Clinical Protocol PRG-042

A Randomized, Double-Blind, Placebo-Controlled Phase IIa Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection
HELP COVID-19

Date: 19 September 2021
Version 1.5

Study Sponsor
ProgenaBiome, LLC 1845 Knoll Drive Ventura, CA 93003

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PROTOCOL APPROVAL PAGE

A Randomized, Double-Blind, Placebo-Controlled Phase IIa Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection
HELP COVID-19

ProgenaBiome, LLC Protocol: PRG-042

Date: 19 September 2021

Chief Executive Medical Officer

Sabine Hazan, MD Date

PROTOCOL SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to all local, legal, and regulatory requirements and ICH guidelines.

The sponsor, all investigators from all clinical sites should sign the signature page as appropriate.

Sponsor Representative:

Name_____

Position/Title_____

Signature_____

Date_____

Principal Investigator:

Name_____

Position/Title_____

Signature_____

Date_____

Investigator:

Name_____

Position/Title_____

Signature_____

Date_____

PROTOCOL

TITLE: Brief Title:	Protocol PRG-042: **A Randomized, Double-Blind, Placebo-Controlled Phase IIa Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection** **HELP COVID-19**
PROTOCOL NO. :	PRG-042
PRIMARY INVESTIGATOR SECONDARY INVESTIGATORS SPONSOR:	Sabine Hazan, MD Alon Steinberg, MD ProgenaBiome, LLC
This study will be performed in compliance with good clinical practices (GCP's) Including the archiving of essential documents.	
ORIGINAL PROTOCOL DATE:	06 May 2020

PROTOCOL SYNOPSIS

Sponsor: ProgenaBiome, LLC
Title of Study: PRG-042 A Randomized, Double-Blind, Placebo-Controlled Phase IIa Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection **Brief Title:** HELP COVID-19
Study Centers: 1
Study Period: 3 Years
Objectives: Prevent COVID-19
Study Design This is a Phase IIa interventional study, with a treatment duration of 12 weeks.
Duration of Subject Participation (Study Visits) Subjects will be recruited though the ProgenaBiome website via a questionnaire, www.clinicaltrials.gov, or may self-refer. Subjects are high-risk individuals (working in healthcare and persons exposed to or living in the same household as a person or persons with a positive COVID-19 test). Subjects who reside with a positive individual will be recruited at the time treatment for that (COVID-19 positive) individual is initiated by the PI. Subjects will be called on the phone for screening, at which time informed consent will be given via the EDC, and baseline history will be collected. After review of all inclusion/exclusion criteria subjects will then be Subjects will be randomized into the Arm 1 (treatment) or Arm 2 (placebo). At this time the associated treatment regimen will be prescribed. Subjects randomized in to Arm 1 will be prescribed hydroxychloroquine, vitamin C, vitamin D, and zinc. Subjects randomized into Arm 2 will be prescribed a placebo, vitamin C, vitamin D, and zinc to achieve nutritional parity. Along with the prescriptions, subjects will be provided with a thermometer for recording temperature, a copy of the daily diary, and a pregnancy test if applicable. On Day 1 first dose of study medications will be taken. Patients will be called this day to teach them how to use the diary in the EDC, discuss the medication dosing regimen, and answer any questions they may have. The next day subjects will be called to ask about AEs and SAE, assess any COVID-19 symptoms, if present, update the list of prior and concomitant medications, and answer any questions they may have. Patients will also be called on Day 10 to ask about AE and SAE, assessment of any COVID-19 symptoms, update the list of prior and concomitant medications, and answer any questions they may have. Weekly afterwards subjects will be called to update the list of concomitant medications, assessment of AEs and SAEs, and assess any COVID-19 symptoms, as well as to answer any questions they may have. During the call on Day 14 patients will be instructed on how to collect a nasal or oropharyngeal swab for RT-PCR testing. This call must be a video call so that visual aids may be used, and the caller may observe the patient collecting the sample. During the Month 1 call, the patient will be reminded to collect a swab. The final visit will occur 12 weeks after Day 1 and will be either an in-clinic visit or videoconference. At this final visit the patient will have an assessment for AE and SAE, the list of prior and concomitant medications will be updated, and a physical examination will be performed (optional). A nasal or oropharyngeal swab will be collected by the study team (or by the patient if this visit is done remotely).

Study Populations

Inclusion Criteria

1. Informed consent, provided electronically via the EDC, demonstrating the subject understands the procedures required for the study and the purpose of the study.
2. Healthy male or female subjects 18 years of age or older that are considered to be high-risk individuals. High-risk individuals are defined as:
    a. All health care workers in hospital Emergency Departments and Intensive Care Units with regular direct contact with COVID-19 patients, or
    b. Individuals exposed to or residing with a person or persons with a positive test for COVID-19
3. Subjects must agree to practice at least two highly effective methods of birth control for the duration of the study This includes condoms with spermicide, oral birth control pills, contraceptive implants, intra-uterine devices, or diaphragms. At least one of these must be a barrier method. Subjects not of reproductive potential will be exempt (e.g. post-menopausal, surgically sterilized)

