Clinical Protocol PRG-044

A Randomized, Double-Blind, Placebo-Controlled Phase IIa Study of Quintuple Therapy to Treat COVID-19 Infection

HAZDpaC

Date: 21 July 2020
Version 1.4

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

PROTOCOL APPROVAL PAGE

ProgenaBiome, LLC Protocol: PRG-044

A Randomized, Double-Blind, Placebo-Controlled Phase IIa Study of Quintuple Therapy to Treat COVID-19 Infection

HAZDpaC

Date: 21 July 2020

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-044: **A Randomized, Double-Blind, Placebo-Controlled Phase IIa Study of Quintuple Therapy to Treat COVID-19 Infection** **HAZDpaC**
PROTOCOL NO. :	PRG-044
PRIMARY INVESTIGATOR FOR SECOND INVESTIGATOR SPONSOR:	Sabine Hazan, MD Dr. 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:	19 March 2020

PROTOCOL SYNOPSIS

Sponsor: ProgenaBiome, LLC

Title of Study: PRG-044
A Randomized, Double-Blind, Placebo-Controlled Phase IIa Study of Quintuple Therapy to Treat COVID-19 Infection

Study Centers: 1

Study Period: 1 year

Objectives:

- Primary: to determine the efficacy of quintuple therapy against COVID-19 infection
- Secondary: To assess the safety and tolerability of treatment with quintuple therapy in Subjects with COVID-19 infection

Study Design

This is a Randomized, Double-Blind, Placebo-Controlled Phase II interventional study that will test the efficacy of quintuple therapy, HAZDpaC (Hydroxychloroquine, Azithromycin, Zinc, Vitamin D, and Vitamin C), in the treatment of Subjects with COVID-19 infection, compared to Subjects given only the vitamins, zinc (to put both groups into nutritional balance), and 2 placebos to match the hydroxychloroquine and azithromycin.

Duration of Subject Participation (Study Visits)

Subjects will be given the opportunity once diagnosis has been made via RT-PCR testing to participate. They may be recruited though the ProgenaBiome website, through a questionnaire. They may also be recruited through www.clinicaltrials.gov. Subjects may be referred by healthcare facilities. Subjects may also self-refer as well. All potential Subjects will be called during the recruitment process for screening assessments. The first step of this will be to obtain informed consent electronically, via the EDC. We will attempt to connect with these Subjects via Zoom/telemedicine. The validity of the test used to diagnose will be verified through medical records. (The diagnosis will be made by the Subject's evaluating physician or evaluation testing center, as part of the standard of care when infection is suspected). Following successful screening, Subjects will be randomized into the Arm 1 (treatment) or Arm 2 (placebo). At this time the associated treatment regimen will be prescribed and shipped to the Subject's home, along with home health equipment (MoMe Kardia II, thermometer, pulse oximeter and pregnancy test). Subjects will take azithromycin for 5 days, and hydroxychloroquine for 10 days, along with vitamin C, vitamin D, and zinc. Starting at Day 11 Subjects will discontinue hydroxychloroquine and reduce the doses of vitamin C, vitamin D, and zinc. The vitamin C, D, and zinc will be taken an additional 20 days at the reduced dose. Subjects will use the home EKG to transmit heart function information to the Study Team to be read by a board-certified cardiologist prior to dosing. The EKG will then be used daily for 10 days and results transmitted to the study team. Subjects will use a home pulse oximeter to monitor oxygen saturation and photographically report these values to the study team via the EDC. Subjects will track their symptoms using a daily diary (provided). Subjects will collect nasal or oropharyngeal swabs on Days 3, 5, 7, 14, and Month 1 and Month 3 for RT-PCR testing. Once Subjects have tested negative following treatment with HAZDpaC, Subjects will present to the clinic at 1, 2, and 3 months post-treatment for viral testing via RT-PCR. Alternatively, these visits may be conducted via videoconference and the subjects may collect these samples at home. At these visits blood will be drawn, a physical exam performed, and vital signs measured (optional). At the month 3 visit a pregnancy test will be given if applicable. Should Subject remain symptomatic at 2 weeks, or return to a positive state at any time during the trial they will be referred to their PCP by a phone call directly from the PI to the PCP. If at any time during the treatment phase or subsequent follow up Subject expresses and demonstrates a worsening or persistence of symptoms, they will be cared for according to standard of care or referred to their primary care provider, according to patient preference. The PI will discuss the case directly with that primary care provider. Subjects will continue to be followed for the remainder of the trial, and documentation of any additional treatments and Subject outcomes will be collected.

Study Populations

Inclusion Criteria

1. Informed consent provided electronically via the EDC, demonstrating that the subject understands the procedures required for the study and the purpose of the study
2. Male or female subjects 18 years of age and up
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)
4. Diagnosis of COVID-19 by at least one of the following:
    a. Physician diagnosis based on clinical presentation
    b. Positive RT-PCR analysis
    c. Positive rapid antigen test

Exclusion Criteria

1. Refusal to provide informed consent
2. Pregnant or breastfeeding women
3. Diarrhea prior to infection
4. Negative test for COVID-19 by RT-PCR or rapid antigen test at screening
5. Any comorbidities which, in the opinion of the investigator, constitute health risk for the subject
6. Any contraindications for treatment with hydroxychloroquine
    a. Hypoglycemic
    b. Known 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. History of QT interval >500msec
    n. History of torsades de pointes
7. Anemia from pyruvate kinase and G6PD deficiencies
8. Abnormal EKG with QT prolongation acquired or from birth
9. Allergies to 4-Aminoquinolines
10. History of jaundice or high fevers prior to developing COVID-19
11. Treatment with any of the medications listed in Appendix II
12. Treatment with any other drug not listed that affects the QT interval
13. Treatment with any anti-epileptics

Number of Subjects
Subjects will be enrolled to ensure that at least 600 complete the study. It is anticipated that screening of 1200 Subjects will be required to achieve this.

Specimen Requirements:
NP swabs (synthetic swab on plastic shaft) placed into 2-3mL of viral transport media.
1 mL of blood in an EDTA and 2 mL of serum in two serum separator tubes spun down

Study Duration
Screening of 1200 Subjects and enrollment of 600 Subjects is expected to take 3 months

Primary Study Objective	Study Endpoints
The rate of recovery from COVID-19 in Subjects using Quintuple Therapy	Number of days from COVID-19 diagnosis to recovery via RT-PCR
Reduction or Progression of Symptomatic Days	Reduction and/or progression of symptomatic days, reduction of symptom severity
Secondary Objectives	**Study Endpoints**
Assess the safety and Tolerability of Quintuple Therapy	Assess the symptom response to study therapy as measured by the survey in the EDC
	EKG response, oxygen saturation, and vital signs at baseline, 2 weeks, 1 month, and two months
	Assess Adverse Events and Serious Adverse Events due to Quintuple Therapy

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.

