

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL
TO EVALUATE THE EFFICACY AND SAFETY OF NITAZOXANIDE
(NTZ) FOR PRE- AND POST-EXPOSURE PROPHYLAXIS OF COVID-19
AND OTHER VIRAL RESPIRATORY ILLNESSES (VRI) IN
HEALTHCARE WORKERS AND OTHERS AT INCREASED RISK OF
SARS-COV-2 INFECTION**

PROTOCOL NO. RM08-3007

Study Sponsor:

The Romark Institute for Medical Research



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INVESTIGATOR’S AGREEMENT

CONFIDENTIALITY

The information in this protocol is provided to you, as an Investigator or consultant, for review by you, your staff, and an applicable institutional review committee. By accepting this document, you agree that information contained herein will be considered confidential and will not be disclosed to others, without written authority from The Romark Institute for Medical Research, except to the extent necessary to obtain: (a) Institutional Review Board approval and (b) informed consent from those persons to whom the investigational medicinal product will be administered.

APPROVAL OF FINAL PROTOCOL

My signature below constitutes agreement with this protocol. I am providing the necessary assurances that this study will be conducted by me and my staff according to all stipulations of the protocol, including all statements regarding confidentiality, and in complete accordance with all applicable regulations including current Good Clinical Practice guidelines and the ethical guidelines set by the World Medical Assembly ([Declaration of Helsinki](#), last amendment in Fortaleza, Brazil October 2013). Furthermore, my signature below indicates that source documents will be available for review by the Sponsor or their designated representative.

Principal Investigator Signature:

Principal Investigator

Date

Print name: _____

With the signature below, the Sponsor approves of this protocol.

Sponsor Signature:

The Romark Institute for Medical Research

Date

Print name: _____

SYNOPSIS

Title:	A Randomized, Double-Blind, Placebo Controlled Trial to Evaluate the Efficacy and Safety of Nitazoxanide (NTZ) for Pre- and Post-exposure Prophylaxis of COVID-19 and Other Viral Respiratory Illnesses (VRI) in Healthcare Workers and Others at Increased Risk of SARS-CoV-2 Infection
Study Number:	RM08-3007
IND Number:	149,166
Indication:	Pre- and post-exposure prophylaxis of COVID-19 and other VRIs
Design:	Multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of NTZ for pre- and post-exposure prophylaxis of COVID-19 and other VRIs.
Number of Subjects:	≥800 up to 4,000 as required to obtain 24 COVID-19 illnesses
Population:	Healthcare workers and others at increased risk of contracting SARS-CoV-2.
Randomization:	1:1 at the subject level
Study Dose and Administration:	<u>Group 1 (NTZ):</u> Two NTZ 300 mg tablets orally twice daily (b.i.d.) for 6 weeks. <u>Group 2 (Placebo):</u> Two placebo tablets orally b.i.d. for 6 weeks. All subjects will receive a B complex vitamin ([REDACTED]) one tablet twice daily to mask potential chromaturia that may be associated with NTZ.
Objective:	Evaluate the effect of NTZ administered 600 mg orally b.i.d. for 6 weeks in preventing symptomatic laboratory-confirmed COVID-19 and other VRIs compared to that of a placebo.
Primary Efficacy Parameters:	<ol style="list-style-type: none">The proportion of subjects with symptomatic laboratory-confirmed COVID-19 identified after start of treatment and before the end of the 6-week treatment period.The proportion of subjects with symptomatic laboratory-confirmed VRI identified after the start of treatment and before the end of the 6-week treatment period

- Secondary Efficacy Parameters:**
- i. Mortality due to COVID-19 or complications thereof.
 - ii. The proportion of subjects (with or without symptoms) testing positive for antibodies to SARS-CoV-2 at either of the Week 6 or Week 8 visits.
- Exploratory Efficacy Parameters:** Proportion of subjects hospitalized due to viral respiratory illness (VRI) or complications thereof; mortality due to VRI or complications thereof; proportion of subjects experiencing acute respiratory illness (ARI); proportion of subjects hospitalized due to ARI or complications thereof; mortality due to ARI or complications thereof.
- Safety Parameters:** Adverse events
- Biological Samples:** Blood and urine samples for safety will be collected for all subjects at baseline, Week 3 and Week 6. Blood samples for pharmacokinetics will be collected at the Week 3 and Week 6 visits. Blood tests for anti-SARS-CoV-2 antibodies will be collected at Baseline, Week 6 and Week 8. Nasopharyngeal swabs will be collected at baseline for all subjects. Additional nasopharyngeal swabs and fecal specimens will be collected by the Investigator at visits for COVID-19/VRI symptoms.
- Study Centers:** Multicenter, USA
- Trial Duration:** April 2020 – April 2021

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
ARI	Acute Respiratory Illness
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
b.i.d.	Twice Daily
BUN	Blood Urea Nitrogen
CMH	Cochran-Mantel-Haenszel
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019 (caused by SARS-CoV-2)
CRF	Case Report Form
EC50	50% Effective Concentration
EDC	Electronic Data Collection
EV/RV	Rhinovirus/Enteroviruses
FDA	Food and Drug Administration
FLU-PRO	InFLUenza Patient-Reported Outcome Questionnaire
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
hMPV	Human Metapneumovirus
IC50	50% Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IL	Interleukin
IRB	Institutional Review Board
LDL	Low Density Lipoprotein
MDCK	Madin-Darby Canine Kidney
NTZ	Nitazoxanide
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
VRI	Viral Respiratory Illness

1. INTRODUCTION

1.1. Viral Respiratory Infections

Respiratory infections are the leading cause of disease globally. There are more than 500 million non-influenza viral respiratory infections or “common colds” each year in the United States, with adults experiencing as many as 2-6 illnesses per year and children experiencing 6-8 (Fendrick et al. 2003, Turner 1997, Worrall 2011). Colds have been reported to account for as much as 40% of time lost from work in the employed population and 30% of school absences (Kirkpatrick 1996). In a study conducted from November of 2000 to February of 2001, the total economic impact of non-influenza viral respiratory tract infections was nearly \$40 billion (Fendrick et al. 2003). Adjusted for inflation (February 2001 to January 2018), the economic impact today would exceed \$56 billion (USDOL Bureau of Labor Statistics 2018). Epidemic outbreaks of VRIs, like SARS-CoV-2, can diminish entire economies and have cost impacts of trillions of dollars.

Common respiratory viral pathogens include adenovirus, human coronavirus, hMPV, EV/RV, influenza, parainfluenza and RSV. In most cases, respiratory viral infections are self-limiting and confined to the upper airways, where they evoke relatively mild symptoms such as sneezing and a runny nose. However, in susceptible individuals, such as newborns, those with pre-existing lung disease, and the elderly, the symptoms can impact on the lower airways, resulting in wheeze, shortness of breath, bronchiolitis or pneumonia (Troy and Bosco 2016).

The EPIC study (Etiology of Pneumonia in the Community) conducted by researchers at the Centers for Disease Control and Prevention was a large multicenter population-based surveillance study conducted in the United States, which used rigorous microbiologic testing in 2259 hospitalized adults with community acquired pneumonia. In this study respiratory viruses were the most common pathogen identified in adults hospitalized with pneumonia accounting for 23% of all pneumonia admissions. Rhinovirus (9%) was the most common pathogen identified followed by influenza A/B (6%), *S. pneumoniae* (5%), hMPV (4%), and RSV (3%). Overall, of the individual organisms identified, viruses accounted for 6 of the 7 most common single as well as co-pathogens. The data further indicated serious VRIs can occur year-round with some intra-virus seasonality (Jain et al. 2015).

Aside from the seasonal prevalence of typical respiratory viruses, outbreaks can occur with these as well as novel strains like SARS-CoV-2 and MERS-CoV. Rhinoviruses have been associated with as much as 59% of outbreaks in long-term care facilities as well as seasonal strains of coronavirus, both leading to severe disease (Longtin et al. 2010, Hand et al. 2018). RSV and hMPV are widely reported to circulate during an influenza season, with RSV infections occurring at 4 times the rate of the general population in the elderly (Ursic et al. 2016, Thompson et al. 2003).

Influenza is the only respiratory virus for which a vaccine exists. Moreover, vaccine efficacy is variable with each season and has demonstrated diminished vaccine responses in the elderly (Centers for Disease Control and Prevention 2019, Goodwin et al. 2006). Despite widespread vaccine availability and uptake, influenza outbreaks are still quite common. For instance, as much as 90% of those residing in long-term care facilities are vaccinated for influenza, yet at least half of these facilities report outbreaks every year (McGeer et al. 2000).

The Infectious Diseases Society of America recommends chemoprophylaxis for institutional outbreaks and in certain situations involving patients at high-risk for complications or unvaccinated personnel in close contact with high-risk patients (Uyeki et al. 2018). However, these recommendations are limited to influenza since there are no available agents for the chemoprophylaxis of other respiratory viruses. Considering the lack of vaccine and chemoprophylaxis availability for most pathogens, inefficacy of influenza vaccination, enhanced rate of spread in certain settings and emergence of novel viral respiratory pathogens a novel broad-spectrum chemoprophylaxis strategy is of paramount importance.

1.1.1. Antivirals Studied for Chemoprophylaxis of Viral Respiratory Infections

The only drugs approved for chemoprophylaxis in this population, for any respiratory virus, are oseltamivir and zanamivir which are only for influenza A and B infections.

In a pooled analysis of two seasonal chemoprophylaxis trials in healthy unvaccinated adults (aged 18 to 65 years), oseltamivir 75 mg once daily taken for 42 days during a community outbreak reduced the incidence of laboratory-confirmed clinical influenza from 5% (25/519) for the placebo group to 1% (6/520) for the oseltamivir group. (TAMIFLU® Prescribing Information 2019, Hayden et al. 1999)

Two seasonal prophylaxis trials assessed zanamivir 10 mg inhaled once daily versus placebo inhaled once daily for 28 days during community outbreaks. The first trial enrolled subjects aged 18 years or older (mean age: 29 years) from 2 university communities. In this trial, the incidence of symptomatic laboratory-confirmed influenza was reduced from 6.1% (34 of 554) for the placebo group to 2.0% (11 of 553) for the group receiving zanamivir. The second seasonal prophylaxis trial enrolled subjects aged 12 to 94 years (mean age: 60 years) with 56% of them older than 65 years. In this trial, the incidence of symptomatic laboratory-confirmed influenza was reduced from 1.4% (23 of 1,685) for the placebo group to 0.2% (4 of 1,678) for the group receiving zanamivir (RELENZA® Prescribing Information 2018).

There are no drugs approved for the treatment or chemoprophylaxis of viral respiratory infections caused by other common respiratory pathogens like coronavirus, RSV, rhinovirus, hMPV, and parainfluenza in this population.

1.2. Nitazoxanide (NTZ)

NTZ is a thiazolide anti-infective with *in vitro* activity against parasites, anaerobic bacteria, and viruses (Anderson and Curran 2007).

ALINIA® (NTZ) for Oral Suspension (patients 1 year of age and older) and ALINIA (NTZ) Tablets (patients 12 years and older) are marketed in the United States for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*. ALINIA for Oral Suspension and ALINIA Tablets have not been shown to be superior to placebo for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients (ALINIA Prescribing Information 2019).

1.2.1. NTZ Inhibits Viral Replication and Cytokine Secretion

Tizoxanide, the active circulating metabolite of NTZ, has been shown to possess antiviral activity in cell culture against a broad range of viruses including influenza A and B viruses, coronaviruses (SARS-CoV-2, MERS-CoV, canine CoV S-378, murine coronavirus, mouse hepatitis virus strain A59 (MHV-A59)), parainfluenza (Sendai) virus, RSV A-2, rotavirus, norovirus, hepatitis C virus genotypes 1a and 1b, Japanese encephalitis virus, dengue fever virus-2, yellow fever virus, hepatitis B virus, and human immunodeficiency virus (HIV) (Rossignol 2014, Rossignol 2016, Wang et al. 2020, Piacentini et al. 2018). Experiments in HeLa R19 cells have shown that NTZ inhibits replication of rhinovirus A serotypes 2 and 16 (Romark Study Report RM01-0434). Concentrations of tizoxanide required to inhibit replication of these viruses by 50% (EC₅₀s) were generally between 0.2 and 3 μM depending upon the test conditions.

