A Prospective Clinical Study of Hydroxychloroquine in the Prevention of SARS-COV-2 (COVID-19) Infection in Health Care Workers after High-Risk Exposures

Protocol Version 1.4 – 28-MAY-2020

Protocol

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A PROSPECTIVE CLINICAL STUDY OF HYDROXYCHLOROQUINE IN THE PREVENTION OF SARS-COV-2 (COVID-19) INFECTION IN HEALTH CARE WORKERS AFTER HIGH-RISK EXPOSURES

VERSION 1.4 – 28-MAY-2020

SPONSOR APPROVAL AND SIGNATURE PAGE

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INVESTIGATOR'S AGREEMENT

I have received and read the package insert for hydroxychloroquine. I have read the BRI-001 clinical study protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

___Peter A. McCullough, MD, MPH _____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Medical and Scientific Leader		
Clinical Study Manager		
Medical Monitor		
SAE Reporting	Safety Hotline: Safety Fax: E-mail	

2. SYNOPSIS

Name of Sponsor/Company:
Baylor Scott and White Research Institute

Name of Investigational Products:
Hydroxychloroquine 200 mg tablets

Title of Study:
A PROSPECTIVE CLINICAL STUDY OF HYDROXYCHLOROQUINE IN THE PREVENTION OF SARS-COV-2 (COVID-19) INFECTION IN HEALTH CARE WORKERS AFTER HIGH-RISK EXPOSURES

Study center(s): Single center

Studied period: 4 months Estimated date first subject enrolled: March 2020 Estimated date last subject completed: July 2020	**Phase of development:** 2

Objectives:

For Healthcare workers with

- One day or more of exposure to suspected and/or positive COVID-19 patients, including but not limited to those working in the Emergency Department or Intensive Care Unit.
  OR
- Unprotected exposure to a known positive COVID-19 patient within 72 hours of screening.

Primary:

- To assess the efficacy of hydroxychloroquine 400 mg (two 200 mg tablets) twice a day on day 1 followed by two 200 mg tablets once a week for a total of 7 weeks in the prevention of COVID-19 infection

Secondary:

- To compare the rate of COVID-19 positive conversion among emergency department workers versus intensive care unit workers

Endpoints:

Primary Efficacy Endpoint:

Rate of COVID-19 positive conversion on weekly nasopharyngeal (NP) sampling

Secondary Efficacy Endpoint:

Time-to-first clinical event consisting of a persistent change for any of the following:

- One positive NP sample
- Common clinical symptoms of COVID-19 infection including fever, cough, and shortness of breath
- Less common signs and symptoms of COVID-19 infection including headache, muscle pain, abdominal pain, sputum production, and sore throat

Exploratory Efficacy Endpoint:

Time-to-first clinical worsening event consisting of any of the following:

- Hospitalization for COVID-19 infection
- Intensive care unit admission for COVID-19 infection
- All cause death

Safety:

Participants will be closely monitored for any occurrence of adverse events or serious adverse events during the trial. Weekly in-person visits will be scheduled to capture the frequency, intensity, and relationship to study drug of (serious) adverse events. Body temperature will also be collected in all follow-up visits.

Methodology:

This prospective open label trial will study the safety, tolerability, and efficacy of hydroxychloroquine 400 mg po in qualified health care workers.

Qualified individuals will be prescribed oral hydroxychloroquine 400 mg twice a day (two 200 mg tablets twice a day) on day 1 followed by two 200 mg tablets once a week for a total of 7 weeks. Dose de-escalation is permitted during the study if indicated clinically. Please refer to Section 7.3.1 for additional details on dose escalation and dose de-escalation.

All study individuals will follow the same visit and assessment schedule. Following study recruitment, participants will be scheduled to be assessed in person during treatment at days 7, 14, 21, 28, 35, 42 and 49.

Healthcare workers who are qualified for the trial but decline participation in receiving the treatment will form the control group and will be offered an observational registry where the same NP COVID-19 sampling schedule and other assessments will be followed with the exception of blood testing. The clinical outcomes will be captured in the same manner and with the same definitions as the clinical arm.

Number of Subjects (planned):

360 individuals will be enrolled into the study with half enrolling in the active treatment study and the other half, those who refuse to get the study treatment, will be entering an observational registry considered as the control group.

Main criteria for inclusion:

1. Adult male and female healthcare workers ≥ 18 to ≤ 75 years of age upon study consent
2. Healthcare workers with
    - One day or more of exposure to suspected and/or positive COVID-19 patients, including but not limited to those working in the Emergency Department or Intensive Care Unit.

    OR

    - Unprotected exposure to a known positive COVID-19 patient within 72 hours of screening.
3. Afebrile with no constitutional symptoms
4. Willing and able to comply with scheduled visits, treatment plan, and other study procedures
5. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study prior to initiation of any subject-mandated procedures

Major exclusion criteria:

1. Participation in other investigational clinical trials for the treatment or prevention of SARS-COV-2 infection within 30days
2. Unwilling to practice acceptable methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) during Screening, while taking study drug, and for at least 30 days after the last dose of study drug is ingested

Note: the following criteria follow standard clinical practice for FDA approved indications of this medication

3. Having a prior history of blood disorders such as aplastic anemia, agranulocytosis, leukopenia, or thrombocytopenia
4. Having a prior history of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency
5. Having dermatitis, psoriasis or porphyria
6. Taking Digoxin, Mefloquine, methotrexate, cyclosporine, praziquantel, antacids and kaolin, cimetidine, ampicillin, Insulin or antidiabetic drugs, arrhythmogenic drugs, antiepileptic drugs, loop, thiazide, and related diuretics, laxatives and enemas, amphotericin B, high dose corticosteroids, and proton pump inhibitors, neostigmine, praziquantel, Pyridostigmine, tamoxifen citrate
7. Allergies: 4-Aminoquinolines
8. Pre-existing retinopathy of the eye
9. Has a chronic liver disease or cirrhosis, including hepatitis B and/or untreated hepatitis
10. Untreated or uncontrolled active bacterial, fungal infection
11. Known or suspected active drug or alcohol abuse, per investigator judgment
12. Women who are pregnant or breastfeeding
13. Known hypersensitivity to any component of the study drug
14. A known history of prolonged QT syndrome or history of additional risk factors for torsades de pointe (e.g., heart failure, requires a lab test , family history of Long QT Syndrome), or the use of concomitant medications that prolong the QT/QTc interval

Investigational product, dosage and mode of administration:

Oral hydroxychloroquine 400 mg twice a day (two 200 mg tabs twice a day) on day 1 followed by two 200 mg tablets once a week for a total of 7 weeks.

Duration of treatment:

Study drug will be administered for 7 weeks.

Criteria for evaluation:

Efficacy: Rate of COVID-19 positive conversion on weekly nasopharyngeal (NP) sampling

Safety: Body temperature measurements, adverse events, and serious adverse events.

Statistical methods:

Sample size: A total sample of 360 individuals (180 in each arm) would provide at least 80% power to detect a relative risk reduction of 40% in the rate of positive NP samples when the anticipated rate of positive conversion among those taking hydroxychloroquine is approximately 30%.

The power calculation, which was based on Pearson Chi Square test, assumes the following:

- One-sided Type I error rate of 0.05
- Anticipated positive NP samples rate of 30% in the clinical arm
- A 40% lower risk of a positive NP sample comparing the hydroxychloroquine group vs the controls
- Loss to follow-up rate of 15%

Primary analysis of efficacy:

The proportion of individuals who tested positive at least once during the study period will be compared between the clinical and the control arms. In addition, the potential effect of hydroxychloroquine on COVID-19 free survival time will also be explored by utilizing appropriate statistical methods. An intent-to-treat approach will be used throughout the analysis with the control group as the referent. A p-value < 0.05 will be considered statistically significant and a risk reduction of 5% will be considered as of smallest clinical importance.

Study Rationale

It is clear that close interaction of health care workers with patients put them at higher risk of getting exposed to infectious diseases. Failing to provide a safe environment for health care workers could cripple the medical system especially during an Epidemic outbreak like COVID-19. It is imperative to make sure that doctors and nurses do not get sick in high numbers; not only because that will contribute to spreading the virus among vulnerable patients but also due to their subsequent role in reducing the number of responding personnel. As a result, it is of utmost importance to provide effective prophylaxis to healthcare workers who are exposed to COVID-19.

Schema for Study of Prophylactic Therapies for COVID-19 Exposure

The trial design is initially for a 7 week treatment period which can be divided into 7 bins of time to allow a flexible design. Given the fluid nature of information flow in this pandemic that for example, new information comes forward clearly showing that 6 days is a sufficient period of time for proven prophylaxis, this trial design can be altered. Conversely if each subsequent qualifying exposure calls for another 6-day bin of time, the protocol can flex to the maximum 7 week period as stated for resource planning.

Once subject's eligibility is approved they may choose to either receive hydroxychloroquine or enter the observational registry. In both cases subjects will be tested for COVID-19 positive conversions on weekly nasopharyngeal (NP) sampling. The swab samples will be collected by trained personnel. Nasopharyngeal swab will be collected in a VCM medium tube or equivalent (UTM) or E-swabs/Amies medium (minitip-NP swab) or M4, M4RT, M5 and M6 transport media. The Roche Cobas test will be utilized for detecting nucleic acids from SARS-CoV-2 in nasopharyngeal swab samples collected from study participants.