Table of Contents

PROTOCOL SYNOPSIS 6
LIST OF ABBREVIATIONS 11
1. BACKGROUND AND RATIONALE 12
2. TRIAL OBJECTIVES 13
3. STUDY PROCEDURES: 13
4. PROHIBITED MEDICATIONS 19
5. SUBJECT PRIVACY: 20
6. SCHEDULE OF EVENTS 20
7. DOSAGE OF INVESTIGATIONAL PRODUCT 22
8. SAMPLE COLLECTION 22
9. SAMPLE STORAGE 22
10. SUBJECT INJURY 22
11. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS 23
11.1 Unexpected Adverse Events 23
11.2 Events Not to be Considered an Adverse Event 23
11.3 Serious Adverse Events 23
11.4 Severity 24
11.5 Relationship to Study 24
11.6 Documentation and Methods of Detecting Adverse Events and Serious Adverse Events 24
11.7 Documentation and Detection of Adverse Events and Serious Adverse Events 25
12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 25
13. RISK/BENEFIT ASSESSMENT 25
13.1 Potential Risks 25
13.2 Potential Benefits to Society 31
14. ETHICAL CONSIDERATIONS 31
14.1 Participant Information and Informed Consent 31
15. STATISTICAL ANALYSIS 32
16. ADVERSE EVENT ANALYSIS 32
17. REGULATORY COMPLIANCE 32
17.1 Principal Investigator 32
17.2 Record Retention 33
18. FINANCIAL OBLIGATIONS AND COMPENSATION 33
18.1 Financial Obligations of the Subjects 33
19. REFERENCES 33
20. APPENDICES 34
20.1 Appendix 1: MoMe Kardia II EKG Specifications and Instructions 34
20.2 Appendix 2: List of Prohibited Medications 38
20.3 Appendix 3: Mitigation of Side Effects 41
20.4 Appendix 4: Subject Stopping Criteria 46

List of Abbreviations

AE	Adverse event
BP	Blood pressure
CFR	Code of Federal Regulations
CRF	Case report form
DNA	Deoxyribonucleic Acid
EDC	Electronic Data Capture
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
mL	Milliliters
NP	Nasopharyngeal
OP	Oropharyngeal
OTC	Over the counter
O_2Sat	Oxygen Saturation
PI	Principal Investigator (at each site)
PPE	Personal Protective Equipment
RR	Respiratory Rate
Rx	Prescription medication
RNA	Ribonucleic Acid
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
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 isolated in Wuhan, China. This disease has rapidly spread to become a worldwide pandemic, as declared by the World Health Organization (WHO). 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 Subjects 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.

It is known that single anti-viral agents work poorly when used alone in other chronic viral infections such as Hepatitis C or HIV infection. So, we know that the greater number of anti-viral agents used in combination, the greater the cure rate.

It has been noted from recently published results that Hydroxychloroquine can be extremely effective against coronavirus 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.

Azithromycin, a commonly prescribed macrolide antibiotic for the past thirty years, has recently been used in clinical trials along with hydroxychloroquine for the treatment of COVID-19. It too has demonstrated an excellent safety profile. P. Gautret, D. Raoult, et al., recently published the results of an open labeled, nonrandomized clinical trial in 80 Subjects at the University Hospital Institute Mediterranean Infection in Marseille, France. Subjects were treated with hydroxychloroquine sulfate 200mg three times a day for 10 days and azithromycin 500mg on day 1 followed by 250mg per day on days 2-5. Professor Didier Raoult found clinical improvement and favorable outcomes in all but two of the Subjects, and 93% had a negative nasopharyngeal viral load RT-PCR test by day 8. Virus cultures from Subject respiratory samples were negative in 97.5% of Subjects at Day 5. Subjects were monitored for QT prolongation and other adverse events. Adverse events were noted to be “rare and minor.” 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.

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 Subjects 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.

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. Reduction of the vitamin C, vitamin D, and zinc doses following treatment with hydroxychloroquine is designed to minimize side effects while maintaining their antiviral effects.

2. Trial Objectives

Primary Study Objective	**Study Endpoints**
The rate of recovery of mild or moderate COVID-19 in Subjects using Quintuple Therapy	Number of Days Recovery from COVID-19 diagnosis to Recover via RT-PCR
Secondary Objectives	**Study Endpoints**
Assess the safety of Quintuple Therapy	Assess the symptom response to study therapy as measured by the survey in the EDC
	EKG response, oxygen saturation, and vital signs at baseline, 2 weeks, 1 month, and two months
Assess Tolerability of Quintuple Therapy	Assess Adverse Events and Serious Adverse Events due to Quintuple Therapy

3. Study Procedures:

- Diagnosis, Medical Review, and Prescription of Therapy (Screening, Day -3 to Day -1):
    - Subject will provide electronic informed consent via the EDC portal.
    - Medical Information
        a. Study staff will review prior and concomitant medications, including over-the-counter medications and supplements.
        b. Investigator will review the Subject's records during the screening process, looking at inclusion/exclusion criteria, gathering data on vital signs, EKG recordings, and oxygen saturation. 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.
    - Diagnosis of COVID-19 will be confirmed
        a. May be based on PCR testing results, rapid antigen testing results, or clinical presentation at screening as assessed by the Principal Investigator including symptoms such as:
            - Fever
            - Cough
            - Anosmia
    - Subject will be provided a daily diary for recording symptoms.
    - Subject will be randomized into Arm 1 or Arm 2
    - Prescription of treatment drugs
        a. Arm 1: Medications will be prescribed for Quintuple Therapy
            - Hydroxychloroquine 200MG BID for 10 days, Azithromycin 500mg on day 1, 250mg day 2-5, Vitamin C 3000mg for 10 days, then 1500mg for 20 days, Vitamin D 3000IU for 10 days, then 1500IU for 20 days, and zinc 50mg for 10 days, then 25mg for 20 days.
        b. Arm 2: Placebos and supplements will be provided (to ensure nutritional parity)
            - Placebo for Hydroxychloroquine BID for 10 days, Placebo for Azithromycin to be taken 2 the on Day 1, then 1 on Days 2-5, Vitamin C 3000mg for 10 days, then 1500mg for 20 days, Vitamin D 3000IU for 10 days, then 1500IU for 20 days, and zinc 50mg for 10 days, then 25mg for 20 days.
        c. Drugs shall be taken first thing in the morning as soon as the patient has eaten. Vitamins will be taken with lunch and dinner, and then the evening dose of drugs will be right before bed.
    - Monitoring equipment provided
        a. Home EKG recording device

b. Pulse Oximeter
c. Thermometer
d. Urine Pregnancy test if applicable

- Subject will be isolated as an outpatient
  a. All CDC recommendations regarding self-quarantine must be followed

- Treatment Period
  - Day 1 following positive test (isolation)
    a. Subject will be video called to ensure they have all study materials and go over:
       - Use of home health equipment
         - Subject will take baseline measurements at this time and record it in the diary
       - Diary and how to transmit its contents
       - Medication dosing
    b. Subject will take pregnancy test if applicable
    c. Subject will use provided equipment to measure vital signs
       - EKG
       - Oxygen Saturation
       - Temperature
    d. Subject will take prescribed regimen

Drug	AM Dose	PM Dose
Hydroxychloroquine (or Placebo)	200mg	200mg
Azithromycin (or Placebo)	500mg	---
Vitamin C	1500mg	1500mg
Vitamin D	1500IU	1500IU
Zinc	25mg	25mg

       - Hydroxychloroquine and azithromycin will be taken early in the morning with breakfast and right before bed. Vitamins and Zinc will be taken with lunch and dinner
  - Day 2
    a. Subject will complete AM and PM diaries
    b. Subject will use provided equipment to measure vital signs
       - EKG
       - Oxygen saturation
       - Temperature
    c. Subject will take prescribed regimen

Drug	AM Dose	PM Dose
Hydroxychloroquine (or Placebo)	200mg	200mg
Azithromycin (or Placebo)	250mg	---
Vitamin C	1500mg	1500mg
Vitamin D	1500IU	1500IU
Zinc	25mg	25mg

  - Day 3
    a. Subject will be called
       - Ask if they are experiencing any difficulties with swab collection
       - Ask about AE/SAE
       - Update list of prior and concomitant medications
       - Ask about symptom resolution or progression

- Instruct how to collect nasal or oropharyngeal swabs
  - Subject will collect first nasal or oropharyngeal swab
- Answer any questions the Subject may have

b. Subject will complete AM/PM diaries
c. Subject will use provided equipment to collect vital signs
- EKG
- Oxygen saturation
- Temperature

d. Subject will take prescribed regimen

Drug	AM Dose	PM Dose
Hydroxychloroquine (or Placebo)	200mg	200mg
Azithromycin (or Placebo)	250mg	---
Vitamin C	1500mg	1500mg
Vitamin D	1500IU	1500IU
Zinc	25mg	25mg