The anti-influenza activity of nitazoxanide and its circulating metabolite, tizoxanide, has been investigated in human (Monocytic U937, T-lymphocytic Jurkat, and Alveolar type II-like A549) and canine (MDCK) cells after infection with multiple different strains of influenza A virus including oseltamivir-resistant and amantadine-resistant strains (Rossignol et al. 2009, Ashton et al. 2010, Sleeman et al. 2014). In a study of the susceptibility of 210 circulating seasonal influenza viruses to tizoxanide demonstrated median EC₅₀ values (±IQR) of 0.48 μM (0.33-0.71), 0.62 μM (0.56-0.75), 0.66 μM (0.62-0.69), and 0.60 μM (0.51-0.67) for A(H1N1)pdm09, A(H3N2), B(Victoria lineage) and B(Yamagata lineage), respectively (Tilmanis et al. 2017).

Laboratory studies to evaluate the potential for resistance of influenza A virus to tizoxanide have been unable to select for resistant virus (Romark Study Report RM01-0417). These studies suggest a low potential for resistance.

Studies in peripheral blood mononuclear cells have also shown tizoxanide suppresses secretion of pro-inflammatory cytokines that are upregulated by VRIs. Concentrations required to suppress cytokine secretion by 50% for IL-2, IL-4, IL-5, IL-6, IL-8, IL-10 and TNF-α ranged from 2.0 to 9.8 μM (Rossignol and van Baalen 2018, Romark Study Report 9264). Nitazoxanide has also been shown to suppress IL-6 production in thioglycollate broth-injected mice (Hong et al. 2012).

Ongoing studies of the mechanism of action of NTZ have shown NTZ and tizoxanide modulate mitochondrial function by uncoupling oxidative phosphorylation. Studies indicate tizoxanide decreases cellular ATP in a dose-dependent manner in MDCK cells and in MDCK cells infected with influenza viruses. Maximum inhibition of ATP in influenza-infected or uninfected MDCK cells reaches up to 45% after 24 hours of exposure to 100 μM tizoxanide. In these experiments, a 10% reduction of ATP achieved by adding less than 10 μM tizoxanide is sufficient to inhibit influenza virus replication by approximately 90%. The decrease in cellular ATP does not affect cell viability and is reversible after eliminating tizoxanide from the culture (Rossignol and van Baalen 2018). Studies of a number of different viruses have shown viral replication is ATP-dependent (Braakman et al. 1992, Braakman et al. 1991, Doms et al. 1987, Chang et al. 2009, Mirazimi and Svensson 2000). In the case of NTZ, key viral proteins like hemagglutinin (influenza), F-protein (RSV and parainfluenza), and N protein (coronavirus) have been identified as potential end targets of this mechanism (Rossignol et al. 2009, Piacentini et

al. 2018, Cao et al. 2015). In addition, inhibition of ATP and its downstream effect on AMP-activated protein kinase activation has been shown to suppress secretion of pro-inflammatory cytokines (Lee et al. 2017, Sag et al. 2008, Wang et al. 2003).

The activity of NTZ in inhibiting replication of a broad range of respiratory viruses as well as the secretion of pro-inflammatory cytokines upregulated during respiratory virus infection has prompted clinical development of NTZ for treatment or prophylaxis of respiratory illness caused by VRIs.

1.2.2. Pharmacokinetics of NTZ in Humans

NTZ is not detectable in the plasma following oral administration of the drug. The main metabolites of NTZ in humans are tizoxanide and tizoxanide glucuronide. Tizoxanide is highly bound to plasma proteins (>99%). The absorption of NTZ in immediate release tablets is significantly enhanced (C_{max} and AUC of tizoxanide and tizoxanide glucuronide in plasma are more than doubled) when it is administered with food. In fasted human volunteers receiving a single 500 mg dose of ^{14}C NTZ, approximately one-third of the dose was excreted in urine as tizoxanide and tizoxanide glucuronide, and two-thirds was excreted in feces as tizoxanide. No other significant metabolites were detected (NTZ 300 mg Tablets Investigators Brochure).

The pharmacokinetics of tizoxanide and tizoxanide glucuronide during repeated oral dosing of NTZ 300 mg extended release tablets administered 600 mg twice daily with food were evaluated in healthy volunteers. Twelve (12) subjects received two NTZ controlled release tablets twice daily with food for 7 days. The pharmacokinetics were studied in plasma up to 12 hours post-dose after the morning dose on Day 1 and Day 7, and before the morning dose on Day 2-6. Based on mixed effect analysis of variance, the steady state tizoxanide and tizoxanide glucuronide plasma concentrations was reached by Day 2, after one day of treatment with NTZ at 600 mg b.i.d. The main pharmacokinetics parameters of tizoxanide and tizoxanide glucuronide are summarized in the table below:

Table 2: Summary of Tizoxanide and Tizoxanide Glucuronide Pharmacokinetics Parameters

PK Parameter (unit)	Tizoxanide		Tizoxanide Glucuronide	
	Day 1 N=12	Day 7 N=12	Day 1 N=12	Day 7 N=12
C_{max} ($\mu\text{g/mL}$)	5.23 \pm 2.71	8.16 \pm 4.16	4.88 \pm 1.72	8.96 \pm 3.48
t_{max} (h)	6.00 (4.00-9.00)	5.00 (3.00-8.00)	6.00 (5.00-11.00)	5.50 (0.00-7.02)
t_{lag} (h)	0.00 (0.00-2.00)	0.00 (0.00-0.00)	0.50 (0.00-2.00)	0.00 (0.00-0.00)
AUC _{0-t} ($\mu\text{g}\cdot\text{h/mL}$)	26.9 \pm 16.1	52.5 \pm 33.7	29.5 \pm 12.1	75.0 \pm 37.8
AUC _{0-T} ($\mu\text{g}\cdot\text{h/mL}$)	28.6 \pm 16.3 ^a	48.3 \pm 31.9 ^b	30.5 \pm 12.2 ^c	75.2 \pm 37.9
C_T ($\mu\text{g/mL}$)	0.709 \pm 0.987	1.72 \pm 2.04	1.39 \pm 0.846	3.89 \pm 2.88
AUC _{0-∞} ($\mu\text{g}\cdot\text{h/mL}$)	27.8 \pm 17.8 ^b	52.3 \pm 35.6 ^b	35.3 \pm 16.5 ^d	62.1 \pm 24.2 ^e
$t_{1/2}$ (h)	1.66 \pm 0.408 ^b	2.19 \pm 0.485 ^b	2.70 \pm 0.848 ^c	4.99 \pm 5.20
λ_z (1/h)	0.441 \pm 0.106 ^b	0.331 \pm 0.0733 ^b	0.282 \pm 0.0902 ^c	0.201 \pm 0.0813
C_{avg} ($\mu\text{g/mL}$)	NA	4.02 \pm 2.66 ^b	NA	6.27 \pm 3.16
C_{min} ($\mu\text{g/mL}$)	NA	1.50 \pm 1.83	NA	3.63 \pm 3.00

PK Parameter (unit)	Tizoxanide		Tizoxanide Glucuronide	
	Day 1 N=12	Day 7 N=12	Day 1 N=12	Day 7 N=12
PTF (%)	NA	193 ± 39.1 ^b	NA	101 ± 40.7
Swing (%)	NA	1039 ± 656	NA	268 ± 194

Values are arithmetic mean ± SD, except median (range) for t_{max} and t_{lag}

N = number of subjects with data; NA = not applicable

^a N=10; ^b N=11; ^c N=11; ^d N=8; ^e N=7

Table 3: Summary of Tizoxanide and Tizoxanide Glucuronide Trough Plasma Concentrations

PK Parameter (unit)	Trough Concentrations (µg/mL Mean (CV%))						
	Day						
Dose Group Nitazoxanide	1 (a)	2	3	4	5	6	7 (b)
Tizoxanide	0.709 (139)	1.55 (100)	2.36 (101)	3.24 (99.7)	3.80 (146)	3.26 (119)	3.02 (98.6)
Tizoxanide Glucuronide	1.39 (61.0)	3.68 (72.3)	4.38 (72.8)	5.35 (77.2)	5.83 (98.8)	5.94 (91.2)	5.65 (68.7)

1.2.3. Clinical Experience with Geriatric Subjects (≥65 Years of Age) Exposed to NTZ 300 mg Extended Release Tablets in Clinical Trials

Of the 3,147 subjects exposed to NTZ 300 mg extended release tablets in clinical trials, 89 were elderly adults aged 65 years and older. Fourteen (14) of these subjects received a single 600 mg dose in a pharmacokinetic study, while 75 subjects were enrolled in Phase 3 clinical trials for the treatment of influenza and common cold due to enterovirus/rhinovirus. In the Phase 3 trials, all were treated with nitazoxanide 600 mg twice daily for 5 days, two of which received nitazoxanide in combination with oseltamivir.

Overall, the type and severity of AEs reported in this population were similar to the total population and the known adverse event profile for the drug. In the pharmacokinetic study only two adverse events were reported in two subjects (headache and diarrhea), both were mild in nature and not considered to be related to nitazoxanide. In Phase 2b/3 and Phase 3 clinical trials, two subjects experienced serious adverse events unrelated to study medication, but rather related to a pre-existing history of a concurrent condition. One of the subjects experienced an exacerbation of congestive heart failure was hospitalized and subsequently recovered. The other subject had a history of severe back and neck pain and was hospitalized for musculoskeletal pain. This subject also recovered. The other adverse events experienced by geriatric subjects were mild to moderate in nature. The most commonly reported AEs (at least 2%) for geriatric subjects receiving nitazoxanide in Phase 3 studies (n = 75) regardless of causality assessment were: diarrhea (9.3%), chromaturia (6.7%), nausea (2.7%), and headache (2.7%). The rates of occurrence of AEs did not differ significantly from those of the placebo.

Population pharmacokinetic data for tizoxanide and tizoxanide glucuronide troughs (prior to next dose) from geriatric subjects receiving nitazoxanide 600 mg twice daily for

5 days is available for 50 subjects enrolled Phase 2b/3 and Phase 3 clinical trials. A comparison of this data to the adult population (18 to 64 years of age) from these studies is presented in the following table (NTZ 300 mg Tablets Investigators Brochure).

Table 4: Population Pharmacokinetics, Trough Data, for Geriatric Subjects ≥ 65 Years of Age from Phase 2b/3 and Phase 3 Clinical Trials

Metabolite	Trough Data Subjects 12 to 17 years	Trough Data Subjects 18 to 64 years
Tizoxanide	0.86 $\mu\text{g/mL}$ (n = 50)	0.81 $\mu\text{g/mL}$ (n = 1305)
Tizoxanide glucuronide	3.08 $\mu\text{g/mL}$ (n = 50)	2.34 $\mu\text{g/mL}$ (n = 1314)

1.2.4. Overview of Other Experience in Clinical Trials and Post-marketing Surveillance

NTZ has been marketed for diarrheal disease caused by *Giardia* or *Cryptosporidium* in the United States since 2003 and in Latin America since 1996. It is estimated that more than 350 million patients have been exposed to NTZ worldwide. No drug-related serious adverse events have been reported during post-marketing experience with NTZ.