Exclusion Criteria

1. Refusal to provide informed consent
2. Any previous positive test for COVID-19 by PCR
3. Symptomatic for COVID-19
4. Pregnant or breastfeeding women
5. Diarrhea prior to the start of treatment
6. Type I or II diabetes
7. Atherosclerotic Coronary Artery Disease
8. Any contraindication for treatment with hydroxychloroquine
    a. Hypoglycemia
    b. G6PD deficiency
    c. Porphyria
    d. Anemia
    e. Neutropenia
    f. Alcoholism
    g. Myasthenia gravis
    h. Skeletal muscle disorders
    i. Maculopathy
    j. Changes in visual field
    k. Liver disease
    l. Psoriasis
    m. Anemia from pyruvate kinase and G6PD deficiencies
    n. Abnormal EKG with QT prolongation acquired or from birth
    o. History of QT interval >500msec
    p. History of torsades de pointes
    q. Allergies to 4-Aminoquinolines
    r. Use of any of the contraindicated medications in Appendix 1
9. Patients taking any anti-epileptics
10. Any comorbidities which, in the opinion of the investigator, constitute health risk for the subject.

Number of Subjects Subjects will be enrolled to ensure that at least 600 complete the study. It is anticipated that 1200 patients will need to be screened to achieve this.
Study Duration Enrollment of at least 600 subjects is expected to take 6 months.

Primary Study Objective	Study Endpoints
Prevention of COVID-19	Negative RT-PCR testing at Day 14, Month 1, and Month 3
Lack of COVID-19 symptoms	Absence of symptoms of COVID-19 as recorded in Patient Diary in the EDC
Assessment of Safety and Tolerability	Assess Adverse Events and Serious Adverse Events

a. Adverse event monitoring will be conducted for 12 weeks
b. Serious adverse event monitoring will be conducted for 12 weeks
c. Should any pregnancy occur, the pregnancy will be followed to its conclusion and the nature of that conclusion (termination, still birth, live birth, presence of absence of any birth defects) will be recorded. Any stillbirth or presence of any birth defects will be recorded as an SAE.

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List of Abbreviations

ACE2	Angiotensin II receptor
AE	Adverse event
BID	Twice a day dosing
BP	Blood pressure
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CMP	Complete Metabolic Panel
CRF	Case report form
DNA	Deoxyribonucleic Acid
EDC	Electronic Data Capture system
EKG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Information Portability and Accountability Act
HR	Heart Rate
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IU	International Units
Mg	Milligrams
mL	Milliliters
NP	Nasopharyngeal
OP	Oropharyngeal
OTC	Over the counter
O_2 saturation	Oxygen Saturation
PCP	Primary Care Provider
PI	Principal Investigator (at each site)
PPE	Personal Protective Equipment
QD	Once a Day Dosing
RR	Respiratory Rate
Rx	Prescription medication
RNA	Ribonucleic Acid
RT-PCR	Real time polymerase chain reaction
SAE	Serious adverse event
SUSAR	Suspected Unexpected Serious Adverse Event
TID	Three times a Day Dosing
WHO	World Health Organization

1. Background and Rationale

COVID-19 is a novel betacoronavirus, the origins of which are still being investigated, and which was first identified and diagnosed in the city of Wuhan, China. This disease has rapidly spread to become a worldwide pandemic. Symptoms of COVID-19, including fever, myalgia, coughing, shortness of breath, headache, and GI symptoms may appear from 2 and 14 days after exposure. However, incubation may be longer. Approximately 20% of patients progress to severe illness, including pneumonia, respiratory distress, and even death. Cases in the US have increased exponentially over the last months. The disease is spreading rapidly, and a cure is desperately needed.

Scientists have identified the molecular structure of the spike glycoproteins on the surface of the virus, which are what allow the virus to "stick" to its target, in this case the human lung. The virus has a very similar sequence and structure to the coronavirus that causes SARS, with the exception of the receptor binding domain. In this domain there is a loopy, flexible glycyl in place of a rigid prolyl, which allows it to tightly bind to a hydrophobic pocket in the receptor, ACE2.

Recently published studies have shown efficacy in treating with Plaquenil (hydroxychloroquine), and thousands of cures have been reported. Of particular interest are several studies out of China and two from France which indicate not only better survival but more rapid recovery and shorter time to viral clearance. The studies in France utilized a dose of 200mg of hydroxychloroquine TID for 10 days. Since the half-life of this drug is 20-80 days, we hypothesize that such large dose is not required for efficacy, and that a slightly lower dose will not only be effective, but will have fewer side effects. Given the long half-life of hydroxychloroquine, treatment with this drug for one day should be sufficient. Should the crisis last a great deal longer, repeat dosing could be considered.

Vitamin C has long been known to enhance the immune response of the host. It has also been shown the have direct antiviral effects, in both acute and chronic infections. Many studies have shown the enhancement of antimicrobial and natural killer cell activities, lymphocyte proliferation, chemotaxis, and delayed-type hypersensitivity. It protects cells from redox reactions and thus the reactive oxygen species generated during respiratory burst and inflammation. Since excess vitamin C is not absorbed, a high dose may be used

Vitamin D has also been shown to have direct antiviral effects, and to enhance the efficacy of other antiviral treatments. Vitamin D levels have also been shown to be a predictor of treatment efficacy in patients with Hepatitis C viral infections. Vitamin D also downregulates the ACEII receptor which is the target of COVID-19 and as such is directly antiviral for this infection. In previous studies, doses have ranged from 160mg-1g (IU * 0.67 = mg)

Deficiency of zinc has been linked to impaired innate immune functions. Supplementation of zinc has been shown to shorten the duration of respiratory infections. The recommended dose for over the counter zinc supplements is up to 79.2mg, placing 50mg well within the accepted range.