- Day 4

a. Subject will complete AM/PM diaries
b. Subject will use provided equipment to collect vital signs
- EKG
- Oxygen saturation
- Temperature

c. Subject will take prescribed regimen

Drug	AM Dose	PM Dose
Hydroxychloroquine (or Placebo)	200mg	200mg
Azithromycin (or Placebo)	250mg	---
Vitamin C	1500mg	1500mg
Vitamin D	1500IU	1500IU
Zinc	25mg	25mg

- Day 5

a. Subject will complete AM/PM diaries
b. Subject will be called
- remind them to collect swab
- Ask about AE/SAE
- Update list of prior and concomitant medications
- Answer any questions

c. Subject will collect nasal or oropharyngeal swab
d. Subject will use provided equipment to collect vital signs
- EKG
- Oxygen saturation
- Temperature

e. Subject will take prescribed regimen

Drug	AM Dose	PM Dose
Hydroxychloroquine (or Placebo)	200mg	200mg
Azithromycin (or Placebo)	250mg	---
Vitamin C	1500mg	1500mg
Vitamin D	1500IU	1500IU
Zinc	25mg	25mg

- Day 6
  a. Subject will complete AM/PM diaries
  b. Subject will use provided equipment to collect vital signs
     - EKG
     - Oxygen saturation
     - Temperature
  c. Subject will take prescribed regimen

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

- Day 7
  a. Subject will be called
     - Ask about AE/SAE
     - Ask about symptom resolution or progression
     - Update list of prior and concomitant medications
     - Answer any questions the Subject may have
  b. Subject will collect nasal or oropharyngeal swab
  c. Subject will complete AM/PM diaries
  d. Subject will use provided equipment to collect vital signs
     - EKG
     - Oxygen saturation
     - Temperature
  e. Subject will take prescribed regimen

Hydroxychloroquine (or Placebo)	200mg	200mg
Vitamin C	1500mg	1500mg
Vitamin D	1500IU	1500IU
Zinc	25mg	25mg

- Day 8
  a. Subject will complete AM/PM diaries
  b. Subject will use provided equipment to collect vital signs
     - EKG
     - Oxygen saturation
     - Temperature
  c. Subject will take prescribed regimen

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

- Day 9
  a. Subject will complete AM/PM diaries
  b. Subject will use provided equipment to collect vital signs
     - EKG
     - Oxygen saturation
     - Temperature

c. Subject will take prescribed regimen

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

- Day 10
  a. Subject will be called
     - Remind them to decrease dosage of vitamins C, vitamin D, and zinc tomorrow
     - Ask about AE/SAE
     - Ask about symptom resolution or progression
     - Update list of prior and concomitant medications
     - Answer any questions the Subject may have
  b. Subject will complete AM/PM diaries
  c. Subject will use provided equipment to collect vital signs
     - EKG
     - Oxygen saturation
     - Temperature
  d. Subject will take prescribed regimen

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

- Day 11-Day 13
  a. Subject will complete AM/PM diaries
  b. Subject will take prescribed regimen

Drug	AM Dose	PM Dose
Vitamin C	750mg	750mg
Vitamin D	750IU	750IU
Zinc	12.5mg	12.5mg

- Day 14
  a. Subject will be called
     - Remind them to collect nasal or oropharyngeal swab
     - Ask about AE/SAE
     - Symptom resolution or progression
     - Answer any questions the Subject may have
  b. Subject will collect nasal or oropharyngeal swab
  c. Subject will complete AM/PM diaries
  d. Subject will take prescribed regimen

Drug	AM Dose	PM Dose
Vitamin C	750mg	750mg

Vitamin D	750IU	750IU
Zinc	12.5mg	12.5mg

- Day 15-30
  a. Subject will complete AM/PM diaries
  b. Subject will take prescribed regimen

Drug	AM Dose	PM Dose
Vitamin C	750mg	750mg
Vitamin D	750IU	750IU
Zinc	12.5mg	12.5mg

- Follow-Up Period (These visits can be conducted via videoconference or in person)
  - Month 1 (outpatient only AFTER negative test)
    a. Vital signs (BP, HR, RR, oxygen saturation, temperature)
    b. Assessment for AE and SAE
    c. EKG (Optional)
    d. Physical exam (Optional)
    e. Blood draw for CBC/Complete metabolic panel/C-Reactive Protein/Blood hydroxychloroquine levels/SARS-CoV Antibody test (All optional)
       - Blood HQ levels will remain blinded from all but unblinded coordinator
    f. Update list of prior and concomitant medications
    g. Study team will collect nasal or oropharyngeal swab (If patient elects to refrain from this in-person visit they will collect this at home)
  - Month 2 (outpatient)
    a. Vital signs (BP, HR, RR, oxygen saturation, temperature)
    b. Assessment for AE and SAE
    c. EKG (Optional)
    d. Physical exam (Optional)
    e. Blood draw for CBC/Complete metabolic panel/C-Reactive Protein (Optional)
    f. Update list of prior and concomitant medications
  - Month 3 (outpatient)
    a. Vital signs (BP, HR, RR, oxygen saturation, temperature)
    b. Assessment for AE and SAE
    c. EKG (Optional)
    d. Physical exam (Optional)
    e. Blood draw for CBC/Complete metabolic panel/C-Reactive Protein (Optional)
    f. Update list of prior and concomitant medications
    g. Study team will collect nasal or oropharyngeal swab (If patient elects to refrain from this in-person visit they will collect this at home)
    h. Pregnancy test (if applicable)
- COVID-19 sample collection
  - Nasal swabs will be collected according to CDC protocol
    a. Synthetic fiber swabs with plastic shafts
       - NP swabs will be collected by insertion of a swab into the nostril parallel to the palate. The swab will be left in place a few seconds to allow it to absorb secretions
    b. Swabs will be immediately placed in sterile tubes with 2-3mL of viral transport media
    c. The tubes will be placed in biohazard bags then boxes. The boxes will be sterilized and then collected by rapid carrier for delivery to the central lab.
  - Oropharyngeal swabs will be collected according to CDC protocol
    a. Synthetic fiber swabs with plastic shafts
       - Swab will be inserted into the mouth and will touch the area near the tonsils five

times.

b. Swabs will be immediately placed in sterile tubes with 2-3mL of viral transport media
c. The tubes will be placed in biohazard bags then boxes. The boxes will be sterilized and then collected by rapid carrier for delivery to the central lab.

- Hospitalization
  - Should Subject's symptoms worsen, they will be referred to their PCP for further evaluation and possible hospitalization

Inclusion Criteria

1. Informed consent provided electronically via the EDC, demonstrating that the subject understands the procedures required for the study and the purpose of the study
2. Male or female Subjects 18 years of age and up
3. Subjects must agree to practice at least one highly effective method 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. Subjects not of reproductive potential will be exempt (e.g. post-menopausal, surgically sterilized)
4. Diagnosis of COVID-19 by at least one of the following:
   a. Physician diagnosis based on clinical presentation
   b. Positive RT-PCR analysis

Positive rapid antigen test **Exclusion Criteria**

1. Refusal to provide informed consent
2. Pregnant or breastfeeding women
3. Diarrhea prior to infection
4. Negative test for COVID-19 by RT-PCR at screening
5. Any comorbidities which, in the opinion of the investigator, constitute health risk for the subject
6. Any contraindications for treatment with hydroxychloroquine
   a. Hypoglycemic
   b. Known 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. History of QT interval >500msec
   n. History of torsades de pointes
7. Anemia from pyruvate kinase and G6PD deficiencies
8. Abnormal EKG with QT prolongation acquired or from birth
9. Allergies to 4-Aminoquinolines
10. History of jaundice or high fevers prior to developing COVID-19
11. Treatment with any of the medications listed in Appendix II
12. Treatment with any other drug not listed that affects the QT interval
13. Treatment with any anti-epileptics

4. Prohibited Medications

Found in Appendix 2

5. Subject privacy:

Subjects will be assigned a unique eight-digit identification number. The first two digits will be the study identification number (44). The next three digits will be the specific test number and the last three digits will be a number sequentially assigned by the site via electronic data capture (EDC). This number will be used to identify the subject on all documents, study equipment, and test samples. 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 secured research facilities per their SOPs.

