A Triple Combination Antiviral Coronavirus Therapy (TriACT) RCT Comparing Nitazoxanide, Ribavirin and Hydroxychloroquine vs. Placebo

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INTERVENTIONAL
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STUDY INFORMATION

- **Title of Project:**
  A Triple Combination Antiviral Coronavirus Therapy (TriACT) RCT Comparing Nitazoxanide, Ribavirin and Hydroxychloroquine vs. Placebo

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Table of Contents

Skip to Section: Hold **CTRL** + **Click (Below)** To Follow Link in **Blue**

1.0 Research Design

1.1 Purpose/Specific Aims

The purpose of this study is to evaluate the efficacy of Nitazoxanide (NTZ), Ribavirin (RBV) and Hydroxychloroquine (HCQ) versus placebo in participants with proven SARS-CoV-2 infection who are asymptomatic or mildly symptomatic with COVID-19. Those with illness requiring hospitalization, or who present with hypoxia (PO2<92%) or shortness of breath at time of enrollment are excluded.

A. Objectives

In participants with proven SARS-CoV-2 infection who are asymptomatic or mildly symptomatic with COVID-19 randomly allocated to nitazoxanide, ribavirin plus hydroxychloroquine (NTZ, RBV + HCQ) or placebo.

Primary Objective:
To assess the rate of decline in viral load over the 10 days after randomization between participants treated with NTZ, RBV + HCQ for COVID-19 and placebo.

Secondary Objective:

1. To compare the proportion of participants with virus below LLOQ at day 10
2. To compare the proportion of participants who are asymptomatic and symptomatic at day 10
3. To compare the time of onset and frequency of the development of fever and other symptoms of COVID-19 in those who were asymptomatic at enrollment
4. To compare the progression in severity of COVID-19 symptoms (hospitalization and length of stay; admission to intensive care unit and number of days in unit; intubation, Death (any cause))
5. To compare the severity of disease in participants who develop symptoms of COVID-19
6. To compare the side effects of NTZ, RBV + HCQ compared to placebo
7. To determine whether baseline viral load predicts response to therapy
8. To assess the rate of decline in viral load over days 3 and 6 after randomization
9. To assess new, self-reported COVID-19 infection in household members

B. Hypotheses / Research Question(s)

We hypothesize that treatment with NTZ, RBV + HCQ decreases viral load and the progression of symptoms, or emergence of symptoms in those who are asymptomatic at baseline, in SARS-CoV-2-positive adults compared to placebo.

1.2 Research Significance

From its origins in late 2019 at a wet seafood market in Wuhan, China, infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has rapidly become a global pandemic [1]. The clinical manifestations of coronavirus disease-2019 (COVID-19) range from asymptomatic carriage and mild upper respiratory symptoms to severe pneumonia, respiratory failure, sepsis, and death [2]. Viral transmission appears to occur predominantly via inhalation or by contact with infectious droplets [3]. In addition to spread from symptomatic persons, pre-symptomatic and asymptomatic hosts also can transmit SARS-CoV-2, complicating efforts to contain its spread [4].

Since the virus is novel in humans and pre-existing immunity appears to be lacking, estimates of its spread are guided by previous pandemics of new influenza strains that could infect 50-70% of the world population within 2 years [5]. SARS-CoV-2 is highly infectious, with estimated R_0 between 2 and 4, and doubling in many countries about every 4 days [6]. The U.S has experienced similar exponential spread, and despite community efforts to encourage social distancing through school and event cancellations, remote workplaces, and self-quarantining, many experts predict that the U.S. health care system, like those in parts

of Europe and Asia, will soon be overwhelmed with new cases, with hospitals and healthcare workers (HCW) facing unprecedented challenges [7, 8]

A triple combination antiviral coronavirus therapy (TriACT) comprised of hydroxychloroquine sulfate, ribavirin, and nitazoxanide for the treatment of acute illness due to SARS-CoV-2 infection is being tested in the study. Each of these drugs is currently available as oral drug product approved for marketing in many of the major world markets. In the US, they are available under the trade names, PLAQUENIL® (hydroxychloroquine sulfate, USP) tablets, for oral use; Rebetol® (ribavirin, USP) capsules and oral solution, for oral use; or Alinia® (nitazoxanide) tablets, for oral use.

The pharmacological rationale for the treatment of SARS-CoV-2 with a triple combination antiviral therapy is based on two distinct rationales: i) high antiviral potency through synergy, in order to block viral replication, and ii) creating a high genetich barrier to antiviral drug resistance. It was previously discovered that by carefully selecting drugs that block sequential steps in viral replication could lead to synergy, or a multiplicative increase in antiviral potency. The triple combination therapy of amantadine, ribavirin and oseltamivir was shown to be 20-fold synergistic, in both in vitro models and in vivo models.[9] This product was evaluated in a global Phase 2 clinical trial conducted by NIH/NIAID, which showed that this three- antiviral drug combination significantly reduced viral load compared to oseltamivir alone.[10] The in vitro pharmacology of hydroxychloroquine sulfate, ribavirin, and nitazoxanide has been examined in SARS-CoV-2 and related viral infections, and have all demonstrated promising, yet modest effects, on slowing viral replication in vitro and in vivo. These drugs sequentially block steps in the SARS-CoV-2 viral replication life cycle, including uncoating, replication and reassembly of virus particles in the host human cells. Each of these drugs exhibit effective antiviral concentrations (or EC50s) ~1 µg/ml based upon in vitro data in corona virus infected cell lines that approximate the blood concentration ranges of their respective labels:

- Hydroxychloroquine: 0.24 to 2.4 µg/ml [11,12]
- Ribavirin: 4 to 8 µg/ml [13]
- Nitazoxanide: 0.3 to 1 µg/ml [14]

In addition to the direct antiviral activity of the triple combination each of the individual drugs has documented immunomodulatory activities that may contribute to the overall impact on the host.[15-17] Combining drugs with both direct antiviral and immunomodulating activity is a rational approach based on the pathophysiology of the infection where immune dysregulation and hyperinflammatory responses contribute to multi-organ dysfunction and death(cytokine storm).

The clinical efficacy, safety, and pharmacokinetics of orally administered hydroxychloroquine sulfate, ribavirin, and nitazoxanide have been investigated as monotherapies in SARS-CoV-2 and related infections.

Hydroxychloroquine has been widely studied in clinical trials for coronaviruses, including COVID19. In a randomized controlled trial (RCT) comparing HCQ (n = 31) versus no HCQ (n = 31) in mild to common COVID-19 (NHC criteria) patients, Chen et al. reported that the HCQ group had shorter time to clinical recovery and radiologic improvement in pneumonia.[18] A non-randomized case-control study in France, which compared HCQ (n = 14) and HCQ plus azithromycin for prevention of bacterial superinfection (n = 6) against a control group (n = 16). At day 6 of treatment, all patients in the HCQ plus azithromycin group tested virus-free, compared to 57.1% in the HCQ-alone group and 12.5% of the control group (P <0.001).[19] Other studies have shown less favorable results. A small non-blinded RCT in China comparing HCQ (n = 15) against a control group (n = 15) in patients with common COVID-19 (NHC criteria) showed that following 7 days of treatment, throat swabs were negative for the virus in 86.7% of the HCQ group compared to 93.3% of the control group (P > 0.05).[20] The mean duration from hospitalization to viral clearance was comparable in both groups. Results of combination therapy from a retrospective cohort study of 368 males from the US Veterans Health Administration medical centers who received either

HCQ, HCQ plus azithromycin or no HCQ for COVID-19 of varying severities showed that the risk of death from any cause was higher in the HCQ group (adjusted hazard ratio (HR) = 2.61; 95% CI: 1.10–6.17; P = 0.03) compared to the no-HCQ group.[21] The risk of ventilation was no different in patients who did not receive HCQ compared to those who received HCQ alone (adjusted HR, 1.43; 95% CI: 0.53–3.79; P = 0.48) or with azithromycin (adjusted HR = 0.43; 95% CI: 0.16–1.12; P = 0.09). The risk of death after ventilation also was not significantly different across the 3 groups.

The safety of HCQ in Covid patients has been examined in multiple studies of varying rigor. HCQ use, with or without azithromycin among patients hospitalized with COVID-19 in retrospective cohort study of 1438 patients hospitalized in metropolitan New York, treatment with HCQ, azithromycin, or both was not associated with significantly lower in-hospital mortality.[22] In another study in New York City, Investigators analyzed 1,376 COVID-19 patients who had been admitted to the hospital , including 811 who received a 5-day course of HCQ.[23] The time-to-event analysis found no greater—or lower—risk of intubation or death with hydroxychloroquine recipients vs. nonrecipients. Three studies have investigated the use of HCQ in severe COVID-19 patients that have reported prolongation of QT intervals. In a prospective case series of 11 severe COVID-19 patients treated with HCQ plus azithromycin, 1 patient discontinued treatment due to prolonged QT interval.[24] In a cohort study of 181 patients with severe COVID-19 within 48 hours of admission, 8 (9.5%) of 84 patients in the HCQ group discontinued HCQ after 4 days due to prolonged QT interval or first-degree atrioventicular block.[25] Perinel et al. examined HCQ dosing in severe to critically ill COVID-19 patients by studying the pharmacokinetic properties of HCQ in 13 COVID-19 ICU patients. In the study, HCQ was withdrawn in 2 (15.4%) patients due to prolonged QT intervals.[26]

Spontaneous reports to pharmacovigilance centers and drug manufacturers provide an additional important source of information that can be used to detect rare adverse events. A summary from the WHO Global Database of Individual Case Safety Reports listed a total of 40 cases of sudden death and/or death as an outcome of TdP/QT interval prolongation following any antimalarial treatment, all of which originated in Europe and North America.[27] In 22 cases, the antimalarial was used for an indication other than malaria, with drug dosages and durations varying accordingly. In 16 cases, concomitant use of another medicine that could potentially increase the risk of QT/QTc interval prolongation was reported. Quinidine was the suspected antimalarial in 16 cases; in 12 of these cases, there was evidence of a cardiac-related indication and/or concomitant medications, suggesting quinidine was used as an antiarrhythmic. Exposure to chloroquine and hydroxychloroquine was reported in six and five cases of sudden death, respectively. In four of these cases, overdose was listed as the indication. Hydroxychloroquine was used to treat rheumatoid arthritis, systemic lupus erythematosus and small cell lung carcinoma in one case each.