Many antiviral treatment studies have shown that drugs used in combination are more effective than single therapies. In short, the whole is greater than the sum of its parts. Thus, we hypothesize that a combination of drugs has greater therapeutic potential, and can be effective in preventing COVID-19.

2. Trial Objectives and Endpoints

Primary Study Objective	Study Endpoints
Prevention of COVID-19	Negative RT-PCR testing at Day 14, Month 1, and Month 3
Lack of COVID-19 symptoms	Absence of symptoms of COVID-19 as recorded in Patient Diary in the EDC
Assessment of Safety and Tolerability	Assess Adverse Events and Serious Adverse Events

3. Study Procedures:

- Screening Period:
  - Day -7 to 1
    - Patient may initiate contact through ProgenaBiome website, www.clincaltrials.gov, be referred by a healthcare professional, or self-refer. Subjects who reside with a positive individual may be informed of the study when the positive individual seeks out treatment from the PI.
    - Patient will provide informed consent electronically via the EDC
      - This will include a HIPAA waiver signed electronically.
      - Special attention should be given to counsel the subject on the risk of hypoglycemia with hydroxychloroquine, and what signs/symptoms to watch out for.
    - Medical records
      - Patient will provide baseline EKG to the study team during screening period
        - Any abnormalities with the Q-T interval will render the subject ineligible and they will be deemed a screen failure
      - Study team will review prior (previous 3 months) and concomitant medications, including over-the-counter medications and supplements.
      - Investigator will review the patient's records during the screening period, looking at inclusion/exclusion criteria, gathering data on BP, HR, and oxygen saturation from the most recent visit. These values will be used to compare to values obtained throughout the study. If any contraindication to participation is found, the study drugs will not be provided and the subject will be deemed a screen failure.
    - Prescription of home health monitoring equipment
      - Thermometer
      - Pregnancy test if applicable
      - Daily diary
    - Prescription of study drugs
      - Arm 1:
        - Hydroxychloroquine 200mg BID for 1 day only
          - To be taken first thing in the morning as soon as subject has

eaten and right before bed.
- To be separated from vitamin dose by at least 2 hours.

- Vitamin C 3000IU per day for 12 weeks
- Vitamin D 3000IU per day for 12 weeks
- Zinc 50mg per day for 12 weeks. This can be reduced to 25 mg if GI upset occurs

- Arm 2:
  - Placebo BID for 1 day only
  - Vitamin C 3000IU per day for 12 weeks
  - Vitamin D 3000IU per day for 12 weeks
  - Zinc 50mg per day for 12 weeks. This can be reduced to 25 mg if GI upset occurs

- Study drugs, thermometer, and pregnancy test (if applicable) will be shipped to patients via rapid carrier.

- Day 1
  - Patient will be called to
    - Teach them how to use the study diary
    - Discuss the medication regimen
    - Answer any questions they may have
    - Teach them how to collect a nasal swab and process the antigen test kit, or package the swab for PCR testing if available
  - Patient will take pregnancy test if applicable
  - Patient will collect temperature reading
  - Patient will complete diary
  - Patient will take prescribed treatment regimen

Drug	AM Dose	PM Dose
Hydroxychloroquine (or placebo)	200mg	200mg
Vitamin C	1500mg	1500mg
Vitamin D	1500 IU	1500 IU
Zinc	25mg	25mg

- Day 2
  - Patient will collect temperature reading
  - Patient will complete diary
  - Patient will be called on the phone for
    - Assessment of AE and SAE
    - Assessment of any COVID-19 symptoms
    - Update list of prior and concomitant medications
    - Answer any question they may have
  - Patient will take prescribed treatment regimen

Drug	AM Dose	PM Dose
Vitamin C	1500mg	1500mg
Vitamin D	1500 IU	1500 IU
Zinc	25mg	25mg

- Days 3-10
  - Patient will collect temperature reading

- Patient will complete diary
- Patient will take prescribed treatment regimen

Drug	AM Dose	PM Dose
Vitamin C	1500mg	1500mg
Vitamin D	1500 IU	1500 IU
Zinc	25mg	25mg

- Day 14
  - Patient will be called for:
    - Assessment COVID-19 symptoms
    - Update list of prior and concomitant medications
    - Remind patient to collect a nasal or oropharyngeal swab
    - Answer any questions they may have
- Week 3
  - Patient will be called on the phone weekly for
    - Assessment for AE and SAE
    - Assessment of any COVID-19 symptoms
    - Update list of prior and concomitant medications
    - Answer any questions they may have
  - Patient will collect temperature readings weekly for the remainder of the trial
  - Patient will complete diary
  - Patient will take prescribed treatment regimen

Drug	AM Dose	PM Dose
Vitamin C	1500mg	1500mg
Vitamin D	1500 IU	1500 IU
Zinc	25mg	25mg

- Week 4
  - Patient will be called on the phone weekly for
    - Assessment for AE and SAE
    - Assessment of any COVID-19 symptoms
    - Update list of prior and concomitant medications
    - Remind patient to collect an oropharyngeal swab
    - Answer any questions they may have
  - Patient will collect temperature readings weekly for the remainder of the trial
  - Patient will complete diary
  - Patient will take prescribed treatment regimen