6. Schedule of Events

On next page

Assessment	Screening (Day -7 to Day 1)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Days 15-30	Month 1 (± 4 days)	Month 2 (± 4 days)	Month 3 (± 4 days)
Informed Consent & Demographics	X																		
Make list of prior and concomitant medications	X			X				X			X				X		X	X	X
Confirmation of COVID-19 diagnosis	X																		
Review of Medical Records	X																		
Prescription of Antimicrobials[a]	X																		
Provide home health equipment[b]	X																		
Pregnancy test[c]		X																	X
Call Subject at home[d]		X		X		X		X			X				X				
Vitals at home[e]		X	X	X	X	X	X	X	X	X	X								
Subject will complete AM/PM diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hydroxychloroquine 200mg BID (or placebo		X	X	X	X	X	X	X	X	X	X								
Azithromycin 500mg (2 tablets) once daily (or placebo)		X																	
Azithromycin 250mg (1 tablet) once daily (or placebo)			X	X	X	X													
Vitamin C 3000mg (2 capsules) twice a day		X	X	X	X	X	X	X	X	X	X								
Vitamin D 3000IU (2 capsules) twice a day		X	X	X	X	X	X	X	X	X	X								
Zinc 50mg (2 capsules) twice a day		X	X	X	X	X	X	X	X	X	X								
Vitamin C 1500mg (1 capsule) twice a day												X	X	X	X	X			
Vitamin D 1500IU (1 capsule) twice a day												X	X	X	X	X			
Zinc 25mg (1 capsule) twice a day												X	X	X	X	X			
Ask about AE and SAE				X				X			X				X		X	X	X
Vitals in-clinic[f]																	X	X	X
Physical exam																	X	X	X
EKG in-clinic																	X	X	X
Swabs for RT-PCR				X		X		X							X		X		X
Bloodwork[g]																	X	X	X
Review list of prior and concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	x	X	X	X	X
SARS-CoV-2 Antibody test (optional, +4 days)																	X		
Blood Hydroxychloroquine level (optional)																	X		

a. To include hydroxychloroquine 200mg tablets (#20), azithromycin 250mg tablets (#6), vitamin C 750mg capsules (#80), vitamin D 750IU capsules (#80), zinc 12.5mg capsules (#80)
b. To include EKG (worn continuously), pulse oximeter, and thermometer
c. If Subject is a woman of childbearing potential
d. To remind them to collect swabs for RT-PCT, ask about AE/SAE, ask about symptoms, and answer any questions
e. To include EKG, oxygen saturation, and temperature
f. Vitals in-clinic to include height (only at first visit), weight, blood pressure (following 5 minutes sitting) pulse, respiratory rate, temperature, and oxygen saturation (Optional)
g. To include CBC, Complete Metabolic Panel, and CRP (details in section 9 Sample Collection) (Optional)

7. Dosage of Investigational Product

Treatment Method	Medication	Dose	Frequency
Quintuple Therapy	Hydroxychloroquine	200mg	BID
	Azithromycin	500mg \Day 1→250mg Day 2-5	Daily
	Vitamin C	1500mg	BID
	Vitamin D	1500IU	BID
	Zinc	25mg	BID
Placebo	Placebo	1 tablet	BID
	Placebo	2 tablets day 1, then 1 tablet day 2-5	Daily
	Vitamin C	1500mg	BID
	Vitamin D	1500IU	BID
	Zinc	25mg	BID

8. Sample Collection

Samples for COVID-19 testing will be collected by the Subject 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 viral transport media. 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.

9. Sample Storage

Samples to be stored by the Cole Laboratories central lab for possible future testing and analysis.

10. 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 in the EDC and in source documents.
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 sponsor. Any malfunction of the medical devices used in this study will be reported to the manufacturer. 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.

11.Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a clinical investigation participant administered a study drug, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug whether or not it is considered related to the study drug.

If the Subject has any abnormal laboratory and other abnormal investigational findings (e.g., physical examination, ECG) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are otherwise considered clinically relevant by the investigator.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In the case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

11.1 Unexpected Adverse Events

An unexpected AE, the nature, severity, specificity, or outcome of which is not consistent with the summary of product characteristics described in the Product Insert

11.2 Events Not to be Considered an Adverse Event

Pre-existing medical conditions/signs/symptoms present 30 days prior to the Screening Period that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions, and are not to be considered AEs. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Not to be Considered an SAE are Hospitalization for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in the absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the investigator will provide information on severity, start and stop dates, relationship to investigation product, rationale of the causality, the action taken regarding IP, and outcome.

11.3 Serious Adverse Events

An SAE is any AE, occurring at any dose level/regimen and regardless of causality that:

- Results in death.
- Is life-threatening: Life-threatening means that the Subject was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form).
- Requires inpatient hospitalization or prolongation of existing hospitalization; however, a hospitalization for an elective procedure will not be considered an SAE.
- Results in persistent or significant disability/incapacity. An AE is incapacitating or disabling if the experience

results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

- Is a congenital anomaly/birth defect: Congenital anomaly/birth defect in a child of a subject or its partner that was exposed to study drug prior to conception or during pregnancy.
- Other, is an important medical event: An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inSubject hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting per regulations, any suspected transmission of an infectious agent via a medical product is by default a suspected unexpected serious adverse reaction (SUSAR) and should be reported in an expedited manner

11.4 Severity

Investigators must evaluate the severity/intensity of AEs and SAEs according to the current active version of the NCI-CTCAE, preferentially using the graded scales. If there is a change in the severity of an AE, it must be recorded as a separate event. If a particular AE's severity/intensity is not specifically graded, the investigator should apply the general guidelines for determination of Grade 1 through Grade 5 as listed in the NCI-CTCAE cover page (as shown below), using their best medical judgment:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate-instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious," which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.
Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.5 Relationship to Study

The investigator must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below. Factors for the assessment of causal relationship include, but are not limited to, the temporal relationship between the AE and the administration of study drug, known side effects of study drug, concomitant therapy, course of the underlying disease and pertinent study procedures.

- Not Suspected: Means a causal relationship of the AE to study drug administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
- Suspected: Means there is a reasonable possibility that the administration of study drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the AE.

11.6 Documentation and Methods of Detecting Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the study. Participants will be

evaluated and questioned generally for AEs during the course of the study, starting at the signing of the informed consent. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. All clearly related signs, symptoms which are either volunteered by participants or observed during or following the course of investigational product administration on the appropriate eCRF. AEs and SAEs reported from the signing of the ICF to the EOS visit are to be reported and documented on the AE eCRF. Any AE related to a protocol procedure should be marked as such on the eCRF.

All AEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the AE eCRF. Any clinically relevant changes in laboratory assessments or other clinical findings as are considered AEs and must be recorded on the AE eCRF. AEs are to be followed for resolution.

It is important that each AE report include a description of the event, duration (onset and resolution dates), severity, relationship with treatment, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of treatment), and outcome. In addition, SAEs should be identified and the appropriate seriousness criteria documented. AEs categorized as SAEs must also be documented within the appropriate SAE section in the eCRF or a paper SAE form if the system is down or otherwise unavailable. Note both methods should not be used beside each other, the paper is for back up reporting only.

11.7 Documentation and Detection of Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the study. Participants will be evaluated and questioned generally for AEs during the course of the study, starting at the signing of the informed consent. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. All clearly related signs, symptoms which are either volunteered by participants or observed during or following the course of investigational product administration on the appropriate eCRF. AEs and SAEs reported from the signing of the ICF to the EOS visit are to be reported and documented on the AE eCRF. Any AE related to a protocol procedure should be marked as such on the eCRF.

All AEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the AE eCRF. Any clinically relevant changes in laboratory assessments or other clinical findings as are considered AEs and must be recorded on the AE eCRF. AEs are to be followed for resolution.

It is important that each AE report include a description of the event, duration (onset and resolution dates), severity, relationship with study drugs, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of study), and outcome. In addition, SAEs should be identified and the appropriate seriousness criteria documented. AEs categorized as SAEs must also be documented within the appropriate SAE section in the eCRF or a paper SAE form if the system is down or otherwise unavailable as described in Section 8.3.4. Note both methods should not be used beside each other, the paper is for back up reporting only.

12. 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.

13. Risk/Benefit Assessment

13.1 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 deidentified 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
    - Subjects 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 azithromycin
  - Dermatologic
    - Generalized rash
    - Pruritis
    - Photosensitivity reaction
    - Stevens-Johnson syndrome
    - Urticaria
    - Dermatitis
    - Dry Skin
    - Hyperhidrosis
    - Eczema
    - DRESS
    - Toxic epidermal necrolysis
    - Erythema multiforme
    - Fungal dermatitis
    - Sweating
    - Vesiculobullous rash

- Maculopapular rash
- Gastrointestinal
  - Diarrhea
  - Nausea
  - Vomiting
  - Abdominal pain
  - Loose stools
  - Flatulence
  - Dyspepsia
  - Stomatitis
  - Gastroenteritis
  - Oral candidiasis
  - Constipation
  - Dysphagia/oral dysphagia
  - Abdominal distention
  - Dry mouth
  - Eructation
  - Mouth ulceration
  - Salivary hypersecretion
  - Pseudomembranous colitis
  - Pancreatitis
  - Tongue discoloration
  - Melena
  - Enteritis
  - Abnormal stools
  - Gastrointestinal disorders
  - Pyloric stenosis
- Genitourinary
  - Vaginitis
  - Vaginal infection
  - Dysuria
  - Intermenstrual bleeding
  - Testicular disorders
- Hematologic
  - Lymphopenia
  - Decreased hematocrit
  - Decreased hemoglobin
  - Neutropenia
  - Eosinophilia
  - Increased platelet count
  - Increased hematocrit
  - Increased lymphocytes
  - Increased basophils
  - Increased monocytes
  - Increased neutrophils
  - Thrombocytopenia
  - Anemia/Hemolytic anemia
  - Decreased platelet count
- Hepatic

        - Hepatitis
        - Increased AST, ALT, GGT, or blood bilirubin
        - Hepatic failure
        - Fulminant hepatitis
        - Hepatic necrosis
    - Hypersensitivity
        - Allergic reaction
        - Angioedema
        - Hypersensitivity
        - Anaphylactic reaction
    - Immunologic
        - Moniliasis
        - Flu syndrome
    - Metabolic
        - Decreased bicarbonate
        - Anorexia
        - Hypernatremia
        - Elevated alkaline phosphatase
        - Elevated bicarbonate
        - Hypochloridemia
        - Elevated lactate dehydrogenase
        - Hyponatremia
        - Hypokalemia
        - Dehydration
    - Musculoskeletal
        - Arthralgia
        - Osteoarthritis
        - Myalgia
        - Back pain
        - Neck pain
        - Elevated creatinine kinase
    - Nervous system
        - Headache
        - Dizziness
        - Paresthesia
        - Dysgeusia
        - Solomnence
        - Hypesthesia
        - Syncope
        - Convulsion
        - Anosmia
        - Ageusia
        - Parosmia
        - Vertigo
        - Myasthenia gravis
        - Taste perversion
        - Hyperkinesia
        - Hyperactivity
    - Optical

        - Visual impairment
        - Conjunctivitis
    - Other
        - Deafness
        - Fatigue
        - Candidiasis
        - Otic disorders
        - Aesthenia
        - Malaise
        - Facial edema
        - Pyrexia
        - Pain
        - Post-procedural complications
        - Fungal or bacterial infection
        - Mucositis
        - Fever
        - Chills
    - Psychiatric
        - Nervousness
        - Insomnia
        - Agitation
        - Aggression
        - Anxiety
        - Delirium
        - Hallucination
        - Emotional lability
        - Irritability
        - Hostility
    - Renal
        - Nephralgia
        - Elevated BUN and creatinine
        - Acute renal failure
        - Interstitial nephritis
    - Respiratory
        - Dyspnea
        - Pneumonia
        - Pharyngitis
        - Rhinitis
        - Epistaxis
        - Bronchospasm
        - Cough
        - Pleural effusion
        - Asthma
        - Bronchitis
        - Reactive airway
- 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: rash, pruritis, edema (especially of the face/tongue/throat), severe dizziness, dyspnea
- Risks associated with Vitamin D
    - Common side effects
        - None
    - Serious side effects
        - Nausea
        - Vomiting
        - Constipation
        - Hypercalcemia
        - Hypercalcemia
        - Polydipsia
        - Polyuria
        - Mental status/mood changes
        - Fatigue
        - Allergic reaction: rash, pruritis, edema (especially of the face/tongue/throat), severe dizziness, dyspnea
- Risks associated with Zinc
    - Common side effects
        - diarrhea
        - Abdominal cramps
        - Vomiting
        - Anosmia
        - Metallic taste
    - Serious side effects
        - Renal damage
        - Gastropathy
        - Decreased copper absorption

13.2 Potential Benefits to Society

- Successful treatment of COVID-19 could save countless lives. The value cannot be calculated

14. Ethical Considerations

14.1 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 a signed Informed Consent Form for each subject prior to initiating any study procedure. Receipt of the 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.

15.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.
PCR results will be compared between the groups as positive or negative

In this study, the meaningful threshold will be calculated as mean change in clinical symptoms as recorded in the diary, from Day 1 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. Ultimately, efficacy will be determined based upon reduction and/or progression of symptomatic days, reduction of symptom severity, as well as analysis of the subject's RT-PCR testing per protocol. These data will be compared to an existing database of de-identified Subject data.

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 Subjects from the treatment group at the end and at baseline, respectively.

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

Sample size was calculated as follows:

$$n = \frac{\log \beta}{\log \rho}$$

Where $\beta = the\ probability\ of\ a\ Type\ II\ error$

$\rho = the\ proportion\ of\ the\ population\ NOT\ affected$

The proportion of the population affected by COVID-19 is 0.005 percent, thus 0.995 percent aren't affected
The probability of a type II error is 0.05
Thus:

$$n = \frac{\log 0.050}{\log 0.995}$$

n=597.647
A sample size of 600 will be used

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

16.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.

17.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.

17.1 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).

17.2 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.

18. Financial Obligations and Compensation

18.1 Financial Obligations of the Subjects

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

19. References

Banjanac, Mihailo, et al. “Anti-Inflammatory Mechanism of Action of Azithromycin in LPS-Stimulated J774A.1 Cells.” *Pharmacological Research*, vol. 66, no. 4, 2012, pp. 357–362., doi:10.1016/j.phrs.2012.06.011.

Cortegiani, Andrea, et al. “A Systematic Review on the Efficacy and Safety of Chloroquine for the Treatment of COVID-19.” *Journal of Critical Care*, 2020, doi:10.1016/j.jcrc.2020.03.005. "...evidence of safety from long-time clinical use for other indications to justify clinical research on chloroquine in Subjects with COVID-19."

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 Subjects 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"

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 Ageage nts*, 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 Subjects and its effect is reinforced by azithromycin."

Gupta, Ritesh, et al. “Clinical Considerations for Subjects 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 ."

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.

