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 IN ELDERLY RESIDENTS OF LONG-TERM CARE FACILITIES (LTCF)

PROTOCOL NO. RM08-3006

Study Sponsor:

The Romark Institute for Medical Research
[redacted]

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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 Post-exposure Prophylaxis of COVID-19 and Other Viral Respiratory Illnesses (VRI) in Elderly Residents of Long-Term Care Facilities (LTCF)
Study Number:	RM08-3006
IND Number:	149,166
Indication:	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 post-exposure prophylaxis of COVID-19 and other VRIs in elderly LTCF residents.
Number of Subjects:	800
Population:	Males and females ≥ 55 years of age residing in LTCFs
Randomization:	1:1 within stratum (LTCF) at the subject level
Study Dose and Administration:	Group 1 (NTZ): Two NTZ 300 mg tablets orally twice daily (b.i.d.) for 6 weeks. Group 2 (Placebo): 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:	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 the start of treatment and before the end of the 6-week treatment period
Secondary Efficacy Parameters:	i. The proportion of subjects hospitalized due to COVID-19 or complications thereof. ii. Mortality due to COVID-19 or complications thereof.

	iii. 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 (VRIs) or complications thereof; mortality due to VRIs or complications thereof; proportion of subjects experiencing acute respiratory illness (ARI); proportion of subjects hospitalized due to ARI or complications thereof, and 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 will be collected by the Investigator at visits for COVID-19/VRI symptoms.
Study Centers:	Multicenter, USA
Trial Duration:	April 2020 – December 2020

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
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
LTCF	Long-Term Care Facilities
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 Illnesses in Long-Term Care Facilities

Respiratory tract infections result in approximately 4 million deaths globally each year. The elderly population is at disproportionate risk due to age-related characteristics such as frailty and immunosenescence. Moreover, this population experiences more severe illnesses, a larger number of hospitalizations and greater mortality rates. The elderly population is growing rapidly and will double by 2050. LTCFs are an important subset of the elderly population, in developed countries approximately 5% live in these facilities. LTCF residents are at elevated risk of acquiring respiratory tract infections due to elevated infection rates, which may be amplified in part due to close living conditions (Childs et al. 2019, McGeer et al. 2000).

An array of viral respiratory pathogens occur in this population, including coronaviruses, RSV, rhinoviruses and hMPV, with infections occurring in as many as 41% of LTCF residents surveyed (Falsey et al. 2008, Checovich et al. 2020). Rhinoviruses have been associated with as much as 59% of LTCF outbreaks and may result in severe disease (Longtin et al. 2010). 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). Outbreaks of seasonal strains of coronavirus have been reported, with the potential to cause severe respiratory illness (Hand et al. 2018). Furthermore, outbreaks of SARS-CoV-2 in LTCFs have been associated with widespread infection amongst residents and high mortality rates (McMichael et al. 2020, Kimball et al. 2020).

Influenza is the only respiratory virus for which a vaccine exists. Moreover, vaccine efficacy is variable, with diminished vaccine responses in the elderly (Goodwin et al. 2006). As much as 90% of those residing in LTCFs are vaccinated for influenza, yet at least half of these facilities report outbreaks every year (McGeer et al. 2000). The Centers for Disease Control and Prevention recommends chemoprophylaxis for all LTCF residents in facilities experiencing an influenza outbreak regardless of vaccination status (Centers for Disease Control and Prevention 2019). 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 this setting and emergence of novel viral respiratory pathogens a novel broad-spectrum chemoprophylaxis strategy is of paramount importance in this population.

1.1.1. Antivirals Studied for Chemoprophylaxis of Viral Respiratory Illnesses

The only drug approved for chemoprophylaxis in this population, for any respiratory virus, is oseltamivir which is only for influenza A and B infections. Oseltamivir was studied in a seasonal (community outbreak) in elderly patients residing in a nursing home. The majority of subjects were vaccinated (>80%), 43% of subjects had cardiac disorders and 14% had chronic airway obstructive disorders. In this study, subjects were given oseltamivir 75 mg once daily for 6 weeks or matching placebo. Oseltamivir treatment resulted in a 92% reduction in the incidence of laboratory-confirmed clinical influenza

compared to placebo (placebo 12/272 (4.4%), oseltamivir 1/276 (0.4%); p=0.002) (TAMIFLU® Prescribing Information 2019, Peters et al. 2001).