The clinical efficacy of ribavirin has been reported in small research studies on the treatment of coronaviruses during the SARS-CoV outbreaks in China and North America, and MERS-CoV outbreaks in the Middle East and Asia. No clinical study has documented a therapeutic benefit of ribavirin monotherapy for treatment of corona virus infections. Results from a retrospective cohort study of the combination of oral ribavirin with interferon alpha significantly improved survival and in the first reported case of MERS-COV in south Korea lead to successful recovery after early treatment.[28,29] In a published case report, triple therapy with Lopinavir/ritonavir, interferon alpha and oral ribavirin in a patient with MERS-CoV infection led to virologic clearance after 6 days of treatment and a full recovery at day 13.[30] In a prospective, open-label, randomized, phase 2 trial in adults with COVID-19 who were admitted to six hospitals in Hong Kong, patients were randomly assigned to a 14-day combination of lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate days (combination group) or to 14 days of lopinavir 400 mg and ritonavir 100 mg every 12 h (control group).[31] Results showed that triple antiviral therapy was safe and superior to lopinavir–ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19. Finally, a large phase 2 study was conducted in influenza patients examining triple combination antiviral drug (TCAD) regimen composed of ribavirin, amantadine, and oseltamivir versus oseltamivir monotherapy with matching placebo. A

significant decrease in viral shedding was observed at day 3 relative to monotherapy, however the difference was not associated with improved clinical benefit.[10]

Hemolytic anemia is a common dose-dependent side effect that frequently complicates prolonged use of ribavirin for treatment of HCV. Two studies have confirmed similar decreases in hemoglobin level that were linearly related to steady-state plasma concentrations of ribavirin and that hemoglobin levels of<8.5 g/dL occurred when the steady-state ribavirin concentration increased above 3.5 mg/mL.[32,33] However, in short courses of treatment for influenza and COVID-19 mentioned above, no significant decrease was reported.[10,31]

Nitazoxanide, in addition to antiparasitic activity, has broad-spectrum in vitro antiviral activity against influenza, RSV, norovirus, rotavirus, and hepatitis B and C viruses and has shown In vitro activity against MERS-CoV and other corona viruses.[14] Clinical results for treatment of viral infections have been mixed. In one phase 2b/3 clinical trial, oral administration of nitazoxanide 600 mg twice daily for five days reduced the duration of clinical symptoms and reduced viral shedding compared to placebo in patients with influenza.[34] However, in a phase 2 study of nitazoxanide + SOC in patients with severe acute respiratory illness (SARI), nitazoxanide did not reduce the duration of hospital stay, supplemental oxygen use, or shedding of respiratory viruses on day 3 in patients with SARI.[35]

Nitazoxanide is generally well tolerated. In the study by Haffizulla et al., adverse events were similar between groups, the most common being headache reported by 24 (11%) of 212 patients enrolled in placebo group, 12 (6%) of 201 patients in the nitazoxanide low-dose group, and 17 (8%) of 211 patients in the nitazoxanide high-dose group, or diarrhea, reported by seven (3%) patients in the placebo group, four (2%) patients enrolled in the nitazoxanide low-dose group, and 17 (8%) patients in the nitazoxanide high-dose group.[34] Similar safety and tolerability was seen in the study by Gamiño-Arroyo et al which reported the similar frequency of adverse events between nitazoxanide and placebo, the most common being gastrointestinal disorders (31.9%), infections and infestations (16.3%) and respiratory and thoracic disorders (16.3%).[35]

The pharmacokinetics of hydroxychloroquine, ribavirin, and nitazoxanide are summarized below.

Following a 200 mg oral dose, hydroxychloroquine reached a Cmax of 129.6ng/mL with a Tmax of 3.26h in the blood and a Cmax of 50.3ng/mL with a Tmax of 3.74h in the plasma. Oral hydroxychloroquine has an absorption half-life of 3-4 hours. A 200 mg oral dose of hydroxychloroquine has a half-life of 537 hours or 22.4 days in blood, and 2963 hours or 123.5 days in plasma. Steady state modelling of steady state dosing of HCQ has been carried out, showing that a 400 mg BID loading dose, followed by 200 mg BID for 5 days results in the unbound Css of 600 ng/ml, with lung concentrations >10,000 ng/ml [11](Smith et al 2020, data on file). Based on a clinical study, hydroxychloroquine is a weak-to-moderate inhibitor of CYP2D6 (causing about a 65% increase in exposure of metoprolol).

After oral ingestion of ribavirin, the plasma concentration exhibits a characteristic three-phase profile, consisting of two rapid phases (absorption and distribution) and one long terminal elimination phase. Ribavirin is promptly absorbed into circulation, with the help of gastrointestinal, sodium-dependent nucleoside transporters in the proximal small bowel. The average time to reach Cmax is 2 hours after oral administration of 1200 mg ribavirin. Following administration of 1200 mg/day with food for 12 weeks mean±SD (n=39; body weight greater than 75 kg) AUC was 25,361±7110 ng·hr/mL and C was 2748±818 ng/mL. The terminal half-life of ribavirin following administration of a single oral dose of ribavirin is about 120 to 170 hours. The total apparent clearance following administration of a single oral dose of ribavirin is about 26 L/h. After 5 days of dosing, Ribavirin levels approaching 3000 ng/ml are achieved with 600 mg BID dosing (Wu, et al, 2018). Ribavirin is eliminated by metabolism and renal elimination, with the latter accounting for about 5–15% of single dose elimination.

The active metabolite of NTZ is tizoxanide (desacetyl-nitazoxanide). The initial reaction in the metabolic pathway of Nitazoxanide is hydrolysis to tizoxanide, followed by conjugation, primarily by glucuronidation to tizoxanide glucuronide. Following a 500mg oral dose, tizaxoadnide reached a Cmax of 10600 ng/mL with a Tmax of 3 h in the plasma. When administered with food, the AUC of tizoxanide and tizoxanide glucuronide in plasma is increased to almost two-fold and the maximum concentration is increased by almost 50% compared to when ingested without food. Following oral administration of a single nitazoxanide tablet every 12 hours for 7 consecutive days, there was no significant accumulation of nitazoxanide metabolites tizoxanide or tizoxanide glucuronide detected in plasma.

In summary, there do not appear to be overlapping or synergistic toxicities among the drugs. It is not expected that co-administration of these drugs will result in increased safety concerns compared to the drugs given individually. Pharmacokinetic interactions are also not expected to occur, given that each is cleared via differing mechanisms. The use of TriACT has not been investigated in clinical studies to date.

1.3 Research Design and Methods

We will conduct a randomized clinical trial enrolling eligible participants who are determined to be SARS-CoV-2-positive (e.g., via Rutgers Corona Cohort [RCC] study, hospital or other screening programs) who volunteer for the study. Specifically, we will enroll 70 participants whose test has been performed within the past 7 days who are either asymptomatic or mildly symptomatic at baseline. Mild COVID-19 symptoms include new cough, sore throat, fever, myalgias, new vomiting or diarrheaor change in smell or taste. Illness requiring hospitalization, or those who present with hypoxia (PO2<92%) or shortness of breath at time of enrollment will be classified as significantly symptomatic and excluded from study participation. People who are allergic or intolerant to NTZ, RBV or HCQ will be excluded. We will randomly allocate participants stratified by presence of mild symptoms to 1) NTZ, RBV and HCQ or 2) placebo. Treatment with the investigational agents or placebo will continue for 5 days. Viral load will be assessed at baseline (day 0) as well as at days 3, 6, and 10 to monitor response to antiviral treatment. Immune status will be determined by antibody testing of blood collected at baseline and day 28. An online symptom questionnaire will be completed daily for 10 days and day 28.

Prior to initiating enrollment, we will prepare two randomization tables for treatment assignment using permuted blocks of six which will be provided to the research pharmacist. One table will be used for participants without symptoms and the other will be used for those with mild symptoms. The pharmacist will prepare kits containing the 5-day supply of study medications (investigational drugs/placebo) which will be sequentially numbered in accordance with the randomization tables. The contents of each kit (investigation drugs/placebo) will be indistinguishable. Study staff will establish symptom status at the baseline visit, and per pharmacy order, provide the participant the next numbered medication kit in the participant's stratum (no symptoms/mild symptoms). The study investigators, staff interacting with the participants and the participants are all masked to treatment assignment

A. Research Procedures

1. Study Procedures:

- ***Day 0/1 – Screening/Baseline Visit (in person)***
  - Pre-screen via online screening form to confirm eligibility
  - Obtain informed consent for trial enrollment
  - Medical history
  - Medication history
  - Document symptoms (if any)

- Take temperature, PO2, Pulse
- Q-T interval assessment
- Obtain urine pregnancy test for females of childbearing potential
- Collect research specimens: mid-turbinate nasal swab and blood for CBC, chem profile and immune status
- Randomize study participant
- Dispense study medication
- Provide Zio AT ECG monitoring device for ongoing Q-T interval assessment
- Provide thermometer and pulse oximeter and home collection kits and provide education on use
- Provide education to participant on how to complete temperature log and confirm medication self-dosing and self-collection of mid-turbinate swab.
- Study participant doses self with prescribed study medications the same day if instructed by the study staff

- ***Days 1-5 – Treatment Period (phone /online)***
  - Study participant doses self with prescribed study medications days 1 to 5
  - Self-collecting of mid-turbinate swab day 3
  - Questionnaire completed by participant daily day 1-day 5
  - Temperature, PO2, and pulse
  - Day 3 telephone call procedure review and confirm self- specimen collection/AEs

- ***Days 6- 10***
  - Questionnaire completed by participant days 6 to10
  - Self-collecting of mid-turbinate swab days 6 and10
  - Temperature, PO2 and pulse
  - Day 6 and 10 telephone call procedure review and confirm self-specimen collection/AEs

- ***Day 14- Follow-up (in person)***
  - In person visit to draw blood sample for CBC and chem panel
  - Return Zio AT ECG monitoring device

- ***Day 28 –Follow-up (in person)***
  - In person visit to draw blood sample for CBC, chem panel, and immune function at 28 days
  - Obtain urine pregnancy test for females of childbearing potential
  - Questionnaire completed by participant
  - Final AE assessment

Study Flow/Schedule of Events:

Procedure	Pre-Screen -5 days	Screening /Baseline (Day 0/1)	Daily x 5 days	Days 6 to 10	Days 3, 6, 10	Day 14 (Office)	Day 28 +/- 4 (Office)
Pre-screen questionnaire	X						
Consent		X					
Baseline questionnaire (inc. Medical History)		X					
Q-T Interval		X	X	X			
Self administered Symptom questionnaire		X	X	X			X
Drug accountability (Treatment compliance)		X	X				X
Temperature		X	X	X			
PO2 and Pulse		X	X	X			
Urine Pregnancy Test		X					X
CBC w/ diff/platelet		X				X	X
Comprehensive metabolic panel		X				X	X
Mid-turbinate self nasal swab for viral shedding		X			X		
Blood test for immune function		X					X
Study medication		X (if day1)	X (BID)				
Telephone Follow-up procedure review & confirm self- specimen collection/					X		
AE Review					X		X

2. Treatment Plan:

- *Dosage and Administration*

  Arm 1: NTZ 1000 mg (2 x 250 mg tablets BID for day one) and then
  1000 mg (2 x 250 mg tablets BID for 4 days)
  RBV 1200 mg (3 x 200 mg capsules BID day one) and then
  RBV 800 mg (2 x 200mg capsules BID for 4 days)
  HCQ 800 mg (2 x 200 mg tablets bid day one) and then
  HCQ 400 mg (1 x 200 mg tablet BID for 4 days)

  Arm 2: Placebo for NTZ (2 tablets BID for day one and then 2 tablets BID for 4 days)
  Placebo for RBV (3 capsules BID day one and then 2 capsules BID for 4 days)
  Placebo for HCQ (2 tablets bid day one and then 1 tablet BID for 4 days)

Hydroxychloroquine sulfate (HCQ)
One hydroxychloroquine sulfate tablet contains 200 mg of hydroxychloroquine sulfate, which is the equivalent to 155 mg base.

Ribavirin (RBV)
One ribavirin capsule contains 200 mg of ribavirin.