20.Appendices

20.1 Appendix 1: MoMe Kardia II EKG Specifications and Instructions

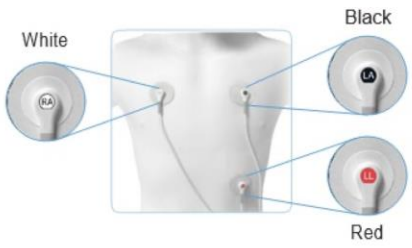
Specification	MoMe® Kardia Device
Battery Life	Provides 24 hours of function before recharging
Operating Temperature	5°C to 40°C
Storage Temperature (power off)	-25°C to 70°C
Operating Humidity	15% to 93% non-condensing
Storage Humidity	15% to 93% non-condensing
Operating Pressure	700 hPa to 1060 hPa
ECG Sampling Rate Digital Resolution Input Dynamic Range Input Offset Dynamic Range	 200 Hz 5uV +/- 10 mV +/- 300 mV
Input Impedance Peak current injection RMS current injection	> 3 MOhm 24 nA (Lead off circuit) DC 29 microA
Data Storage Capacity	Minimum 30 days
Dimensions	108 mm x 67 mm x 17 mm max
Weight	80 +/- 5 g
Communication Means	HSPA+, UMTS, GPRS, EDGE 800/850, AWS1700, 1900
Ingress Protection Rating	IPX0
Display	Type: LED Matrix, Size: 24 X 7
Memory	Internal microSD card up to 32 GB, Not user accessible
Battery	Li-Ion 1900mAh battery pack Min 24 hour battery life

Benefits

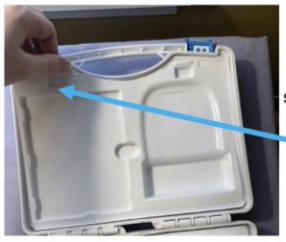
- 3-in-1 outpatient mobile cardiac monitor: Holter, MCT, and event monitor
- Lightweight, one piece, sleek form factor
- Eliminates intermediaries in patient enrollments and IDTF data delays, which may provide faster time to diagnosis
- On-demand, full disclosure wireless device with automated analysis in the cloud
- Practices gain full control over diagnostic workflow, including billing

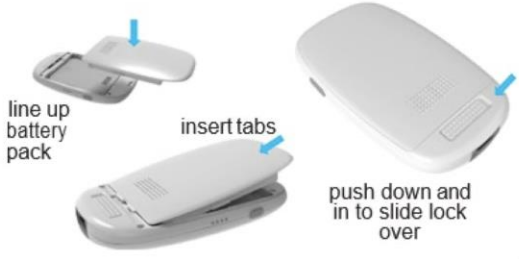
Distributed by
BIOTRONIK
excellence for life

LEADSET 2



ATTACHMENTS





https://youtu.be/L0oKWp_PHbI

RECORD

Press and hold the Record Button for 3 seconds to record

VOLUME

BATTERY

Replace the battery with a fully charged one when the BATT LOW notification is displayed

Patient Instructions

- This is not a life-saving device and is only monitoring your heart rhythm
- DO NOT Get MoMe Kardia Wet – remove before bathing
- Change Battery every 24 Hours and replace used battery on charger
- Contact your physician's office directly with questions/problems

CHARGING

WARNINGS

- MoMe® Kardia is not intended for use as an emergency medical response system. Call 911 if you feel you are having a medical emergency.
- The MoMe® Kardia Device is not defibrillation-proof. Remove MoMe® Kardia Device and disconnect patient leads before external defibrillation.
- Do not service or repair any components of the MoMe® Kardia system. Removal of or tampering with any component may alter device performance and cause device malfunction or failure.
- The MoMe® Kardia contains a cellphone. If you have an implantable device, follow your implantable device manufacturer's recommendations for use with a cellphone.

CAUTIONS

- Electrodes may cause skin irritation. Follow your physician's instructions on what to do if skin irritation occurs.
- Use only with the supplied battery packs, charging dock, and wall adapter
- MoMe® Kardia is not waterproof:
  - Do not get device wet. Never bathe, shower, or swim while wearing the MoMe® Kardia Device (while bathing or swimming, store MoMe® Kardia equipment in a safe, dry location)
  - Protect all MoMe® Kardia parts from water, liquids or moisture which will damage equipment and affect system operation;
  - Do not immerse any part of the MoMe® Kardia system in water or fluids. Do not spray device with cleaners or other liquids;
- Do not drop or subject MoMe® Kardia parts to extreme physical shock.
- Keep the system out of reach of children and pets.
- The MoMe® Kardia provided for use in the U.S. will not transmit recorded data if you travel outside of the U.S.

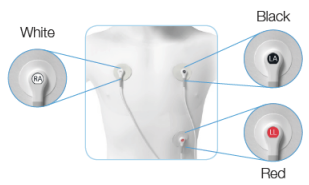
INFOBIONIC®

MoMe® Kardia
Patient Quick Reference Guide

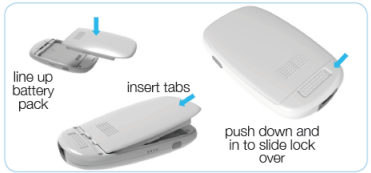
10609a

Your physician prescribed you a MoMe® Kardia device. It is important you wear the device according to your doctor's instructions.

LEADSET



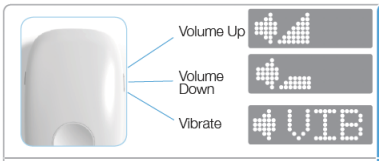
ATTACHMENTS



Slide device into Belt Clip to lock into position

Attach the leadset as shown above.

VOLUME



RECORD

Press and hold the Record Button for 3 seconds to record

NOTIFICATIONS

BATT LOW

Replace the battery with a fully charged one when the BATT LOW notification is displayed

CHARGING

WARNINGS

- MoMe® Kardia is not intended for use as an emergency medical response system. Call 911 if you feel you are having a medical emergency.
- The MoMe® Kardia Device is not defibrillation-proof. Remove MoMe® Kardia Device and disconnect patient leads before external defibrillation.
- Do not service or repair any components of the MoMe® Kardia system. Removal of or tampering with any component may alter device performance and cause device malfunction or failure.
- The MoMe® Kardia contains a cellphone. If you have an implantable device, follow your implantable device manufacturer's recommendations for use with a cellphone.

CAUTIONS

- Electrodes may cause skin irritation. Follow your physician's instructions on what to do if skin irritation occurs.
- Use only with the supplied battery packs, charging dock, and wall adapter
- MoMe® Kardia is not waterproof:
  - Do not get device wet. Never bathe, shower, or swim while wearing the MoMe® Kardia Device (while bathing or swimming, store MoMe® Kardia equipment in a safe, dry location)
  - Protect all MoMe® Kardia parts from water, liquids or moisture which will damage equipment and affect system operation;
  - Do not immerse any part of the MoMe® Kardia system in water or fluids. Do not spray device with cleaners or other liquids;
- Do not drop or subject MoMe® Kardia parts to extreme physical shock.
- Keep the system out of reach of children and pets.
- The MoMe® Kardia provided for use in the U.S. will not transmit recorded data if you travel outside of the U.S.

MoMe® Kardia
Patient Quick Reference Guide

MoMe® Kardia

Specification Sheet

Product Highlights

MoMe® Kardia is an advanced 3-in-1 outpatient mobile cardiac monitoring solution that allows physicians to dynamically switch between Holter, MCT, and event monitoring modes for up to 30 days of continuous monitoring.

MoMe® Kardia is the first and only FDA cleared remote cardiac monitoring platform that provides near real-time full disclosure data.