Drug	AM Dose	PM Dose
Vitamin C	1500mg	1500mg
Vitamin D	1500 IU	1500 IU
Zinc	25mg	25mg

- Week 5-11
  - Patient will be called on the phone weekly for

- Assessment for AE and SAE
- Assessment of any COVID-19 symptoms
- Update list of prior and concomitant medications
- Answer any questions they may have

- Patient will collect temperature readings weekly for the remainder of the trial
- Patient will complete diary
- Patient will take prescribed treatment regimen

Drug	AM Dose	PM Dose
Vitamin C	1500mg	1500mg
Vitamin D	1500 IU	1500 IU
Zinc	25mg	25mg

- Week 12
  - Patient will present to the clinic (or or have a telehealth visit) for evaluation to include
    - Assessment for AE and SAE
    - Update list of prior and concomitant medications
    - Physical exam (Optional, on if in-clinic visit occurs)
    - Nasal or oropharyngeal swab collection (if patient elects to conduct final visit by videoconference, they will collect this sample at home)

COVID-19 sample collection

- To be overseen by study staff on Day 1, Day 14, and Month 1
- To be conducted by study staff at the Month 3 visit unless this is a telehealth visit
  - As this is not standard of care, ProgenaBiome will cover the cost of this test
    - If such testing becomes standard of care in the future, patient insurance will be charged for these tests.
- Samples for COVID-19 testing will be collected using synthetic swabs with plastic shafts. Nasal or oropharyngeal swabs will be collected and immediately be placed into a sterile vial with 2-3 mL of sterile saline. These will be placed into biohazard bags, boxed up, the box sterilized, and picked up for shipment to the central laboratory. Samples will be tested by RT-PCR. Samples may alternatively be tested with a rapid antigen test in the subject's home.

Inclusion Criteria

1. Informed consent, provided electronically via the EDC, demonstrating the subject understands the procedures required for the study and the purpose of the study.
2. Healthy male or female subjects 18 years of age or older that are considered to be high-risk individuals. High-risk individuals are defined as:
   a. All health care workers in hospital Emergency Departments and Intensive Care Units with regular direct contact with COVID-19 patients
   b. Individuals exposed to or residing with a person or persons with a positive test for COVID-19
3. Subjects must agree to practice at least two highly effective methods of birth control for the duration of the study This includes condoms with spermicide, oral birth control pills, contraceptive implants, intra-uterine devices, or diaphragms. At least one of these must be a barrier method. Subjects not of reproductive potential will be exempt (e.g. post-menopausal, surgically sterilized)

Exclusion Criteria

1. Refusal to provide informed consent
2. Any previous positive test for COVID-19 by RT-PCR
3. Symptomatic for COVID-19
4. Pregnant or breastfeeding women
5. Diarrhea prior to the start of treatment
6. Type I or II diabetes
7. Atherosclerotic Coronary Artery Disease
8. Any contraindication for treatment with hydroxychloroquine including:
    a. Hypoglycemia
    b. G6PD deficiency
    c. Porphyria
    d. Anemia
    e. Neutropenia
    f. Alcoholism
    g. Myasthenia Gravis
    h. Skeletal muscle disorders
    i. Maculopathy
    j. Changes in the visual field
    k. Liver disease, with ALT/AST > 2.5 upper limit normal and total bilirubin >2.5 upper limit normal
    l. Psoriasis
    m. Anemia from pyruvate kinase and G6PD deficiencies
    n. Abnormal EKG with QT prolongation acquired or from birth
    o. History of QT interval >500msec
    p. History of torsades de pointes
    q. Allergies to 4-Aminoquinolines
    r. Use of any of the contraindicated medications in Appendix 1
9. Treatment with any anti-epileptic mediation
10. Any comorbidities which, in the opinion of the investigator, constitute health risk for the subject.

4. Prohibited Medications

Found in Appendix 1

5. Subject privacy:

Subjects will be assigned a unique eight-digit identification number. The first two digits will be the study identification number (42). The next three digits will be the site number and the last three digits will be a number sequentially assigned by the site via the EDC. This number will be used to identify the subject on all documents. Only personnel on the delegation log will have access to study documents. These documents will be stored in password-protected computers, and physical documents will be stored in locked fireproof cabinets.

6. Schedule of events

Assessment	Screening (Day -7 to Day 1)	Day 1	Day 2	Day 3-10	Day 14	Week 3	Week 4/Month 1	Week 5	Week 6	Week 7	Week 8/Month 2	Week 9	Week 10	Week 11	Week 12/Month 3
Informed Consent & Demographics	X														
Initial Review of Prior and Concomitant Medications	X														
Medical Records review, including baseline EKG	X														
Randomization	X														
Prescription of Hydroxychloroquine or placebo, vitamin C, vitamin D, and zinc	X														
Provision of daily diary, thermometer and pregnancy test	X														
Pregnancy Test if applicable		X													
Temperature at home		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete daily diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hydroxychloroquine 200mg		X													
Vitamin C 3000mg		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitamin D 3000 IU		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Zinc 50mg[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone/video call to patient[b]	X	X	X		X	X	X	X	X	X	X	X	X	X	
Update list of prior and concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ask about AE and SAE		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of COVID-19 symptoms		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Swabs for antigen test or RT-PCR		X			X		X								X
Vitals in-clinic[c]															X
Physical Exam															X

a. May be reduced to 25mg if GI upset occurs
b. Will occur weekly Weeks 2-11
c. Vitals in-clinic to include height, weight, blood pressure (following 5 minutes sitting) pulse, respiratory rate, temperature, and oxygen saturation

7. Provision of Study Drug

Hydroxychloroquine has been made available for this study by the United States Government. The vitamin C, vitamin D, and zinc will be provided by Mickey Fine Pharmacy.