The safety of the study participants will be ensured by closely monitoring the (serious) adverse events occurring during the trial. In addition, we will comply with the standard of care for regular prescribing of hydroxychloroquine which does not require a routine assessment of subject's health status especially for short-term use. However, since the package insert for hydroxychloroquine cautions on using antimalarial

compounds for individuals with hepatic disease, alcoholism, G-6-PD and severe blood disorder we will not include individuals having those diseases in our study.

Subjects who choose to enter the clinical arm of the study will receive hydroxychloroquine for a total of 7 weeks. The study drug supply will be maintained either through Baylor Scott & White pharmacies or directly from a manufacturer.

The logistics of drug dispensing will be specified based on the availability of drug supplies and also the mechanism through which the drug would be accessed. If there is enough supply of hydroxychloroquine we will dispense the drug as feasible in advance for future visits, otherwise a weekly supply would be provided to participants at each visit.

At the end of the study, after the last subject visit is completed. All collected data will be analyzed with the study population being those who either received hydroxychloroquine or entered the observational registry.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATS	American Thoracic Society
AUC	Area under the concentration-time curve
BMI	Body mass index
BP	Blood Pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations (US)
CK	Creatine kinase
CKD	Chronic kidney disease
C_{max}	Maximum drug concentration in plasma
CT	Computed tomography
DSMB	Data safety monitoring board
EC	Ethics Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HCV	Hepatitis C virus
Hgb	Hemoglobin
ICH	International Conference on Harmonization
INR	International normalized ratio
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
IWRS	Interactive Web Response System
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MMRM	Mixed model repeated measures
PK	Pharmacokinetic
RBC	Red blood cell
ROS	Reactive oxygen species
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-36	36-item short form survey
SRC	Sample size re-calculation committee
TBL	Total bilirubin
T_{max}	Time when maximum drug concentration in plasma is achieved
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of child bearing potential

5. INTRODUCTION

New major epidemic foci of coronavirus disease 2019 (COVID-19), have been identified and are rapidly expanding in Europe, North America, Asia, and the Middle East, with the first confirmed cases being identified in African and Latin American countries.[1] By March 16, 2020, the number of cases of COVID-19 outside China had increased drastically and the number of affected countries, states, or territories reporting infections to WHO was 143.1 On the basis of"alarming levels of spread and severity, and by the alarming levels of inaction", on March 11, 2020, the Director-General of WHO characterized the COVID-19 situation as a pandemic.

The WHO Strategic and Technical Advisory Group for Infectious Hazards (STAG-IH) regularly reviews and updates its risk assessment of COVID-19 to make recommendations to the WHO health emergencies programme.[2] STAG-IH's most recent formal meeting on March 12, 2020, included an update of the global COVID-19 situation and an overview of the research priorities established by the WHO Research and Development Blueprint Scientific Advisory Group that met on March 2, 2020, in Geneva, Switzerland, to prioritize the recommendations of an earlier meeting on COVID-19 research held in early February, 2020.

To respond to COVID-19, many countries are using a combination of containment and mitigation activities with the intention of delaying major surges of patients and levelling the demand for hospital beds, while protecting the most vulnerable from infection, including elderly people and those with comorbidities. Activities to accomplish these goals vary and are based on national risk assessments that many times include estimated numbers of patients requiring hospitalization and availability of hospital beds and ventilation support. Most national response strategies include varying levels of contact tracing and self-isolation or quarantine; promotion of public health measures, including handwashing, respiratory etiquette, and social distancing; preparation of health systems for a surge of severely ill patients who require isolation, oxygen, and mechanical ventilation; strengthening health facility infection prevention and control, with special attention to nursing home facilities; and postponement or cancellation of large-scale public gatherings.

Based on more than 500 genetic sequences submitted to GISAID (the Global Initiative on Sharing All Influenza Data), the virus has not drifted to significant strain difference and changes in sequence are minimal. There is no evidence to link sequence information with transmissibility or virulence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19.

SARS-CoV-2, like other emerging high-threat pathogens, has infected health-care workers in China and several other countries. To date, however, in China, where infection prevention and control was taken seriously, nosocomial transmission has not been a major amplifier of transmission in this epidemic. Epidemiological records in China suggest that up to 85% of human-to-human transmission has occurred in family clusters and that 2055 health-care workers have become infected, demonstrating that patient to healthcare worker is tractable. However, there have been no major nosocomial outbreaks and some supporting evidence that some health-care workers may have acquired infection or transmitted the infection to their families. These findings suggest that close and unprotected exposure is required for transmission by direct contact or by contact with fomites in the immediate environment of those with infection. Continuing reports from outside China suggest the same means of transmission to close contacts

and persons who attended the same social events or were in circumscribed areas such as office spaces or cruise ships. It has been suggested that a healthcare worker that had 15-30 min of exposure within 6 feet of an infected patient without PEP could acquire the infection.

Intensified case finding and contact tracing are considered crucial by most countries and are being undertaken to attempt to locate cases and to stop onward transmission. Confirmation of infection at present consists of PCR for acute infection, and although many serological tests to identify convalescent antibodies which confer potential immunity are being developed they require validation with well characterized sera before they are reliable for general use.

From studies of viral shedding in patients with mild and more severe infections, shedding seems to be greatest during the early phase of disease. The role, if any, of asymptomatic carriers in transmitting infection is not yet completely understood. Pre-symptomatic infectiousness is a concern among healthcare workers and many countries are now using 1–2 days of symptom onset as the start day for contact identification.

A comprehensive report published by the Chinese Center for Disease Control and Prevention on the epidemiological characteristics of 72,314 patients with COVID-19 confirmed previous understanding that most known infections cause mild disease, with a case fatality ratio that ranged from 2·9% in Hubei province to 0·4% in the other Chinese provinces. This report also suggested that elderly people, particularly those older than 80 years, and people with comorbidities, such as cardiac disease, respiratory disease, and diabetes, are at greatest risk of serious disease and death. The case definition used in China changed several times as COVID-19 progressed, making it difficult to completely characterize the natural history of infection, including the mortality ratio. Information on mortality and contributing factors from outbreak sites in other countries varies greatly, and seems to be influenced by such factors as age of patients, associated comorbidities, availability of isolation facilities for acute care for patients who need respiratory support, and surge capacity of the health-care system. Individuals in care facilities for older people are at particular risk of serious disease as shown in the report of a series of deaths in an elderly care facility in Washington State.

The pandemic of COVID-19 has clearly entered a new stage with rapid spread in countries outside China and all members of society must understand and practice measures for self-protection and for prevention of transmission of infection to others. STAG-IH makes the following recommendations.

First, countries need to rapidly and robustly increase their preparedness, readiness, and response actions based on their national risk assessment and the four WHO transmission scenarios for countries with no cases, first cases, first clusters, and community transmission and spread (4Cs).

Second, all countries should consider a combination of response measures: case and contact finding; containment or other measures that aim to delay the onset of patient surges where feasible; and measures such as public awareness, promotion of personal protective hygiene, preparation of health systems for a surge of severely ill patients, stronger infection prevention and control in health facilities, nursing homes, and long-term care facilities, and postponement or cancellation of large-scale public gatherings.

Third, countries with no or a few first cases of COVID-19 should consider active surveillance for timely case finding; isolate, test, and trace every contact in containment; practice social distancing; and ready their health-care systems and populations for spread of infection.

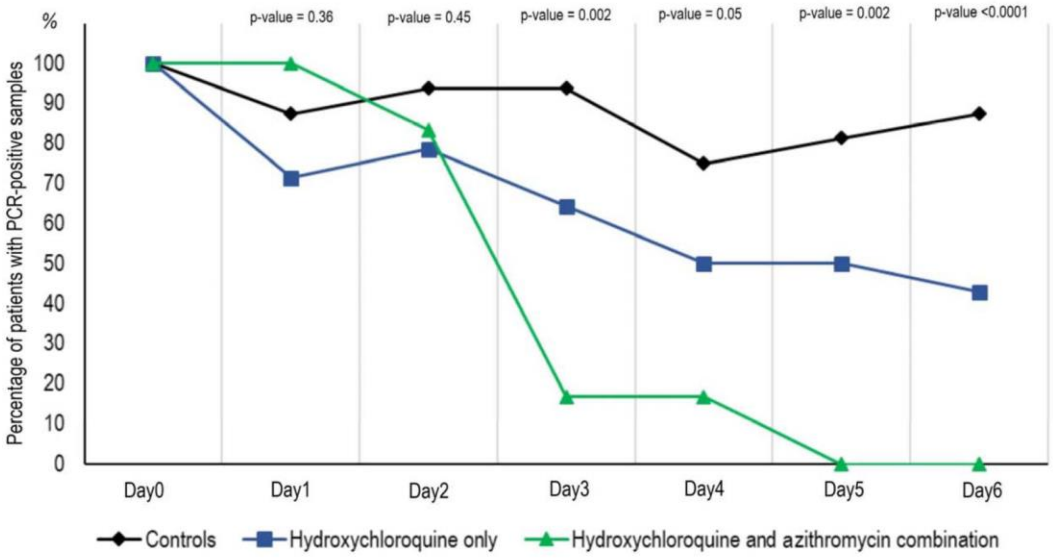
None of these suggested by STAG-IH address the issue of healthcare workers with concern over high-risk exposures such as those who would qualify for this trial.