20.2 Appendix 2: List of Prohibited Medications

abarelix
abiraterone
acetohexamide
adalimumab
adenosine
ado-trastuzumab emtansine
afatinib
albuterol
alfuzosin
afatinib
aliskiren
aluminum carbonate
aluminum hydroxide
amifampridine
amiodarone
amisulpride
amitriptyline
amoxicillin
amoxapine
ampicillin
anagrelide
anisindione
apalutamide
apomorphine
arformoterol
aripiprazole
arsenic trioxide
asenapine
asparaginase erwinia chrysanthemi
asparaginase escherichia coli
astemizole
atomoxetine
atorvastatin
attapulgite
auranofin
aurothioglucose
bacampicillin
balsalazide
bcg
bedaquiline
benznidazole
bepridil
betrixaban
bicalutamide
binimetinib
bisacodyl
bitolterol
black cohosh
bortezomib
bosutinib
brentuximab
buprenorphine
cabazitaxel
cabergoline
cabozantinib
calaspargase pegol
calcium carbonate
cannabidiol
carbenicillin
carboplatin
carfilzomib
casanthranol
cascara sagrada
castor oil
ceritinib
cerivastatin
certolizumab
cevimeline
chloramphenicol
chloroquine
chlorpromazine
chlorpropamide
cholera vaccine, live
cimetidine
ciprofloxacin
cisapride
cisplatin
citalopram
clarithromycin
clofarabine
clofazimine
clomipramine
cloxacillin
clozapine
codeine
colchicine
crizotinib
cyclosporine
dapsone
darifenacin
dasatinib
daunorubicin
daunorubicin liposomal
deferiprone
degarelix
desipramine
deutetrabenazine
didanosine
digoxin
dihydroxyaluminum sodium carbonate
dabigatran
daclizumab
dasatinib
daunorubicin
daunorubicin liposomal
degarelix
desipramine
deutetrabenazine
dicloxacillin
dicumarol
digitoxin
digoxin
dihydroergotamine
dinutuximab
disopyramide
disulfiram
docetaxel
dofetilide
dolasetron
donepezil
doxepin
doxepin topical
doxorubicin liposomal
dronedarone
droperidol
duloxetine
edoxaban
efavirenz
elotuzumab
encorafenib
enfortumab vedotin
entrectinib
enzalutamide
epirubicin
eribulin
ergonovine
ergotamine
erythromycin
escitalopram
estradiol
etanercept
ethambutol
ethinyl estradiol
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
halofantrine
haloperidol
halothane
histrelin
hydralazine
hydroxyzine
ibutilide
idarubicin
idelalisib
iloperidone
imipramine
indacaterol
indium oxyquinoline in-111
infliximab
inotuzumab ozogamicin
interferon alfa-2a
interferon alfa-2b
interferon alfa-n1
interferon beta-1a
interferon beta-1b
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
lomitapide
loperamide
lovastatin
lusutrombopag
macimorelin
magaldrate
magnesium carbonate
magnesium citrate
magnesium hydroxide
magnesium oxide
maprotiline
mefloquine
mesoridazine
metaproterenol
methadone
methicillin
methotrexate
methotrimeprazine
methylergonovine
methysergide maleate
metoprolol
metronidazole
mezlocillin
midostaurin
mifepristone
mineral oil
mipomersen
mirtazapine
moxifloxacin
mycophenolate mofetil
mycophenolic acid
nateglinide
n nadolol
nafcillin
naldemedine
naloxegol
naltrexone
nefazodone
nelarabine
nelfinavir
nilotinib
nilutamide
nitrofurantoin
norfloxacin
nortriptyline
ofloxacin
olanzapine
olodaterol
ondansetron
osilodrostat
osimertinib
oxacillin
oxaliplatin
oxtriphylline
paclitaxelpaclitaxel
protein-bound
paliperidone
palonosetron
panobinostat
papaverine
pasireotide
pazopanib
pegaspargase
peginterferon alfa-2a
peginterferon alfa-2b
peginterferon beta-1a
penicillamine
penicillin g benzathine
penicillin g potassium
penicillin g sodium
penicillin v potassium
pentamidine
perflutren
perphenazine
phenolphthalein
pimavanserin
pimozide
piperacillin
pirbuterol
pitavastatin
pitolisant
polatuzumab vedotin
polyethylene glycol 3350
polyethylene glycol 3350
with electrolytes
pomalidomide
ponatinib
posaconazole
pravastatin
primaquine
probucol
procainamide
procaine penicillin
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
riociguat
risperidone
ritodrine
rivaroxaban
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
talazoparib
tamoxifen
telavancin
telbivudine
telithromycin
teniposide
terbutaline
terfenadine
teriflunomide
tetrabenazine
thalidomide
thioguanine
thioridazine
theophylline
ticarcillin
timolol ophthalmic
tinidazole
tizanidine
tocilizumab
tolazamide
tolbutamide
tolterodine
toremifene
trabectedin
tramadol
trazodone
triclabendazole
trifluoperazine
triflupromazine
trimeprazine
trimipramine
triptorelin
typhoid vaccine, live
ubrogepant
valbenazine
vandetanib
vardenafil
vasopressin
vemurafenib
venlafaxine
vigabatrin
vinblastine
vincristine
vincristine liposome
vinorelbinz
vismodegib
voriconazole
warfarin
zafirlukast
zalcitabine
zidovudine
ziprasidone

20.3 Appendix 3: Mitigation of Side Effects

- 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 Subject Diary
- Auditory
    - Tinnitus and deafness
        - Subjects experiencing either of these symptoms will be referred to their primary care physician for treatment.
- Dermatological
    - Rash or pruritis, including Vesiculobullous rash or Maculopapular rash
        - Subject will be prescribed appropriate treatment depending on the type of rash or pruritis
    - Photosensitivity reaction
        - Subject will be advised to avoid sunlight for the duration of treatment. If Subject must go out, they should wear pants and long sleeves.
    - Stevens-Johnson syndrome, DRESS syndrome, TEN
        - Subject will be referred to a hospital for evaluation treatment
    - Urticaria
        - Will be treated with antihistamines and observed. If this treatment is not effective, the Subject will be re-evaluated by PI for further treatment and/or referral
    - Dermatitis including exfoliative dermatitis
        - Subject 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
    - Dry Skin
        - Subject will be provided with a skin care recommendation depending on the degree of severity
    - Hyperhidrosis
        - Subject will be referred to their PCP for evaluation
    - Eczema
        - Subject will be provided with topical treatment if necessary
    - Erythema multiforme
        - Subject will be observed, as this condition usually resolves without treatment. The efficacy of glucocorticoids in this condition is debated
    - Fungal dermatitis
        - Subject will be prescribed appropriate antifungal medication
    - 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
        - Subject will be prescribed appropriate therapy depending on type and severity of symptoms
    - Angioedema
        - Treatment will depend on the severity. If severe, Subject 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
    - Subject will be medically managed. If severe treatment may be discontinued.
  - Nausea
    - Subject will be prescribed anti-nausea medication if needed
  - Loose Stools & Diarrhea
    - Subject will be prescribed anti-diarrheal medication if needed
  - Vomiting
    - Subject will be prescribed anti-emetic medication if needed
  - Flatulence
    - Subject will be advised to try over-the-counter anti-flatulence medication if needed
  - Dyspepsia
    - Subject will be prescribed appropriate therapy such as an H2 receptor antagonist or PPI if needed
  - Stomatitis
    - If needed Subject will be advised to:
      - Avoid hot beverages and foods as well as salty, spicy, and citrus-based foods.
      - Use pain relievers like Tylenol or ibuprofen.
      - Gargle with cool water or suck on ice pops if they have a mouth burn.
  - Gastroenteritis
    - Subject will be prescribed appropriate therapy if needed
  - Oral candidiasis
    - Subject will be prescribed appropriate antifungal medications if needed
  - Constipation
    - Subject will be prescribed stool softening medication if needed
  - Dysphagia/ oral dysphagia
    - Depending on the severity Subject might be managed with medication such as PPI
  - Abdominal distention
    - Subject will be medically managed. If severe Subject will have teleconference with PI and may be referred for in-person visit with PI and/or hospitalization.
  - Dry mouth
    - Subject will be advised to drink water and chew gum
  - Eructation
    - Subject will be advised to eat and drink slowly and avoid carbonated beverages. If this does not work, PPI may be prescribed if needed
  - Mouth ulceration
    - If mild Subject will be advised to:
      - Avoid hot beverages and foods as well as salty, spicy, and citrus-based foods.
      - Use pain relievers like Tylenol or ibuprofen.
      - Gargle with cool water or suck on ice pops if they have a mouth burn.
    - If moderate or severe Subject will be medically managed
  - Salivary hypersecretion
    - Should resolve when treatment is completed
  - Pseudomembranous colitis
    - Subject will be medically managed
  - Pancreatitis
    - Subject will be referred for hospital for evaluation