8. Subject Injury

In the event of any untoward medical occurrence in a subject directly caused by procedures performed pursuant to this protocol, it is the responsibility of the Investigator to record all relevant information regarding the medical occurrence on the Sample Collection Study.
The Investigator is responsible for the proper reporting of any potential adverse events (AE) or serious adverse events (SAE) (as defined by general medical standards) to the appropriate medical device manufacturer related to the study. AEs/SAEs related procedures should be reported directly to the clinic and/or investigator. The investigator is responsible for ensuring that adequate medical care is provided to a subject for any untoward medical occurrence resulting from this clinical protocol.

9. Direct Access to Source Data/Documents

The investigator involved in this study will agree to allow direct access to authorized auditors, IRB reviewers, and all applicable regulatory bodies as necessary to study relevant source data and documents including study relevant portions of the subject's medical record if necessary.

10. Risk/Benefit Assessment

10.1 Potential Risks

- Confidentiality Risks: All data (clinical, demographic, etc.) for individual subjects will be provided to ProgenaBiome. Information obtained during the study will not be shared outside the study personnel except in scientific reports or publications in aggregated and de-identified form.
- Risks associated with hydroxychloroquine
    - Auditory
        - Tinnitus
        - Hearing loss
    - Cardiovascular
        - Cardiomyopathy (can result in fatal cardiac failure)
        - biventricular hypertrophy
        - Prolongation of Q-T Interval
    - Dermatologic
        - Pigmentary changes in skin and mucous membranes
            - Usually reversible upon discontinuation of medication
        - Bleaching of hair
            - Usually reversible upon discontinuation of medication
        - Alopecia
            - Usually reversible upon discontinuation of medication
        - Rash/pruritus
        - AGEP
            - Usually reversible upon discontinuation of medication
        - Outbreak of psoriasis, occasionally associated with fever and hyperleukocytosis
        - Urticaria

- Angioedema
- Bullous eruptions including
  - Erythema multiforme
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
- DRESS syndrome
- Photosensitivity
- Exfoliative dermatitis

- Gastrointestinal
  - Abdominal pain
  - Nausea
  - Diarrhea
  - Vomiting
- Hematologic
  - Bone marrow suppression
  - Anemia
  - Aplastic anemia
  - Agranulocytosis
  - Leukopenia
  - Thrombocytopenia
- Hepatic
  - Fulminant hepatic failure
- Metabolic
  - Anorexia
  - Hypoglycemia
  - Exacerbation or precipitation of porphyria
- Musculoskeletal
  - Sensorimotor dysfunction
  - Skeletal muscle myopathy or neuromyopathy
    - May be reversible by stopping medication but recovery could take months
  - Depression of tendon reflexes
  - Abnormal nerve conduction studies
- Nervous system
  - Headache
  - Dizziness
  - Seizure
  - Vertigo
  - Auditory nerve dysfunction
  - Ataxia
- Optical
  - Blurred vision
    - Dose dependent and reversible upon discontinuation of medication
  - Retinopathy with changes in pigmentation and other visual field defects
    - Patients with retinal changes may be asymptomatic initially, or may have scotomatous vision with paracentral, pericentral ring types, temporal scotomas, and abnormal color vision.
  - Corneal changes including edema and opacities can be symptomless or may

cause disturbances such as haloes, blurring of vision, or photophobia. They may be transient and are reversible when therapy is discontinued.
- Maculopathies, and macular degeneration (may be irreversible), extra-ocular muscle palsies (reversible), nystagmus
  - Maculopathies, and macular degeneration, can occur from 3 months to several years of exposure to this drug and may be irreversible

- Psychiatric
  - Affect lability
  - Nervousness
  - Psychosis
  - Suicidal behavior
- Respiratory
  - Bronchospasm

- Risks associated with Vitamin C
  - Common side effects
    - Diarrhea
    - Nausea
    - Vomiting
    - Abdominal cramps/pain
    - heartburn
  - Serious side effects
    - Dysuria
    - Pink or bloody urine
    - Allergic reaction: including rash, pruritis, edema (especially of the face/tongue/throat), severe dizziness, dyspnea
- Risks associated with Vitamin D
  - Common side effects
    - None
  - Serious side effects
    - Vomiting
    - Nausea
    - Constipation
    - Increased thirst
    - Increased urination
    - Mental/mood changes
    - Unusual tiredness
    - Allergic reaction: including rash, itching, swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing
- Risks associated with Zinc
  - Common side effects
    - Vomiting
    - Diarrhea
    - Metallic taste
  - Serious side effects
    - Renal damage

        - Gastropathy
        - Decreased copper absorption
- Risks associated with COVID-19 infection
    - Fever
    - Cough
    - Shortness of breath
    - Pneumonia
    - Difficulty breathing
    - Persistent pain or pressure in the chest
    - Multiple organ failure
    - Need for mechanical ventilation
    - Death

10.2 Potential Benefits to Society

A prophylactic treatment could save countless lives, and billions of dollars in healthcare costs and lost productivity. The value cannot accurately be calculated

11. Ethical Considerations: Participant Information and Informed Consent

The Informed Consent Forms and any other related documents (including a HIPAA Authorization) must be approved by the IRB prior to study initiation. The Principal Investigator or his/her designee must obtain an electronic Informed Consent for each subject prior to initiating any study procedure. Receipt of the electronically signed Informed Consent Form will be documented in the CRFs and the original signed consent will be retained by the Investigator. A copy of the signed Informed Consent Form is offered to each subject. The site research staff will comply with the study protocol and will be responsible for the administration of informed consent and for acting in accord with the Health and Information Portability and Accountability Act (HIPAA) requirements. The study site is responsible for the accuracy and completeness of the data submitted and for making medical records and source documents available to the regulatory bodies.