Azithromycin may have direct and indirect antiviral effects on human cells infected with pathogenic strains of viruses that could apply in COVID-19 infection.[3] [4] [5] [6] [7] [8]

Hydroxychloroquine and chloroquine are antimalarial agents that have been used for decades for both active treatment and prophylaxis. Several sources of data and rationale have been developed to support the notion that hydroxychloroquine may have activity against COVID-19.[9] [10] [11] [12] [13]

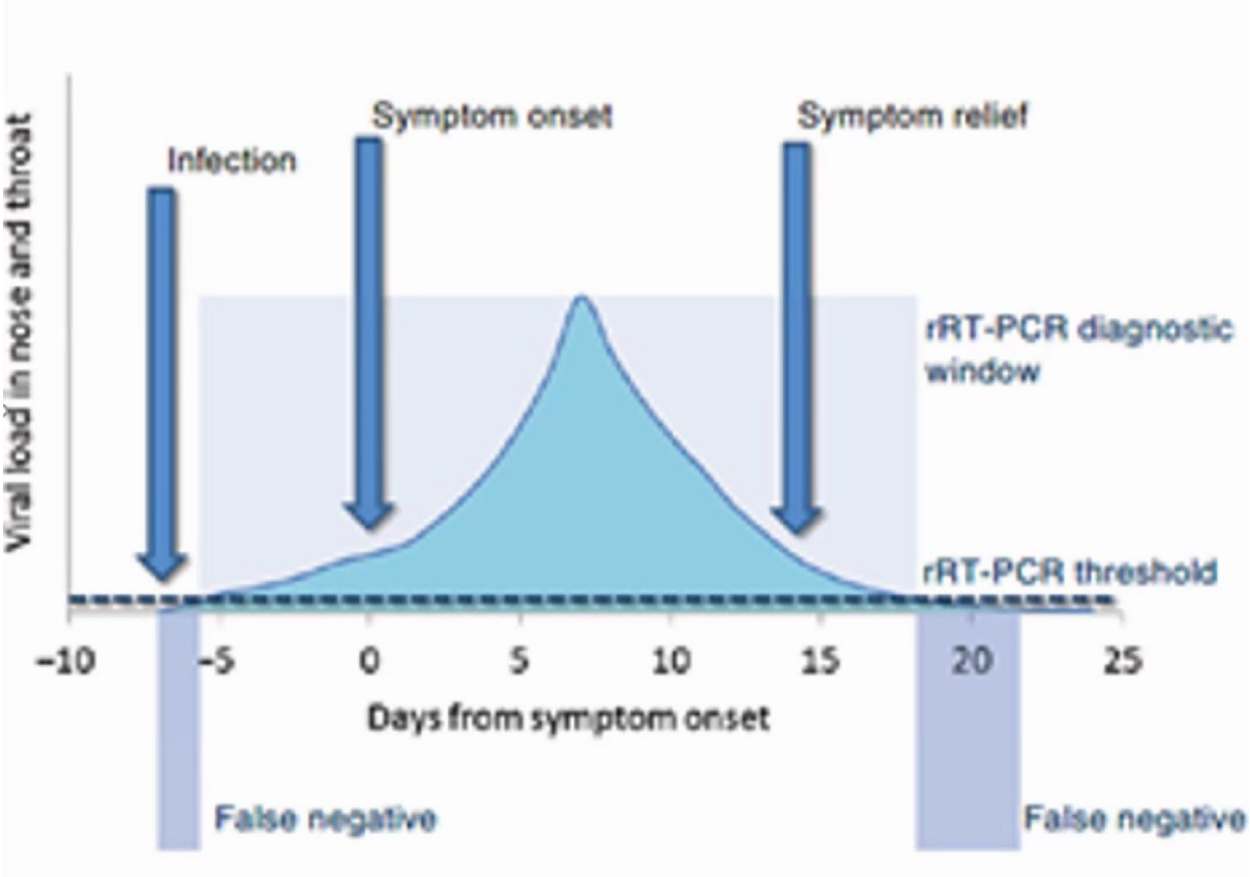
A prospective open-label trial from France evaluated the efficacy of hydroxychloroquine alone and in combination with azithromycin in symptomatic, hospitalized patients with positive COVID-19. The study composed of 36 patients, out of which 20 received 600 mg of hydroxychloroquine daily for 10 days. The remaining 16 patients who either refused the treatment or were not eligible to receive it because they were at other centers in France were considered as the control group. The primary endpoint was virological clearance of NP sampling at six days. Six patients who received hydroxychloroquine contributed incomplete NP sampling to the analysis because three worsened and were transferred to the intensive care unit, one patient died, one patient left the hospital, and one patient could not tolerate the study medication due to nausea. At day 6, 70% of hydroxychloroquine-treated patients were virologically cured comparing with 12.5% in the control group ($p= 0.001$). The investigators found the rate of recovery in patients taking hydroxychloroquine to be approximately 5 times more than that of patients in the control group. Six patients were additionally treated with Azithromycin for presumed superimposed bacterial infection. The figure below, demonstrates the efficacy of hydroxychloroquine alone and in combination with azithromycin according to the French study[14]:

Figure 2. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine only, in COVID-19 patients treated with hydroxychloroquine and azithomycin combination, and in COVID-19 control patients.



Please cite this work as Gautret et al. (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents – In Press 17 March 2020 – DOI : 10.1016/j.ijantimicag.2020.105949

Finally, research gaps about COVID-19 should be addressed in prospective, clinical trials as proposed in this study. The present study will leverage information concerning the infectious curve associated with COVID-19 exposure as illustrated in the figure.



5.1. Clinical Experience with Hydroxychloroquine

Please refer to the package insert.

5.1.1. Safety and Tolerability

Please refer to the package insert for a detailed discussion of safety findings for studies in healthy subjects, rheumatology, infectious diseases, and other illnesses patients with hydroxychloroquine.

5.1.2. Clinical Experience with hydroxychloroquine

Please refer to the package insert for a detailed discussion of clinical experience and efficacy findings for studies in healthy subjects, rheumatology, infectious diseases, and patients with other illnesses

5.1.3. Transaminase and GGT Elevations

In clinical studies of hydroxychloroquine, patients may have increases of transaminase enzymes above baseline upon initiation of treatment, please refer to the package insert for a detailed discussion.

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5.1.4. Muscle Discomfort

In clinical studies of hydroxychloroquine, patients may have increases in muscle discomfort above baseline upon initiation of treatment, please refer to the package insert for a detailed discussion.

5.1.5. Anemia

Clinical studies of hydroxychloroquine, patients may have reductions in hemoglobin from baseline upon initiation of treatment, please refer to the package insert for a detailed discussion.

5.1.6. Prolonged QT and Risk for Arrythmias

Hydroxychloroquine may prolong the QT interval. Please refer to the package insert for a detailed discussions.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

For healthcare workers with

- One day or more of exposure to suspected and/or positive COVID-19 patients, including but not limited to those working in the Emergency Department or Intensive Care Unit.

OR

- Unprotected exposure to a known positive COVID-19 patient within 72 hours of screening.

6.1.1. Primary Objective

To assess the efficacy of hydroxychloroquine 400 mg twice a day (two 200 mg tablets twice a day) on day 1 followed by two 200 mg tablets once a week for a total of 7 weeks in the prevention of COVID-19 infection

6.1.2. Secondary Objective

To compare the rate of COVID-19 positive conversion among emergency department workers versus intensive care unit workers

6.2. Endpoints

6.2.1. Primary Efficacy Endpoint

Rate of COVID-19 positive conversion on weekly nasopharyngeal (NP) sampling

6.2.2. Secondary Efficacy Endpoints

Time-to-first clinical event consisting of a persistent change for any of the following:

- One positive NP sample
- Common clinical symptoms of COVID-19 infection including fever, cough, and shortness of breath
- Less common signs and symptoms of COVID-19 infection including headache, muscle pain, abdominal pain, sputum production, and sore throat

6.2.3. Exploratory Efficacy Endpoints

Time-to-first clinical worsening event consisting of any of the following:

1) Hospitalization for COVID-19 infection
2) Intensive care unit admission for COVID-19 infection
3) All cause death

6.2.4. Safety Endpoints

Frequency, intensity, and relationship to study drug of adverse events and serious adverse events, change from baseline in body temperature.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This prospective open label trial will study the safety, tolerability, and efficacy of hydroxychloroquine in qualified health care workers.

Qualified individuals will be administered hydroxychloroquine twice a day on day 1 (two 200 mg twice a day) and once a week (two 200 mg) afterwards for a total of 7 weeks. Dose de-escalation is permitted during the study if indicated clinically. Please refer to Section 7.3.1 for additional details on dose de-escalation.

All study individuals will follow the same visit and assessment schedule. Following study enrollment, participants will be scheduled to be assessed in person at Days 7, 14, 21, 28, 35, 42 and 49.