Over 7,500 subjects have been treated with NTZ in clinical trials, including 3,147 subjects 12 years of age and older who have been exposed to the NTZ 300 mg extended release tablets (as monotherapy, n = 2,659, or in combination with oseltamivir, n = 488). Of the 3,147 subjects, 2,686 were given a dose of 600 mg twice daily for 5 days. The most commonly (at least 2% of treated subjects) reported adverse events (AEs) regardless of causality assessment were: chromaturia (10.8%), diarrhea (6.3%), abdominal pain/abdominal pain upper/abdominal pain lower (2.8%), bronchitis (2.8%), nausea (2.7%), and headache (2.3%). In the placebo-controlled trials, the rates of occurrence of AEs did not differ significantly from those of placebo except for chromaturia (10.8% compared to 0.8% for placebo). Less than 1% of subjects discontinued therapy because of AEs (NTZ 300 mg Tablets Investigators Brochure).

1.3. Rationale for the Study

There is an important need for therapies to prevent VRIs, especially in outbreak situations, and particularly in healthcare workers caring for seriously ill patients. VRIs are a critical health concern especially in those at risk for complications. Of the most common viruses associated with VRI, chemoprophylaxis therapies and vaccines are only commercially available for influenza.

NTZ's broad-spectrum of activity against respiratory viruses makes it a good candidate for chemoprophylaxis as it has demonstrated activity against the common pathogens associated with VRI. Importantly, previous studies have demonstrated NTZ has a favorable safety profile and low risk for developing viral resistance.

This study will be conducted during a time when COVID-19 (caused by SARS-CoV-2) is circulating and posing significant risk. There is an important need for an oral medication that could be administered as chemoprophylaxis of COVID-19.

This study is a multicenter randomized, double-blind, placebo-controlled trial designed to evaluate efficacy and safety of NTZ 600 mg administered orally twice daily for 6 weeks

compared to a placebo for pre- and post-exposure prophylaxis of COVID-19 and other VRIs in healthcare workers and others at high risk of contracting SARS-CoV-2 infection.

2. STUDY OBJECTIVES

The primary objectives of this study are to evaluate the effect of NTZ administered orally 600 mg twice daily for 6 weeks in preventing symptomatic laboratory-confirmed COVID-19 and other VRIs in healthcare workers and others at high risk of contracting SARS-CoV-2 infection compared to that of a placebo.

The secondary objectives of this study are to evaluate the effect of NTZ administered orally 600 mg twice daily for 6 weeks in (i) preventing mortality due to COVID-19 or complications thereof, and (ii) reducing the proportion of subjects (with or without symptoms) testing positive for antibodies to SARS-CoV-2 at either of the Week 6 or Week 8 visits.

Exploratory objectives include (i) hospitalization due to VRI or complications thereof, (ii) mortality due to VRI or complications thereof, (iii) proportions of subjects experiencing acute respiratory illness (ARI), (iv) hospitalization due to ARI or complications thereof, and (v) mortality due to ARI or complications thereof.

Other important objectives include evaluation of the safety of NTZ by analysis of adverse events and evaluation of relationships between pharmacokinetics and clinical or virologic responses.

3. STUDY DESIGN

The study will be a multicenter, stratified, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of NTZ for pre- and post-exposure prophylaxis of COVID-19 and other VRIs.

Subjects will be stratified according to their most likely location of exposure, which is a proxy for exposure to SARS-CoV-2 and other VRIs. The strata are:

- Emergency Department
- Intensive Care Unit
- COVID-specific Care Unit
- Walk-in Clinic
- Paramedics and other first responders (e.g., firefighter/EMT)
- Social Activities (3-5 per week)
- Social Activities (>5 per week)

Within strata, subjects will be randomized 1:1 to one of the following groups:

- Group 1 (NTZ): Two NTZ 300 mg tablets b.i.d. for 6 weeks
- Group 2 (Placebo): Two placebo tablets b.i.d. for 6 weeks

This study is expected to run from April 2020 through April 2021.

Rationale for important issues in the study design is described below:

- *Rationale for study design.* *In vitro* data suggest NTZ may be effective against the most common viruses associated with VRIs including SARS-CoV-2. Except for influenza, there are no drugs or vaccines commercially available to prevent VRIs, especially pandemic and outbreak strains of non-influenza viruses like SARS-CoV-2. In the case of influenza these drugs are limited to only the neuraminidase inhibitors for chemoprophylaxis and the vaccine has been demonstrated to be less effective in elderly patients. This study is designed to determine if a drug with broad-spectrum antiviral activity like NTZ can prevent VRIs.
- *Choice of NTZ dose and duration of treatment.* The dose of NTZ was selected based upon safety, tolerability and pharmacokinetics data from prior clinical experience with nitazoxanide. Extended release tablets at a dose of 600 mg administered twice daily with food will be used to achieve and maintain steady state plasma concentrations of tizoxanide above the concentrations required to inhibit respiratory viruses in cell cultures. The tablets will be administered with a B complex vitamin to mask potential chromatemia that may be observed due to the yellow color of nitazoxanide metabolites. A treatment duration of 6 weeks is expected to be sufficient to capture transmission of COVID-19 yet short enough to avoid unnecessary exposure to the medication. Studies of oseltamivir for prophylaxis of influenza have employed a 6-week treatment duration. That treatment duration is supported by safety data from prior studies of NTZ and past experience noting prolonged activity of non-influenza viruses that extended for several months (Monto et al. 1987, Falsey et al. 2008, TAMIFLU® Prescribing Information 2019, NTZ 300 mg Tablets Investigators Brochure).
- *Choice of control groups.* A placebo control is appropriate for the study due to lack of any approved active control.
- *Choice of patient population.* The population to be studied includes healthcare workers and others at high risk of contracting SARS-CoV-2 and other respiratory virus infections. There are no approved antivirals or vaccines for the prevention of non-influenza respiratory viruses, subjects will not be prevented from being prescribed rescue medication for complications if warranted. Therefore, participation in the study will not pose unreasonable risk to any eligible subject. To avoid the potential for sharing medications among subjects in the same household, subjects will be excluded if they reside in a household with a family member currently enrolled as a participant in the study.
- *Choice of Vitamin B Complex Supplement.* All subjects will receive a vitamin B complex supplement ([REDACTED]) one tablet twice a day with study medication. This dose follows the manufacturer's labeled dosing. The purpose of the supplement is to help mask any chromatemia attributed to NTZ and aid in maintaining study blinding. The supplement will supply each subject with the following Percent Daily Values based on a 2,000 calorie diet: vitamin B1 1,333%, vitamin B2 824%, vitamin B3 240%, vitamin B5 360%, vitamin B6 1000%, vitamin B7 100%, vitamin B12 15,000%, folate 100%, and vitamin C 267%. Considering this supplement will provide well beyond the needed

daily allowance of these water-soluble vitamins, excess amounts are expected to be excreted in the urine and provide discoloration.

- *Choice of Patient-Reported Outcome Instrument.* This clinical trial will use the InFLUenza Patient-Reported Outcome Questionnaire (FLU-PRO[®]).

FLU-PRO[®] was developed with the support of the U.S. Department of Health and Human Services through the National Cancer Institute and the National Institutes of Allergy and Infectious Diseases, National Institutes of Health, in response to the need for improved metrics to evaluate treatment effect in clinical trials of drugs for the treatment of influenza and other respiratory tract viral diseases. It was developed and validated in accordance with FDA's guidance, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims." It has also been validated for use on an electronic device as part of an electronic diary ("eDiary") that can time stamp diary entries to ensure timely recording, thereby mitigating risks of recall bias. We will use an electronic diary for this clinical trial. FLU-PRO[®] was separately validated for use in a population with non-influenza like illness and also has recently been used in vaccine studies with older adults for the prevention of RSV (Powers et al. 2018, Yu et al. 2020).

- *Choice of ARI Definition.* The primary endpoint of this trial requires a determination that an ARI has occurred. We have defined ARI as "≥0.5 increase from baseline in mean symptom score for the chest/respiratory FLU-PRO domain or ≥0.5 increase from baseline in mean symptom score for at least two of the following FLU-PRO[®] domains: body/systemic, nose, throat." In arriving at this definition, we reviewed published mean FLU-PRO[®] symptom score data over the course of RSV illness (Yu et al. 2020) as well as data from recently completed clinical trials in approximately 3,000 subjects with colds and influenza (Romark, data on file). The ARI definition requires an increase in symptom scores from baseline, although the magnitude of the required increase (≥0.5) in mean domain scores is low, and we are requiring that the increase in mean score be achieved for only one or two of the four domains.

4. SUBJECT SELECTION

The criteria for inclusion and exclusion are defined below:

4.1. Inclusion Criteria

1. Males and females at least 18 years of age or of legal consenting age based on local requirements.
2. Persons at increased risk of contracting COVID-19, including:
 - a. Healthcare workers with known direct occupational exposure to COVID-19 within 7 days prior to enrollment. A qualifying person (i) provides healthcare to patients and/or (ii) typically positions themselves within 6 feet of patients ("close contact") and (iii) is a full-time employee (average of ≥ 24 hrs/week) in a high contact area (Emergency Department, Intensive Care Unit, COVID-specific Care Unit, Walk-in Clinic, Paramedic/First Responder).

- b. Persons participating in social activities without the practice of generally accepted social distancing practices at least three times per week. Qualifying activities include the presence of at least 10 people in close (<6 feet) proximity to each other without masks or other personal protective equipment (e.g., socializing at bars or community/social centers, in-home social gatherings, classes or trainings, etc.). These subjects must have engaged in such activities at least three times in the past 7 days and plan to continue these activities during the study.
3. Must have a smartphone, tablet, computer, or other qualifying internet-enabled device and daily internet access.
4. Occupational exposure to a person infected with SAR-CoV-2 within 7 days prior to enrollment or social interaction as defined in criterion 2(b).
5. Willing and able to provide written informed consent and comply with the requirements of the protocol, including completion of the subject diary.

4.2. Exclusion Criteria

1. Subjects not at increased risk of contracting SARS-CoV-2 from occupational or social behaviors.
2. Subjects with known severe heart, lung, neurological or other systemic disease that the Investigator believes could preclude safe participation.
3. Subjects with a history of COVID-19 or known to have developed anti-SARS-CoV-2 antibodies or received a SARS-CoV-2 vaccine.
4. Subjects who experienced a previous episode of acute upper respiratory tract infection, otitis, bronchitis or sinusitis or received antibiotics for these conditions or antiviral therapy for influenza within two weeks prior to and including study day 1.
5. Subjects residing in the same household with another family member currently participating in the study.
6. Receipt of any dose of NTZ within 7 days prior to screening.
7. Treatment with any investigational drug or vaccine therapy within 30 days prior to screening and willing to avoid them during the course of the study.
8. Known sensitivity to NTZ or any of the excipients comprising the study medication.
9. Subjects unable to swallow oral tablets or capsules.
10. Females of childbearing potential who are either pregnant or sexually active without the use of birth control. Female subjects of child-bearing potential that are sexually active must have a negative baseline pregnancy test and must agree to continue an acceptable method of birth control for the duration of the study and for 1 month post-treatment. A double barrier method, oral birth control pills administered for at least 2 monthly cycles prior to study drug administration, an IUD, or medroxyprogesterone acetate administered intramuscularly for a minimum of one month prior to study drug administration are acceptable methods of birth control for inclusion into the study. Female subjects are considered of childbearing potential unless they are postmenopausal (absence of

menstrual bleeding for 1 year - or 6 months if laboratory confirmation of hormonal status), or have had a hysterectomy, bilateral tubular ligation or bilateral oophorectomy.

11. Females who are breastfeeding.
12. Subjects with active respiratory allergies or subjects expected to require anti-allergy medications during the study period for respiratory allergies.
13. Subjects taking medications considered to be major CYP2C8 substrates, refer to [Table 7](#).
14. Subjects who, in the judgment of the Investigator, will be unlikely to comply with the requirements of this protocol including completion of the subject diary.