The risks and benefits of participating in this study will be explained to each potential subject, prior to entering into the study. The Informed Consent Form must be written in language readily understood by the subject.

12. Statistical analysis

The treated patients in this study will be compared to the placebo group. Measurements will include PCR test results, presence or absence of symptoms, and symptom severity.

The change of these measurements from the end to the baseline (post–pre) will be used as the primary outcome, for example, $\mu e = \mu_{e1} - \mu_{e0}$, where μ_{e1} and μ_{e0} are the outcome of patients from the treatment group at the end and at baseline, respectively.

$$H_0 : \Delta \leq \delta_0 \text{against } H_a : \Delta > \delta_0$$

where δ_0 is a clinically meaningful threshold to measure the disease symptoms. In this study, that meaningful threshold will be calculated as mean change in clinical symptoms as recorded in the diary, from baseline through week 12. Each category in the diary will be assigned a number, 0 for None, 1 for Mild, 2 for Moderate and 3 for severe. Each category will be analyzed independently and they will be analyzed as a group.

Categorical variables will be summarized by presenting the number (n) and percent (%) of subjects in each category. All Statistical tests for the analysis will be performed using the $p<0.05$ level of significance. All confidence intervals will be one-sided.

Since these are healthcare workers who are exposed to COVID-19 at every shift, efficacy will be determined by RT-PCR testing, as well as the presence or absence of symptoms as recorded in the patient diary via EDC.

Additional details can be found in the Statistical Analysis Plan that will be developed prior to database lock.

13. Adverse Event Analysis

All adverse events and serious adverse events will be analyzed to determine likelihood of association with treatment. Likely and known Treatment Emergent Events will be tabulated and summarized by presenting the incidence number (number and percentage of subjects) in each treatment group. No inferential analyses will be performed on safety parameters.

14. Regulatory Compliance

This study will be conducted in accordance with protocol and applicable requirements outlined in FDA Code of Federal Regulations (CFR) Title 21 and the International Conference on Harmonization (ICH) E6 Good Clinical Practice.

Principal Investigator

The Principal Investigator, together with any designated Sub-Investigators, has the overall responsibility for the conduct and compliance of this clinical trial according to this protocol and Good Clinical Practice (GCP).

Record Retention

Per FDA and ICH GCP requirements, ProgenaBiome requires that all study related documentation be retained up to 2 years after the last sample has been processed or as mandated by the institution, whichever is longer.

15. Financial Obligations and Compensation

15.1 Financial Obligations of the Subjects

The subjects will not incur financial obligations by participation in this study.

16. References

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3. Gao, Jianjun, et al. “Breakthrough: Chloroquine Phosphate Has Shown Apparent Efficacy in Treatment of COVID-19 Associated Pneumonia in Clinical Studies.” *BioScience Trends*, vol. 14, no. 1, 2020, pp. 72–73., doi:10.5582/bst.2020.01047. "results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control

treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus- negative conversion, and shortening the disease course according to the news briefing"

4. Gautret, Philippe, et al. “Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomized Clinical Trial.” *International Journal of Antimicrobial Agents*, 2020, p. 105949., doi:10.1016/j.ijantimicag.2020.105949. "Despite its small sample size our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin."
5. Gupta, Ritesh, et al. “Clinical Considerations for Patients with Diabetes in Times of COVID-19 Epidemic.” *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, vol. 14, no. 3, 2020, pp. 211–212., doi:10.1016/j.dsx.2020.03.002. "Zinc nanoparticles were shown to have inhibitory effects on H1N1 viral load, though their effect in COVID-19 is unknown and untested. Vitamin C supplementation has some role in prevention of pneumonia and its effect on COVID-19 needs evaluation ."
6. Zhang, Lei, and Yunhui Liu. “Potential Interventions for Novel Coronavirus in China: A Systematic Review.” *Journal of Medical Virology*, vol. 92, no. 5, 2020, pp. 479–490., doi:10.1002/jmv.25707. Highlights Vitamin D Role in maturation of immune cells, lower rates of pneumonia in Vitamin C supplemented groups in three clinical trials, and the role of zinc in both humoral and cell-mediated immunity.