7.2. Number of Subjects

A total of 360 subjects will be enrolled

7.3. Treatment Assignment

Qualified individuals may choose which group they want to be in. Subjects in the treatment group will receive hydroxychloroquine for 7 weeks. Those who decide to opt out of receiving treatments will compose the control group.

7.3.1. Dose and Dose De-Escalation

Subjects receiving hydroxychloroquine will start at fixed doses unless contraindicated clinically. The investigator may choose to decrease the subject's dose to one-half of the prior doses if clinically indicated. Dose de-escalation can occur more than once, but the minimum dose permitted is 200 mg of hydroxychloroquine. Reasons for dose de-escalation should be discussed with the medical monitor prior to changing dose.

Unscheduled visits due to dose de-escalation should include assessments detailed in Section 9.5.

7.4. Criteria for Study Termination

Although the Sponsor intends to complete the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons, or if required by regulatory agencies. If the Sponsor discontinues the study, all study drug will be discontinued and the investigator will be responsible for securing any alternative therapy to be administered, as appropriate.

7.5. Schedule of Assessments

Table 3 lists the overall schedule of assessments for the study.

Table 3: Schedule of Assessments

Study Day (Day) / Assessment	Screen A[a]	Day 1[b]	Day 7 Day 7±3	Day 14 Day 14±3	Day 21 Day 21±3	Day 28 Day 28±3	Day 35 Day 35±3	Day 42 Day 42±3	Day 49[j] Day 49±3 (End of study visit)
Informed consent	X								
Inclusion/ exclusion	X	X[c]							
Self-reported Pregnancy Status[d]	X	X	X	X	X	X	X	X	X
Demographics and baseline disease characteristics	X								
Prior and Concomitant medications	X	X	X	X	X	X	X	X	X
Current background medications	X	X	X	X	X	X	X	X	X
Medical history	X								
Self-reported Height	X								
Self-reported Weight	X								
Body temperature	X	X	X	X	X	X	X	X	X
Study drug administration		X	X	X	X	X	X	X	
Dispense study drug[e]		X	X	X	X	X	X	X	
Collect study drug[f]			X	X	X	X	X	X	X
nasopharyngeal (NP) sampling		X	X	X	X	X	X	X	X
Adverse event collection		X[g]	X	X	X	X	X	X	X
Visual analogue scale (VAS) for cough severity	X	X	X	X	X	X	X	X	X
Exposure assessment	X	X	X	X	X	X	X	X	X
Virus serology[h]	X			X		X		X[j]	

[a] Total Screening period should not exceed 30 days. Screening and Day 1 can be completed in the same visit.

[b] Day 1 is the day of administration of the first dose. **On Day 1, all procedures should be performed before study drug administration.**

[c] Screening eligibility procedures do not need to be repeated on Day 1; however, a review of any changes in eligibility criteria should be evaluated prior to Day 1 procedures

[d] Female participants will be asked with respect to their pregnancy as a verbal check

[e] Depending on the availability of the drug supply, the schedule of drug dispensing might change

[f] If the schedule for drug dispensing changes, the arrangements for drug collection will change accordingly

[g] AE assessments on Day 1 should be performed following study drug administration

[h] Only applicable to those who choose to participate in the optional viral serology study

[i] Individuals who terminate from the study prior to the Day 49 study visit should return to the clinic as soon as possible for early termination assessments (*i.e.*, Day 49 Day Prior and end-of-treatment visits). Participants should complete the end-of-treatment procedures, including assessments, prior to any adjustments being made to their treatment regimen.

[j] If final serology draw not collected at Day 42, it can be collected at day 49

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

1. Adult male and female healthcare workers ≥ 18 to ≤ 75 years of age upon study consent
2. Healthcare workers with
   - One day or more of exposure to suspect and/or positive COVID-19 patients, including but not limited to those working in the Emergency Department or Intensive Care Unit.

   OR

   - Unprotected exposure to a known positive COVID-19 patient within 72 hours of screening.
3. Afebrile with no constitutional symptoms
4. Willing and able to comply with scheduled visits, treatment plan, and other study procedures
5. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study prior to initiation of any subject-mandated procedures

8.2. Subject Exclusion Criteria

1. Participation in other investigational clinical trials for the treatment or prevention of SARS-COV-2 infection within 30days
2. Unwilling to practice acceptable methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) during Screening, while taking study drug, and for at least 30 days after the last dose of study drug is ingested

Note: the following criteria follow standard clinical practice for FDA approved indications of this medication

3. Having a prior history of blood disorders such as aplastic anemia, agranulocytosis, leukopenia, or thrombocytopenia
4. Having a prior history of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency
5. Having dermatitis, psoriasis or porphyria
6. Taking Digoxin, Mefloquine, methotrexate, cyclosporine, praziquantel, antacids and kaolin, cimetidine, ampicillin, Insulin or antidiabetic drugs, arrhythmogenic drugs, antiepileptic drugs, loop, thiazide, and related diuretics, laxatives and enemas, amphotericin B, high dose corticosteroids, and proton pump inhibitors, neostigmine, praziquantel, Pyridostigmine, tamoxifen citrate
7. Allergies: 4-Aminoquinolines
8. Pre-existing retinopathy of the eye
9. Has a chronic liver disease or cirrhosis, including hepatitis B and/or untreated hepatitis

10. Untreated or uncontrolled active bacterial, fungal infection
11. Known or suspected active drug or alcohol abuse, per investigator judgment
12. Women who are pregnant or breastfeeding
13. Known hypersensitivity to any component of the study drug
14. A known history of prolonged QT syndrome or history of additional risk factors for torsades de pointe (e.g., heart failure, requires a lab test , family history of Long QT Syndrome), or the use of concomitant medications that prolong the QT/QTc interval

8.3. Subject Re-Screening

Subjects may repeat the Screening procedures to qualify for the study with approval from the medical monitor.

8.4. Subject Discontinuation and Termination

Subjects have the right to discontinue study drug or withdraw from the study at any time for any reason, without prejudice to their medical care. Furthermore, the investigator may discontinue a subject from study drug. Consultation with the medical monitor should occur prior to study drug discontinuation or withdrawing a subject from the study. The reason for a subject's discontinuation from study drug or study termination will be recorded in the electronic case report form (eCRF).

8.4.1. Subject Discontinuation Criteria

Discontinuation refers to a subject's stopping administration of study drug. Reasons for study drug discontinuation may include the following:

- Confirmed clinical worsening event
- Occurrence of an AE or change in medical status that leads the investigator to be concerned about the subject's welfare
- Administrative reasons (*e.g.*, inability to continue)
- Sponsor termination of the study
- Voluntary withdrawal
- Females who become pregnant during the study
- A positive COVID-19 test

Subjects who are discontinued from study drug should still continue in the study, completing all study visits and undergo all scheduled study assessments, if possible.

8.4.2. Subject Termination Criteria

Termination refers to a subject's stopping study drug and all study assessments and visits. Reasons for study termination include the following:

- Loss to follow-up

- Death
- Withdrawal of consent

Every reasonable effort should be made to contact individuals who do not return for a scheduled visit. The investigator should inquire about the reason for withdrawal, request the subject return all unused investigational product, request the subject return for end-of-treatment and follow-up visits (if applicable), and follow up with the subject regarding any unresolved AEs.

9. TREATMENT OF SUBJECTS

9.1. Select Management Guidelines

The following guidelines apply to the management of study participants:

9.1.1. Management of Ongoing Exposures

Study participants will continue to adhere to good clinical practice to avoid infection with COVID-19 according to the CDC and other applicable guidance.

9.1.2. Management of Muscle Discomfort

Basic symptomatic relief is the first step in managing muscle spasm, including walking, adequate hydration, wearing socks, and stretching before bedtime. Assessment of levels of electrolytes such as magnesium, calcium and potassium may indicate the need for replacement. If vitamin D levels are low, supplementation may be warranted. Muscle relaxants may also help relieve symptoms.

9.1.3. Diarrhea

In instances where an individual experiences diarrhea consideration will be made with respect to the doses of the study medications as well as concomitant medications.

9.1.4. Nausea

Nausea may occur with higher doses of hydroxychloroquine.. Nausea adverse events are typically mild and reversible within a few Days after treatment initiation. If symptoms do not resolve, dose de-escalation, with consultation of the medical monitor, may be necessary.

9.1.5. Management of COVID-19 positive test

If the result of an NP swab test demonstrates the presence of SARS-CoV-2, the subject will be directed to immediately receive appropriate medical care and will discontinue study treatment and procedures, however the sponsor will continue to follow the subject until their condition is resolved or death. Patient management following a positive test during the study will not be directed by study procedures and will be at the discretion of the subject's physician.

9.2. Description of Study Drug

Hydroxychloroquine (BRI-001) drug product information is shown in Table 4.

Table 4: Hydroxychloroquine Drug Product Information

Description	Hydroxychloroquine tablets
Ingredients	Hydroxychloroquine sulfate
Route of Administration	Oral

9.3. Concomitant Medications

9.3.1. Excluded Medications

Subjects taking these medications or treatments will be ineligible for enrollment:

- Any other investigational drug or device as part of an interventional study;
- Taking Digoxin, Mefloquine, methotrexate, cyclosporine, praziquantel, antacids and kaolin, cimetidine, ampicillin, Insulin or antidiabetic drugs, arrhythmogenic drugs, antiepileptic drugs, loop, thiazide, and related diuretics, laxatives and enemas, amphotericin B, high dose corticosteroids, and proton pump inhibitors, neostigmine, praziquantel, Pyridostigmine, tamoxifen citrate

Subjects who take excluded medications during the study should not discontinue study drug solely on this basis. Consultation with the medical monitor should occur prior to study drug discontinuation or withdrawing a subject from the study.