5. STUDY PROCEDURES

5.1. Screening Evaluation (Day -30 to Day 1)

Before screening, subjects will be informed of the nature of study, and written consent must be obtained prior to participation. After giving informed consent, the subject will be assigned a subject number, and the following procedures will be carried out:

1. Survey of COVID-19 exposure.
2. Complete medical history.
3. Physical examination including body weight and vital signs (blood pressure, pulse, respiratory rate and body temperature).
4. Collection of demographic information and smoking history.
5. Urine pregnancy test for all females of childbearing potential (must be performed Day 1).
6. Evaluation according to eligibility (inclusion and exclusion) criteria.

The information collected during the screening period must be current through the time of randomization.

5.2. Baseline (Day 1, may be same day as screening evaluation)

At baseline, the following procedures will be carried out:

1. Collection of a nasopharyngeal swab sample using a single nylon flocced dry swab inserted into both nostrils for RT-PCR.
2. Collection of blood sample for laboratory safety tests and anti-SARs-CoV-2 antibodies.
3. Collection of a urine sample for routine urinalysis (appearance, glucose, protein and blood).
4. Review and recording of any concomitant medications.
5. Provision of an electronic symptom diary to subject and subject completion of baseline electronic diary under supervision and instruction of study site personnel.

6. Randomization and dispensing of study medication (medication assigned in sequential order).
7. Administration of the first dose of study medication with food (< 1 hour after food intake) and a B complex vitamin ([REDACTED]) under observation of Investigator or a member of Investigator's staff, and entry in the medication administration record.
8. Instruct subject regarding:
 - a. *Administration of study medication.* Subjects will be instructed to take the study medication (two tablets) twice daily with the morning and evening meals, approximately every 12 hours (< 1 hour after food intake, preferably a high-fat meal but at a minimum a cereal bar) and a B complex vitamin ([REDACTED]).
 - b. *Completion of subject diary.* Subjects will be instructed on completion of the electronic diary.
 - c. *Use of birth control.* Female subjects of childbearing potential, if sexually active, will be instructed to continue an acceptable method of birth control for the duration of the study and for 1 month post-treatment. Acceptable methods of birth control include a double barrier method, oral birth control pills, an IUD, or medroxyprogesterone acetate administered intramuscularly.
 - d. *Follow-up visits:* Subjects will be instructed on the study schedule and follow up visits at Week 3, Week 6 and Week 8.
 - e. *Seeking emergency care or contacting the study physician or nurse:* Subjects must be informed to seek emergency medical care or contact the study physician or nurse if they develop any of the following symptoms listed below during the full 8-week study and follow-up period.

CONTACT STUDY PHYSICIAN, IF:

- Trouble breathing including shortness of breath
 - Severe headache, stiff neck, confusion or excessive somnolence
 - If fever ($\geq 99^{\circ}\text{F}$ or $\geq 37.2^{\circ}\text{C}$) returns after being absent for 24 hours
 - Increased difficulty breathing
 - Wheezing develops
 - New pain develops or pain localizes to one area, such as an ear, the throat, the chest, or the sinuses
 - Symptoms become more severe or frequent
 - Symptoms recur or any difficulty breathing following 5-10 days resolution of illness
 - An allergic-like reaction occurs or is suspected
 - Abnormal behavior
- f. *Local public health guidelines:* Subjects will be advised to follow local public health guidelines for SARS-CoV-2 infection control.

5.3. Daily Day 1 through Week 6

Subjects will keep a daily diary to chart study medication and answer the question, “do you feel like you have symptoms of a cold or flu?” If the subject responds “yes”, they will be prompted to complete a full symptom diary questionnaire (FLU-PRO[®]) and contact the Investigator. A study physician, nurse or other designated site personnel will review each subject’s electronic diary entries daily to ensure compliance with collection of diary data. If a subject has not completed his/her diary or if errors are suspected, the study personnel will contact the subject to implement appropriate corrective actions.

If the subject reports (i) at least one of the Lower Respiratory Symptoms presented in [Table 5](#) below or (ii) at least one symptom from each of the Upper Respiratory Symptoms and Systemic Symptoms categories presented in [Table 5](#) below, the subject will then contact the study physician to complete a “Suspected ARI Visit” with the procedures provided below. All subjects meeting this criteria will complete a “Suspected ARI Visit” as soon as possible, but in any event within 5 days of the first diary at which these criteria are met for each episode of suspected ARI regardless of patient or physician assessment of illness nature or severity.

Table 5: Clinical Illness Required for Diagnosis of ARI¹ (adapted from [Yu et al. 2020](#))

Upper Respiratory Symptoms	Lower Respiratory Symptoms	Systemic Symptoms
<ul style="list-style-type: none"> • Nasal congestion/rhinorrhea (runny or dripping nose, congested or stuffy nose, head congestion, sinus pressure)² • Sore throat (sore or painful throat)² 	<ul style="list-style-type: none"> • Cough (coughing, chest congestion, chest tightness, dry or hacking cough, wet or loose cough)² • Dyspnea (shortness of breath)² • Sputum (coughing up sputum or phlegm)² • Wheezing 	<ul style="list-style-type: none"> • Myalgias or arthralgias (body aches or pains)² • Fatigue (weak or tired, sleeping more than usual)² • Headache • Decreased appetite (lack of appetite, did not feel like eating)² • Feverishness (felt hot, chills or shivering, felt cold, sweating)²

¹ Suspected ARI requires self-reporting of any Lower Respiratory Symptom, or at least one Upper Respiratory Symptom together with one Systemic Symptom.

² Lay language used in the FLU-PRO[®] questionnaire is presented in parentheses.

5.4. Suspected ARI Visit

Subjects requiring Suspected ARI Visit will be evaluated as follows:

1. Physical examination as warranted by the Investigator for any change from baseline.
2. Body weight and collection of vital signs to include blood pressure, pulse, respiratory rate and body temperature.

3. Collect a nasopharyngeal swab sample using a single nylon flocculated dry swab inserted into both nostrils for RT-PCR at the Suspected ARI Visit, 24 to 36 hours later, and then again 4 to 5 days later.
4. Collect a fecal specimen for RT-PCR at the Suspected ARI Visit, 24 to 36 hours later, and then again 4 to 5 days later.
5. The subject will complete a FLU-PRO[®] symptom diary daily until he/she responds “yes” to the FLU-PRO[®] question, “Have you returned to your usual health?” for 3 consecutive days or until the Week 8 Visit, whichever occurs first. The daily FLU-PRO[®] diary will be completed between 7:00 pm and 11:00 pm.
6. Review and recording of concomitant medications.
7. Review and recording of adverse events/side effects.
8. Laboratory investigations for safety may be performed as warranted based upon the Investigator’s judgment.
9. If a subject tests positive for a respiratory virus by RT-PCR, that subject may receive standard of care as clinically warranted by the Investigator.

Regardless of symptoms or laboratory data, the subject will continue treatment until the 6-week treatment period has ended.

5.5. Week 3 (±7 days) and Week 6 Evaluations (±2 days)

Subjects will attend in-clinic visits at Week 3 and Week 6, and the following procedures will be performed:

1. Physical examination as warranted by the Investigator for any change from baseline.
2. Body weight and collection of vital signs to include blood pressure, pulse, respiratory rate and body temperature.
3. Collection of blood sample for laboratory safety tests, pharmacokinetics (pre-dose, at least six hours after the most recent previous dose) and anti-SARs-CoV-2 antibodies (antibody testing at Week 6 visit only).
4. Collection of urine sample for routine urinalysis.
5. Review of compliance with study medication, collection of medication bottle with any unused medications (Week 6 visit only), and completion of the pill count log form.
6. Review and recording of concomitant medications.
7. Review and recording of adverse events/side effects and complications. Note that all adverse events and complications must be followed until their resolution or stabilization even beyond the 8-week study period.
8. Review of number and type of social activities.
9. Advise subjects to follow local public health guidelines for SARS-CoV-2 infection control.

5.6. Week 8 Evaluation (+7 days)

Subjects will attend in-clinic visits at Week 8 and the following procedures will be performed:

1. Physical examination as warranted by the Investigator for any change from baseline.
2. Collection of blood sample for anti-SARs-CoV-2 antibodies.
3. Review and recording of concomitant medications.
4. Review and recording of adverse events/side effects and complications. Note that all adverse events and complications must be followed until their resolution or stabilization even beyond the 8-week study period.
5. Document any infections diagnosed during the follow-up period.

5.7. Unscheduled Visit

Subjects requiring an unscheduled visit due to worsening symptoms or adverse events will be evaluated at the discretion of the Investigator as is medically warranted. Tests and/ or procedures performed at this visit may include, but are not limited to, the following:

1. Physical examination as warranted by the Investigator for any change from baseline.
2. Body weight and collection of vital signs to include blood pressure, pulse, respiratory rate and body temperature.
3. Collection of a nasopharyngeal swab sample using a single nylon flocced dry swab inserted into both nostrils for RT-PCR.
4. Collection of blood sample for laboratory safety tests.
5. Collection of urine sample for routine urinalysis.
6. Review of compliance with study medication.
7. Review and recording of concomitant medications.
8. Review and recording of adverse events/side effects.

5.8. Study Discontinuation

Rules for discontinuation of a subject or for discontinuing the study are provided in Section 11.2. All subjects discontinued from the study before Week 6 will be evaluated at study discontinuation using the procedures described above for the Week 6 evaluation. Those discontinued after Week 6 will be evaluated as warranted by the Investigator.

5.9. Plan for Laboratory Safety Tests

A central laboratory will be used for laboratory safety testing. Blood tests will include hemoglobin, hematocrit, complete blood count (total and differential), platelet count, random blood sugar, total cholesterol, HDL, LDL, triglycerides, albumin, AST, ALT, GGT, alkaline phosphatase, bilirubin (total/direct), BUN, creatinine, sodium, potassium, chloride. Routine urinalysis will include appearance, glucose, protein, and blood.

5.10. Plan for Virology Testing and Monitoring Resistance

Blood samples collected at Baseline, Week 6 and Week 8 will be tested for anti-SARS-CoV-2 antibodies at a central laboratory using a validated assay (when such become available).

Virology testing of nasopharyngeal swab samples will be conducted as described below.

1. Collection of samples:

Two nasopharyngeal swabs will be collected from each subject at Baseline (Day 1), at each Suspected ARI Visit, 24 to 36 hours after each Suspected ARI Visit, 4 to 5 days after each Suspected ARI Visit, and as warranted by the Investigator.

A fecal specimen will be collected from each subject at each Suspected ARI Visit, 24 to 36 hours after each Suspected ARI Visit, and 4 to 5 days after each Suspected ARI Visit.

2. Testing of biological samples:

Each nasopharyngeal swab sample will be subjected to RT-PCR using the [REDACTED] [REDACTED] to detect influenza A (non-specific as to subtype); influenza A H1, H1N1 (2009), H3 subtypes; influenza B; RSV A and B; parainfluenza 1, 2, 3 and 4; hMPV; adenovirus; human EV/RV; coronavirus NL63, HKU1, 229E and OC43; *Chlamydomphila pneumoniae*; and *Mycoplasma pneumoniae*. The [REDACTED] [REDACTED] will be used to test for SARS-CoV-2.

Each fecal sample will be subjected to RT-PCR using the [REDACTED] [REDACTED] [REDACTED] will be used to test for SARS-CoV-2.

3. Drug susceptibility testing:

If any Suspected ARI Visit nasopharyngeal swab sample is positive for a VRI, the virus will be isolated (if possible) and tested for susceptibility to tizoxanide.

4. Storage of samples: All samples collected during the study will be stored for at least 2 years for potential future testing.