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

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% (EC_{50}s) 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} (µg/mL)	5.23 ± 2.71	8.16 ± 4.16	4.88 ±1.72	8.96 ±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} (µg.h/mL)	26.9 ± 16.1	52.5 ± 33.7	29.5 ± 12.1	75.0 ± 37.8
AUC_{0-T} (µg.h/mL)	28.6 ± 16.3[a]	48.3 ± 31.9[b]	30.5 ± 12.2[c]	75.2 ± 37.9
C_T (µg/mL)	0.709 ± 0.987	1.72 ± 2.04	1.39 ± 0.846	3.89 ± 2.88
$AUC_{0-\infty}$ (µg.h/mL)	27.8 ± 17.8[b]	52.3 ± 35.6[b]	35.3 ± 16.5[d]	62.1 ± 24.2[e]
$t_{1/2}$ (h)	1.66 ± 0.408[b]	2.19 ± 0.485[b]	2.70 ± 0.848[c]	4.99 ± 5.20
λ_z (1/h)	0.441 ± 0.106[b]	0.331 ± 0.0733[b]	0.282 ± 0.0902[c]	0.201 ± 0.0813
C_{avg} (µg/mL)	NA	4.02 ± 2.66[b]	NA	6.27 ± 3.16
C_{min} (µg/mL)	NA	1.50 ± 1.83	NA	3.63 ± 3.00
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%)						
Dose Group Nitazoxanide	Day						
	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 ≥65 years	Trough Data Subjects 18 to 64 years
Tizoxanide	0.86 µg/mL (n = 50)	0.81 µg/mL (n = 1305)
Tizoxanide glucuronide	3.08 µg/mL (n = 50)	2.34 µg/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 at-risk populations like those in living in LTCFs. VRIs in LTCFs are a critical health concern due to the burgeoning patient population, increased morbidity and mortality in elderly adults and the lack of available treatments for a broad array of viruses. Oseltamivir is available for treatment and chemoprophylaxis, yet it is limited to only influenza infections while data indicates multiple other non-influenza viruses are a significant cause of VRI in this population.

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 posing significant risk to elderly patients with underlying health conditions. There is an important need for an oral medication that could be administered as chemoprophylaxis of COVID-19 in patients in LTCFs.

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 post-exposure prophylaxis of COVID-19 and other VRIs in elderly LTCF residents.

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 elderly LTCF residents compared to that of a placebo.

Secondary objectives are to evaluate the effect on (i) hospitalization due to COVID-19 or complications thereof, (ii) mortality due to COVID-19 or complications thereof, and (iii) 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, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of NTZ for post-exposure prophylaxis of COVID-19 and other VRIs in elderly LTCF residents.

Subjects will be randomized within strata 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 December 2020.

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 in at risk elderly subjects residing in LTCFs.
- *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 (Super B-Complex™, Igennus Healthcare Nutrition, Cambridge, UK) to mask potential chromaturia 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 in the LTCF population 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, Peters et al. 2001, Falsey et al. 2008, 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 is at high risk for COVID-19 and other VRIs and related complications and are likely to derive the most benefit from chemoprophylaxis. COVID-19 has been associated with high rates of mortality in this population, and therefore, effective post-exposure prophylaxis is needed (McMichael et al. 2020). 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.
- *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 chromaturia 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." 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. Male and female residents of LTCFs at least 55 years of age.
2. Willing and able to provide written informed consent and comply with the requirements of the protocol.
3. At least one symptomatic laboratory-confirmed COVID-19 illness identified among residents or staff of the LTCF within 10 days prior to randomization.

4.2. Exclusion Criteria

1. Alzheimer's disease, dementia, or other mental incapacity which precludes comprehension of the study requirements or symptom diary.
2. Subjects expected to require hospitalization within the 8-week treatment and follow-up period.
3. Subjects with a history of COVID-19 or known to have developed anti-SARS-CoV-2 antibodies.
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. Receipt of any dose of NTZ within 7 days prior to screening.
6. Treatment with any investigational drug or vaccine within 30 days prior to screening or unwilling to avoid them during the course of the study.
7. Known sensitivity to NTZ or any of the excipients comprising the study medication.
8. Subjects unable to swallow oral tablets or capsules.
9. Subjects taking medications considered to be major CYP2C8 substrates, refer to Table 7 .
10. Subjects who, in the judgment of the Investigator, will be unlikely to comply with the requirements of this protocol.