9.3.2. Permitted Medications

Allowed concomitant medications include the following:

- Daily multivitamins or recommended daily supplements;
- Other medications intended to manage concurrent diseases, as authorized by the treating physician;
- Oral, implantable, or injectable contraceptives.

Subjects taking medication chronically should be maintained on those same doses and dose schedules throughout the study period and should not have additions or changes made to their medications, as medically feasible.

The use of the other therapies which may affect walking distance, are permitted during the study, provided the subjects have been receiving a stable dosage for at least 30 days prior to Day 1. Unless medically indicated and discussed with the medical monitor, the doses of these agents should remain unchanged during the study.

9.4. Treatment Compliance

The investigator or his/her designated and qualified representatives will only dispense study drug to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol. Subjects who miss more than 25% of the total number of expected doses will not be considered treatment-compliant.

9.4.1. Study Monitoring Committee

A study monitoring team including a qualified physician, a monitor from BSWRI, and a statistician will be responsible to monitor the safety and integrity of the study and to make recommendations as appropriate. They will start reviewing the collected data approximately 4

weeks after the first subject is enrolled and will continue to do so quarterly until the last dose of the last subject enrolled.

The study monitoring committee will be responsible for reviewing the progress of the study and the accumulating of the data while the study is ongoing. They may recommend that the study continue as is, be modified to protect subject safety, or be terminated. However, investigators, will make decisions concerning the need for laboratory investigations, ECG, and intra-subject dose-escalation decisions throughout the study for each subject and may choose to decrease the subject's dose (to one-half of the prior dose).

9.5. Unscheduled Visits

Unscheduled visits are allowed for the following reasons:

- Management of an adverse event or serious adverse event;
- Dose de-escalation;
- Any time the investigator feels that it is clinically appropriate for subject safety.

At a minimum, unscheduled visits should include collection of adverse events and vital signs. Additional conversations may be necessary with the medical monitor following an unscheduled visit to assess subject safety.

9.6. Pregnancy

9.6.1. Women of Childbearing Potential

Women will be asked to self-report their pregnancy status at screening. We are relying on self-reporting of pregnancy because we do not want to delay the preventive treatment for COVID-19 to those who are working in a high-risk environment. The study investigators believe that the risk of contracting COVID-19 may be worse than taking hydroxychloroquine.

Women of childbearing potential (WOCBP) are those who are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy) do not have fallopian inserts with confirmed blockage, have not had reproductive potential terminated by radiation, and are not postmenopausal for at least 1 year.

9.6.2. Methods of Birth Control

During Screening, while taking study drug and until 30 days following administration of the final dose of study medication, WOCBP must practice one of the following acceptable methods of birth control:

- Use double barrier contraception method defined as male use of a condom and female use of a barrier method (*e.g.*, contraceptive sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream]);

- Use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 90 days prior to start of study drug administration;
- Use of an intrauterine device;
- monogamous partner with a vasectomy;
- Abstain from sexual intercourse completely. Complete abstinence from sexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

During Screening, while taking study drug and until 30 days after the final dose of study medication is taken, males who have female partners of childbearing potential must practice one of the following methods of birth control:

- Have had a vasectomy (at least 6 months earlier);
- Use double barrier contraception method, defined as male use of a condom and female use of a barrier method (*e.g.*, contraceptive sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream]);
- Partner use of an intrauterine device;
- Partner use of hormonal contraceptives (oral, parenteral, vaginal or transdermal) for at least 90 days prior to start of study drug administration;
- Abstain from sexual intercourse completely. Complete abstinence from sexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

9.6.3. Suspected Pregnancy

During the study, all WOCBP must be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, late or missed menstrual period). Male subjects must be instructed to contact the investigator if a sexual partner suspects she may be pregnant.

If a subject or investigator suspects that the subject may be pregnant, the study drug must be withheld until the results of a serum pregnancy test are available. If the serum pregnancy test confirms the pregnancy, the subject must permanently discontinue taking study drug. The investigator must immediately report to the medical monitor a pregnancy associated with study drug exposure. The early discontinuation protocol-required procedures outlined for End-of-treatment and Follow-up visits must be performed on the subject.

Pregnancy is not considered an AE; however, the investigator must follow a pregnant subject, or the pregnant female partner of a male subject (if consenting), and report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 Days. BSWRI or designee may contact the investigator to request additional information throughout the course of the pregnancy.

The following pregnancy outcomes must be considered SAEs and will require additional reporting in the eCRF and reported as a serious adverse event:

- Congenital anomaly/birth defect;
- Stillbirth;
- Spontaneous miscarriage.

9.7. Serious Toxicities

In the case of serious toxicities, the investigator may choose to interrupt treatment with hydroxychloroquine. Dose reductions are permitted to manage tolerability issues. Once a subject's dose has been reduced, that dose should be maintained until the Day 49 visit. Subjects who resume therapy after an interruption will follow the originally planned study schedule.

9.8. Study Procedures

The following sections describe each assessment. The timing of these assessments is noted in Table 3. All Day 1 procedures, except AE assessments, should be completed prior to administration of first dose of study drug.

9.8.1. Informed Consent

Written informed consent (see Section 15.3) must be obtained from the subject before any study-related procedures are performed, and again if there is a change in the study procedures that would affect the subject's willingness to participate.

9.8.2. Informed Consent For Optional Viral Serology Sub-Study

Individuals who are willing to participate in the viral serology sub-study, which is optional, will sign a separate consent form prior to the collection of samples.

9.8.3. Inclusion/Exclusion

Inclusion and exclusion criteria must be reviewed as indicated in Table 3. Subjects must meet all of the inclusion and none of the exclusion criteria for entry in the study. Investigators should contact the medical monitor with any questions regarding eligibility prior to enrolling the subjects on Day 1.

9.8.4. Demographics and Baseline Disease Characteristics

Demographic data including sex, age, race, and ethnicity, will be collected as indicated in Table 3. Baseline disease characteristics will be collected as indicated in Table 3.

9.8.5. Prior and Current Concomitant Medications

The name, dose, and frequency must be recorded for all medications that the subject is taking. All allowed and excluded medications should be recorded including all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Trade or generic drug names should be used where possible. Concomitant medications will be reviewed as indicated in Table 3 and all changes will be recorded.

9.8.6. Current Background Medications

The name, dose, and frequency must be recorded for all background medications that the subject is taking. Trade or generic drug names should be used where possible. Additional background PAH medications may only be prescribed after a clinical worsening event is confirmed.

9.8.7. Medical History

A complete medical history (*e.g.*, per subject report) that includes all medical history within the past 5 years must be collected. Medical history will be recorded as indicated in Table 3.

9.8.8. Height

Height will be self-reported as indicated in Table 3.

9.8.9. Weight

Weight will be self-reported as indicated in Table 3.

9.8.10. Body Temperature Measurements

Body temperature will be measured as indicated in Table 3.

9.8.11. Cough Visual Analog Scale

Cough visual analogue scale (VAS, 0–100 mm) will be recorded as indicated in Table 3 to assess cough severity in patients with chronic cough. Please refer to appendix II for cough visual analogue scale template.

9.8.12. Exposure Assessment

Subjects will be questioned about potential exposure to COVID-19 infection over the past 7 days as indicated in Table 3 to quantify ongoing risk of infection. Please refer to Appendix III for more details on exposure assessment questionnaire.

9.8.13. Pregnancy Test

WOCBP (see Section 9.6) will self-report on their pregnancy status. Any subject who becomes pregnant during the study must discontinue taking study drug immediately. See Section 9.6.3 for a description of procedures to be followed in case of pregnancy.

9.8.14. Study Drug Administration

Subjects should self-administer two capsules on day 1 following by two capsules once a week after that (preferably in the morning) until the end of the study. A bottle of tablets will be included in each subject's study drug kit.

A vomited dose must not be replaced. A double dose (*e.g.*, missed dose from previous week and dose for current week) must not be taken.

9.8.15. Study Drug Dispensation and Collection

Study drug will be dispensed to the subject and collected from the subject as indicated in Table 3. The dispensing schedule will be subject to availability. Dispensed treatment kits from each visit should be returned to the site for collection at the subsequent visit.

9.8.16. Adverse Event Collection

Subjects will be observed for general appearance, presence of illness or injury, or signs indicative of a concurrent illness as indicated in Table 3. Subjects must be instructed to volunteer any information regarding AEs on or after the first dose of study drug or query the subjects with an open question regarding any AEs they may be experiencing (*e.g.*, "How have you been feeling since your last visit?"). Any findings are to be documented. Subjects must be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Responses must be documented in the source documents.