5. Clinical virology laboratory for diagnostic testing:

[REDACTED]
[REDACTED]
[REDACTED]

6. Clinical virology laboratory for drug susceptibility testing:

[REDACTED]
[REDACTED]
[REDACTED]

6. RANDOMIZATION

Subjects will be randomized 1:1 to receive either NTZ or placebo. An independent third party will prepare master randomization lists for each of the strata and maintain the masking of the study. Subjects who qualify for the study will be assigned to treatment using

centralized randomization procedures. The treatment numbers will appear on the bottles containing the masked study medication. The randomization list will be masked to study participants including Sponsor, Investigators, study monitors, statisticians, subjects and laboratory personnel. Unmasking procedures will be detailed in the Medical Monitoring Plan and Investigators will be provided instructions for unmasking.

7. DATA MANAGEMENT

7.1. Electronic Data Entry

Data will be transcribed from source documents into an electronic data capture (EDC) system.

The responsible study monitor(s) will verify data according to the Clinical Monitoring Plan, either remotely or at the clinical study site. The Investigator will ensure that the data recorded are accurate and complete.

Queries emerging during data cleaning will be generated within the EDC system by data management or clinical research associates. The Investigator or his/her designee will answer the queries and update the source data, if needed.

Adverse events and comorbid conditions will be coded by data management using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded by data management using the World Health Organization (WHO) Drug Dictionary.

After the last subject's last visit has taken place, the database will be cleaned as necessary. As soon as the database is considered clean, it will be locked. The locked database will be used in the final statistical analysis for study reporting. Measures will be undertaken to protect subject data handled during inspections against disclosure to unauthorized third parties. Subject confidentiality will be maintained at all times.

7.2. Protocol Deviations

Protocol deviations will be documented by the Investigator, reported to the institutional review board (IRB) as appropriate, and also reviewed by the assigned clinical research associate. Deviations will be reported in the clinical trial management system or applicable EDC. Each deviation will be classified as major or minor according to the following definitions:

Major protocol deviation: A deviation that has an impact on subject safety, may substantially alter risks to subjects, may have an effect on the integrity of the study data, or may affect the subject's willingness to participate in the study

Minor protocol deviation: All other protocol deviations.

7.3. Data Quality Assurance

The accuracy and reliability of the study data will be assured by the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the

Investigator and associated personnel prior to the study, and by periodic monitoring visits by the Sponsor or Sponsor's representatives. Written instructions will be provided for collection, preparation, and shipment of samples.

The monitor will review the source data for accuracy and completeness, and any discrepancies will be resolved with the Investigator or designee, as appropriate.

The Sponsor will be entitled to inspect and audit the facilities used in the clinical and laboratory parts of the study, as well as to make anonymized copies of all the data files pertaining to the study. Similar procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

8. STATISTICAL CONSIDERATIONS

8.1. Sample Size Calculations

For purposes of calculating our sample size, we assume that the proportion of subjects experiencing COVID-19 over a 6-week period is 1% and that the proportion of subjects experiencing any VRI is 2%. Current illness rates in the trial are approximately 1.2% for COVID-19 and 2.8% for VRIs. We further assume that effective prophylaxis will result in 80% reduction of the illness rate. Influenza prophylaxis studies of oseltamivir have resulted in approximately 80% reduction of influenza illness (see Tamiflu[®] prescribing information).

Using these assumptions, a Cox proportional hazards regression model (fitting the strata and treatment arm as a set of indicator variables) can be used to generate the number of events (COVID-19 cases) needed for 90% power to detect a hazard ratio of 0.8 versus a hazard ratio of 1. This number is 17 events. Earlier iterations of this protocol were sized on the assumption of a 3% overall rate for COVID-19 cases. Because the infection rate is much lower than anticipated, the Sponsor has decided to power the trial based on event counts. The intent is to keep the Cochran-Mantel-Haenszel (CMH) analysis previously planned. The expected sample size was generated from the event count required and the current illness rate approximating 1%. The power of the CMH analysis was then evaluated.

The expected sample size is 2842 subjects assigned equally to strata and to treatment arm within strata. This (fixed) sample size has 80.6% power for a CMH test of equal illness rates in the two treatment arms. When determining the fixed sample size necessary for 90% power for the CMH test under the current rates and effect size, a sample size of approximately 4000 is required. Under current assumptions this results in 23 expected events in the study – very near the number of events originally hypothesized based upon 800 total subjects and a blended illness rate of 3% for the two treatment arms.

A study-wide event count of 24 COVID-19 cases was chosen. This proposed event count results in power for the VRI endpoint (at the expected sample size) of 98.2%.

8.2. Efficacy Variables

Primary Efficacy Parameters:	<ul style="list-style-type: none"> i. The proportion of subjects with symptomatic laboratory-confirmed COVID-19 identified after start of treatment and before the end of the 6-week treatment period ii. The proportion of subjects with symptomatic laboratory-confirmed VRI identified after start of treatment and before the end of the 6-week treatment period
Secondary Efficacy Parameters:	<ul style="list-style-type: none"> i. Mortality due to COVID-19 or complications thereof ii. The proportion of subjects (with or without symptoms) testing positive for antibodies to SARS-CoV-2 at either of the Week 6 or Week 8 visits
Exploratory Efficacy Parameters:	Hospitalization due to VRI or complications thereof, mortality due to VRI or complications thereof, proportions of subjects experiencing acute respiratory illness (ARI), hospitalization due to ARI or complications thereof, mortality due to ARI or complications thereof.

8.3. Response Definitions

ARI:	≥ 0.5 increase from baseline in mean symptom score for the chest/respiratory FLU-PRO domain or ≥ 0.5 increase from baseline in mean symptom score for at least two of the following FLU-PRO [®] domains: body/systemic, nose, throat.
COVID-19:	ARI after start of treatment and before the end of the 6-week treatment period associated with detection of SARS-CoV-2 by RT-PCR assay of nasopharyngeal swab.
VRI:	ARI after start of treatment and before the end of the 6-week treatment period associated with detection of any respiratory virus by RT-PCR assay of nasopharyngeal swab.

8.4. Statistical Methodology

The statistical methodology is described briefly below and will be described in detail in the Statistical Analysis Plan.

8.4.1. Efficacy Analyses

Efficacy analyses will be based on a population consisting of all subjects randomized without a laboratory-detected viral respiratory infection at the baseline visit (intention-

to-treat or ITT population). All chi-square analyses will be calculated with appropriate continuity corrections.

There will be two primary efficacy analyses:

- The proportion of subjects experiencing COVID-19 in the NTZ treatment group will be compared to that of the placebo treatment group using a two-sided Cochran-Mantel-Haenszel (CMH) chi-square test ($\alpha = 0.049$).
- The proportion of subjects experiencing VRI in the NTZ treatment group will be compared to that of the placebo treatment group using a two-sided CMH chi-square test ($\alpha = 0.001$).

Secondary analyses will be performed as follows:

- The proportion of subjects experiencing COVID-19 or VRI for treatment vs control will be tested within strata using Pearson chi-square tests at an unadjusted $\alpha = 0.05$.
- Confidence intervals (95% confidence level) will be produced for the overall odds ratio and for the odds ratios for NTZ vs placebo for each stratum.
- Proportions of subjects experiencing mortality due to COVID-19 or complications thereof will be compared by treatment group using a two-sided Pearson chi-square test (unadjusted $\alpha = 0.05$).
- Proportions of subjects (with or without symptoms) testing positive for antibodies to SARS-CoV-2 at either of the Week 6 or Week 8 visits will be compared by treatment group using a two-sided Pearson chi-square test (unadjusted $\alpha = 0.05$).

Exploratory analyses will be performed as follows:

- Proportions of subjects experiencing each of the following will be compared by treatment group using a two-sided Pearson chi-square test (unadjusted $\alpha = 0.05$): (i) hospitalization due to VRI or complications thereof, (ii) mortality due to VRI or complications thereof, (iii) proportions of subjects experiencing acute respiratory illness (ARI), (vi) hospitalization due to ARI or complications thereof, (v) mortality due to ARI or complications thereof.

8.4.2. Population Pharmacokinetics Analysis

On Week 3 and 6, the plasma samples will be collected before the morning dose (at the trough). These data will allow for analysis of relationships between trough plasma concentrations and clinical and virologic response.

Trough plasma concentrations of tizoxanide and tizoxanide glucuronide will be summarized descriptively for each of the treatment groups. Exploratory analyses will be conducted to evaluate the relationships between plasma concentrations and age, race, gender, body weight, body mass index, VRI and adverse events.

8.4.3. Safety Analyses

All randomized subjects who receive the study medication will be evaluated for drug safety. Safety analyses will be done descriptively.

9. INVESTIGATIONAL PRODUCTS

9.1. Drug Regimens, Administration and Duration

Group 1 (NTZ): Subjects will receive two NTZ 300 mg tablets b.i.d. with food (< 1 hour after food intake) and a B complex vitamin ([REDACTED]) b.i.d. for 6 weeks.

Group 2 (Placebo): Subjects will receive two placebo tablets b.i.d. with food (< 1 hour after food intake) and a B complex vitamin ([REDACTED]) b.i.d. for 6 weeks.

The food prior to drug intake should preferably be a high-fat meal, but at minimum a cereal bar.

All subjects will receive a vitamin B complex supplement one tablet twice a day (manufacturer's labeled dosing) to help mask any potential chromaturia attributed to NTZ and aid in maintaining study blinding.

9.2. Identity of Investigational Products

The active formulation for this study is a yellow, film-coated tablet that contains 300 mg NTZ plus standard excipients. The placebo tablet will have the same appearance and inactive ingredients as the active tablet.

The vitamin B complex supplement is [REDACTED] manufactured by [REDACTED]. The supplement will supply each subject with the following Percent Daily Values based on a 2,000-calorie diet: vitamin B1 1,333%, vitamin B2 824%, vitamin B3 240%, vitamin B5 360%, vitamin B6 1000%, vitamin B7 100%, vitamin B12 15,000%, folate 100%, and vitamin C 267%.

9.3. Packaging and Labeling

NTZ or placebo tablets will be packaged in white 30 cc HDPE bottles, each containing 20 tablets. Each subject will receive a boxed kit containing 180 tablets (9 bottles). The subjects will take two tablets with food at each dosing time point. The kits will be stored at room temperature and will bear labels with the following information:

Table 6: Study Medication Labels

External Box Label

		Principal Investigator:
9 Bottles (20 Tablets Each)		
180 Tablets Total	Study N° RM08-3007	Treatment N°: XXXX
Lot:		
<p>Take 2 Tablets by Mouth <u>with Food</u> Twice Daily Caution: New Drug-Limited by Federal Law to Investigational Use STORE AT ROOM TEMPERATURE • DO NOT USE BEYOND END OF STUDY KEEP OUT OF REACH OF CHILDREN Study Sponsor: The Romark Institute for Medical Research</p>		

Individual Bottle Label

20 Tablets	Study N° RM08-3007	Treatment N°: XXXX
Lot:		
<p>Take 2 Tablets by Mouth <u>with Food</u> Twice Daily Caution: New Drug-Limited by Federal Law to Investigational Use STORE AT ROOM TEMPERATURE • DO NOT USE BEYOND END OF STUDY KEEP OUT OF REACH OF CHILDREN Study Sponsor: The Romark Institute for Medical Research</p>		

9.4. Drug Accountability

Medication will be dispensed at baseline. Medication compliance will be reviewed with each subject at each scheduled and unscheduled visit, subjects will be asked to return the bottles in which the medication was dispensed along with any unused medication.

The Investigator or designee is required to maintain adequate records of the disposition of all study drug, including dates, quantity and use by subject. Unused supplies must be returned to the Sponsor.

9.5. Subject Compliance

Subject compliance with the protocol will be checked by the Investigator and recorded in the EDC system at each visit.

Subjects will be considered non-compliant if they have missed more than 20% of the doses of the study medication (major protocol violation). Non-compliance will not be cause for discontinuation of subject participation in the study.