5. STUDY PROCEDURES

All study visits are to occur in the subject's home facility.

5.1. Screening Evaluation (Day-90 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. Complete medical history.
2. Physical examination including body weight and vital signs (blood pressure, pulse, respiratory rate and body temperature).
3. Collection of demographic information and smoking history.
4. 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 two nasopharyngeal swabs (one from each nostril) using nylon flocked dry swabs 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. Complete baseline symptom diary entries.
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) and a B complex vitamin ([redacted]) 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).
   b. *Follow-up visits:* Subjects will be instructed on the study schedule and follow up visits at Week 1, Week 3, Week 6 and Week 8.
   c. *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 (≥99°F or ≥37.2°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

5.3. Daily Day 1 through Week 6

A caregiver will record the time of each study medication intake. Once daily, the caregiver will (i) inquire regarding the health of the subject, (ii) record any concomitant medications, and (iii) ask the subject once daily, "do you feel like you have symptoms of a cold or flu?" If the subject responds "yes", the caregiver will have the subject complete a FLU-PRO© diary to evaluate the subject's symptoms. 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 caregiver will then contact the study physician or nurse to complete a "Suspected ARI Visit" with the procedures provided below.

Table 5: Clinical Symptoms Required for Suspected ARI[1] (adapted from Yu et al. 2020)

Upper Respiratory Symptoms	Lower Respiratory Symptoms	Systemic Symptoms
• Nasal congestion/rhinorrhea (runny or dripping nose, congested or stuffy nose, head congestion, sinus pressure)[2] • Sore throat (sore or painful throat)[2]	• 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	• 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. Collection of two nasopharyngeal swabs using nylon flocked dry swabs for RT-PCR.
4. Collect two nasopharyngeal swabs 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 4:00 pm and 8:00 pm. A caregiver may assist the subject with completing the diary if needed.

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 1, Week 3, and Week 6 Evaluations (±2 days)

A study physician, nurse or other study personnel will visit each subject at Week 1, 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. Week 3 and Week 6 only, collection of blood sample for laboratory safety tests, pharmacokinetics (pre-dose) and anti-SARs-CoV-2 antibodies (antibody testing at Week 6 visit only).
4. Week 3 and Week 6 only, 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.

5.6. Week 8 Evaluation (+7 days)

A study physician, nurse or other study personnel will visit each subject 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 record concomitant medications.
4. Review and record 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 two nasopharyngeal swabs using nylon flocked dry swabs 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.

2. Testing of biological samples:

   Each nasopharyngeal swab sample will be subjected to RT-PCR using the ePlex® Respiratory Pathogen Panel (GenMark, Carlsbad, CA) 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; *Chlamydophila pneumoniae*; and *Mycoplasma pneumoniae*. The Aptima® SARS-CoV-2 Assay (Hologic, Inc, San Diego, CA) 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]

6. Clinical virology laboratory for drug susceptibility testing:

   [redacted]

6. RANDOMIZATION

Subjects will be randomized 1:1 by stratum to receive either NTZ or placebo. An independent third party will prepare a master randomization list 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 study-specific 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 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

Recent reports of COVID-19 in long-term care facilities in the United States have suggested a high rate of transmission of the SARS-CoV-2 virus, but infection control procedures may significantly decrease transmission (McMichael et al. 2020, Kimball et al. 2020). A recent study of 264 elderly volunteers (≥65 years of age) reported 1.6 respiratory tract infections (not laboratory-confirmed) per person-year indicating approximately a 20% probability of respiratory tract infection over a given 6-week period (Mannick et. al, 2018). Infection control procedures in place during the period covered by this clinical trial are also expected to reduce the transmission of other respiratory viruses.

For purposes of calculating our sample size, we assume that the proportion of subjects experiencing COVID-19 over a 6-week period is 5%, the proportion of subjects experiencing any VRI is 10%, and that effective prophylaxis will reduce the rate of COVID-19 and other VRIs by 80%. Influenza prophylaxis studies of oseltamivir have resulted in approximately 80% reduction of influenza illness among residents of long-term care facilities (see Tamiflu® prescribing information).