Nitazoxanide (NTZ)
One nitazoxanide tablet contains 500 mg of nitazoxanide.

Take all tablets/capsules with a meal or a glass of milk.

All study drugs should be stored at room temperature 20°-25° (68°-77 °F).

Concomitant Medications & Supportive Guidelines
Study participants can receive full supportive care therapies concomitantly during the study. We will advise rest, fluids, hot/ showers/baths. We will recommend NO antipyretics since they make infections worse by interfering with the generation of fever--which is considered beneficial until it reaches 102 degrees F.

B. Participant Enrollment

We will identify asymptomatic or mildly symptomatic participants who test positive for SARS-CoV-2 from the Rutgers Coronavirus Cohort (RCC) and hospital screening programs, or from the community through advertisements at our medical center, university, and in local publications. The recruiting materials will direct the potential participants to online materials that include information about the trial, consent forms, and a screener questionnaire to assess eligibility. If eligible for the trial, we will answer any questions and provide as much time as needed to review all study materials. The participant may then electronically sign the consent or, as an alternative, wait until the initial visit to re-review and sign the consent. The consenting process will be primarily performed remotely to protect research personnel.

As soon as possible after consent, the participant will participate in an in person visit for baseline biospecimen collection. On arrival, research staff wearing PPE will re-review the consent, confirm/obtain signatures, measure the PO2, do a urine pregnancy test in women with potential to be pregnant and measure the baseline QTc interval with the Kardia Mobile 6L (AliveCor, Inc). A 6 lead EKG is obtained when the patient places their fingers on 2 electrode sensors while holding

the device on their leg. The ECG is uploaded to an iPhone and the tracing is sent to the Electrophysiologist cardiologist who will calculate the QT and QTc. The device is approved by the FDA for QTc measurements. The participant will be excluded if the Q-T interval is prolonged beyond 450 Msec. We will also exclude anyone who has a PO2<92% or a positive pregnancy test. We will randomly allocate the participant, provide the assigned medications, and obtain mid-turbinate self nasal swab and blood samples. We will also take the participant's temperature and pulse. We will provide education to the patient on how to complete all at-home study procedures and use all ancillary study supplies which we will provide (self nasal swab specimen kits, thermometer, and pulse oximeter).

We will telephone the participant about 2 hours after the initial medication dose to confirm that the Zio AT patch has been triggered for the one-time 2 hour reading (see the Risks of Harm/Potential for Benefits to Subjects to Subjects section, page 35), review the BID dosing schedule, study procedures, and any participant questions. We will also call on days 3, 6, and 10 for procedure review and to confirm self- specimen collection and AE review. We will have an in person visit on day 14 to collect a blood specimen and on day 28 to collect a blood specimen and urine pregnancy test, review medical status and AEs Self collection of mid-turbinate nasal swab to measure viral shedding will be on days 3, 6 and10 post randomization.

QT interval will be measured on an ongoing basis through day 10 via the Zio AT mobile cardiac telemetry device describe in section 4.7 E. If the corrected QT - QTc interval increases from baseline of > 60msec or QT > 500 msec, the medications, if still being taken, will discontinued at that time. Participant QTc intervals will be monitored every 6 hours until the interval returns to baseline. If a serous arrhythmia is detected during the continuous monitoring, the study cardiologist and participant will be promptly contacted, and the participant will be directed to seek medical treatment as appropriate.

C. Study Safety Assessments

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

1. Definitions:
   - Adverse Events:
     An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

   - Serious Adverse Events:
     A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfills one or more of the following criteria:
     - Results in death
     - Is immediately life-threatening
     - Requires in-patient hospitalization or prolongation of existing hospitalization
     - Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.
- The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to the FDA via MedWatch form, if applicable.

2. Recording of Adverse Events
   Non-serious adverse events and SAEs will be determined from the time the study drug is given, throughout the treatment period and up to and including the one month follow-up period. All grade 3 or higher AEs will be recorded. Grade 1 – 2 AEs do not need to be recorded. After withdrawal from treatment, participants must be followed-up for all existing and new AEs for 60 calendar days after the last dose of trial drug and/or until event resolution. All new AEs occurring during that period must be recorded (if SAEs, they must be reported to Data Safety Monitoring Board (DSMB) and Rutgers IRB as per SOPs.).

   All study-related toxicities/ SAEs must be followed until resolution, unless in the Treating Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

3. Reporting of Serious Adverse Events
   Investigators and other site personnel must inform the DSMB and Rutgers IRB. FDA will be informed as required accordance with the reporting obligations of 21 CFR 312.32. It is the responsibility of the principal investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines.

   All SAEs meeting the criteria for expedited reporting will be reported to the Rutgers IRB within the mandated time frames. All SAEs within the safety follow-up window (e.g., within 30 days after the last dose of study medications) established in the protocol will be reported.

4. Clinical Safety Assessments
   - Recording of Adverse Events
     Non-serious adverse events and SAEs will be determined from the time the study drug is given, throughout the treatment period and up to and including the 28-day follow-up period. All grade 3 or higher AEs will be recorded. Grade 1-2 AEs do not need to be recorded. After withdrawal from treatment, participants must be followed-up for all existing and new AEs for 28 calendar days after the last dose of trial drug and/or until event resolution. All new AEs occurring during that period must be recorded (if SAEs, they must be reported to the Data Safety Monitoring Committee and Rutgers IRB).

   - Adverse Events Based on Signs and Symptoms
     When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

D. Data Points

Case Report Forms

Completion of the electronic case report forms (eCRFs) will be done in accordance with the instructions outlined in the study specific data capture plan. All eCRFs are considered the primary

data collection document for the study and are stored in REDCap in a confidential format. Only key personnel who are delegated in the delegation of authority log are permitted to make entries, changes, or corrections in the eCRF. All users will complete user training, as required or appropriate per regulations. An audit trail will be maintained automatically by the electronic CRF management system.

Data Points to be collected:

- Baseline medical history
- Treatment compliance
- Daily temperatures
- Symptoms of disease
- Adverse events
- Concomitant medications
- Any standard of care treatments or procedures to manage COVID-19
- Viral load from saliva specimen
- Viral load from mid-turbinate self-nasal swab
- SARS-CoV-2 infections confirmed or suspected in household members

Data Submission Timeline and Forms
Completion of eCRFs will occur within 72 hours of study time point unless otherwise indicated. Baseline (pre-study) eCRFs (e.g., enrollment, medical history, concomitant medications, etc.) will be completed no later than 24 hours after the start of treatment.

E. Study Duration
Study participants will be treated for five (5) days and will then remain on follow-up for up to 28 days after entry into the study. The estimated time to complete the entire study including data analysis is 3-6 months

F. Endpoints
Primary endpoint:

1. Rate of decline in viral load over the 10 days after randomization

Secondary:

1. Proportion of participants with virus below LLOQ at day 10
2. Proportion of participants asymptomatic at day 10.
3. For those who were asymptomatic at baseline: Progression to symptoms--presence or absence of key symptoms: fever ≥ 100.4^0 F ($38\ ^0$ C); sore throat, cough, shortness of breath, myalgias, vomiting or diarrhea, or change in smell or taste
4. Proportion of participants with progression of severity of COVID-19 symptoms (hospitalization and length of stay; admission to intensive care unit and number of days in unit; Intubation; Death (any cause))
5. Comparison of severity of disease in participants who develop symptoms of COVID-19 at all timepoints
6. Assessment of medication toxicity as measured by standard metrics
7. Q-T interval from baseline of > 60msec or QT > 500 msec)
8. Number of participants with undetectable viral load and absence of symptoms
9. Rate of decline in viral load at study days 3 and 6
10. New, self-reported COVID infection in household members

1.4 Preliminary Data

There are data supporting the antiviral activity of NTZ, RBV and HCQ as single agents as summarized in Section 1.2. There is no previous human experience with this triple combination.

1.5 Sample Size Justification

Primary outcome:

Rate of decline in viral load. We expect a gradual decay in viral loads (depending on when in the infection's natural history participants are enrolled. Participants will be detected as being SARS-CoV-2-positive by our screen at varying points in the infection (some early, some late). Based on the 4 manuscripts with measurements, including Hung et al [31] and Gautret et al [19], we can calculate an expected decline rate. One outcome would be a greater than expected fall in viral load in the active arms vs the SoC arm (e.g., 0.3 $\log_{10}$ /day greater decline =0.9 $\log_{10}$ in 3 days).

We will compare rate of decline in viral load Arm 1 (NTZ, RBV + HCQ) to Arm 2 (placebo) with the aim of determining if the combination of NTZ, RBV + HCQ is superior to placebo. We plan to enroll 35 participants in each arm of the trial for a total of 70. We assume data are collected at baseline and 3, 6 and 10 days after enrollment.

Power calculations were obtained from simulated data, where:

- Baseline log10 VL was generated from uniform (3,9) distribution (i.e., at baseline, people were equally likely to have log10 VL anywhere from 3 to 9. This is consistent with Hung et al [31]
- For the control group, average change per day was set to either -0.3 or -0.4. In Hung et al [31] it appears to be about -0.37.
- For the treatment group, the average decline per day was greater (steeper) than the control group by either 0.2 or 0.3. In Hung et al [31]the difference in slopes appears to be about 0.2
- Within person SD was set to either 0.5 or 1.
- SD of the slope between individuals was set to 0.2. In Hung et al [31] the within-group IQR of log10 VL was relatively small, so we do not expect a large amount of variation in slopes between participants.

Power was calculated using the following steps: (1) generate 1000 data sets in each scenario; (2) fit random slope and intercept models to the simulated data; (3) record the proportion of times that the test of the interaction between treatment and slope was rejected.

Results: Power (%) based on a sample size of 30 per group

		treatment effect	
Slope SoC group	**SD**	**-0.2**	**-0.3**
-0.3	0.5	94	99
-0.4	0.5	94	99
-0.3	1	87	99
-0.4	1	84	99

In all of these scenarios we would have >80% power to detect a difference in the slope between groups.

1.6 Study Variables

A. Primary Outcome:

Viral load at 10 days post randomization

B. Other measures

Age,
Gender
Race/ethnicity
BMI
Co-morbidity:

- Diabetes mellitus
- Hypertension
- Chronic bronchitis, emphysema, or chronic obstructive pulmonary disease (COPD)
- Other lung disease
- Coronary artery disease, peripheral artery disease, angina, or heart attack (myocardial infarction)
- Congestive heart failure
- Stroke or transient ischemic attack (TIA)
- Atrial fibrillation
- Cancer other than non-melanoma skin cancer
- Chronic kidney disease (CKD)
- Crohn's disease, ulcerative colitis, or inflammatory bowel disease (IBD)
- Rheumatoid arthritis (RA), psoriasis, systemic lupus, multiple sclerosis, or another autoimmune disorder
- Allergic rhinitis

Medications
Symptoms
Household infection (confirmed or suspected)

List variables of interest

Treatment Variables:

- Treatment Compliance
- Adverse Events (number/percentage/grade)

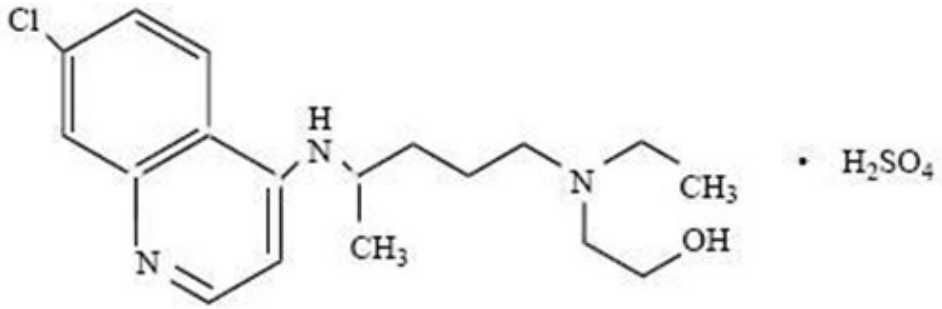
1.7 Drugs/Devices/Biologics

Generic name: Hydroxychloroquine sulfate
Commercial name: Plaquenil

For complete information please refer to the package inserts at
http://dailymed.nlm.nih.gov/dailymed/Hydroxychloroquine

Chemical name: 7-Chloro-4-[4-[ethyl-(2-hydroxyethyl) amino]-1-methylbutylamino] quinolone

Source: Commercially available



C18H26ClN3O•H2SO4 Molecular Weight: 433.95

Hydroxychloroquine sulfate tablets, USP contain 200 mg hydroxychloroquine sulfate, equivalent to 155 mg base, and are for oral administration.