9.8.17. Optional Viral Serology Study

Infection with SARS-COVID-2 may range from asymptomatic to disease requiring hospitalization. Given a high number of asymptomatic or minimally symptomatic infections, it is possible that a proportion of the population could have been exposed and recovered, especially in the weeks before active testing and surveillance became available in the United States. Moreover, healthcare workers who work in the "frontline" or directly with patients infected with SARS-COVID-2, are at higher risk of infection.

Another important aspect of finding detectable IgG antibody titers is the use of plasma from recovered patients with COVID-19 in a similar fashion as it has previously been used to treat outbreaks other potentially lethal infectious diseases such as SARS, Ebola, diphtheria, measles, etc. before a vaccine was available. On March 24, 2020, the FDA announced a pathway to facilitate access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections. This therapy relies on circulating serum antibodies that are able to, either prevent infection via blocking interaction of the virus with the host cell receptor, or that can potentiate antibody-dependent cell-mediated cytotoxicity (ADCC).

Hypothesis: A proportion of healthcare workers have previously been exposed and recovered from SARS-COVID-2. Detectable IgG antibodies against SARS-COVID-2 would indicate evidence of past infection. Moreover, the development of IgM or IgG antibodies during the study period would indicate exposure to the virus.

Inclusion criteria:

- All healthcare workers participating in the chemoprophylaxis trial will be offered participation.

Accordingly, the Biotechnology Center within the Baylor Institute for Immunology Research has initiated a viral serology study to collect serum/plasma samples from those participating in the study that also agree to have blood samples obtained. The donors that have the highest titers of

antibodies directed to SARS-COV-2 proteins will have the highest potential for eliciting potent therapeutic benefit.

Individuals who agree to participate in the viral serology sub-study will be required to sign a separate ICF before collection of the samples. Subjects are not required to participate in the viral serology sub-study in order to enroll in the primary study. Samples for viral serology sub-study should be collected on day 1/baseline (pre-dose) and on days 14, 28 and 42 as indicated in Table 3.

Healthcare worker blood sampling: Initial blood sampling for plasma collection will be planned via staff at the BSWRI BPM core laboratory, which is classified as a Bio Safety Level 2 lab (BSL-2). The Core will manage documentation, storage, and appropriate dispersal of the collected materials.

Serology testing: Samples will be processed by the BPM Core staff for viral inactivation. Serology at the Biotechnology Center will be undertaken with read out of SARS-COV-2-specific plasm pan-Ig and/or or IgG. If needed for throughput, samples can be pooled and assayed to identify positive pools, followed by deconvolution.

Biotechnology Center will run serology tests using either solid phase ELISA or bead-based Luminex™ multiplexed assay (the latter is ~10-fold more sensitive). Recombinant protein components of SARS-COV-2 are the basis of these assays, and these will either be purchase commercially (Sinobiologicals) or made in house. If commercial assay kits become available, then they will be used for testing or validation of in-house assays.

Serology study Endpoints:

- The primary endpoint is to determine the proportion of healthcare workers that have detectable SARS-COVID-2 IgG at baseline
- Secondary endpoint: determine the proportion of healthcare workers who seroconvert as evidenced by detectable IgM and/or IgG levels throughout the study.

Considerations/Interventions:

- All serum samples will be paired with a Nasopharyngeal swab PCR as this is performed weekly.
- Participants with detectable IgM and no detectable IgG against SARS-COVID-2 will be considered recently infected and will require further evaluation by Employee health.
- Participants who have only detectable IgG will be considered previously exposed and with resolved infection.
- Participants with detectable IgG and IgM will be considered to have been infected and on recovery phase.

Study termination:

- Participants may elect to stop participation at any time.

Management of COVID-19 positive cases:

- Those who become infected during the trial will be encouraged to do the serology testing two weeks after they become positive, if feasible.

Management of missed visits:

Subjects who miss the Day 42 serology for any reason (subject availability, had to leave before completing visit, etc.) will be reminded during the Day 49 visit that they did not have their final serology draw done at Day 42. They will be asked if they wish to have the final draw done at the final visit ("today"). This will allow them to receive at least the "before and after" results of their antibodies during the study (all subjects consented to Day 1 serology draws and had at least 1 sample collected) in addition to any samples they consented to have collected during the study, and they will be informed that this helps the researcher gather more data on the prevalence of antibodies in healthcare workers at high risk of COVID-19 infection.

In all cases, this conversation will be documented on the Day 49 source documents, including that it was not done at Day 42 and why, and that the subject is agreeing or refusing to have it drawn at Day 49. For subjects that did have some procedures at Day 42 but were not able to complete the serology sample collection, this is additionally documented in the Day 42 source documents. For subjects who missed Day 42 entirely, there will be a notation in the subject file that the visit was missed.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Hydroxychloroquine tablets will be used in this study.

10.2. Study Drug Packaging and Labeling

The study drug will be supplied in high-density polyethylene (HDPE) bottles. Each bottle will contain a desiccant insert that must not be ingested. Labeling on each kit bottle will contain at minimum the following information:

- Medication ID number;
- Protocol BSWRI-001;
- Caution Statement: Keep out of sight and reach of children;
- Control or lot number
- Store at 20° – 25°C (68° – 77°F), short term excursions allowed to 15° – 30°C (59° – 86°F);
- BSWRI, Dallas, TX.

A double panel label will be presented on the treatment kit carton containing this and other information as well.

10.3. Study Drug Storage

The stability of the drug product has been and is currently being evaluated in ongoing studies.

Investigative sites must store the investigational product in a secure location with room temperature conditions of 20° - 25°C (68° - 77°F), with brief excursions allowed to 15° – 30°C (59° – 86°F).

10.4. Study Drug Administration

Please refer to Section 9.8.14 for details on study drug administration. Clear instructions will be provided to the subject regarding the number and type of capsules to be ingested at each study drug administration time point listed in Table 3. Subjects must be instructed to continue taking study drug twice on day 1 (two 200 mg twice a day) and once weekly (two 200 mg) after that for a total of 7 weeks unless: (1) subject has been otherwise instructed by the investigator or (2) the subject has been formally discontinued from the study.

10.5. Study Drug Accountability

The investigator, or designee, will maintain a record of all study drug received, dispensed, and returned to the Sponsors' designee. No study drug shall be destroyed by the clinical site unless directed in writing to do so by the Sponsor's quality assurance department. Study drug bottles and any unused capsules should be returned to the study staff for eventual disposition by the Sponsor. The number of capsules returned at each visit will be recorded for each bottle in the kit.

10.6. Study Drug Handling and Disposal

At the conclusion of the study or in an instance of planned study drug replacement, the Sponsor or its designee will direct the site regarding the final disposition of study drug.

11. SAFETY ASSESSMENTS

11.1. Safety Parameters

To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety assessments. Safety parameters include vital sign measurements, adverse events and serious adverse events.

11.2. Adverse and Serious Adverse Events

11.2.1. Definition of Adverse Events

11.2.1.1. Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject regardless of its causal relationship to study drug. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study-drug related. Included in this definition are any newly-occurring events or previous condition that has increased in severity or frequency since the administration of study drug.

All AEs that are observed or reported by the subject during the study (from time of administration of the first dose at the Day 1 visit until the final visit indicated in Table 3 must be reported, regardless of their relationship to study drug or their clinical significance.

11.2.1.2. Serious Adverse Event

A serious adverse event (SAE) is any AE occurring at any dose and regardless of causality that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly or birth defect in an offspring of a subject taking study drug;
- Is an important medical event.

The term "life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not meet any of the criteria defined above; however, they may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies that occur during the study (from the time of the first dose of study drug until the final visit

indicated in Table 3, as appropriate). Certain pregnancy outcomes will require submission as an SAE (See Section 9.6).

The investigator is responsible for reporting to BSWRI or designee all AEs and SAEs that are observed or reported by the subject during the study (from the time of administration of the first dose of study drug until the final visit indicated in Table 3, as appropriate), regardless of their relationship to study drug or their clinical significance.

The Sponsor, or the Contract Research Organization (CRO) on the behalf of the Sponsor, must be notified immediately regarding the occurrence of any SAE that occurs after the subject is enrolled and throughout the study, regardless of study drug administration, including SAEs resulting from protocol-associated procedures, as defined in relevant legislation. The procedures for reporting all SAEs, regardless of causal relationship, are as follows:

- Record the SAE on the AE eCRF and complete the "Serious Adverse Event Report" form within the electronic database.
- In the event the electronic database is not functional, a paper SAE form will be available for the reporting of SAEs.

The Sponsor may request additional information from the investigator to ensure the timely completion of accurate safety reports.

All SAEs reported or observed during the study must be followed to resolution or until the investigator deems the event to be chronic or the subject to be stable. BSWRI or designee may contact the investigator to obtain additional information on any SAE which has not resolved at the time the subject completes the study.

11.3. Eliciting Adverse Event Information

At every study visit, subjects must be asked a standard, non-directed question, such as, "How have you been feeling since your last visit?" to elicit any medically related changes in their well-being. They may also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Responses must be documented in the source documents.

In addition to subject observations, AEs must be documented for any clinically significant diagnosis resulting from abnormal laboratory test values, physical examination findings, or ECG abnormalities, or from other documents that are relevant to subject safety.

11.4. Assessment of Causality

The investigator must use the following classifications and criteria to characterize the relationship or association of the study drug in causing or contributing to the AE:

Not Related: This relationship suggests that there is no association between the study drug and the reported event.