A Cochran-Mantel-Haenszel (CMH) chi-square test stratifying by 20 LTCFs will have 92.8% statistical power to detect the difference between 5% and 1% rates of occurrence of COVID-19 over all strata at an alpha of 0.049 with a total sample size of 800, allocated equally to strata (LTCFs) and treatment groups within strata. The statistical power remains >92% when the number of LTCFs is 5, 10, 16 or 20. The CMH chi-square test has 93.9% power to detect the difference between 10% and 2% rates of occurrence of VRIs over all strata at an alpha of 0.001 with 800 subjects allocated equally to 20 LTCFs. 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.

A sample size of 800 subjects (400 per treatment group) was selected.

8.2. Efficacy Variables

Primary Efficacy Parameters:

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:

i. The proportion of subjects hospitalized due to COVID-19 or complications thereof

ii. Mortality due to COVID-19 or complications thereof

iii. 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, and 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).

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 (α =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 (α =0.001).

Secondary analyses will be performed as follows:

- Proportions of subjects experiencing hospitalization due to COVID-19 or complications thereof will be compared by treatment group using a two-sided CMH Chi-square test (unadjusted α =0.05).
- Proportions of subjects experiencing mortality due to COVID-19 or complications thereof will be compared by treatment group using a two-sided CMH Chi-square test (unadjusted α =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 CMH Chi-square test (unadjusted α =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 CMH Chi-square test (unadjusted α =0.05): (i) hospitalization due to VRI or complications thereof; (ii) mortality due to VRI or complications thereof, (iii) acute respiratory illness (ARI), (vi) hospitalization due to ARI or complications thereof; and (v) mortality due to ARI or complications thereof.

Other analyses may be performed as outlined in the study Statistical Analysis Plan.

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° RM08-3006 Treatment N°: XXXX
Lot:

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
[redacted]

Individual Bottle Label

20 Tablets Lot:	Study N° RM08-3006	Treatment N°: XXXX

Take 2 Tablets by Mouth with Food 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
[redacted]

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, NSB5 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
[redacted]

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 ≥ 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 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 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. The IDMC will closely monitor the incidence of diarrhea as it could potentially be a vehicle for the spread of SARS-CoV-2. Enrollment will be paused while the IDMC conducts its first interim analysis of safety and futility. The IDMC may also conduct analyses of safety, futility and effectiveness if the number of COVID-19 illnesses is higher than anticipated.

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.

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 ([redacted])		
Name:	[redacted]	
Title:	Executive Director, Global Clinical Development	
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]PS	
Title:	VP, Medical Affairs (Romark)	
Tel.:	[redacted]	
Mobile:	[redacted]	
Fax:	[redacted]	
E-mail:	[redacted]	