Pharmacokinetics: Following a single 200 mg oral dose of hydroxychloroquine sulfate to healthy males, the mean peak blood concentration of hydroxychloroquine was 129.6 ng/mL, reached in 3.26 hours with a half-life of 537 hours (22.4 days). In the same study, the plasma peak concentration was 50.3 ng/mL reached in 3.74 hours with a half-life of 2963 hours (123.5 days). Urine hydroxychloroquine levels were still detectable after 3 months with approximately 10% of the dose excreted as the parent drug. Results following a single dose of a 200 mg tablet versus I.V. infusion (155 mg), demonstrated a half-life of about 40 days and a large volume of distribution.

Mechanism of Action: The precise mechanism by which hydroxychloroquine exhibits activity against *Plasmodium* is not known. Hydroxychloroquine, like chloroquine, is a weak base and may exert its effect by concentrating in the acid vesicles of the parasite and by inhibiting polymerization of heme. It can also inhibit certain enzymes by its interaction with DNA.

Warnings:

Ocular: Irreversible retinal damage has been observed in some patients who had received hydroxychloroquine sulfate. Significant risk factors for retinal damage include daily doses of hydroxychloroquine sulfate greater than 6.5 mg/kg (5 mg/kg base) of actual body weight, durations of use greater than five years, subnormal glomerular filtration, use of some concomitant drug products such as tamoxifen citrate and concurrent macular disease.

Cardiac Effects, including Cardiomyopathy and QT prolongation: Post-marketing cases of life-threatening and fatal cardiomyopathy have been reported with use of hydroxychloroquine sulfate as well as with use of chloroquine. Hydroxychloroquine sulfate prolongs the QT interval. Ventricular arrhythmias and torsades de pointes have been reported in patients taking hydroxychloroquine sulfate (see OVERDOSAGE). Therefore, hydroxychloroquine sulfate should not be administered with other drugs that have the potential to prolong the QT interval.

Worsening of psoriasis and porphyria

Proximal Myopathy and Neuropathy

Neuropsychiatric events, including suicidality

Hypoglycemia: Hydroxychloroquine sulfate has been shown to cause severe hypoglycemia including loss of consciousness that could be life threatening in patients treated with or without antidiabetic medications

General precautions: General: Use with caution in patients with gastrointestinal, neurological, or blood disorders, and in those with a sensitivity to quinine.

Hepatic/Renal Disease: Antimalarial compounds should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs. A reduction in dosage may be necessary in patients with hepatic or renal disease, as well as in those taking medicines known to affect these organs.

Hematologic Effects/Laboratory Tests: Antimalarial compounds should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs. Periodic blood cell counts should be performed if patients are given prolonged therapy.

Hydroxychloroquine sulfate should be administered with caution in patients having glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

Dermatologic Effects: Dermatologic reactions to hydroxychloroquine sulfate may occur and, therefore, proper care should be exercised when it is administered to any patient receiving a drug with a significant tendency to produce dermatitis.

Drug Interactions (include but not limited to): Digoxin, Insulin or antidiabetic drugs, Drugs that prolong QT interval and other arrhythmogenic drugs, Mefloquine and other drugs known to lower the convulsive threshold, Antiepileptics, Methotrexate, Cyclosporin, Praziquantel, Antacids and kaolin, Cimetidine, Ampicillin.

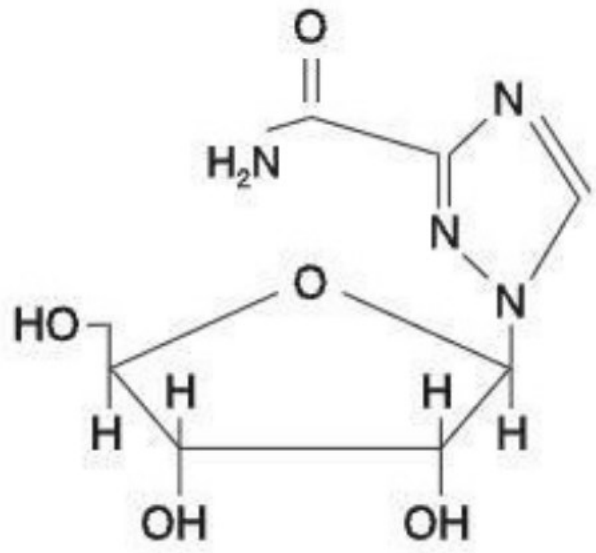
Availability: FDA approved; commercially available hydroxychloroquine sulfate will be supplied free of charge to all patients enrolled.

Generic name: Ribavirin
Commercial name:

For complete information please refer to the package inserts at
http://dailymed.nlm.nih.gov/dailymed/ribavirin

Chemical name: 1-β-Dribofuranosyl-1H-1,2,4-triazole-3-carboxamide

Source: Commercially available



$C_8 H_{12} N_4 O_5$ and the molecular weight is 244.2

Ribavirin, USP is white, crystalline powder. It is freely soluble in water and slightly soluble in dehydrated alcohol. Each film-coated ribavirin tablet intended for oral administration contains 200 mg or 400 mg or 500 mg or 600 mg of ribavirin. In addition, each tablet contains the following inactive ingredients: crospovidone, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, silicon dioxide, talc, and titanium dioxide.

Pharmacokinetics
Multiple dose ribavirin pharmacokinetic data are available for HCV patients who received ribavirin in combination with peginterferon alfa-2a. Following administration of 1200 mg/day with food for 12 weeks mean±SD (n=39; body weight greater than 75 kg) AUC was 25,361±7110 ng·hr/mL and C was 2748±818 ng/mL. The average time to reach C was 2 hours. Trough ribavirin plasma concentrations following 12 weeks of dosing with food were 1662±545 ng/mL in HCV infected patients who received 800 mg/day (n=89), and 2112±810 ng/mL in patients who received 1200 mg/day (n=75; body weight greater than 75 kg). The terminal half-life of ribavirin following administration of a single oral dose of ribavirin is about 120 to 170 hours. The total apparent clearance following administration of a single oral dose of ribavirin is about 26 L/h. There is extensive accumulation of ribavirin after multiple dosing (twice daily) such that the C at steady state was four-fold higher than that of a single dose.

Contraindications:

Ribavirin
Pregnancy: Women who are or may become pregnant. Ribavirin may cause fetal harm when administered to a pregnant woman. women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus Men whose female partners are pregnant.
Hemoglobinopathies: Patients with hemoglobinopathies (e.g., thalassemia major or sickle-cell anemia).

In combination with didanosine: Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials.

Ribavirin and peginterferon alfa-2a combination therapy is contraindicated in patients with:

Autoimmune hepatitis.

Hepatic decompensation (Child-Pugh score greater than 6; class B and C) in cirrhotic CHC mono infected patients before treatment.

Hepatic decompensation (Child-Pugh score greater than or equal to 6) in cirrhotic CHC patients coinfected with HIV before treatment.

Warnings:

Significant adverse reactions associated with ribavirin/peginterferon alfa-2a combination therapy include severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, ophthalmologic disorders, cerebrovascular disorders, pulmonary dysfunction, colitis, pancreatitis, and diabetes. The Peginterferon alfa-2a Package Insert should be reviewed in its entirety for additional safety information prior to initiation of combination treatment.

Pregnancy
Ribavirin may cause birth defects and/or death of the exposed fetus. Ribavirin has demonstrated significant teratogenic and/or embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy.

Anemia
The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 13% of all ribavirin/peginterferon alfa-2a- treated participants in clinical trials. Anemia associated with ribavirin occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in hemoglobin may be significant, it is advised that hemoglobin or hematocrit be obtained pretreatment and at week 2 and week 4 of therapy or more frequently if clinically indicated. Patients should then be followed as clinically appropriate. Caution should be exercised in initiating treatment in any patient with baseline risk of severe anemia (e.g., spherocytosis, history of gastrointestinal bleeding). Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin.

Hepatic Failure
Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons, including peginterferon alfa-2a. Cirrhotic CHC patients coinfected with HIV receiving highly active antiretroviral therapy (HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART.

Hypersensitivity
Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, and

anaphylaxis) have been observed during alpha interferon and ribavirin therapy. If such a reaction occurs, therapy with peginterferon alfa-2a and ribavirin should be discontinued immediately, and appropriate medical therapy instituted. Serious skin reactions including vesiculobullous eruptions, reactions in the spectrum of Stevens-Johnson Syndrome (erythema multiforme major) with varying degrees of skin and mucosal involvement and exfoliative dermatitis (erythroderma) have been reported in patients receiving peginterferon alfa-2a with and without ribavirin. Patients developing signs or symptoms of severe skin reactions must discontinue therapy

Pulmonary Disorders
Dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, and pneumonia have been reported during therapy with ribavirin and interferon. Occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, patients should be closely monitored and, if appropriate, combination ribavirin/peginterferon alfa-2a treatment should be discontinued.

Bone Marrow Suppression
Pancytopenia (marked decreases in RBCs, neutrophils, and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of pegylated interferon/ribavirin and azathioprine. In this limited number of patients (n=8), myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of both HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone. peginterferon alfa-2a, ribavirin, and azathioprine should be discontinued for pancytopenia, and pegylated interferon/ribavirin should not be re-introduced with concomitant azathioprine.

Pancreatitis
Ribavirin and peginterferon alfa-2a therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.

Impact on Growth in Pediatric Patients
During combination therapy for up to 48 weeks with peginterferon alfa-2a plus ribavirin, growth inhibition was observed in pediatric participants 5 to 17 years of age. Decreases in weight for age z-score and height for age z-score up to 48 weeks of therapy compared with baseline were observed. At 2years post-treatment, 16% of pediatric participants were more than 15 percentiles below their baseline weight curve and 11% were more than 15 percentiles below their baseline height curve. The available longer term data on participants who were followed up to 6 years post-treatment are too limited to determine the risk of reduced adult height in some patients [see Clinical Studies Experience

Drug interactions: Didanosine, zidovudine

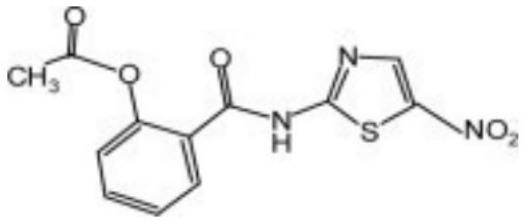
Availability: FDA approved; commercially available Ribavirin will be supplied free of charge to all patients enrolled.