9.6. Disallowed Medication

During the active treatment course of the study, concomitant use of medications considered major CYP2C8 substrates are prohibited, see below.

Table 7: Major CYP2C8 Substrates

Generic Name	Brand Name(s)	Therapeutic Use and/or Drug Class
Amodiaquine	BASOQUIN, CAMOQUIN, FLAVOQUIN	Antimalarial
Daprodustat (GSK1278863)	*	Antianemic, prolyl hydroxylase inhibitor
Dasabuvir (ABT-333)	EXVIERA	Antiviral, NS5B inhibitor
Enzalutamide	XTANDI	Anticancer, antiandrogen
Montelukast	SINGULAIR	Antiasthmatic, LTRA
Pioglitazone	ACTOS	Antidiabetic, PPAR- γ agonist
Repaglinide	NOVONORM, PRANDIN	Antidiabetic, meglitinide analog
Source: Backman et al. 2016 .		
*Currently listed as investigational only and not yet granted a trade name by the manufacturer.		

Subjects are also prohibited from taking hydroxychloroquine, chloroquine, NTZ (except as the blinded investigational medication) or any other investigational medication or vaccine during the study. Since tizoxanide is highly protein-bound and may compete with plasma protein binding sites, co-administration of NTZ and warfarin should be avoided if reasonably possible. If co-administration of NTZ and warfarin cannot be avoided, the investigator must monitor prothrombin time and international normalized ratio (PT/INR) in subjects taking warfarin as clinically warranted.

Medications for pre-existing conditions that are not excluded (see exclusion criteria) should be continued as prescribed. The use of such medication will be recorded in the EDC system.

10. ADVERSE EVENTS

The term “adverse event” is defined for purposes of this study as any unwanted physical, psychological or behavioral change experienced by a subject during the course of the study and after taking the first dose of study medication regardless of its severity or relation to the study. Adverse events may include symptoms, signs, unexpected worsening of pre-existing conditions, clinically significant changes in laboratory values, diseases and syndromes, and significant and unexpected failures of pharmacological action of other medications. Symptoms of VRIs (cough, sore throat, nasal obstruction, fatigue, headache, myalgia, feverishness) and complications of VRIs will not be reported as adverse events.

Adverse events will be recorded on the appropriate EDC forms throughout the study, and the severity of each adverse event will be graded on a four-point scale: mild, moderate, severe, or life-threatening (See [Appendix II](#)). The duration of the adverse event and relationship to the study drug will also be recorded. All adverse events must be followed until their resolution or stabilization even beyond the planned study period.

10.1. Definitions

The following definitions will apply to the reporting of adverse events:

1. Serious Adverse Event: Any adverse experience occurring at any dose that is fatal or life threatening; requires in-patient hospitalization or prolongation of an existing hospitalization; is a persistent significant disability/incapacity; is a congenital anomaly or birth defect; or is an important medical event that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
2. Unexpected Adverse Event: Any adverse experience that is not identified in nature, severity, or frequency in the Investigator's Brochure for NTZ.
3. Severity of adverse events will be assessed by the Investigator using the Toxicity Grading Scale Tables provided in [Appendix II](#) (derived and adapted from "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", US Dept. of HHS, FDA, CDER, September 2007 and the National Institutes of Health, National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0).
4. Causality (relationship to treatment) will be assessed as follows:
 - *Definitely Related*: The adverse event is clearly related to the investigational agent(s) or research intervention: the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known pattern of response, and no alternative cause is present.
 - *Probably Related*: The adverse event is likely related to the investigational agent(s) or intervention: the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known or suspected pattern of response, but an alternative cause may be present.
 - *Possibly Related*: There is a reasonable possibility that the event may have been caused by or is linked in a significant way to the research; the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a suspected pattern of response, but an alternative cause is present.
 - *Unrelated (or Not Related)*: The adverse event is clearly NOT related to the investigational agent(s) or intervention: the adverse event has no temporal relationship to the administration of the investigational agent(s) or research intervention, follows no known or suspected pattern of response, and an alternative cause is present.

Under double-blind treatment conditions, it should be assumed that all subjects are taking the test drug.

10.2. Clinical Adverse Events

At the time of each return visit, the subject will be questioned regarding the occurrence and nature of any adverse events. All events must be recorded in the subjects' medical records and in the EDC system. Any subject affected will be examined by the Investigator as deemed necessary to ascertain the course of the event and any residual effects.

All moderate and severe adverse events will be reviewed by the Principal Investigator who will determine using his/her best clinical judgment whether they warrant the subject to be discontinued from the study. The Sponsor will be notified immediately if a subject is discontinued from the study. For all adverse events that require the subject to be discontinued from the study, relevant clinical assessments and laboratory tests will be repeated as clinically indicated until final resolution or stabilization of the event(s).

All subjects will be instructed to contact the Investigator, Investigator's assistants, or clinical personnel should the subject have any serious adverse experiences. Serious adverse events, including death regardless of the cause, must be reported to the Sponsor immediately (within 24 hours of the initial report).

A serious event requiring immediate notification by telephone is an event that:

- results in death
- is life threatening
- requires inpatient hospitalization or prolongation of an existing hospitalization
- is a persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

An overdose is defined as any intentional or unintentional consumption of the drug by any route that exceeds the highest dose stated in the Investigator's Brochure or in an investigational protocol, whichever dose is larger. Overdoses without an associated adverse event should be recorded, but not reported as an adverse event.

10.3. Reporting Requirement

The Principal Investigator is required to notify The Romark Institute for Medical Research (Sponsor) immediately of any unexpected, fatal, or life-threatening experience and all unusual, alarming, or serious reactions to medication regardless of any opinions as to the cause/effect relationship. All serious adverse events will also be reported to the IRB. Adverse events should be reported to:

The Romark Institute for Medical Research
Medical Affairs

██
██
██
██

10.4. Medication Modification/Withdrawal Due to an Adverse Event

If a severe adverse reaction develops during therapy, the study medication should be discontinued, and the subject should be withdrawn from the study.

10.5. Medication Errors

A medication error is defined as any preventable event related to dosing instructions, product labeling, or packaging that causes or leads to inappropriate medication use or subject harm while the medication is in the control of the investigative site or subject. Medication errors which result in adverse events should be recorded and reported as adverse events. All other medication errors should be reported to the study Sponsor through the Medical Affairs department within 7 days of identification by the site.

11. DISCONTINUATION

11.1. Study Discontinuation

The study may be discontinued under the following circumstances:

1. The Sponsor reserves the right to discontinue the study at any time.
2. Adverse event listings will be produced for safety monitoring at least once every two weeks during recruitment. The data will be tested to determine if there are greater than 20% of the subjects who have had \geq Grade 3 adverse events considered by the Investigator to be possibly, probably or definitely related to the study drug (defined by the Toxicity Grading Scale Tables provided in [Appendix II](#)).

If greater than 20% of the subjects have at least one Grade 3 or Grade 4 adverse event considered to be possibly, probably or definitely related to the study drug by the study Medical Monitor, then the study must be stopped and the Institutional Review Boards, and FDA's Division of Anti-Infectives will be notified. All safety and activity data will be submitted to the FDA in a timely manner.

11.2. Subject Discontinuation

Treatment will be discontinued for individual subjects for the following reasons:

1. An allergic reaction occurs or is suspected.
2. Medical conditions that may require study discontinuation in the Investigator's judgment.
3. Subject desire to discontinue participation.

In the case of an allergic reaction or other medical condition requiring subject discontinuation, appropriate treatment will be instituted by the Investigator.

12. ELECTRONIC DATA COLLECTION (EDC) SYSTEM

An EDC system will be used for this study. Prior to study initiation, site staff and authorized Romark personnel will be trained to use this system.

All source forms are to be filled out completely by the examining site staff and reviewed and signed off on by the Investigator(s).

13. RETENTION OF RECORDS

Essential Documents are documents that individually and collectively permit evaluation of the conduct of a trial and quality of the data produced. They demonstrate the compliance of the Investigator, Sponsor, and monitor with the GCP standards and with all applicable regulatory requirements.

In compliance with the ICH/GCP guidelines, the Investigator/institution will maintain all CRFs and all EDC source forms and source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). A list of these documents is found in [Appendix III: List of Essential Document for the Investigative Site](#). The Investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents listed in [Appendix III](#) must be retained for the duration required by applicable regulatory authorities or until the Sponsor informs the Investigator/institution these documents are no longer needed.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator must permit access to such reports.

The Sponsor is responsible for organizing and maintaining the Trial Master File which is a clear documentation of the course of the study.

14. MONITORING THE STUDY

Monitoring will be conducted by the Sponsor and/or a contract research organization according to standard operating procedures. Site visits will be conducted on-site or remotely by the Sponsor or their representatives at regular intervals to conduct inspections.

A full description of the monitoring procedures for this study will be detailed in the Clinical Monitoring Plan.

The Investigator will grant representatives of the Sponsor's clinical operations team and quality team, as well as regulatory agencies and ethical committees access to inspect facilities and records (including subject charts) relevant to this study and agrees to assist the monitors in their activities, if requested.

An Independent Data Monitoring Committee (IDMC) will be organized to monitor safety and futility for this study. A full description of the IDMC procedures for this study will be detailed in the Medical Monitoring (Safety) Plan and IDMC Charter.

15. INFORMED CONSENT

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The informed consent form (ICF) must be signed before performance of any study-related activity. The informed consent form will be approved by both the Sponsor and by the reviewing IRB. They will be in accordance with principles that

originated in the [Declaration of Helsinki](#), current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the Investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care he/she will receive. Finally, they will be told that the Investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized Sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, and agrees to allow his or her study physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained, if permitted by local law.

Assent from any minor (≤ 18 years of age or as local regulations apply) enrolled into the study will be obtained along with documented consent from their parent/legal guardian to allow the minor to participate in the study. The assent and consent forms must be signed prior to the performance of any study related activity.

Signed ICFs must remain in the subject's file(s) and be available for verification by representatives of Romark, the IRB, and FDA/relevant regulatory agencies at any time.

16. ETHICS

The clinical trial will be performed in accordance with the guidelines set by the World Medical Assembly ([Declaration of Helsinki](#), last amendment in Fortaleza, Brazil, October 2013). Prior written approval of the study protocol and of the informed consent form will be obtained from the appropriate local Medical Ethics Review Board.

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and during the study subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able

to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

16.2. Investigator Responsibilities

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that originated in the [Declaration of Helsinki](#), and that the clinical study data are credible.

16.3. Institutional Review Board (IRB)

Before the start of the study, the Investigator (or Sponsor where required) will provide the IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IRB)
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IRB requests to fulfill its obligation

This study will be undertaken only after the IRB has given full approval of the final protocol, amendments (if any), the ICF, applicable recruiting materials, and subject compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IRB and the documents being approved.

During the study, the Investigator (or Sponsor where required) will send the following documents and updates to the IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable

- Investigator's Brochure addenda or new edition(s)
- Summaries of the status of the study at intervals stipulated in guidelines of the IRB (at least annually)
- Reports of AEs that are serious, unlisted, and associated with the investigational drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the Investigator's care
- Notification if a new Investigator is responsible for the study at the site
- Annual IND Update Report, Short Term Study Specific Safety Summary and Line Listings, where applicable
- Any other requirements of the IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable informed consent form and assent form revisions must be submitted promptly to the IRB for review and approval before implementation of the change(s), except when necessary to eliminate immediate hazard to the study subjects. If a deviation from, or a change to the protocol was implemented to eliminate an immediate hazard to study subjects, then the implemented deviation or change, the reasons for it, and, if appropriate, the protocol amendment should be submitted to the IRB as soon as possible.

The re-approval of the clinical study by the IRB should be documented in writing.

At the end of the study, the Investigator (or Sponsor where required) will notify the IRB about the study completion.