Unlikely Related: This relationship suggests that the temporal sequence of the event with study drug administration makes a causal relationship improbable and/or other factors also provide plausible explanations.

Possibly Related: This relationship suggests that treatment with the study drug caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from the time of study drug administration, and/or, follows a known response pattern to the study drug, but could have been produced by other factors.

Probably Related: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with study drug administration seems likely.

Definitely Related: This relationship suggests that a definite causal relationship exists between the drug administration and the AE, and other conditions (*e.g.*, concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

11.5. Assessment of Severity

The investigator will grade the severity of the AEs as mild, moderate, or severe using the following definitions:

Mild: Symptoms causing no or minimal interference with usual social and functional activities

Moderate: Symptoms causing greater than minimal interference with usual social and functional activities

Severe: Symptoms causing inability to perform usual social and functional activities

11.6. Recording Adverse Events

All conditions present prior to the administration of the first dose of study drug (Day 1) should be documented as medical history. After the first dose, documentation of adverse events (AEs) shall continue until 49 days following administration of the final dose of study medication, regardless of the relationship of the AE to study drug. Information to be collected includes type of event, date of onset, date of resolution, investigator-specified assessment of severity and relationship to study drug, seriousness, as well as any action taken.

While an AE is ongoing, changes in the severity (*e.g.*, worsening and improving) should be noted in the source documents, but when documenting the AE, only the total duration and greatest severity should be recorded in the eCRF. AEs characterized as intermittent require documentation of onset and duration.

All drug-related (possibly, probably, or definitely related, see Section 11.4) AEs and abnormal laboratory test results reported or observed during the study must be followed to resolution (either return to baseline or within normal limits). All other AEs will be followed through the final visit indicated in Table 3, as appropriate.

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Preexisting conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the subject experiences a

worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (*e.g.*, "worsening of…"). Any improvement in condition should be documented per Section **Error! Reference source not found.**.

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory test values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s). Changes in laboratory test values are only considered AEs if they are judged to be clinically significant (*i.e.*, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiological fluctuation). If abnormal laboratory test values are the result of pathology for which there is an overall diagnosis (*e.g.*, increased creatinine levels in renal failure), only the diagnosis should be reported as an AE.

Elective procedures (surgeries or therapies) that were scheduled prior to the start of AE collection are not considered AEs. These elective procedures should not be recorded as AEs, but should be documented in the subject's source documents as elective (*e.g.*, elective periodontal surgery). However, if a pre-planned procedure is performed early (*e.g.*, as an emergency) because of a worsening of the preexisting condition, the worsening of the condition should be captured as an AE.

11.7. Reporting Serious Adverse Events

Any AE the investigator considers serious according to the previously described criteria must be reported within 24 hours from the time the site personnel first learn about the event. The eCRF system within the clinical database is the preferred method of reporting an SAE.

To report the SAE, the investigator will complete the SAE form in the clinical database and submit to BSWRI Safety (Refer to Table 5) within 24 hours of awareness. If the clinical database is down for any reason, the manual SAE forms should be used; however, sites are responsible for ensuring the information on the manual SAE forms is entered into the clinical database once available.

Table 5: SAE Reporting Contact Information

BSWRI Safety Hotline North America Safety Hotline: Safety Fax: E-mail:

For questions regarding SAE reporting, contact your study manager, monitor, or BSWRI Safety.

Follow-Up Reports

The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of new information, the SAE form should be updated within the clinical database and submitted along with any supporting documentation (*e.g.*, subject discharge summary or autopsy reports) to BSWRI Safety NA (refer to Table 5). If the clinical database is down for any reason, the manual SAE forms should be used; however, sites are responsible for ensuring the updated information on the manual SAE forms is entered into the clinical database once available.

The Sponsor or designee will notify regulatory agencies of any fatal or life-threatening unexpected events associated with the use of the study drug as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within the timeframe established by the appropriate regulatory agency. For other SAEs that do not meet the fatal or life-threatening unexpected criteria, but are reported to be associated with the use of the study drug, BSWRI or designee will notify the appropriate regulatory agencies in writing within the timeframe established by those regulatory agencies. BSWRI or designee will provide copies of any reports to regulatory agencies regarding serious and unexpected SAEs to the investigators for review and submission to their institutional review board (IRB) or Ethics Committee (EC), as appropriate.

Principal investigators are responsible for informing their IRB/EC of any SAEs at their site. SAE correspondence with regulatory authorities or IRBs/ECs must be submitted to the Sponsor or designee for recording in the study file.

These events will be reviewed on a regular basis in aggregate and will be reported in an expedited manner if a safety signal is detected. Regular safety study updates will be reported to regulatory authorities according to local guidelines.

12. STATISTICS

12.1. Sample Size

A total sample of 360 individuals (180 in each arm) would provide at least 80% power to detect a relative risk reduction of 40% in the rate of positive NP samples when the anticipated rate of positive conversion among those taking hydroxychloroquine is approximately 30%.

The power calculation, which was based on Pearson Chi Square test, assumes the following:

- One-sided Type I error rate of 0.05
- Anticipated positive NP samples rate of 30% in the clinical arm
- A 40% lower risk of a positive NP sample comparing the hydroxychloroquine group vs the controls
- Loss to follow-up rate of 15%

12.1.1. Efficacy Variables

Result of COVID-19 weekly nasopharyngeal (NP) test **.**

12.1.2. Safety Variables

The safety variables include results of vital sign measurements, adverse events, and serious adverse events.

12.2. Statistical Analyses

A statistical analysis plan (SAP) detailing the analyses will be developed prior to the database lock. All statistical analyses and data summaries will be performed using SAS® (Version 9.1 or higher) or other validated software. The SAP will serve as the final arbiter of all statistical analyses. Data will be summarized overall using descriptive statistics. Continuous data will be summarized with number of subjects (n), mean, median, minimum, maximum, relevant quartiles, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages. Chi Square or Fisher exact test will be used for comparing binary outcomes between treatment and control groups. Continuous variables will be compared between the study groups by means of two sample T test or Wilcoxon-rank-sum test.

12.2.1. Primary Analysis of Efficacy

All subjects who received at least one dose of study medication, will be used as the primary population for assessment of efficacy. The proportion of people whose NP sample becomes positive at least once during the trial will be compared between the study groups using Chi square or Fisher exact test. Survival analysis will be utilized to estimate the potential effects of hydroxychloroquine on COVID-19 free survival times. We will apply generalized linear mixed models to compare the positive conversion rate of COVID-19 between the study arms while controlling for other confounding factors. AIC and BIC criteria will be used to choose an appropriate covariance structure between the measurements collected at consecutive visits. An

interaction effect between time and study group will be added to the model to evaluate whether the relative risk of a positive conversion changes from visit to visit.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Audits and Inspections

Principal investigators and institutions involved in the study will permit study-related monitoring, audits, and IRB/EC review, and regulatory inspections, by providing direct access to all study records. In the event of an audit, the principal investigator agrees to allow the Sponsor, representatives of the Sponsor, the US Food and Drug Administration (FDA), and other relevant regulatory authorities access to all study records.

The principal investigator should promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or designee.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Quality Assurance

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, BSWRI may conduct a quality assurance audit of the investigator's clinical site, including CTM/IMP storage facilities.

14.2. Financial Disclosure

Principal investigators and sub-investigators are required to provide financial disclosure information prior to starting the study. In addition, the principal investigator and sub-investigators must provide the Sponsor or designee with updated information, if any relevant changes occur during the course of the investigation and for one year following the completion of the study.

No potential investigator who has a vested financial interest in the success of this study may participate in this study.

14.3. Sponsor Obligations

The Sponsor or designee is not financially responsible for further testing/treatment of any medical condition that may be detected during the Screening process. In addition, in the absence of specific arrangements, the Sponsor or designee is not financially responsible for treatment of the subject's underlying disease.

14.4. Investigator Documentation

Before beginning the study, the principal investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the Code of Federal Regulations (CFR) by providing the essential documents to the Sponsor or designee, which include but are not limited to the following:

- An original investigator-signed investigator agreement page of the protocol;
- The IRB/EC approval of the protocol;
- The IRB- or EC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardians;
- A Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572;
- Curricula vitae for the principal investigator and each sub-investigator listed on Form FDA 1572. A curricula vitae and current licensure, as applicable, must be provided. The curricula vitae must have been signed and dated by the principal investigators and sub-investigators within 2 years before study start-up to indicate the documents are accurate and current;
- Completed financial disclosure forms (Section 14.2) to allow the Sponsor or designee to submit complete and accurate certification or disclosure statements required under US Title 21 CFR 54. In addition, the investigators must provide to the Sponsor or

designee a commitment to update this information promptly if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study;

- Laboratory certifications and normal ranges for any laboratories used by the site for the conduct of this study.

14.5. Clinical Study Insurance

In accordance with the respective national drug laws, the Sponsor has taken out subject liability insurance for all subjects who give their consent and enroll in this study. This insurance covers potential fatalities, physical injuries, or damage to health that may occur during the clinical study.

14.6. Use of Information

All information regarding hydroxychloroquine supplied by the Sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. Furthermore, the investigator is obligated to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of hydroxychloroquine/azithromycin and may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required.