Generic name: Nitazoxanide
Commercial name: ALINIA

For complete information please refer to the package inserts at
http://dailymed.nlm.nih.gov/dailymed/nitazoxanide

Chemical name: 2-acetyloxy- N-(5-nitro-2-thiazolyl) benzamide

Source: Commercially available



C_{12} H_9 N_3 O_5 S and the molecular weight is 307.3

Nitazoxanide is a light yellow crystalline powder. It is poorly soluble in ethanol and practically insoluble in water.

ALINIA Tablets contain 500 mg of nitazoxanide and the following inactive ingredients: maize starch, pregelatinized corn starch, hydroxypropyl methylcellulose, sucrose, sodium starch glycollate, talc, magnesium stearate, soy lecithin, polyvinyl alcohol, xanthan gum, titanium dioxide, D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, and FD&C Blue No. 2 Aluminum Lake.

ALINIA for Oral Suspension, when reconstituted with 48 mL of water, produces 60 mL of a homogeneous suspension with a pink color that contains 100 mg nitazoxanide per 5 mL and the following inactive ingredients: sodium benzoate, sucrose, xanthan gum, microcrystalline cellulose and carboxymethylcellulose sodium, anhydrous citric acid, sodium citrate dihydrate, maltodextrin, modified food starch, triacetin, FD&C Red No. 40 and artificial strawberry flavoring.

Pharmacokinetics
Absorption Single Dosing: Following oral administration of ALINIA Tablets or Oral Suspension, the parent drug, nitazoxanide, is not detected in plasma.

Multiple dosing: Following oral administration of a single ALINIA Tablet every 12 hours for 7 consecutive days, there was no significant accumulation of nitazoxanide metabolites tizoxanide or tizoxanide glucuronide detected in plasma.

Bioavailability: ALINIA for Oral Suspension is not bioequivalent to ALINIA Tablets. The relative bioavailability of the suspension compared to the tablet was 70%. When ALINIA Tablets are administered with food, the AUC of tizoxanide and tizoxanide glucuronide in plasma is increased almost two-fold and the C_{max} is increased by almost 50%. When ALINIA for Oral Suspension was administered with food, the AUC of tizoxanide and tizoxanide glucuronide increased by about 45-50% and the C_{max} increased by ≤10%.

Distribution: In plasma, more than 99% of tizoxanide is bound to proteins.
Elimination Metabolism: Following oral administration in humans, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide (desacetyl-nitazoxanide). Tizoxanide then undergoes conjugation, primarily by glucuronidation.

Excretion: Tizoxanide is excreted in the urine, bile, and feces, and tizoxanide glucuronide is excreted in urine and bile. Approximately two-thirds of the oral dose of nitazoxanide is excreted in the feces and one-third in the urine.

Contraindications:

Hypersensitivity: ALINIA Tablets and ALINIA for Oral Suspension are contraindicated in patients with a prior hypersensitivity to nitazoxanide or any other ingredient in the formulations.

Drug interactions: Highly Protein Bound Drugs with Narrow Therapeutic Indices i.e. Tizoxanide, warfarin

Availability: FDA approved; commercially available Ribavirin will be supplied free of charge to all patients enrolled.

There is no current data that assess the risks of the use of all three drugs in combination.

A. Drug/Device Accountability and Storage Methods
Drug accountability logs and pharmacy records must be maintained at each pharmacy location and must be available for review upon request. Drug accountability logs and pharmacy records will be reviewed during monitoring visits and by the Research Pharmacist

B. Treatment Compliance
The study medication will be given in accordance with the protocol and the instructions of the treating investigator. The study drugs will be provided to participants to be self-administered. Participants will be asked to confirm medication dosing each day on daily logs and on the day 3 and day 6 call with research staff.

1.8 Specimen Collection

A. Primary Specimen Collection
The research specimens collected will be for:

1. Viral load
2. Antibody testing
3. Safety (CBC and chemistry)

- **Types of Specimens**:
  - Mid-turbinate self nasal swab will be collected at baseline and days 3, 6 and 10
  - Blood specimen will be collected at baseline, day 14 and day 28

- **Annotation**: Specimens will be uniquely identified and marked with the participant's study ID and study time point. All primary collection devices (blood and nasal swab kits) will have a unique barcode that is linked to the participant study ID at the time of collection and sample registration.

- **Transport**: Nasal-swabs specimens (live virus is fully deactivated by the transport media) will placed in the packing materials supplied by the research laboratory (TGen) or designee shipped to Altasciences via Fed Ex promptly following specimen collection at the clinic and at home. The nasal swab specimens will be batched at Altasciences and shipped to TGen on a frequency to be determined by study enrollment. All shipping material, instructions and transport supplies will be provided to the participant within the collection kit. All blood specimens will be collected during clinic visits and transported for testing in accordance with institutional policy. Blood for clinical analyses (cbc, chem panel, magnesium will be directly transported to the RWJUH laboratory by the study staff. Blood drawn for antibody testing will be packaged and sent to RUCDR via UPS, using the materials and instructions provided by RUCDR. These samples will be processed, frozen, and stored at RUCDR until transport to the Gennaro Lab for analysis.

- **Processing**: All specimen processing will be in accordance with institutional policy.

- **Storage**: The blood specimens and the nasal swab specimens will be stored at their respective laboratories until the time of testing.

- **Disposition**: The antibody blood specimens and nasal swab specimens will be maintained until the end of study. Leftover specimens may be de-identified and may be used for other future research, e.g., validating viral load measurements with improved technologies or viral sequencing analysis.

B. Secondary Specimen Collection
N/A

1.9 Data Collection

A. Primary Data Collection
Data collection will occur at a baseline visit with follow-up data collected over the subsequent month as described below.

- **Location**: Study site visits (baseline, day 14 & day 28) will take place at the designated RWJMS study location at 93 French St, New Brunswick, NJ which is an Institutional Biosafety Committee (IBC) approved location to meet with SARS-Cov-2 positive individuals. Consent and all questionnaires will be completed electronically online. This questionnaire will include items on health and medical history, lifestyle, employment and patient contact, and demographics. At baseline, contact information (e-mail/phone) for the participant will be collected as well as contact information of 2 individuals who know the participant well who we can reach out to in case the participant falls ill.

  Follow-up questionnaires will be administered daily for 10 days and on day 28 after entering the study. Follow-up questionnaires will include items on symptoms of COVID-19, reactions to the study medications and health status of household members since the last questionnaire Up to 3 daily automated reminders will be sent to remind participants to complete the surveys. In addition, participants will self-report their body temperature, PO2, and pulse daily through REDcap, daily for the first 10 days of the study period. Participants will receive automated email/text reminders to record this information daily. We will also call on days 3, 6 and 10 to confirm self specimen collection, check medical status and study drug dosing (on days 3 & 6) and questionnaire completion compliance. On day 14 participants will return for a blood draw and to return the ZIO AT monitoring device. On day 28, participants will return to the clinic for a final symptom assessment, a blood draw for immune function and CBC, pregnancy test, if applicable and final study drug accountability.

- **Process of Data Collection**: All in-person data collection will be overseen by the clinical study coordinator team conducting study visits, with questionnaires self-administered by participants. The blood specimens will be collected at the in-person visits (baseline, day 14 & 28). Participants will be responsible for reporting their own daily temperatures, PO2 and pulse.
- **Timing and Frequency**: Following the baseline visit and questionnaire, self-administered questionnaire data will be collected on for the first 10 days and on day 28 after entering the study. Data on temperature, PO2, pulse will be reported through REDCap daily for 10 days..
- **Procedures for Audio/Visual Recording**: N/A, no recordings planned
- **Study Instruments**: As described earlier, the questionnaires will collect demographic and health history and behaviors at baseline. They follow-up questionnaires will capture current signs and symptoms of potential infection and infection in household members.
- **Ethnographic Studies, Interviews, Or Observation**: N/A

- **Participant Identifiers**: Biospecimen and questionnaire data will be coded by study ID. A link between study ID and participant name/date of birth will be retained and available to approved study staff to link specimens to participants.

B. Secondary Data Collection

For participants who develop symptoms or seek clinical care for any medical, and grant permission to obtain records, we will access medical records related to their infection and subsequent care. We will review hospital records from acute illness resulting from COVID-19 including discharge summary, imaging, laboratory studies, and treatments. No medical records will be reviewed for participants who remain asymptomatic, and no data will be abstracted on unrelated conditions or previous health history.

- **Type of Records**: In those developing symptoms, medical records related to the possible infection will be abstracted. Relevant fields include diagnoses, lab values, imaging data, medications and other interventions, other inpatient care related to the infection, and disposition (e.g., discharge, death).
- **Location**: Study staff with authorized access to the RBHS and hospital electronic records will access those records directly. Records that are at outside locations or to which the researchers do not have authorized access will be requested directly from the facility. At the time of consent, each participant will be asked to sign a form authorizing the release of these data.
- **Inclusion/Exclusion**: Records will be abstracted from the date of randomization forward until the end of the 28-day active follow-up period. Charts will be reviewed by trained clinical study coordinators using secure connections.
- **Data Abstraction Form(s):** Each participant will be assigned a unique study identification number that will be linked to each completed electronic questionnaire as well as to the collected biospecimens. All questionnaires will be administered via and stored in REDCap software hosted by Rutgers Robert Wood Johnson Medical School [17].

1.10 Timetable/Schedule of Events

All study procedures will be performed according to the scheduled outlined in the Study Flow Table

2.0 Project Management

2.1 Research Staff and Qualifications

Dr. Jeffrey Carson is the Provost, New Brunswick at Rutgers Biomedical Health Science, Distinguished Professor of Medicine, and the Richard C. Reynolds, M.D. Chair in General Internal Medicine at Rutgers Robert Wood Johnson Medical School. Dr. Carson has led multiple clinical trials funded by the NIH and recognized leader in research related to indications of red blood cell transfusion. Dr. Carson was a member of Clinical Trials Review Committee at the National Heart, Lung and Blood Institutes and served as Chair during his 5th year. He will serve as a PI on this MPI NIH proposal.

Dr. Reynold Panettieri, Vice Chancellor for Clinical and Translational Medicine and a pulmonologist, has 28 years of clinical research experience. He has been a PI or Co-Investigator in over 60 clinical trials, enrolling over 300 study participants. He also serves as the Program Director for NJ Alliance for Clinical and Translational Science, our CTSA Hub. He will serve as a PI on this MPI NIH proposal.

Dr. Martin Blaser has been involved in medical research since 1981. He has been the principal investigator of multiple protocols involving human participants, including the present U01AI122285 cooperative agreement with the NIH Clinical Center, involving antibiotic effects on the microbiome in human volunteers. Prior to coming to Rutgers, he served as Professor of Medicine at Vanderbilt and at New York University, where he served as Chair of Medicine for 12 years. He will serve as a PI on this MPI NIH proposal.