17.Appendices:

17.1 Appendix 1: Prohibited Medications

abarelix
abiraterone
acetohexamide
adalimumab
adenosine
ado-trastuzumab emtansine
albuterol
alfuzosin
aluminum carbonate
aluminum hydroxide
amifampridine
amiodarone
amisulpride
amitriptyline
amoxapine
anagrelide
apalutamide
apomorphine
arformoterol
aripiprazole
arsenic trioxide
asenapine
astemizole
atomoxetine
atorvastatin
attapulgite
auranofin
aurothioglucose
bedaquiline
benznidazole
bepridil
bicalutamide
bisacodyl
bitolterol
bortezomib
bosutinib
brentuximab
buprenorphine
cabazitaxel
cabozantinib
calcium carbonate
carboplatin
carfilzomib
casanthranol
cascara sagrada
castor oil
ceritinib
cerivastatin
certolizumab
cevimeline
chloramphenicol
chloroquine
chlorpromazine
chlorpropamide
cimetidine
ciprofloxacin
cisapride
cisplatin
citalopram
clarithromycin
clofazimine
clomipramine
clozapine
codeine
colchicine
crizotinib
dapsone
darifenacin
dasatinib
daunorubicin
daunorubicin liposomal
deferiprone
degarelix
desipramine
deutetrabenazine
didanosine
digoxin
dihydroxyaluminum sodium carbonate
dinutuximab
disopyramide
disulfiram
docetaxel
dofetilide
dolasetron
donepezil
doxepin
doxepin topical
doxorubicin
doxorubicin liposomal
dronedarone
droperidol
duloxetine efavirenz
elotuzumab
encorafenib
enfortumab vedotin
entrectinib
enzalutamide
epirubicin
eribulin
erythromycin
escitalopram
etanercept
ethambutol
ethionamide
etoposide
etravirine
ezogabine
famotidine
fesoterodine
fingolimod
flecainide
fluconazole
fludarabine
fluoxetine
fluphenazine
flutamide
fluvastatin
formoterol
foscarnet
galantamine
gatifloxacin
gemifloxacin
gilteritinib
glasdegib
glimepiride
glipizide
glyburide
glycerin
gold sodium thiomalate
golimumab
goserelin
granisetron
grepafloxacin
ibutilide
idarubicin
iloperidone
imipramine
indacaterol
infliximab
inotuzumab ozogamicin
interferon alfa-2a
interferon alfa-2b
interferon alfa-n1
interferon alfacon-1
iodoquinol
ipilimumab
isoetharine
isoniazid
isoproterenol
ivabradine
ivosidenib
ixabepilone
ixazomib
kaolin
ketoconazole
lactitol
lactulose
lanthanum carbonate
lapatinib
lefamulin
leflunomide
lenvatinib
leuprolide
levalbuterol
levodopa
levofloxacin
levomethadyl acetate
linezolid
lithium
lofexidine
lomefloxacin
loperamide
lovastatin
macimorelin
magaldrate
magnesium carbonate
magnesium citrate
magnesium hydroxide
magnesium oxide

maprotiline
mefloquine
mesoridazine
metaproterenol
methadone
methotrexate
methotrimeprazine
metoprolol
metronidazole
midostaurin
mifepristone
mineral oil
mirtazapine
moxifloxacin
nateglinide
nelarabine
nilotinib
nilutamide
nitrofurantoin
norfloxacin
nortriptyline
ofloxacin
olanzapine
olodaterol
ondansetron
osilodrostat
osimertinib
oxaliplatin
paclitaxel
paclitaxel protein-bound
paliperidone
palonosetron
panobinostat
papaverine
pasireotide
pazopanib
peginterferon alfa-2a
peginterferon alfa-2b
penicillamine
pentamidine
perflutren
perphenazine
phenolphthalein
pimavanserin
pimozide
pirbuterol
pitavastatin
pitolisant
polatuzumab vedotin
polyethylene glycol 3350
polyethylene glycol 3350 with electrolytes
pomalidomide
ponatinib
posaconazole
pravastatin
primaquine
probucol
procainamide
prochlorperazine
promazine
promethazine
propafenone
propofol
propoxyphene
protriptyline
quetiapine
quinapril
quinidine
quinine
rabies vaccine, human diploid cell
rabies vaccine, purified chick embryo cell
ranolazine
red yeast rice
repaglinide
ribociclib
rilpivirine
risperidone
ritodrine
rivastigmine
romidepsin
rosuvastatin
salmeterol
saquinavir
secnidazole
senna
sertraline
sevoflurane
simvastatin
siponimod
sodium iodide i-123
sodium iodide-i-131
solifenacin
sorafenib
sotalol
sparfloxacin
stavudine
sulfamethoxazole
sunitinib
tacrine
tacrolimus
tamoxifen
telavancin
telbivudine
telithromycin
teniposide
terbutaline
terfenadine
teriflunomide
tetrabenazine
thalidomide
thioridazine
timolol ophthalmic
tinidazole
tizanidine
tocilizumab
tolazamide
tolbutamide
tolterodine
toremifene
trabectedin
tramadol
trazodone
triclabendazole
trifluoperazine
triflupromazine
trimeprazine
trimipramine
triptorelin
typhoid vaccine, live
valbenazine
vandetanib
vardenafil
vasopressin
vemurafenib
venlafaxine
vigabatrin
vinblastine
vincristine
vincristine liposome
vinorelbine
voriconazole
zafirlukast
zalcitabine
zidovudine
ziprasidone