  - Tongue discoloration
    - Will be monitored
  - Melena
    - Medical management will be utilized first if needed. If this is unsuccessful, Subjects will be evaluated and treated based on current standards of care
  - Enteritis
    - Will be symptomatically managed. If symptoms persist, Subject may be referred for hospitalization
  - Abnormal stools
    - Subject will be medically managed
  - Gastrointestinal dysfunction
    - Subject will be symptomatically managed
  - Pyloric stenosis
    - Subject will be referred to PCP for evaluation and standard of care therapy
- Genitourinary
  - Vaginitis/Vaginal infection
    - Subject will be prescribed appropriate antibiotic or antifungal therapy
  - Dysuria
    - Urinalysis will be performed to check for bladder infection. If one is found it will be treated with appropriate antibiotics. If UTI is not found, diagnostics such as vaginal/urethral culture will be run to test for other causes. If these are found, they will be medically managed.
  - Intermenstrual bleeding
    - Subjects will be advised that this should end once treatment is completed. Subject will be referred to a gynecologist if needed.
  - Testicular disorder
    - Subject will be referred to a specialist
- Hematologic
  - Any hematological abnormalities found during treatment or after will be followed by subsequent CBCs. If the problem is severe, Subject may be medically managed or referred for hematology consultation and possible hospitalization.
- Hepatic
  - Hepatitis
    - Medication will be discontinued, and Subject will be monitored. If liver values do not return to normal Subject will be referred to a specialist
  - Elevated AST, ALT, GGT, and/or bilirubin
    - Follow-up metabolic panels will be run. Subjects will be advised to refrain from drinking alcohol for the duration of the trial. If values do not return to normal, Subject will be referred to their PCP or GI specialist
  - Hepatic failure/fulminant hepatic failure/fulminant hepatitis/hepatic necrosis
    - Subject will be referred for hospitalization
- Hypersensitivity
  - Allergic reaction/hypersensitivity
    - Subject will be medically managed with antihistamines and standard-of-care
  - Angioedema
    - Subject's airway will be managed. Subject will be treated with antihistamines and if necessary, glucocorticoids.
  - Anaphylactic reaction
    - Subject will be emergently treated with epinephrine and referred for hospitalization if necessary

- Immunologic
  - Moniliasis
    - Subject will be treated with appropriate antifungal therapy.
  - Flu syndrome
    - Subject will be tested for influenza. If positive, Subject will be prescribed appropriate antiviral regimen
- Metabolic
  - Abnormal blood chemistry values including below will be monitored. If they do not return to normal Subject will be treated accordingly
    - Decreased bicarbonate
    - Hypernatremia
    - Elevated alkaline phosphatase
    - Elevated bicarbonate
    - Hyperchloridemia
    - Elevated lactate dehydrogenase
    - hyponatremia
    - Hypokalemia
    - Decreased copper absorption
  - Dehydration
    - Subject will be advised to increase fluids and possibly electrolyte intake. If this does not solve the problem, or it is severe, Subject may be referred for hospitalization
  - Anorexia
    - Subject will be monitored for resolution of symptoms. If they do not resolve on their own, Subject will be medically managed
- Musculoskeletal
  - Sensorimotor disorders
    - Subject will be referred to a specialist
  - Skeletal muscle myopathy or neuromyopathy
    - May be reversible by stopping medication but recovery can take months. Subject will be referred to a specialist
  - Depression of tendon reflexes/ Abnormal nerve conduction studies
    - Subject will be referred to a specialist
  - Arthralgia/myalgia/neck pain/back pain
    - Subject will be medically managed
  - Osteoarthritis
    - Subject will be medically managed. If the condition worsens Subject will be referred to a specialist
  - Elevated creatine kinase
    - Subject will be monitored. If condition persists or worsens, Subject will be referred to a specialist
- Nervous system
  - Headache/dizziness/vertigo
    - Subject will be medically managed
  - Seizure
    - Subject will be referred to a neurologist for diagnostics and treatment
  - Ataxia
    - Subject will be referred to a neurologist for diagnostics and treatment
  - Auditory nerve dysfunction
    - Subject 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
    - Subjects with retinal changes may be asymptomatic initially, or may have scotomatous vision with paracentral, pericentral ring types, temporal scotomas, and abnormal color vision.
    - Subjects 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 Subject will be referred to an ophthalmologist
- Other
  - Fatigue/Aesthenia/Malaise/fever/chills
    - Subject will be monitored. If this does not resolve with treatment Subject will undergo further diagnostics to determine the etiology
  - Candidiasis
    - Subject will be treated with appropriate antifungal therapy
  - Ear disorder
    - Subject will be referred to a specialist
  - Face edema
    - Subject will have bloodwork and urinalysis done. Depending on findings Subject may be medically managed or referred to a specialist and treatment discontinued.
  - Pain
    - Subject will be medically managed
  - Post-procedural complications
    -
  - Fungal or bacterial infection
    - Subject will be treated with appropriate antimicrobial therapy
  - Mucositis
    - Should resolve with completion of treatment. Will be medically and symptomatically managed
- Psychiatric
  - Affect lability
    - Subject will be referred to a specialist
  - Nervousness
    - Subject will be referred to a specialist
  - Psychosis
    - Subject will be referred to a specialist
  - Suicidal behavior
    - Subject will be referred to a specialist
  - Insomnia
    - Subject will be medically managed. If this fails Subject will be referred to a specialist

- Agitation
  - Subject will be referred to a specialist
- Aggression
  - Subject will be referred to a specialist
- Anxiety
  - Subject will be referred to a specialist
- Delirium
  - Subject will be referred to a specialist, possibly for hospitalization
- Hallucination
  - Subject will be referred to a specialist, possibly for hospitalization
- Irritability
  - Subject will be referred to a specialist
- Hostility
  - Subject will be referred to a specialist

- Renal
  - Renal pain
    - Subject will be medically managed
  - Increased BUN and creatinine
    - Subsequent labs will be run. If the values do not return to normal treatment will be discontinued. Will be followed until values return to normal.
  - Acute renal failure
    - Treatment will be discontinued. Subject will be referred for hospitalization
  - Interstitial nephritis
    - CBC will be run to determine if there is an infectious etiology. Treatment will be discontinued. Subject will be treated with corticosteroids.
- Respiratory
  - Dyspnea/pneumonia/pleural effusion
    - Subject will be referred for hospitalization
  - Pharyngitis
    - Subject will be given a rapid strep test and if this is positive will be treated with appropriate antibiotics. If negative Subject will be symptomatically medically managed
  - Rhinitis
    - Subject will be medically managed
  - Respiratory disorder
    - Subject will undergo clinical evaluation to determine the nature of the disorder. If determined to be other than COVID-19 will be medically managed
  - Epistaxis
    - Subject will apply pressure to the nasal alae for at least 10 minutes or until bleeding stops. If severe Subject will be evaluated for blood loss and possibly be referred for hospitalization
  - Bronchospasm
    - Treatment will be discontinued, and Subject will be treated with antihistamines
  - Cough
    - Subject will be advised to use lozenges. If the symptom is severe, cough syrup may be prescribed
  - Asthma
    - Treatment will be discontinued, and Subject will be given supportive care
    - BronchitisSubject will be medically managed with supportive treatment.

20.4 Appendix 4: Subject Stopping Criteria

- QT interval >500msec
- Increase in QT >30-60msec
- Presence of torsades de pointes
- Occurrence of unexpected drug related SAE
- Any other risk which the Investigator deems necessary to discontinue the study drugs