PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE EFFICACY AND SAFETY OF NITAZOXANIDE IN THE TREATMENT OF MILD OR MODERATE COVID-19

PROTOCOL NO. RM08-3008

Study Sponsor:

The Romark Institute for Medical Research
[redacted]

Version: Final v4.0

January 11, 2021

STATEMENT OF COMPLIANCE

This study will be conducted in compliance with this protocol, current International Conference on Harmonization Good Clinical Practice (ICH GCP), United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR 50, 21 CFR Part 312), and applicable regulatory requirements.

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: _____

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1. PROTOCOL SUMMARY

1.1. Synopsis

Title of Study:	A Phase 3, Randomized, Double-Blind, Placebo Controlled Trial to Evaluate the Efficacy and Safety of Nitazoxanide in the Treatment of Mild or Moderate COVID-19
Name of Test Drug:	Nitazoxanide 300 mg Tablets
Name of Active Ingredient:	Nitazoxanide
Study Sponsor:	The Romark Institute for Medical Research
IND Number:	149,166
STUDY DETAILS	
Anticipated Study Period:	July 2020 – January 2021
Protocol & Amendments:	Original Protocol, version 1.0: July 14, 2020 Amendment 1, version 2.0: July 23, 2020 Amendment 2, version 3.0: September 16, 2020 Amendment 3, version 4.0: January 11, 2021
Investigators:	Multiple in the US.
OBJECTIVES	
Primary Objective:	To evaluate the effect of NTZ in reducing the time to Sustained Response compared to placebo in subjects with mild or moderate COVID-19
Secondary Objectives:	To evaluate the effect of NTZ in reducing the rate of progression to Severe COVID-19 Illness compared to placebo
Exploratory Objectives:	To evaluate: i. The proportion of subjects positive for SARS-CoV-2 by Aptima® SARS-CoV-2 Assay at each of Days 4 and 10 ii. The change from baseline in quantitative SARS-CoV-2 RNA measured by RT-PCR at each of Days 4 and 10 iii. The effect of NTZ in reducing the rate of hospitalization compared to placebo iv. The effect of NTZ in reducing the rate of mortality compared to placebo
Safety Objectives:	Safety will be assessed by analysis of adverse events.
METHODOLOGY	
Study Design:	Multicenter, randomized, double-blind trial

Treatments:	Subjects will be randomized 1:1 to one of the following groups: Group 1 (NTZ): Two NTZ 300 mg tablets b.i.d. for 5 days administered orally with food. Group 2 (Placebo): Two placebo tablets b.i.d. for 5 days administered orally with food.
Study Duration:	Subjects will receive 2 tablets b.i.d. for 5 days (10 doses). The follow up period will extend through the end of study visit at study Day 28.

SUBJECT POPULATION

Number of Subjects Planned: At least 350 up to 400 subjects with laboratory-confirmed SARS-CoV-2-infection. This may require enrollment of up to 800 total subjects.

Inclusion Criteria:

1. Male or female at least 12 years of age
2. [*Criterion removed in protocol amendment 2. See Appendix 1 for revision history.*]
3. Presence of clinical signs and/or symptoms consistent with worsening or stable mild or moderate COVID-19 (one of the following is required):
   a. Presence of at least two respiratory symptom domains (head, throat, nose, chest, cough) with a score of ≥2 as determined by Screening FLU-PRO OR
   b. Presence of at least one respiratory symptom domain (head, throat, nose, chest, cough) with a score of ≥2 as determined by Screening FLU-PRO with pulse rate ≥90 OR
   c. Presence of at least one respiratory symptom domain (head, throat, nose, chest, cough) with a score of ≥2 as determined by Screening FLU-PRO with respiratory rate ≥16

   AND patient reported assessment that symptoms are present, the symptoms are not consistent with the subject's usual health, the symptoms interfere with daily activities, and the symptoms have worsened or remained the same relative to the previous day, as confirmed by responses to questions in the Screening FLU-PRO.
4. Onset of symptoms no more than 72 hours before enrollment in the trial. Onset of symptoms is defined as the earlier of the first time at which the subject experienced subjective fever or any respiratory symptom (headache/head congestion, throat symptoms, nasal symptoms, chest symptoms, cough).
5. Willing and able to provide written informed consent (including assent by legal guardian if under 18 years of age) and comply with the requirements of the protocol, including completion of the subject diary and all protocol procedures.