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21. APPENDICES

21.1. Appendix I: Study Schedule

Table 9: Schedule of Assessments

	Screening (Day-90 to Day 1)	Baseline (Day 1)	Day 1-Week 6	Weeks 1, 3, 6	Week 8	Suspected ARI Visit	Unsched-uled Visit
Signed informed consent	X						
Complete medical history	X						
Physical examination	X			X[1]	X	X[1]	X
Body weight/vital signs[2]	X			X		X	X
Demographics/smoking history	X						
Record body temperature	X			X		X	X
Evaluate according to inclusion/exclusion criteria	X						
Collect nasopharyngeal swabs		X				X[3]	X
Blood sample for pharmacokinetics[4]				X			
Blood sample for laboratory safety tests[5]		X		X			X
Blood sample for antibody testing		X		X[7]	X		
Urine sample for routine urinalysis[5]		X		X			X
Record concomitant medications		X	X	X	X	X	X
Randomization/dispense study medication		X					
Complete symptom diary		X	X[6]			X	
First dose, then study medication twice daily for 6 weeks		X	X				
Instructions re: dosing, concomitant medications, follow-up visits and seeking emergency care		X		X			X
Review/record adverse events		X		X	X	X	X
Inquire regarding cold/flu symptoms and refer for Suspected ARI visit if yes			X				
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 are to be collected at a Suspected ARI Visit and repeat swabs collected 24 to 36 hours and 4 to 5 days later.
[4] Week 3 and 6 visit only, blood sample to be collected pre-dose.
[5] Week 3 and 6 visit only, aboratory 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] 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 4 pm and 8 pm each day until the subject returns to usual health for 3 consecutive days or until the Week 6 Visit, whichever comes first. A caregiver may assist the subject with the diary entry if needed.
[7] Week 6 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 – hypophosphatemia 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: RM08-3006	
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: • 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 • 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: • 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: • 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: • 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: RM08-3006	
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	
Amendment 1	
Purpose:	Incorporating FDA's recommended updates to the protocol and other minor changes.
Effective Date:	24APR2020
Change 1	Summary, Section 8.1: Increased number of subjects to be enrolled from 600 to 800.
Change 2	Summary, Sections 3, 6, 8.1: Changed randomization scheme from cluster randomization by facility to 1:1 randomization at the subject level and updated protocol language accordingly.
Change 3	Summary, 3, 5.2 (Items 7 & 8), 9.1: Added language to clarify all subjects will receive a B complex vitamin [redacted] one tablet twice daily with study medication to mask potential chromaturia that may be associated with NTZ.
Change 4	Summary, Sections 2, 8.2, 8.4.1: Added a Secondary Efficacy Parameter, "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."
Change 5	Summary, Sections 5.2, 5.5, 5.6, Table 9: Added the collection of anti-SARS-CoV-2 antibodies at Baseline, Week 6 and Week 8.
Change 6	Table 1: Added "CMH Cochran-Mantel-Haenszel" and "IDMC Independent Data Monitoring Committee". Removed "DSMB Data and Safety Monitoring Board".
Change 7	Section 3: • Replaced "Within 24 hours after symptomatic laboratory-confirmed COVID-19 is identified in an LTCF, that LTCF…" with "Subjects…" • Removed "All subjects enrolled at a given LTCF will receive the same treatment (NTZ or Placebo)." • Replaced "October" with "August". • Added the italicized language "The tablets will be administered with a B complex vitamin [redacted] to mask potential chromaturia that may be observed due to the yellow color of nitazoxanide metabolites. • Removed the bullet point and contents titled "Choice of LTCF as the Randomization Unit" • Added the bullet point titled "*Choice of Vitamin B Complex Supplement* ", and contents therein.

Summary of Changes	
Change 8	Section 4.1: Revised Inclusion Criteria #3 to "At least one symptomatic laboratory-confirmed COVID-19 illness identified among residents or staff of the LTCF within 10 days prior to randomization."
Change 9	Section 4.2: • Revised Exclusion Criteria #2 to "Subjects expected to require hospitalization within the 8-week treatment and follow-up period." • Added Exclusion Criteria #3, "Subjects with a history of COVID-19 or known to have developed anti-SARS-CoV-2 antibodies." Other Exclusion Criteria were moved down one number accordingly.
Change 10	Section 5.1: • Revised the Screening Evaluation window from Day -30 to Day -90. • Removed on item #4 , "…repeat at Baseline if screening is not performed the same day as Baseline." • Added, "The information collected during the screening period must be current through the time of randomization."
Change 11	Section 5.2: • Item #1, removed "(Copan Diagnostics)". • Item #2, added "…and anti-SARs-CoV-2 antibodies." • Item 8b, added "…and Week 8."
Change 12	Section 5.3: • Replaced, "If the subject reports at least one symptom from any 2 of the 3 symptom categories presented in Table 5 below, the caregiver will then contact the study physician or nurse,…" with "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 caregiver will then contact the study physician or nurse to complete a "Suspected ARI Visit" with the procedures provided below." • Removed, the rest of the paragraph and the next paragraph before Table 5. This information was added to section 5.4.
Change 13	Table 5: Revised footnote 1 to read, "Suspected ARI requires self-reporting of any Lower Respiratory Symptom, or at least one Upper Respiratory Symptom together with one Systemic Symptom."
Change 14	Added, "Section 5.4 Suspected ARI Visit" and contents therein.
Change 15	Section 5.5 (formerly 5.4): • Item #3, added "…and anti-SARs-CoV-2 antibodies (antibody testing at Week 6 visit only)." • Item #7, revised to "…8-week study period."
Change 16	Added, "Section 5.6 Week 8 Evaluation (+7 days)" and contents therein.