15. ETHICS

15.1. Institutional Review Board (IRB) or Ethics Committee Review

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Each investigator must provide the Sponsor or its designee a signed and dated statement that the protocol and informed consent have been approved by the IRB/EC for that site before consenting subjects. Prior to study initiation, the investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with this protocol and to give access to all relevant data and records to the Sponsor, its designee, and regulatory authorities as required.

The IRB/EC chairperson or designee must sign all IRB/EC approvals and must identify the IRB/EC by name and address, the clinical protocol, and the date approval and/or favorable opinion was granted.

The principal investigator is responsible for obtaining reviews of the clinical research at intervals specified by the IRB/EC, but not exceeding 1 year. The principal investigator must supply the Sponsor or designee with written documentation of reviews of the clinical research.

15.2. Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (*e.g.*, US Code of Federal Regulations Title 21, European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

The principal investigator agrees to conduct the study in accordance with the International Conference on Harmonization (ICH) for Guidance for Industry on Good Clinical Practice (GCP) ICH E6(R1) [http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf] and the principles of the Declaration of Helsinki [http://www.wma.net/en/30publications/10policies/b3/]. The principal investigator must conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

15.3. Written Informed Consent

Because the study will be conducted under a United States Investigational New Drug Application, a signed informed consent form, in compliance with Title 21 of the United States Code of Federal Regulations (CFR) Part 50, will be obtained from each subject before the subject enters the study. For sites outside of the United States, the signed consent will be obtained in accord with local regulations, ICH E6 (R1), and principles of the Declaration of Helsinki. An informed consent template may be provided by the Sponsor or designee to the investigators. The consent must be reviewed by the Sponsor or designee before IRB/EC submission. Once reviewed, the consent will be submitted by the principal investigator to his or her IRB/EC for review and approval before the start of the study. If the informed consent form is revised during the course of the study, all participants affected by the revision must sign the revised IRB/EC-approved consent form.

Before enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved informed consent form. Once the principal investigator or designee is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the informed consent form.

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/EC-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (*i.e.*, all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Any changes to the proposed consent form suggested by the investigator must be agreed to by the Sponsor before submission to the IRB/EC, and a copy of the approved version and the notice of approval must be provided to the Sponsor's designated monitor after IRB/EC approval.

The principal investigator or designee will provide a copy of the informed consent form (signed copy to be provided per applicable law) to the subject and/or legal guardian. The original form will be maintained in the subject's medical records at the site.

15.4. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA or applicable regulatory authorities, or the IRB/EC.

The principal investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to them for the purpose of the study. Prior written agreement from the Sponsor or designee must be obtained for the disclosure of any said confidential information to other parties.

15.5. Modification of the Protocol

Any changes that arise after the approval of the protocol must be documented as protocol amendments. The FDA or other applicable regulatory agencies must be notified of protocol amendments. The changes will become effective only after approval of the Sponsor, the investigator, the IRB/EC, and where necessary, the applicable regulatory agency. In cases when the protocol is modified to enhance subject safety, changes may be implemented and the amendment must be immediately submitted to the IRB/EC.

The investigator is responsible for informing the IRB/EC of all problems involving risks to subjects according to national legislation. In case of urgent safety measures, the Sponsor will immediately notify the investigators and relevant regulatory agencies, including FDA in accord with 21 CFR 312.32.

15.6. Protocol Deviations

The principal investigator or designee must document any protocol deviation. The IRB/EC must be notified of all protocol deviations in a timely manner by the principal investigator or designee as appropriate. Protocol deviations will be documented by the responsible monitor during monitoring visits, and those observations will be communicated to the investigator.

If there is an immediate hazard to a subject the principal investigator may deviate from the protocol without prior Sponsor and IRB/EC approval. The Sponsor and IRB/EC must be notified of the deviation.

16. DATA HANDLING AND RECORDKEEPING

16.1. Retention of Records

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application submission or 2 years after formal discontinuation of the clinical development of the investigational product. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

16.2. Case Report Forms

All case report form data will be entered in paper or electronic forms at the investigational site. A 21 CFR Part 11 compliant Electronic Data Capture system (EDC) will be used to capture data electronically for all subjects.

17. PUBLICATION POLICY

The Sponsor supports communication and publication of study results whatever the findings of the study.

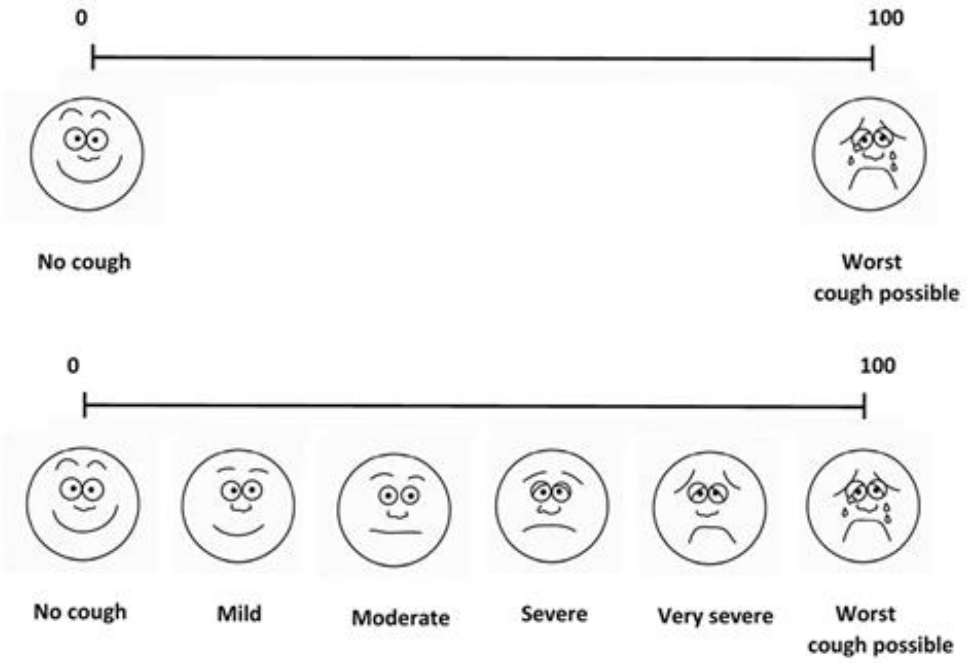
The Sponsor reserves the right to review all planned communications and manuscripts based on the results of this study. This reservation of the right is not intended to restrict or hinder publication or any other dissemination of study results, but to allow the Sponsor to confirm the accuracy of the data, to protect proprietary information, and to provide comments based on information that may not yet be available to the study investigators. The Sponsor also encourages disclosure of any conflict of interest from all authors or investigators when manuscripts are submitted for publication. Those individuals, who have contributed greatly to this study, including lead external advisors and select principal investigators, may serve on any potential publications committee for the study.

18 APPENDICES

18.1 Appendix I: Registry for Screened and Not Randomized

For healthcare workers who have been screened and who would have qualified as eligible subjects but decline participation because of personal choice or logistical reasons, a registry will be offered with the same baseline data collection, schedule of NP sampling, and capture of outcomes. This will serve as a form of community surveillance for the medical center and will have a sample size that will not be pre-specified and limited only by the availability of NP COVID-19 sampling. For those who develop a positive NP test, the current guidance from the medical center administration and in concert with guidance from the U.S Federal Government, State and Local Authorities, Centers for Disease Control, and State and Local Health Departments, will all be applied in terms of next steps in monitoring and control of COVID-19 viral spread.

18.2 Appendix II: Cough Visual Analog Scale



18.3 Appendix III: Exposure Assessment Questionnaire

Exposure Questions		**Visit:**						**Date**
#	**Question**	**Details**						**Comments**
1	Number of shifts worked in the last 7d (in ICU/ED, +other COVID-19 unit)		Number of hours worked in last 7 d? (in ICU/ED, +COVID unit)					
2	Were you present in the room for a procedure likely to generate higher concentrations of respiratory secretions or aerosols[1]?	□ no □ yes	**If yes:**	List details (procedures, frequency, duration, etc.)				
3	Did you have extensive body contact with a +COVID-19 pt (e.g. rolling the patient, assisting in ADLs)?	□ no □ yes	**If yes:**	List details (activity, frequency, duration, etc.)				
4	Did you have <u>prolonged close contact</u> with a suspected/confirmed +COVID-19 pt (within 6 feet for > 15 min cumulatively in 1 or more shifts)?	□ no □ yes	**If yes:**	Were you in contact with secretions and/or excretions?	□ no □ yes	**If Yes,** did secretions contact unprotected:	☐ Mouth ☐ Eyes ☐ Nose ☐ hands	

[1] Examples: CPR, manual respiration, intubation, extubation, bronchoscopy, nebulizer therapy, or sputum induction

Staff initials:_____

Exposure Questions -*continued*				**Visit:**	**Date**
#	**Question**	**Details**	**Comments**		
5	Do you feel your PPE has been adequate?	□ no □ yes	**If *no*:**	Please describe:	
6	Did you have unprotected exposures not described above (eg incomplete PPE for any duration with COVID19 patient):				

Staff initials:_____

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