16.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the Investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

17. DATA CONFIDENTIALITY, DISCLOSURE OF DATA, AND PUBLICATION

Data generated for the study should be stored by the Investigator in a limited-access file area and be accessible only to representatives of the study site, Romark, the IRB, and FDA/relevant regulatory agencies. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare.

No information that can be related to a specific individual subject may be released or used in any fashion without the signed written consent of that subject. All reports and communications relating to study subjects will identify subjects only by initials and subject identification number. The Investigator will keep complete subject identification for purposes of long-term follow-up, if needed. This information will be treated with strict adherence to professional standards of confidentiality.

Site personnel will enter data relating to each subject's participation in the study into the EDC system provided by the Sponsor. In the EDC system, identification numbers and initials will be used to identify subjects. Subject names will not be used in the CRFs. Management of data from the EDC system and the production of the clinical study report will be the responsibility of the Sponsor. Access to the database will be restricted to employees who have been trained to use the system. Access to the EDC system and study report will be limited to the IRB, FDA or other regulatory agencies and the Sponsor.

Presentation and/or publication of the results of the study is encouraged provided that The Romark Institute for Medical Research is notified in advance of the author's intent and is given the opportunity to review the manuscript or abstract 45 days prior to its submission for presentation at a scientific meeting or for publication in a scientific journal. The Investigators will have complete autonomy regarding the content and wording of any abstracts, presentations, and scientific publications arising from this study, including the decision of whether or not to publish.

18. DATA AND REPORT REQUIREMENTS

Data required by The Romark Institute for Medical Research prior to approval and initiation of the study are as follows:

1. Curriculum vitae of the Principal Investigator and all Co-Investigators.
2. Copy of the IRB-approved Informed Consent and subject information forms.
3. Copy of the IRB approval for the conduct of the study.

Data and materials required by The Romark Institute for Medical Research before the study can be considered complete and terminated are as follows:

1. Pre- and post-treatment history, physical examination and subject evaluations.
2. Pre- as well as interim and post-treatment laboratory findings and all special test results.
3. EDC forms properly completed and signed by the Principal Investigator.
4. Drug Inventory Logs indicating drug dispensed and return of the unused supplies to the Sponsor or destruction by study site.

5. Signed Informed Consent/Assent from each subject.

19. CONTACT INFORMATION

Table 8: Contact Information

Medical Monitors		
Name:	[REDACTED]	
Title:	Medical Monitor	
Tel.:	[REDACTED]	
Fax:	[REDACTED]	
E-mail:	[REDACTED]	
Sponsor Medical Affairs		
Name:	[REDACTED]	
Title:	VP, Medical Affairs (Romark)	
Tel.:	[REDACTED]	
Mobile:	[REDACTED]	
Fax:	[REDACTED]	
E-mail:	[REDACTED]	
Sponsor Project Management		
Name:	[REDACTED]	
Title:	Clinical Operations Lead	
Tel.:	[REDACTED]	
Mobile:	[REDACTED]	
Fax:	[REDACTED]	
E-mail:	[REDACTED]	
Central Laboratory ([REDACTED])		
Name:	[REDACTED]	
Title:	Project Manager	
Tel.:	[REDACTED]	
Fax:	[REDACTED]	
E-mail:	[REDACTED]	
Investigational Product Supplier		
Name:	[REDACTED]	
Title:	VP, Medical Affairs (Romark)	
Tel.:	[REDACTED]	
Mobile:	[REDACTED]	
Fax:	[REDACTED]	
E-mail:	[REDACTED]	

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21. APPENDICES

Appendix I: Study Schedule

Appendix II: Toxicity Grading for Adverse Events

Appendix III: List of Essential Documents for the Investigative Site

Appendix IV: Protocol Revision History

Appendix V: Declaration of Helsinki

21.1. Appendix I: Study Schedule**Table 9: Schedule of Assessments**

	Screening (Day -30 to Day 1)	Baseline (Day 1)	Day 1- Week 6	Weeks 3, 6	Week 8	Suspected ARI Visit	Unscheduled Visit
Signed informed consent/assent	X						
Complete medical history	X						
Physical examination	X			X ¹	X ¹	X ¹	X
Body weight/vital signs ²	X			X		X	X
Demographics/smoking history	X						
Urine pregnancy test (Day 1)	X						
Record body temperature	X			X		X	X
Evaluate according to inclusion/exclusion criteria	X						
Review number and type of social activities ⁹	X			X			
Collect nasopharyngeal swabs		X				X ³	X
Collect fecal specimen						X ³	
Blood sample for pharmacokinetics ⁴				X			
Blood sample for laboratory safety tests ⁵		X		X			X
Blood sample for anti-SARS-CoV-2 Ab		X		X ⁶	X		
Urine sample for routine urinalysis ⁵		X		X			X
Record concomitant medications		X	X	X	X	X	X
Complete symptom diary		X	X ⁷				
Randomization/dispense study medication		X					
First dose, then study medication twice daily for 6 weeks		X	X				
Instructions re: dosing, swab collection concomitant medications, subject diary, follow-up visits, seeking emergency care and local public health guidelines		X		X			X
Review/record adverse events		X		X	X	X	X
Review electronic subject diary entries						X ⁸	X ⁸
Review compliance with study medication, collect container with unused medication, complete pill count log form				X			
Document any infections diagnosed during follow-up period					X		

¹ Physical examination as warranted by the Investigator for any change from Baseline.

² Body weight and collection of vital signs to include blood pressure, pulse, respiratory rate and body temperature.

³ Nasopharyngeal swabs and a fecal specimen are to be collected at a Suspected ARI Visit and then again 24 to 36 hours and 4 to 5 days later.

⁴ Blood sample to be collected pre-dose.

⁵ Laboratory safety tests include hemoglobin, hematocrit, complete blood count (total and differential), platelet count, random blood sugar, total cholesterol, HDL, LDL, triglycerides, albumin, AST, ALT, GGT, alkaline phosphatase, bilirubin (total/direct), BUN, creatinine, sodium, potassium, chloride and routine urinalysis (appearance, glucose, proteins and blood).

⁶ Blood samples for anti-SARS-CoV-2 antibodies are to be collected at Baseline, Week 6 and Week 8 only.

⁷ If the subject meets the criteria for a Suspected ARI, then he/she will be asked to complete a symptom diary, and then continue daily with the symptom diary between 7 pm and 11 pm each day until the subject returns to usual health for 3 consecutive days or until the Week 8 Visit, whichever comes first.

⁸ Site staff will contact subjects as needed during study to ensure timely completion of electronic diary.

⁹ Subjects who qualify for the study based upon social risk only.

21.2. Appendix II: Toxicity Grading for Adverse Events

[Derived and adapted from “Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”, US Dept. of HHS, FDA, CDER, September 2007]

Table 10: Table for Clinical Abnormalities: Vital Signs

Vital Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)** (°F)**	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia – beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Table 11: Table for Clinical Abnormalities: Systemic (General)

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2-3 loose stools or <400 gms/24 hours	4-5 stools or 400-800 gms/24 hours	6 or more watery stools or >800 gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Table 12: Table for Clinical Abnormalities: Systemic Illness

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters.

Table 13: Table for Laboratory Abnormalities: Serum

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Chloride – mEq/L**	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemi a mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Liver Function Tests – GGT** increase by factor	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol**	ULN – 300 mg/dL	>300 – 400 mg/dL	>400 – 500 mg/dL	>500 mg/dL

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Triglycerides – mg/dL**	150 mg/dL – 300 mg/dL	>300 mg/dL – 500 mg/dL	>500 mg/dL - 1000 mg/dL	>1000 mg/dL
HDL – mg/dL**	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
LDL – mg/dL**	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** Derived from the National Institutes of Health, National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. ADL- Activities of Daily Living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. selfcare ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note: “ULN” is the upper limit of the normal range.

Table 14: Table for Laboratory Abnormalities: Hematology

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) – gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) – gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hematocrit - %**	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
WBC Increase - cell/mm ³	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm ³	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm ³	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm ³	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm ³	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm ³	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** Derived from the National Institutes of Health, National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. ADL- Activities of Daily Living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. selfcare ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note: “ULN” is the upper limit of the normal range.

Table 15: Table for Laboratory Abnormalities: Urine

Urine*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 – 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

21.3. Appendix III: List of Essential Documents for the Investigative Site**Table 16: List of Essential Documents for the Investigative Site**

Study No: RM08-3007	
Title of Document	
1.	Investigator's Brochure and Updates
2.	Signed protocol (all versions) and amendments, if any, and sample EDC forms
3.	Information given to trial subject: <ul style="list-style-type: none"> • Informed consent form (all versions), any other written information, advertisement for subject recruitment (if used)
4.	Financial agreement between the Investigator/institution and the Sponsor for the trial
5.	Signed agreement between involved parties <ul style="list-style-type: none"> • Financial Disclosure of Investigator/institution and Sponsor • Confidential Disclosure Agreement of Investigator/institution and Sponsor
6.	Dated, documented approval/favorable opinion of IRB of the following: <ul style="list-style-type: none"> • Protocol and any amendments • EDC system (if applicable) • Informed consent form and any revisions • Any other written information to be provided to the subjects • Advertisement for subject recruitment (if used) • Subject compensation (if any) • Any other documents given approval • Continuing review of the trial
7.	Institutional Review Board composition
8.	Regulatory notice of Principal Investigator and sub-Investigators, FDA Form 1572
9.	Curriculum vitae and/or other relevant documents evidencing qualifications of Investigator and sub-Investigators
10.	Normal values/ranges and updates for medical/laboratory/technical procedures and/or tests included in the protocol
11.	Medical/laboratory technical procedures/tests and updates: <ul style="list-style-type: none"> • certification or • accreditation or • established quality control and/or external quality assessment or • other validation (where required)
12.	Shipping records for investigational product(s) and trial-related materials
13.	Site initiation monitoring report
14.	Relevant communications other than site visits: <ul style="list-style-type: none"> • Letters/ emails • Meeting notes • Notes of telephone calls
15.	Signed informed consent forms
16.	Source documents
17.	Signed, dated, and completed EDC forms to include documentation of EDC form corrections
18.	Notification by originating Investigator to Sponsor of serious adverse events and related reports
19.	Notification by Investigator, where applicable, to IRB of unexpected serious adverse drug reactions and of other safety information
20.	Notification by Sponsor to Investigator of safety information

Study No: RM08-3007	
Title of Document	
21.	Interim or annual reports to IRB
22.	Subject Screening log
23.	Subject identification code list
24.	Subject enrollment log
25.	Investigational product accountability records (receipt, storage, dispensing, shipment)
26.	Signature sheet
27.	Record of retained body fluids/tissue samples (if any)
28.	Final report by Investigator/institution to IRB

21.4. Appendix IV: Protocol Revision History

Table 17: Protocol Revision History

Summary of Changes	
<i>Amendment 1</i>	
Purpose:	Incorporating FDA’s recommended updates to the protocol and correction of typos.
Effective Date:	17MAY2020
Change 1	Section 3 and Section 8.3, revised to read, “ARI: ≥ 0.5 increase from baseline in mean symptom score for the chest/respiratory FLU-PRO domain or ≥ 0.5 increase from baseline in mean symptom score for at least two of the following FLU-PRO [©] domains: body/systemic, nose, throat.”
Change 2	Section 3, added the italicized language, “...mean score be achieved for only <i>one or two</i> ...”
Change 3	Section 5.4, changed “...or until the Week 6 Visit...” to “...or until the Week 8 Visit...”
Change 4	Section 8.1, added the following text, “We further assume that effective prophylaxis will result in 80% reduction of the illness rate. Influenza prophylaxis studies of oseltamivir have resulted in approximately 80% reduction of influenza illness (see Tamiflu [®] prescribing information).”
Change 5	Section 8.1, added in two locations, “Adjusting the stratum size to assume unequal allocation while holding the effect size and total sample size constant results in negligible changes (i.e., changes in the third significant figure) in the study power.”
Change 6	Section 9.6, added, “Since tizoxanide is highly protein-bound and may compete with plasma protein binding sites, co-administration of NTZ and warfarin should be avoided if reasonably possible. If co-administration of NTZ and warfarin cannot be avoided, the investigator must monitor prothrombin time and international normalized ratio (PT/INR) in subjects taking warfarin as clinically warranted.”
Action:	A revised protocol version 2.0 dated May 17, 2020 was generated.
<i>Amendment 2</i>	
Purpose:	To expand the study population to include persons at high risk of SARS-CoV-2 infection due to social behaviors and to clarify duration of diary completion if symptoms persist at the end of treatment visit.
Effective Date:	27AUG2020