Dr. Emily Barrett, co-Investigator and co-Director of the Epidemiology Core, is an Associate Professor in the Rutgers School of Public Health, Department of Biostatistics and Epidemiology and Director of the Human Exposures and Outcomes Core of the Rutgers Center for Environmental Exposures and Disease. Dr. Barrett studies the impact of environmental exposures on health and disease. She currently leads two existing NIH-funded cohort studies and has extensive experience with human participants research including recruitment, retention, protocol development, biospecimen collection, and survey research.

Dr. Daniel Horton, Co-Director of the Epidemiology Core, is an Assistant Professor of Pediatrics and Epidemiology, Chancellor's Scholar, and founding core faculty member of the Center for Pharmacoepidemiology and Treatment Science at Rutgers. He is currently Principal Investigator of an NIH/NIAMS-funded observational cohort study of the microbiome in children with juvenile idiopathic arthritis that includes prospective collection and analysis of clinical data, survey data, and biospecimens (K23-AR070286). Through this project and others, he has experience working with large clinical and biologic datasets and with multidisciplinary teams, investigators, and units across the University, including at the School of Public Health, RWJMS, RWJUH, and RUCDR.

Dr. Jason Roy is Chair & Professor, Department of Biostatistics and Epidemiology. He is interested in methodological research in developing flexible Bayesian methods for large, observational studies, especially data from EHR and mobile health. He is particularly interested in causal inference problems, where Bayesian nonparametric methods can be used in conjunction with g-computation. He is also interested in functional clustering methods, which can be very useful for extracting features from intensively collected data (such as from mobile devices).

James Coromilas, MD is Professor of Medicine and Chief of the Division of Cardiology and Hypertension at Rutgers Robert Wood Johnson Medical School. Dr. Cormilas has subspecialty training and certification in electrophysiology. He will serve as Co-Investigator on the trial and interpret ECG for the QT interval and review the monitored rhythm twice per day.

2.2 Research Staff Training

We will provide training to all clinical research staff prior to any contact with study participants including:

- Overview of protocol and study organization
- Consent process
- Completion of study questionnaires
- Use of study ancillary supplies (Zio AT ECG, thermometer, pulse oximeter, home specimen collection and shipping)
- Use of REDCap

For those research staff collecting specimens or otherwise exposed to potentially infectious individuals, we will provide training for:

- Sample collection and handling of sample collection kits;
- Sample collection and processing activities;
- Use of personal protective equipment (PPE).

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2.3 Resources Available

Nitazoxanide, Ribavirin, Hydroxychloroquine sulfate and corresponding placebo tablets will be provided at no charge to the study participants. The study required devices (Zio AT monitoring device, pulse oximeter, thermometer) as well as at home specimen collection materials and associated shipping materials will also be provided without expense to the study participants.

Staffing and coordination of the study will be run through clinical coordinating staff lead by Dr. Carson with supplemented by our CTSA hub (NJ Alliance for Clinical and Translational Science [NJ ACTS]) directed by PI Dr. Reynold Panettieri. Dr. Carson's team has led large international trials including over 100 sites funded by NIH. NJ ACTS runs the 5 CRUs in which most study visits will occur and a highly experienced team of has 22 clinical research coordinators who can be deployed for this work. These coordinators are facile in the use of iPad-based electronic consents (eConsents) and clinical report forms (eCRFs). Additional coordinators will be recruited from the University employees.

The biospecimen management and storage of CBC and chemistry blood samples will occur at Robert Wood Johnson University Hospital. Blood specimen for SARS-CoV-2 antibody testing will be packaged and shipped to RUCDR (who will provide the collection kits), where it will be processed, frozen and stored prior to transport to the Genarro Lab for analysis.

The nasal swab specimens testing will occur at The Translational Genomics Research Institute (TGen), an affiliate of City of Hope. TGen will provide Sample collection kits and Viral Load Testing in support of the primary endpoint for this study.

2.4 Research Sites

Division of General Internal Medicine, Rutgers Robert Wood Johnson Medical School,
New Brunswick, NJ
RWJ Barnabas Health – Robert Wood Johnson University Hospital

The antibody testing specimens will be stored and analyzed at:

RUCDR Infinite Biologics
145 Bevier Rd
Piscataway, NJ 08854

Gennaro Lab
W250G
The International Center for Public Health
225 Warren Street
Newark NJ 07103

The nasal swab biospecimens will be stored and analyzed at:

Altasciences
6605 Merrill Creek Pkwy
Everett, WA 98203

The Translational Genomics Research Institute (TGen)
3051 W. Shamrell Blvd
Flagstaff, AZ 85005

The safety blood analyses will be performed at:

Robert Wood Johnson Hospital Laboratory
New Brunswick, NJ 08901

3.0 Multi-Center Research

N/A

4.0 Participant Considerations

4.1 Participant Selection and Enrollment Considerations

A. Method to Identify Potential Participants

The study population will consist of those with a known positive test for SARS-CoV-2 who have no or mild symptoms of infection. We anticipate these individuals will be identified due to their participation in ongoing (and upcoming) screening programs (e.g., the RCC study, hospital wide screenings, first responder screenings). We will develop relationships with these screening programs and, if agreeable, the programs will have participants self-identify as interested in volunteering for future research. We will reach out directly to potentially eligible participants identified in this manner. We will determine if they are asymptomatic or mildly symptomatic and, if eligible, offer participation in the trial. We will also recruit participants from the general public through advertisements in local press, letters to local clinicians, and emails to university staff and faculty. Interested participants will review the trial methods and complete the eligibility questionnaire. We will also send an email to employees of Robert Wood Johnson University Hospital, University Hospital, and Rutgers University seeking volunteers with SARS-CoV-2-positive tests within the past 7 days.

B. Recruitment Details

We will recruit eligible participants from the RCC study or participants identified from the community who test positive for SARS-CoV-2. The recruiting materials will direct the potential participants to online materials that include information about the trial, consent forms, and a screening questionnaire to assess eligibility.

C. Participant Screening

We will require all volunteers to complete an on-line screening questionnaire which will identify eligible participants. Based on the responses to the screening questionnaire, the volunteers will be notified if they could be eligible for the study. Eligible participants will be asked to provide their name, e-mail address, and phone number so that study staff may follow up with them to further assess their willingness to participate in the trial.

The participant will then come to the study location at 93 French in New Brunswick to complete final screening for the trial eligibility. P02 will be measured and 6 lead portable electrocardiogram will be performed; if PO2<92% or QT interval is QTc interval > 450 mSEC the participant will be excluded. Females of childbearing potential will have a urine test to confirm that they are not pregnant.

Inclusion Criteria

1. Documented SARS-CoV-2 infection by qPCR assay without symptoms or with mild symptoms consistent with COVID-19 performed within the past 7 days
2. Age ≥21

Exclusion Criteria

1. COVID-19 symptoms requiring hospitalization
2. PO2 < 92%
3. Short of breath at time of enrollment
4. Retinal eye disease
5. Known glucose-6 phosphate dehydrogenase (G-6-PD) deficiency
6. Known chronic kidney disease, stage - 5 or receiving dialysis
7. Current use of:
   - Class 3 AAD (amiodarone, dronaderone, dofetilide, sotalol)
   - Class 1A AAD (procainamide, quinidine, disopyramide)
   - Flecainide
   - SSRI: citalopram (Celexa), Escitalopram (Lexapro)
   - chlorpromazine
   - Cilostazol (Pletal)
   - Donepezil (Aricept)
   - Droperidol
   - Fluoconazole
   - Methadone
   - Ondansetron (Zofran)
   - Thioridazine
   - Macrolides (clarithromycin, erythromycin)
   - Fluroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)
   - Tamoxifen citrate
8. Pregnancy or women who are breast feeding
9. Inability to tolerate oral medications
10. Allergy or prior adverse reaction to either hydroxychloroquine sulfate, ribavirin, or nitazoxanide
11. Allergy to adhesives
12. QTc interval > 450 mSEC for men and women
13. History of Torsade de Pointes VT or prior cardiac arrest or congenital long QT interval
14. Non-English-speaking

4.2 Secondary Participants

N/A

4.3 Number of Participants

A. Total Number of Participants

70

B. Total Number of Participants If Multicenter Study

All participants will be enrolled at Rutgers, Robert Wood Johnson Medical School.

C. Feasibility

Given the current incidence rate of SARS-CoV-2 positivity, we anticipate that enrollment will be completed within 2-6 months.

4.4 Consent Procedures

A. Consent Process

- **Location of Consent Process**
  Eligible individuals will complete the consent online following discussion with research coordinators by telephone. Remote consent will be utilized to protect the safety of the research personnel and others. At the baseline visit, the study staff will review the consent document and study procedures, answer any remaining questions, confirm the participant's signature, and also sign the consent.
- **Ongoing Consent**
  Participants will undergo intensive follow-up over the 28 day study period, particularly over the first days of active treatment. There will not be ongoing written informed consent obtained, but study staff will make it clear that participants may ask questions about the research or cease their participation at any time.
- **Individual Roles for Researchers Involved in Consent**
  All consent will be done online by participants (see 1.3A for details) or by the NJ ACTS and other RBHS clinical research coordinators who conduct the study visits.
- **Consent Discussion Duration**
  It is anticipated that consent will take approximately 30 minutes to complete. However, we recognize that in some cases, additional time may be needed to answer questions or address concerns with a study team member. We will answer any questions and provide as much time as needed to review all study materials.
- **Coercion or Undue Influence**
  Participants self-initiate interest in study participation by completing the online screening survey. We will make it clear that participation is voluntary and that electing not to participate will not impact clinical care or employment status.
- **Participant Understanding**
  At the time the research coordinators obtain the electronic consent, they will query to the participant to be certain they understand they questionnaire completion and specimen collection obligations. Similarly, research coordinators will verify the understanding of these procedures of participants who completed an online eConsent before proceeding with biospecimen collection.

B. Waiver or Alteration of Consent Process

N/A

C. Documentation of Consent

- **Documenting Consent**
  Prospective participants who are deemed eligible after completing the online screening survey may read through the consent form. Study staff will contact each individual who provides their contact information and express interest in participation. The consent, eligibility and exclusion criteria and study procedures will be reviewed, and questions will be answered. The participant will may then electronically sign the consent or, as an alternative, wait until the initial visit to re-review and sign the consent. The consent will be also be signed by the person obtaining consent. The signed consent will be stored in the REDCap database. The consenting process will be primarily performed remotely to protect research personnel.

- **Waiver of Documentation of Consent (i.e., will not obtain participant's signature)**
  N/A

4.5 Special Consent/Populations

A. Minors-Participants Who Are Not Yet Adults

N/A

B. Wards of the State
N/A

C. Non-English-Speaking Participants
We will only enroll English-speaking participants.

D. Adults Unable to Consent / Decisionally Impaired Adults
N/A

4.6 Economic Burden and/or Compensation for Participants

A. Expenses
The study drugs will be provided at no charge. At the initial visit we will provide each participant with a Zio AT mobile cardiac telemetry device. Participants will return the device at their day 28 visit. Study participants will not be charged for the cost of any research procedures which are conducted as part of this study. Participants and/or their insurance carriers (or Charity Care in the absence of insurance) will be expected to pay for the standard of care costs related to COVID-19 treatment and follow-up and for any other medical treatment (e.g., drug reactions) they require.