Summary of Changes	
Change 17	Section 5.7 (formerly 5.5): Item #3, removed "(Copan Diagnostics)".
Change 18	Section 5.8 (formerly 5.6): Added "Those discontinued after Week 6 will be evaluated as warranted by the Investigator."
Change 19	Section 5.10 (formerly 5.8): • Added "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)." • Item #2, removed "human bocavirus" and "Legionella pneumophilia". • Item #2, replaced "The ePlex SARS-CoV-2 Test (GenMark, Carlsbad, CA)..." with "The Panther Fusion® SARS-CoV-2 Assay (Hologic, Inc, San Diego, CA)…"
Change 20	Section 6: Revised to read "Subjects will be randomized 1:1 to receive either NTZ or placebo. An independent third party will prepare a master randomization list 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."
Change 21	Section 8.1: The contents are new to represent the revised randomization and enrollment scheme.
Change 22	Section 8.4.1: The contents are new to represent the revised randomization and enrollment scheme.
Change 23	Section 9.2: Added, "The vitamin B complex supplement is [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%."
Change 24	Section 11.1: Revised in two places, "…greater than 5% of the subjects…" with "…greater than 20% of the subjects…".
Change 25	Section 14: Last paragraph revised to read, "An Independent Data Monitoring Committee (IDMC) will be organized for this study. A full description of the DSMB procedures for this study will be detailed in the Medical Monitoring (Safety) Plan and IDMC Charter. The IDMC will closely monitor the incidence of diarrhea as it could potentially be a vehicle for the spread of SARS-CoV-2. Enrollment will be paused while the IDMC conducts its first interim analysis."
Change 26	Table 8: Added Central Laboratory contact information.
Change 27	Table 9: Revised to represent the addition of a Week 8 visit and antibody testing.
Action:	A revised protocol version 2.0 dated April 24, 2020 was generated.
Amendment 2	
Purpose:	Language to clarify procedures and correct typos

Summary of Changes	
Effective Date:	07MAY2020
Change 1	Section 5: Added, "All study visits are to occur in the subject's home facility."
Change 2	Section 14: Changed "DSMB" to "IDMC"
Change 3	Table 9: Changed "Day -30" to "Day -90"
Action:	A revised protocol version 2.1 dated May 7, 2020 was generated.
Amendment 3	
Purpose:	Incorporating FDA's recommended updates to the protocol and correction of typos.
Effective Date:	17MAY2020
Change 1	Synopsis, added the italicized language, "1:1 *within stratum (LTCF)* at the subject level"
Change 2	Section 3, added the italicized language, "Subjects will be randomized *within strata* 1:1 to one of the following groups:"
Change 3	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 4	Section 3, added the italicized language, "…mean score be achieved for only *one or* two…"
Change 5	Section 5.4, changed, "…or until the Week 6 Visit..." to "…or until the Week 8 Visit..."
Change 6	Section 6, added the italicized language, "Subjects will be randomized 1:1 *by stratum* to receive either NTZ or placebo."
Change 7	Section 8.1, added the following text, "Influenza prophylaxis studies of oseltamivir have resulted in approximately 80% reduction of influenza illness among residents of long-term care facilities (see Tamiflu® prescribing information)."
Change 8	Section 8.1, added, "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 9	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."
Change 10	Section 14, added, "…of safety and futility. The IDMC may also conduct analyses of safety, futility and effectiveness if the number of COVID-19 illnesses is higher than anticipated."
Action:	A revised protocol version 3.0 dated May 17, 2020 was generated.

Summary of Changes	
Amendment 4	
Purpose:	Revision of inclusion age and visit assessments.
Effective Date:	26AUG2020
Change 1	Synopsis and Section 4.1, changed age to ≥ 55 years.
Change 2	Synopsis, Section 5.5 and Section 8.4.2, removed Week 1 blood and urine sample collection.
Change 3	Revised trial dates to April 2020 – December 2020.
Change 4	Section 5.10, changed "Panther Fusion® SARS-CoV-2 Assay" to "Aptima® SARS-CoV-2 Assay".
Change 5	Table 9, revised footnotes to reflect changes to laboratory collection.
Action:	A revised protocol version 4.0 dated August 26, 2020 was generated.

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 provided 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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