Summary of Changes	
Change 1	<p>Pages 1 & 7</p> <p>Updated title of the study from “<i>A Randomized, Double-Blind, Placebo Controlled Trial to Evaluate the Efficacy and Safety of Nitazoxanide (NTZ) for Post-exposure Prophylaxis of COVID-19 and Other Viral Respiratory Illnesses (VRI) in Healthcare Workers</i>” to “<i>A Randomized, Double-Blind, Placebo Controlled Trial to Evaluate the Efficacy and Safety of Nitazoxanide (NTZ) for Pre- and Post-exposure Prophylaxis of COVID-19 and Other Viral Respiratory Illnesses (VRI) in Healthcare Workers and Others at Increased Risk of SARS-CoV-2 Infection</i>”</p>
Change 2	<p>Page 7, <i>Synopsis</i></p> <ul style="list-style-type: none"> • Updated indication from “<i>Post-exposure prophylaxis</i>” to “<i>Pre- and post-exposure prophylaxis</i>” • Updated population from “<i>Healthcare workers at increased risk of occupational exposure to COVID-19</i>” to “<i>Healthcare workers and others at increased risk of contracting SARS-CoV-2</i>” • Updated trial duration from “<i>April 2020 – August 2020</i>” to “<i>April 2020 – December 2020</i>”
Change 3	<p>Page 16, <i>1.3 Rationale for the Study</i></p> <p>Updated “<i>post-exposure prophylaxis of COVID-19 and other VRIs in healthcare workers at high risk of occupational exposure to SARS-CoV-2</i>” to “<i>pre- and post-exposure prophylaxis of COVID-19 and other VRIs in healthcare workers and others at high risk of contracting SARS-CoV-2 infection</i>”</p>
Change 4	<p>Page 16, <i>2. Study Objectives</i></p> <p>Updated “<i>healthcare workers at high risk of occupational exposure</i>” to “<i>healthcare workers and others at high risk of contracting SARS-CoV-2 infection</i>”</p>
Change 5	<p>Page 16, <i>3. Study Design</i></p> <ul style="list-style-type: none"> • Updated “<i>post-exposure</i>” to “<i>pre- and post-exposure</i>” • Updated “<i>Subjects will be stratified according to their workspace</i>” to “<i>Subjects will be stratified according to their most likely location of exposure</i>” • Added “<i>Social Activities</i>” stratum • Updated expected end month from August to December
Change 6	<p>Page 17, <i>Choice of Patient Population</i></p> <ul style="list-style-type: none"> • Updated “<i>healthcare workers at high risk of occupational exposure to COVID-19</i>” to “<i>healthcare workers and others at high risk of contracting SARS-CoV-2 and other respiratory virus infections</i>”

Summary of Changes	
	<ul style="list-style-type: none"> Updated “<i>subjects will be excluded if they reside in a household with another subject enrolled as a participant in the study</i>” to “<i>subjects will be excluded if they reside in a household with a family member currently enrolled as a participant in the study</i>”
Change 7	<p>Pages 18 & 19, 4.1 Inclusion Criteria</p> <ul style="list-style-type: none"> Updated “<i>Males and females at least 18 years of age</i>” to “<i>Males and females at least 18 years of age or of legal consenting age based on local requirements</i>” Updated Inclusion Criteria 2 from: <ol style="list-style-type: none"> 2. <i>Healthcare workers at increased risk for direct occupational exposure to COVID-19.</i> <ol style="list-style-type: none"> a. <i>Subject meets the definition of “healthcare worker”</i> <ul style="list-style-type: none"> • <i>Provides healthcare to patients and/or</i> • <i>Typically positions themselves within 6 feet of patients (“close contact”) and</i> • <i>Is a full-time employee (average of ≥ 24 hrs/week) in a high contact area (Emergency Department, Intensive Care Unit, COVID-specific Care Unit, Walk-in Clinic, Paramedic/First Responder)</i> <p>To:</p> <ol style="list-style-type: none"> 6. <i>Persons at increased risk of contracting COVID-19, including:</i> <ol style="list-style-type: none"> a. <i>Healthcare workers with known direct occupational exposure to COVID-19 within 7 days prior to enrollment. A qualifying person (i) provides healthcare to patients and/or (ii) typically positions themselves within 6 feet of patients (“close contact”) and (iii) is a full-time employee (average of ≥ 24 hrs/week) in a high contact area (Emergency Department, Intensive Care Unit, COVID-specific Care Unit, Walk-in Clinic, Paramedic/First Responder).</i> b. <i>Persons participating in social activities without the practice of generally accepted social distancing practices at least three times per week. Qualifying activities include the presence of at least 10 people in close (<6 feet) proximity to each other without masks or other personal protective equipment (e.g., socializing at bars or community/social centers, in-home social gatherings, classes or trainings, etc.). These subjects must have engaged in such activities at least three times in the past 7 days and plan to continue these activities during the study.</i> <ul style="list-style-type: none"> Added “<i>or social interaction as defined in criterion 2(b)</i>” to Inclusion Criteria 4

Summary of Changes	
Change 8	<p>Page 19, 4.2 <i>Exclusion Criteria</i></p> <ul style="list-style-type: none"> Updated Exclusion Criteria 1 from “<i>Subjects not meeting the study definition of healthcare worker</i>” to “<i>Subjects not at increased risk of contracting SARS-CoV-2 from occupational or social behaviors.</i>” Updated Exclusion Criterion 5 from “<i>Subjects residing in the same household with another subject participating in the study</i>” to “<i>Subjects residing in the same household with another family member currently participating in the study</i>”
Change 9	<p>Pages 20, 22 & 24</p> <p>Updated “<i>Collection of two nasopharyngeal swabs (one from each nostril) using nylon flocked dry swabs for RT-PCR</i>” to “<i>Collection of a nasopharyngeal swab sample using a single nylon flocked dry swab inserted into both nostrils for RT-PCR</i>”</p>
Change 10	<p>Page 22, 5.3 <i>Daily Day 1 through Week 6</i></p> <p>Added “<i>All subjects meeting this criteria will complete a “Suspected ARI Visit” regardless of patient or physician assessment of illness nature or severity.</i>”</p>
Change 11	<p>Page 23, 5.5 <i>Week 3 (±7 days) and Week 6 Evaluations (±2 days) and 5.6 Week 8 Evaluation (+7 days)</i></p> <p>Updated “<i>A study physician, nurse or other study personnel will visit each subject</i>” to “<i>Subjects will attend in-clinic visits</i>”</p>
Change 12	<p>Page 25, 2. <i>Testing of Biological Samples</i></p> <p>Updated “<i>Panther Fusion</i>” to “<i>Aptima</i>” as the SARS-CoV-2 assay used for nasopharyngeal swabs and fecal samples.</p>
Change 13	<p>Page 25, 6. <i>Randomization</i></p> <ul style="list-style-type: none"> Updated number of strata from “<i>five</i>” to “<i>six</i>” Added “<i>Social risk</i>” to the list of strata
Change 14	<p>Page 36, 14. <i>Monitoring the Study</i></p> <p>Added “<i>on-site or remotely</i>” to clarify the location of site visits.</p>
Amendment 3	
Purpose:	<p>To require that subjects be advised to follow local public health guidelines for SARS-CoV-2 infection control.</p> <p>To stratify randomization by and collect information regarding on-study number and type of social activities.</p>
Effective Date:	28SEP2020

Summary of Changes	
Change 1:	Page 16, 3. <i>Study Design</i> Updated stratification options from “ <i>Social Activities</i> ” to “ <i>Social Activities (3-5 per week)</i> ” and “ <i>Social Activities (>5 per week)</i> ”
Change 2:	Page 21, 5.2 <i>Baseline (Day 1, may be same day as screening evaluation)</i> Added: “ <i>f. Local public health guidelines: Subjects will be advised to follow local public health guidelines for SARS-CoV-2 infection control</i> ”
Change 3:	Page 23, 5.5 <i>Week 3 (±7 days) and Week 6 Evaluations (±2 days)</i> Added: “ <i>8. Review of number and type of social activities.</i> <i>9. Advise subjects to follow local public health guidelines for SARS-CoV-2 infection control.</i> ”
Change 4:	Page 25, 6. <i>Randomization</i> Updated: “ <i>for each of the six strata (Emergency Department workers, Intensive Care Unit workers, COVID-specific Care Unit workers, walk-in clinic workers, paramedics and other first responders, Social risk)</i> ” to: “ <i>for each of the strata</i> ”
Change 5:	Page 46, Table 9. <i>Schedule of Assessments</i> Added: “ <i>Review number and type of social activities (Subjects who qualify for the study based upon social risk only)</i> ” Added: “ <i>Instruct subject regarding [...] local public health guidelines</i> ”
Amendment 4	
Purpose:	To update sample size requirements using an event-based approach based on observed COVID-19 illness rates. To update expected trial duration based on revised sample size requirements. To add SARS-CoV-2 vaccination as an exclusion criterion. To clarify the acceptable time window in which a suspected ARI visit should be completed. To clarify the meaning of “pre-dose” for the purpose of blood sample collection for pharmacokinetics.
Effective Date:	26OCT2020

Summary of Changes	
Change 1:	<p>Page 7, <i>Synopsis</i> Updated Number of Subjects from 800 to “≥ 800 up to 4,000 as required to obtain 24 COVID-19 illnesses”</p> <p>Page 27, <i>8.1 Sample Size Calculation</i> Updated description of the sample size calculation using an event-based approach to require 24 COVID-19 illnesses.</p>
Change 2:	<p>Page 8, <i>Synopsis</i> & Page 16, <i>Study Design</i> Updated expected trial duration from “<i>April 2020-December 2020</i>” to “<i>April 2020-April 2021</i>”</p>
Change 3:	<p>Page 19, <i>Exclusion Criteria</i> Added “<i>or received a SARS-CoV-2 vaccine</i>” to exclusion criterion #3</p>
Change 4:	<p>Page 22, <i>5.3 Daily Day 1 through Week 6</i> Updated: “<i>All subjects meeting this criteria will complete a “Suspected ARI Visit” regardless of patient or physician assessment of illness nature or severity.</i>” to: “<i>All subjects meeting this criteria will complete a “Suspected ARI Visit” as soon as possible, but in any event within 5 days of the first diary at which these criteria are met for each episode of suspected ARI regardless of patient or physician assessment of illness nature or severity.</i>”</p>
Change 5:	<p>Page 23, <i>5.5 Week 3 (± 7 days) and Week 6 Evaluations (± 2 days)</i> Added: “<i>at least six hours after the most recent previous dose</i>” to instructions for the pre-dose pharmacokinetics blood sample.</p>

21.5. Appendix V: Declaration of Helsinki

Special Communication

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
 29th WMA General Assembly, Tokyo, Japan, October 1975
 35th WMA General Assembly, Venice, Italy, October 1983
 41st WMA General Assembly, Hong Kong, September 1989
 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
 53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
 59th WMA General Assembly, Seoul, Republic of Korea, October 2008
 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the

best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent pro-

vided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

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