B. Compensation/Incentives

Participants will receive a ClinCard at the initial study visit, which will be preloaded with money to pay for that day's parking. On the day 14 and 28 day visits, we will add money to that card to cover the parking costs on those days as well.

We will add additional money to the card at the final (day 28) study visit (maximum amount $50). The amount of they receive will be based on completion of the study tasks: $25 for completing all of the self-collected specimens (days 3, 6, & 10) and $25 for completing both the day 24 and day 28 (final) study visit and returning ZioAT monitoring device.

Participants will also keep the thermometer and the pulse oximeter provided at the initial study visit,

C. Compensation Documentation
None

4.7 Risks of Harm/Potential for Benefits to Participants

A. Description of Risks of Harm to Participants

- **Reasonably Foreseeable Risks of Harm**

Hydroxychloroquine Sulfate Adverse Events:
The package labeling does not provide as clear a percent incidence as modern labels since hydroxychloroquine is an old medication. The following Council for International Organizations of Medical Sciences (CIOMS) frequency rating is used, when applicable: Very common ≥ 10 %; Common ≥ 1 and <10 %; Uncommon ≥ 0.1 and < 1 %; Rare ≥ 0.01 and <0.1 %; Very rare < 0.01 %; Not known (frequency cannot be estimated from available data).

- **Blood and lymphatic system disorders**
  Not known: Bone marrow depression, anemia, aplastic anemia, agranulocytosis, leucopenia, and thrombocytopenia (see Warnings and Precautions, Hematologic).

- **Cardiac disorders**
  Not known: Cardiomyopathy, which may result in cardiac failure and in some cases a fatal outcome. Chronic toxicity should be considered when conduction disorders (bundle branch block/ atrioventricular heart block) as well as biventricular hypertrophy are found. Drug discontinuation may lead to recovery (see Warnings and Precautions, Cardiovascular, Drug Interactions, and Symptoms and Treatment of Over dosage). Hydroxychloroquine prolongs the QT, PR and/or QRS intervals which may lead to an arrhythmia. Ventricular arrhythmias and torsade de pointes have been reported in patients taking hydroxychloroquine (see Warnings and Precautions, Cardiovascular, Drug Interactions, and Symptoms and Treatment of Over dosage).

- **Ear and labyrinth disorders**
  Uncommon: ≥ 0.1 and < 1 %: Vertigo, tinnitus.
  Not known: Hearing loss, including cases of irreversible hearing loss.

- **Eye disorders**
  Common: ≥ 1 and <10 %*:* Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible (see WARNINGS AND PRECAUTIONS, Ophthalmologic).
  Uncommon: ≥ 0.1 and < 1 %*:* Maculopathies, which may be irreversible. Retinopathy with changes in pigmentation and visual field defects (see Warnings and Precautions, Ophthalmologic). In its early form it appears reversible upon discontinuation of the drug. If allowed to develop however, there may be a risk of progression even after treatment withdrawal. Patients with retinal changes may be asymptomatic initially, or may have scotomatous vision with paracentral, pericentral ring types, temporal scotomas, abnormal color visions, reduction in visual acuity, night blindness, difficulty reading and skipping words. Corneal changes including edema and opacities. They are either symptomless or may cause disturbances such as halos around lights especially at night, blurring of vision, vision disturbances, or photophobia. They may be transient or are reversible upon discontinuation of therapy (see Warnings and Precautions, Ophthalmologic).
  Not known: Macular degeneration, which may be irreversible.

- **Gastrointestinal disorders**
  Very common: ≥ *10 %*: Abdominal pain, nausea.
  Common: Diarrhea, vomiting.
  These symptoms usually resolve immediately upon reducing the dose or upon stopping the treatment.

- **Hepatobiliary disorders**
  Uncommon: ≥ 0.1 and < 1 %: Abnormal liver function tests.
  Not known: Fulminant hepatic failure (see Warnings and Precautions, Hepatic/Biliary/Pancreatic).

- **Immune system disorders**
  Not known: Urticaria, angioedema, bronchospasm.

- **Metabolism and nutrition disorders**
  Common: ≥ *1 and <10 %*: Anorexia (usually resolves immediately upon reducing the dose or upon stopping the treatment).
  Not known: hypoglycemia (see Warnings and Precautions, Endocrine and Metabolism).
  Hydroxychloroquine may exacerbate porphyria (see Warnings and Precautions, General).

- **Musculoskeletal and connective tissue disorders**
  Uncommon: ≥ 0.1 and < 1 %: Sensori motor disorders.
  Not known: Skeletal muscle palsies or skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups. Depression of tendon reflexes, abnormal results of nerve conduction tests. Myopathy may be reversible after drug discontinuation, but recovery may take many months (see Warnings and Precautions, Musculoskeletal).

- **Nervous system disorders**
  Common: ≥ *1 and <10 %*: Headache.
  Uncommon: Dizziness.
  Not known: Convulsions. Extrapyramidal reactions such as: akathisia, dystonia, dyskinesia, gait disturbance, tremor.

- **Psychiatric disorders**
  Common: ≥ *1 and <10 %*: Affect lability.
  Uncommon: ≥ 0.1 and < 1 %: Nervousness.
  Not known: Psychosis, suicidal behavior.

- **Skin and subcutaneous tissue disorders**
  Common: ≥ *1 and <10 %*: Skin rash, pruritus.
  Uncommon: ≥ 0.1 and < 1 %*:* Pigmentary changes in skin and mucous membranes, bleaching of hair, alopecia. These usually resolve readily upon cessation of therapy.
  Not known: Bullous eruptions (including urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum), toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, Drug Rash with Eosinophilia and Systemic Symptoms (Dress syndrome), photosensitivity, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP) (see Warnings and Precautions, Skin).

- **Risk of Harm from an Intervention on a Participant with an Existing Condition**
  N/A

- **Other Foreseeable Risks of Harm**
  N/A

- **Observation and Sensitive Information**
  N/A

RIBAVIRIN Adverse Events

Significant adverse reactions associated with Ribavirin/peginterferon alfa-2a combination therapy include severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, ophthalmologic disorders, cerebrovascular disorders, pulmonary dysfunction, colitis, pancreatitis, and diabetes.

Pregnancy
Ribavirin may cause birth defects and/or death of the exposed fetus. Ribavirin has demonstrated significant teratogenic and/or embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of Ribavirin.

Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Patients should be instructed to use at least two forms of effective contraception during treatment and for 6 months after treatment has been stopped. Pregnancy testing should occur monthly during Ribavirin therapy and for 6 months after therapy has stopped.

Anemia

The primary toxicity of Ribavirin is hemolytic anemia, which was observed in approximately 13% of all Ribavirin/peginterferon alfa-2a- treated participants in clinical trials. Anemia associated with Ribavirin occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in hemoglobin may be significant, it is advised that hemoglobin or hematocrit be obtained pretreatment and at week 2 and week 4 of therapy or more frequently if clinically indicated. Patients should then be followed as clinically appropriate. Caution should be exercised in initiating treatment in any patient with baseline risk of severe anemia (e.g., spherocytosis, history of gastrointestinal bleeding)

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by Ribavirin. Patients should be assessed for underlying cardiac disease before initiation of Ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use Ribavirin.

Hepatic Failure

Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons, including peginterferon alfa-2a. Cirrhotic CHC patients coinfected with HIV receiving highly active antiretroviral therapy (HAART) and interferon alfa-2a with or without Ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART. In Study NR15961 among 129 CHC/HIV cirrhotic patients receiving HAART, 14 (11%) of these patients across all treatment arms developed hepatic decompensation resulting in 6 deaths. All 14 patients were on NRTIs, including stavudine, didanosine, abacavir, zidovudine, and lamivudine. These small numbers of patients do not permit discrimination between specific NRTIs or the associated risk. During treatment, patients' clinical status and hepatic function should be closely monitored for signs and symptoms of hepatic decompensation. Treatment with peginterferon alfa-2a/ Ribavirin should be discontinued immediately in patients with hepatic decompensation

Hypersensitivity

Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, and anaphylaxis) have been observed during alpha interferon and Ribavirin therapy. If such a reaction occurs, therapy with peginterferon alfa-2a and Ribavirin should be discontinued immediately, and appropriate medical therapy instituted. Serious skin reactions including vesiculobullous eruptions, reactions in the spectrum of Stevens-Johnson Syndrome (erythema multiforme major) with varying degrees of skin and mucosal involvement and exfoliative dermatitis (erythroderma) have been reported in patients receiving peginterferon alfa-2a with and without Ribavirin. Patients developing signs or symptoms of severe skin reactions must discontinue therapy.

Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, and pneumonia have been reported during therapy with Ribavirin and interferon. Occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, patients should be closely monitored and, if appropriate, combination Ribavirin/peginterferon alfa-2a treatment should be discontinued.

Bone Marrow Suppression
Pancytopenia (marked decreases in RBCs, neutrophils, and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of pegylated interferon/Ribavirin and azathioprine. In this limited number of patients (n=8), myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of both HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone. peginterferon alfa-2a, Ribavirin, and azathioprine should be discontinued for pancytopenia, and pegylated interferon/Ribavirin should not be re-introduced with concomitant azathioprine.

Pancreatitis
Ribavirin and peginterferon alfa-2a therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.

Impact on Growth in Pediatric Patients
During combination therapy for up to 48 weeks with peginterferon alfa-2a plus Ribavirin, growth inhibition was observed in pediatric participants 5 to 17 years of age. Decreases in weight for age z-score and height for age z-score up to 48 weeks of therapy compared with baseline were observed. At 2 years post-treatment, 16% of pediatric participants were more than 15 percentiles below their baseline weight curve and 11% were more than 15 percentiles below their baseline height curve.

The available longer term data on participants who were followed up to 6 years post-treatment are too limited to determine the risk of reduced adult height in some patients.

NITAZOXANIDE Adverse Events

Gastrointestinal
Gastrointestinal side effects have included abdominal pain (6.6% to 7.8%), diarrhea (2.1% to 4.2%), and nausea (3%). Side effects occurring in less than 1% of patients have included vomiting, anorexia, flatulence, dyspepsia, constipation, dry mouth, and thirst.

The incidence of gastrointestinal side effects may be dose related. Abdominal pain, diarrhea and discolored urine occurred more often in participants receiving higher doses (1 gram twice daily).

Nervous system
Nervous system side effects have included headache (3.1%). Dizziness, somnolence, insomnia, tremor, and hypesthesia have been reported by less than 1% of the patients.

Other
Adverse effects affecting the body as a whole have included asthenia, fever, pain (pelvic/back), flu syndrome, earache, and chills in less than 1% of patients.

Metabolic
Metabolic side effects have included increased creatinine and SGPT in less than 1% of patients.

Dermatologic
Dermatologic side effects have included pruritus, rash, and sweat in less than 1% of patients.

Ocular
Ocular side effects have included pale yellow eye discoloration (<1%).

Respiratory
Respiratory side effects have included epistaxis, rhinitis, lung disease, and pharyngitis.

Genitourinary
Genitourinary side effects have included discolored urine, dysuria, amenorrhea, metrorrhagia, and edema labia.

General
In general, side effects have been mild and transient in nature. The most frequent side effects have included abdominal pain, diarrhea, vomiting, and headache, and the rates of occurrence were not significantly different from placebo.

