is complete/closed, source documentation may be archived for long-term storage.

7.9 Data or Specimen Storage/Security

Electronic study data shall be maintained in a (21 CFR Part 11) compliant application. Paper records shall be stored in the investigator/designee restricted access area.

All study specimens shall be stored in Honor Health Research Laboratory facilities with restricted access only to authorized research laboratory staff. All study specimens shall be de-identified. The Sponsor shall maintain information on specimen transfer to other facilities.

7.10 Retention of Records

Records and documents pertaining to the conduct of this study, including eCRFs, electronic or paper data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for the length of time required federal, state and local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

7.11 Study Monitoring

All aspects of the study will be carefully monitored with respect to all applicable regulations and Institutional Policies and Procedures. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator or designee.

Protocol deviations will be handled in accordance with Institutional Policies and Procedures.

7.12 Data Safety Monitoring Plan

No formal Data Safety Monitoring Committee is planned. Members of the study team and the principal investigator shall meet at least every 2 weeks to discuss study participants, clinical management and the need for study amendments/closure and other study administrative matters.

7.13 Study Modification

Amendments must be sent to the IRB for approval prior to implementation (as appropriate). Actions to ensure the safety of subjects may be implemented prior to receiving IRB approval, but the IRB must be notified promptly.

All study modifications must be approved by the IRB of record before implementing, except in cases where the implementation of the modification will directly impact on the safety of study participants. The Clinical Investigator(s) in consultation with the Sponsor and Institutional Review Boards (IRBs), may determine that the protection of a participant's safety, welfare, and rights is best served by modifying the study conduct. Such decisions will depend on specific circumstances. These decisions must be clearly documented in the study records. It is critical that trial participants are kept informed of changes to the study that could impact them.

7.14 Study Discontinuation

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB, investigational product safety problems and/or availability or at the discretion of the Sponsor.

7.15 Study Completion

The study shall be considered completed when:

- All patients have completed treatment/study assessments
- Study data has been entered in CRF
- Safety data has been verified in the CRFs
- Notification from IRB has been received acknowledging study completion

7.16 Conflict of Interest Policy

The Investigator and key study personnel must complete a Clinical Investigator Financial Certification/Disclosure Statement to report financial interests and arrangements as per HonorHealth Institutional Policy.

7.17 Funding Source

There is no external funding for this study. The Sponsor shall cover administrative costs for this study.

7.18 Publication Plan

The results of this study may be published or presented at scientific meetings by the investigator at any time. For all publications relating to the study, the principal investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

Furthermore, authorship of publications will be determined by mutual agreement between investigators and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in clinical study agreements, the publication policy set-put in this section shall not apply.

List of Tables

Title
Table 1. Schedule of Assessments
Table 2 Clinical Laboratory Assessments

References

1. Liao X, Wang B & Kang Y. Novel coronavirus infection during the 2019-2020 epidemic: preparing intensive care units-the experience in Sichuan Province, China. Intensive Care Medicine 2020; 46:357.

2. Farag A, Wang P, Ahmed M, Sadek H. Identification of FDA Approved Drugs Targeting COVID-19 Virus by Structure-Based Drug Repositioning. ChemRxiv 2020; doi: 10.26434/chemrxiv.12003930.v.

3. Gielen V, Johnston, SL, Edwards, MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. European Respiratory Journal 2010; 36:646.

4. 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. International Journal of Antimicrobial Agents

5. Krause PJ, Lepore T, Sikand VK et al. Atovaquone and Azithromycin for the Treatment of Babesiosis. New England Journal of Medicine 2000; 343:1454.

6. Liao X, Wang B & Kang Y. Novel coronavirus infection during the 2019-2020 epidemic: preparing intensive care units-the experience in Sichuan Province, China. Intensive Care Medicine 2020; 46:357.