17.2 Appendix 2: Side Effect Mitigation

- All side effects will be recorded as AEs or SAEs and reported accordingly
- AE and SAE will be inquired about in both phone conversations and in the Patient Diary
- Auditory
    - Tinnitus and hearing loss
        - Patients experiencing either of these symptoms will be referred to their primary care physician for treatment.
- Cardiovascular
    - Cardiomyopathy (can result in fatal cardiac failure
        - Patient data will be evaluated by board certified study cardiologist and treatment initiated if deemed necessary
    - biventricular hypertrophy
        - Patient data will be evaluated by board certified study cardiologist and treatment initiated if deemed necessary
    - Prolongation of Q-T Interval
        - Patient data will be evaluated by board certified study cardiologist and treatment initiated if deemed necessary
- Dermatological
    - Rash or pruritis, including Vesiculobullous rash or Maculopapular rash
        - Patient will be prescribed appropriate treatment depending on the type of rash or pruritis
    - Photosensitivity reaction
        - Patient will be advised to avoid sunlight for the duration of treatment. If patient must go out, they should wear pants and long sleeves.
    - Stevens-Johnson syndrome, DRESS syndrome, TEN
        - Patient will be referred to a hospital for evaluation treatment
    - Urticaria
        - Will be treated with antihistamines and observed. If this treatment is not effective, the patient will be re-evaluated by PI for further treatment and/or referral
    - Dermatitis including exfoliative dermatitis
        - Patient will be evaluated by the PI and treatment will be initiated based on the type of dermatitis. Therapies could include topical hydrocortisone cream, antihistamines, and glucocorticoids
    - Pigmentary changes in skin and mucous membranes
        - Usually reversible upon discontinuation of medication
    - Bleaching of hair
        - Usually reversible upon discontinuation of medication
    - Alopecia
        - If severe, medication may be discontinued. This condition is usually reversible upon discontinuation of medication
    - AGEP
        - Usually reversible upon discontinuation of medication
    - Outbreak of psoriasis, occasionally associated with fever and hyperleukocytosis
        - Patient will be prescribed appropriate therapy depending on type and severity of symptoms
    - Angioedema
        - Treatment will depend on the severity. If severe, patient will be referred to the hospital for evaluation and treatment. If less, severe may be treated with antihistamines, anti-inflammatories, or glucocorticoids.

- Gastrointestinal
  - Abdominal pain
    - Patient will be medically managed. If severe treatment may be discontinued.
  - Nausea
    - Patient will be prescribed anti-nausea medication if needed
  - Diarrhea
    - Patient will be prescribed anti-diarrheal medication if needed
  - Vomiting
    - Patient will be prescribed anti-emetic medication if needed
- Hematologic
  - Any hematological abnormalities found during treatment or after will be followed by subsequent CBCs. If the problem is severe, patient may be medically managed or referred for hematology consultation and possible hospitalization.
- Hepatic
  - Fulminant hepatic failure
    - Patient will be referred for hospitalization
- Hypersensitivity
  - Allergic reaction/hypersensitivity
  - Anaphylactic reaction
    - Patient will be emergently treated with epinephrine and referred for hospitalization if necessary
- Metabolic
  - Abnormal blood chemistry values, including hypoglycemia, reported to study staff will be monitored. If they do not return to normal patient will be treated accordingly
  - Anorexia
    - Patient will be monitored for resolution of symptoms. If they do not resolve on their own, patient will be medically managed
  - Exacerbation or precipitation of porphyria
    - Patient will be referred to their PCP for evaluation and possible treatment
- Musculoskeletal
  - Sensorimotor disorders
    - Patient will be referred to a specialist
  - Skeletal muscle myopathy or neuromyopathy
    - May be reversible by stopping medication but recovery can take months. Patient will be referred to a specialist
  - Depression of tendon reflexes or abnormal nerve conduction studies
    - Patient will be referred to a specialist
- Nervous system
  - Headache/dizziness/vertigo
    - Patient will be medically managed
  - Seizure
    - Patient will be referred to a neurologist for diagnostics and treatment
  - Ataxia
    - Patient will be referred to a neurologist for diagnostics and treatment
  - Auditory nerve dysfunction
    - Patient will be referred to a specialist for evaluation and treatment
- Optical
  - Blurred vision

        - Dose dependent and reversible upon discontinuation of medication
        - Medication will be discontinued
    - Retinopathy with changes in pigmentation and visual field defects
        - Patients with retinal changes may be asymptomatic initially, or may have scotomatous vision with paracentral, pericentral ring types, temporal scotomas, and abnormal color vision.
        - Patients will be referred to an ophthalmologist
    - Corneal changes including edema and opacities can be symptomless or may cause disturbances such as haloes, blurring of vision or photophobia. They may be transient and are reversible when therapy is discontinued.
        - Therapy will be discontinued
    - Maculopathies and macular degeneration (may be irreversible), extra-ocular muscle palsies (reversible), nystagmus
        - Maculopathies and macular degeneration can occur from 3 months to several years of exposure to this drug and may be irreversible
        - Treatment will be discontinued, and patient will be referred to an ophthalmologist
- Psychiatric
    - Affect lability
        - Patient will be referred to a specialist
    - Nervousness
        - Patient will be referred to a specialist
    - Psychosis
        - Patient will be referred to a specialist
    - Suicidal behavior
        - Patient will be referred to a specialist
- Respiratory
    - Bronchospasm
        - Treatment will be discontinued, and patient will be treated with antihistamines

17.3 Appendix 3: Subject Stopping Criteria

- QT interval >500msec
- Presence of torsades de pointes
- Occurrence of unexpected drug related SAE
- Any other risk which the Investigator deems necessary to discontinue the study drugs