Exclusion Criteria:

1. Persons with any clinical sign or symptoms suggestive of severe systemic illness with COVID-19, including the following:
   a. shortness of breath at rest,
   b. resting pulse ≥125 beats per minute,
   c. resting respiratory rate ≥30 breaths per minute, or
   d. $SpO_2 \leq 93\%$ on room air at sea level.

2. Subjects who experienced a previous episode of acute upper respiratory tract infection, otitis, bronchitis or sinusitis or received antibiotics for these conditions within two weeks prior to and including study day 1.
3. Severely immunodeficient persons including:
    a. Subjects with immunologic disorders or receiving immunosuppressive therapy (e.g., for organ or bone marrow transplants, immunomodulatory therapies for certain autoimmune diseases)
    b. Subjects with untreated HIV infection or treated HIV infection with a CD4 count below 350 cells/mm^3 in the last six months
    c. Subjects actively undergoing systemic chemotherapy or radiotherapy treatment for malignancy
    d. Subjects using steroids as maintenance therapy for a chronic condition
4. Subjects with active respiratory allergies or subjects expected to require anti-allergy medications during the study period for respiratory allergies.
5. Females of childbearing potential who are either pregnant or sexually active without the use of birth control.
6. Subjects with a history of COVID-19 or known to have developed anti-SARS-CoV-2 antibodies.
7. Subjects residing in the same household with another subject participating in the study.
8. Treatment with any investigational drug or vaccine therapy within 30 days prior to screening and willing to avoid them during the course of the study.
9. Receipt of any dose of NTZ within seven days prior to screening.
10. Known sensitivity to NTZ or any of the excipients comprising the study medication.
11. Subjects unable to swallow oral tablets or capsules.
12. Subjects with known severe heart, lung, neurological or other systemic disease that the Investigator believes could preclude safe participation.
13. Subjects likely or expected to require hospitalization unrelated to COVID-19 during the study period.
14. Subjects taking medications considered to be major CYP2C8 substrates. Refer to Table 5 in Section 6.5.
15. Subjects who, in the judgment of the Investigator, will be unlikely to comply with the requirements of this protocol including completion of the subject diary.

ASSESSMENTS

Efficacy:

- Subjects will complete a diary recording oral temperature twice daily and the FLU-PRO© patient reported outcomes instrument once daily in the evening for 21 days for efficacy evaluation.
- Subjects will be contacted daily by site staff on study days 2-7 to screen for progression to severe illness or other complications.

Virology: Nasopharyngeal swab samples will be collected on each of study Days 1, 4, and 10 for analysis of virology endpoints.
Safety: The safety of study drug administration will be monitored by assessment of adverse events from baseline through the Day 28 study exit, clinical laboratory testing at baseline and on Day 10, physical examinations and vital signs assessments at screening, Day 10 and Day 22 and telephone monitoring/at home visits during Day 2 through Day 7 and Day 28.
Pharmacokinetics: On the morning of Day 4 prior to dosing, trough plasma samples will be collected.