Musculoskeletal
Musculoskeletal side effects have included myalgia, leg cramps, and spontaneous bone fracture.

Cardiovascular
Cardiovascular side effects have included tachycardia, syncope, and hypertension.

Hematologic
Hematologic side effects have included anemia and leukocytosis.

Renal
Renal side effects have included kidney pain.

B. Procedures which Risk Harm to Embryo, Fetus, and/or Pregnant Participants

Women who are pregnant or unwilling to stop breast feeding are excluded from this trial due to the absence of data which demonstrates that this therapy changes morbidity or mortality.

The US FDA labelling for hydroxychloroquine sulcate risk states the following:
Teratogenic Effects**:** Human pregnancies resulting in live births have been reported in the literature and no increase in the rate of birth defects has been demonstrated. Embryonic deaths and malformations of anophthalmia and microphthalmia in the offspring have been reported when pregnant rats received large doses of chloroquine.

Nursing Mothers: Caution should be exercised when administering PLAQUENIL to nursing women. It has been demonstrated that hydroxychloroquine administered to nursing women is excreted in human milk and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines."

The US FDA Labelling for ribavirin states the following: may cause birth defects and/or death of the exposed fetus. Ribavirin has demonstrated significant teratogenic and/or embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of Ribavirin. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients.

All patients must be made fully aware of the information relating to the potential for reproductive toxicity as detailed in the Informed Consent Form. Patients of childbearing potential and their

partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 6 months after last dose of study drug(s).

Women of childbearing potential
Females of childbearing potential should use reliable methods of contraception from the time of screening until 6 months after discontinuing study treatment. Acceptable methods of contraception include abstinence, tubal ligation, combined oral, transdermal, or intra-vaginal hormonal contraceptives, medroxyprogesterone injections (e.g., Depo-Provera), copper-banded intra-uterine devices, hormone impregnated intra-uterine systems and vasectomised partners. All methods of contraception (except for total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse.

Males
Male patients must use a condom during sexual intercourse with all sexual partners including a pregnant female partner during the study and for 4 weeks after discontinuing study treatment. However, where a sexual partner of a male participant is a woman of childbearing potential who is not using effective contraception, men must use a condom during sexual intercourse during the; study and for 6 months after discontinuing study treatment. Male patients should avoid procreation during the trial and for 6 months after discontinuing study treatment.

C. Risks of Harm to Non-Participants

When evaluating the patient during the visit, research personnel will wear appropriate personal protective equipment (PPE) as recommended by the CDC. This includes the following:

- Gown
- Gloves
- Eye/face protection (i.e., goggles, face shield)
- If available, National Institute for Occupational Safety and Health (NIOSH)-certified disposable N95 or better respirator. The CDC has stated that surgical (face) masks have been determined to be an acceptable alternative to N95 or better respirators, when the supply chain of respirators cannot meet the demand so long as procedures that are likely to generate respiratory aerosols are not being performed. The use of mid-turbinate nasal swabs to collect viral load specimens during this study is not considered an aerosolizing procedure.

D. Assessment of Social Behavior Considerations

N/A

E. Minimizing Risks of Harm

Once participants are started on study drug, monitoring for prolongation of QTc or development of polymorphic ventricular tachycardia is required. The Zio AT (iRhythm Technologies, Inc.) is a mobile cardiac telemetry device that allows continuous monitoring of the QTc interval and heart rhythm abnormalities. The Zio AT consists of a small transdermal patch that is applied on the participant's upper chest and a gateway device (size of a cell phone) that has to be kept within 10 feet of the participant. The ECG signal is transmitted to iRhythm technologies via the internet using the gateway. The participant does not have to change batteries or do anything to the device for the 10-day monitoring interval. We have used this device clinically and participant compliance is excellent. The rhythm is monitored continuously for arrhythmias and our EP-cardiology team will be notified immediately for any run of ventricular tachycardia (VT) greater than 4 complexes and other significant arrhythmias (pauses greater than 3 seconds, heart block, atrial fibrillation). We are monitoring for any run of VT since we have found that most episodes of torsade de pointes VT are preceded by shorter runs of polymorphic VT. The participant can also

trigger a transmission by pressing a small button on the transdermal patch if they experience any cardiac symptoms. We will monitor the QTc with this device. We will obtain a baseline transmission at the initial visit after the participant has been deemed to be eligible based on the Kardia Mobile 6L QTc measurement. We will ask the participant to do a transmission for QTc measurement 2 hours after the first dose of study drug. These will be reviewed and QTc measured by our EP cardiology team. We will then monitor the QTc interval twice a day at two predetermined times. This type of monitoring is equivalent to what can be done in the hospital on telemetry and in practice may be superior since the protocol will be strictly adhered to and measurements made by an electrophysiologist. If QT interval increases from baseline of > 60msec or QT > 500 msec, the medications, if still being taken, will discontinued at that time. Participant QT will be monitored every 6 hours until the interval returns to baseline. If a serous arrhythmia is detected during the continuous monitoring, the study cardiologist and participant will be promptly contacted, and the participant will be directed to seek medical treatment as appropriate.

Hemolytic anemia has been associated with long-term use of ribavirin. The study participants will receive only a 5 day course of medication. As an added safety measure hemoglobin level will be checked at baseline, day 14 and then again at day 28. A comprehensive metabolic panel will be drawn at baseline, day 14, and day 28.

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- **Certificate of Confidentiality**
  N/A

- **Provisions to Protect the Privacy Interests of Participants**
  Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors from Rutgers), may review patients records and as required.

  Patients will be required to sign a HIPAA authorization, providing permission to use identifiable health information to be used and/or disclosed for research purposes. Provisions for protecting the privacy interests of include:
  - Ensuring that the conditions under which a procedure is performed, or information is collected (e.g., physical locations, telephone contact, mail, or email solicitations) afford protections against interactions with participants being witnessed, overheard or inadvertently intercepted or viewed.
  - Limiting the information being collected to only the minimum amount of data necessary to accomplish the research purposes.

  The research team will make all efforts to ensure confidentiality is maintained by:
  - Protecting PHI against public viewing;
  - Proper storage and disposal of documents that contain PHI;
  - Safeguarding computer workstations and databases that access PHI.

F. Potential Benefits to Participants

There may be direct benefit to the patient for participation in this study because the study participant may receive hydroxychloroquine sulfate ribavirin and nitazoxanide, which are FDA approved and have been shown to have potential activity in patients with COVID-19, although this does not guarantee that each individual participant will benefit.

Data gathered from this study may allow us to identify an effective treatment for COVID-19 that could result in benefit to the patient or society as a whole in the future.

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)

The Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. In accordance with the Health Information Portability and Accountability Act (HIPAA), the written Informed Consent Form must include a participant authorization to release medical information to a regulatory authority, or Institutional Review Board (IRB), to grant access to participant's medical information that includes all hospital records relevant to the study, including participants' medical history.

The core elements included in the HIPAA authorization are:

- A description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion;
- The name or other specific identification of the person(s), or class of persons, authorized to make the requested use or disclosure;
- The name or other specific identification of the person(s), or class of persons, to whom the covered entity may make the requested use or disclosure;
- A description of each purpose of the requested use or disclosure;
- An expiration date or an expiration event that relates to the individual or the purpose of the use or disclosure;
- Signature of the individual and date.

5.2 Family Educational Rights and Privacy Act (FERPA)

N/A

5.3 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

N/A

5.4 General Data Protection Regulation (GDPR)

N/A

5.5 NJ Access to Medical Research Act (Surrogate Consent)

N/A

6.0 Data Management Plan

6.1 Data Analysis

We will follow intention-to-treat principles and analyze the groups as randomized. A summary table of baseline variables will be created with means and standard deviations for continuous variables or percentages for categorical variables, all stratified by treatment group.

Primary outcome. We will have repeated measures of log10 VL for each participant. These measurements will occur on day 0 (baseline) and at about days 3, 6 and 10. We will fit a linear mixed effects model, where log10 VL is the outcome, indicators for treatment group (SoC reference), time, and treatment by time interactions are the predictors. The model will include a random slope and intercept, to account for within participant correlation. The robust sandwich variance will be used to estimate standard errors. Because we are estimating within participant changes over time from randomization, we can estimate a treatment effect at any particular day. Our primary hypotheses involve the change over time, which we will assess with the treatment by time interaction terms. If participants drop out from the study

before the day 10 visit, we will use all of their preceding data. Linear mixed effects models rely on the assumption that missing data are missing at random.

Secondary outcomes. For binary outcomes, such as progression to having symptoms, intubation, death, hospitalization, and admission to intensive care unit, we will fit logistic regression models. The covariates will include the treatment group indicators. We will report odds ratios and 95% confidence intervals. For change variables, such as change in viral shedding or change in Q-T interval, we will fit linear mixed effects models (similar to primary outcome).

6.2 Data Security

Data will be entered into electronic case report forms (eCRFs) through REDCap. These eCRFs are used to record participant data generated by participant events: including labs, study medication administration, or procedures of the protocol. Access to the database is limited to the research staff on a need to know basis. Each authorized user accesses the software using his/her Rutgers NetID and password. Audit trails are built into the software to track when data entry was started, when the form was declared complete, when the form was monitored/queried, amended, and then finalized.

6.3 Data and Safety Monitoring

A. Data/Safety Monitoring Plan

We will convene an independent DSMB comprised of experts in infectious disease, biostatistics, and ethics. The DSMB will review the study protocol and provide recommendations. Recruitment will be initiated after the DSMB approves the study protocol.

B. Data/Safety Monitoring Board Details

The DSMB will review recruitment, retention, data completeness, protocol deviations, adverse events (AEs), severe adverse events (SAEs) and unexpected problems (UPs) when ½ of the participants have been enrolled and will provide written recommendations to the PI.

Adverse events will be monitored in following ways: 1) the DSMB will review all reported adverse events and monitor the incidence rates after ½ participants are enrolled, 2) the expedited review of unexpected SAEs related to the protocol and unanticipated problems (UP). If unexpected safety concerns arise from the trial data or from external research or literature, then safety data reporting will be expanded and examined on an ad-hoc basis. The investigators will work with the DSMB to ensure that the board members have sufficient information to comprehensively monitor patient safety throughout the trial. The DSMB may advise early termination of the trial for safety reasons, efficacy of the primary outcome or other modifications to the protocol.

6.4 Reporting Results

A. Individual Participants' Results

We will provide each participant the results their immune testing at the end of the trial.

B. Aggregate Results

Aggregate research results will be shared with the study participants.

C. Professional Reporting

The policies and procedures of Rutgers University's legal department (see: Investigator's Handbook) will govern publication of the trial. It is expected that the results of this trial will be submitted for publication in a timely manner following the conclusion.

D. Clinical Trials Registration, Results Reporting and Consent Posting

ClinicalTrials.Gov Registration and Data Reporting: Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are participant to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

This is a research study which prospectively assigns human participants to health related interventions. The study will be registered on clinicaltrials.gov per FDA Regulations within 21 days of enrollment of the first participant and updated at least every 6 months.

6.5 Secondary Use of the Data

N/A

7.0 Research Repositories – Specimens and/or Data

There will be no research repositories established from this research.

8.0 Approvals/Authorizations

Approval will be obtained from the Rutgers University Biosafety Committee and the Robert Wood Johnson University Hospital Research Utilization Group (RUG)

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