1.2. Schedule of Assessments

Table 1: Schedule of Assessments

	Screening	Baseline	Treatment Period	Diary Period	Follow-Up Visits				Unscheduled
Assessment	**Day 1**	**Day 1**	**Day 2-7**	**Day 1-21**	**Day 4±1**	**Day 10±3**	**Day 22+3**	**Day 28+3**	**As Needed**
Signed informed consent/assent[1]	X								
Demographics, smoking & medical history[2]	X								
Urine pregnancy test[7]	X								
Physical examination[3]	X				X[4]	X[4]	X[4]		X[4]
Body weight and resting vital signs[5]	X				X	X	X		X
Complete Screening FLU-PRO[6]	X								
Evaluate eligibility[7]	X								
Collect nasopharyngeal swabs[8]		X			X	X			
Collect blood sample for lab safety tests[8]		X					X		X
Collect blood sample for antibody tests[8]		X					X		
Collect blood sample for pharmacokinetics[8]					X				
Collect urine sample for routine urinalysis[8]		X					X		X
Record concomitant medications		X			X	X	X		X
Randomize & dispense study medication[9]		X							
First dose and practice diary in-office[9,10]		X							
Review/record adverse events[11]		X			X	X	X		X
Instructions re: dosing, concomitant medications, diary completion, follow-up visits, and emergency care[12]		X	X		X	X	X		X
Contact subject to screen for complications			X[13]					X[14]	
Complete diary (subject responsibility)[10]				X					
Review subject diary entries (site responsibility)[15]				X					

[1] See Section 8.1.1 [2] See Section 8.1.2 [3] See Section 8.1.3 [4] Completed as necessary, see Section 8.1.3 [5] See Section 8.1.4 [6] See Section 8.1.5 [7] See Section 5.0
[8] See Section 8.2 [9] See Section 8.1.6 [10] See Section 8.3.1 [11] See Section 8.4 [12] See Section 8.1.7 [13] See Section 8.1.8 [14] See Section 8.1.9
[15] See Section 8.3.2

2. INTRODUCTION

2.1. Coronavirus Disease 2019 (COVID-19)

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel *betacoronavirus*, was isolated in December 2019 from patients presenting with unidentified viral pneumonia (Zhu et al. 2020). As of early June 2020, the virus resulted in more than 7 million infections and nearly 500,000 deaths worldwide (Johns Hopkins Coronavirus Resource Center 2020).

Infection with SARS-CoV-2 produces illness known as Coronavirus Disease 2019 or "COVID-19". Commonly reported symptoms include fever, chills, cough, shortness of breath, difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, vomiting, and diarrhea (U.S. CDC 2020a). The severity of illness ranges from mild and self-limited to very severe or fatal, with the current U.S. hospitalization rate of 82 per 100,000 cases and 255 per 100,000 in those over 65 years of age (U.S. CDC 2020b).

Seroprevalence studies conducted in U.S. metropolitan areas have estimated between 5% and 14% population-level exposure to SARS-CoV-2, indicating that a significant proportion of the population is still at risk for a first infection (Sood et al. 2020, Goldberg 2020). Continued social distancing and "safer at home" measures aimed at reducing transmission of the virus has resulted in record unemployment in the U.S., and the SARS-CoV-2 pandemic is expected to result in a more than 10% reduction in U.S. domestic GDP in 2020 (OECD 2020).

Remdesivir for intravenous administration has received emergency use authorization in the U.S. for hospitalized patients with COVID-19, but no antiviral has been authorized or approved for mild or moderate illness.

2.2. 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).

2.2.1. 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, HCoV-229E, HCoV-OC43, HCoV-NL63, 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, Romark data on file). Experiments in HeLa R19 cells have shown that NTZ inhibits replication of rhinovirus A serotypes 2 and 16 (Romark Study Report RM01-0434). Concentrations of tizoxanide required to inhibit replication of these viruses by 50% (EC50s) were generally between 0.2 and 3 µM depending upon the test conditions.

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

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

Studies in peripheral blood mononuclear cells have also shown tizoxanide suppresses secretion of pro-inflammatory cytokines that are upregulated by viral respiratory infections (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.

2.2.2. 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 (Cmax 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 14C 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
Cmax (µg/mL)	5.23 ± 2.71	8.16 ± 4.16	4.88 ±1.72	8.96 ±3.48
tmax (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)
tlag (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)
AUC0-t (µg.h/mL)	26.9 ± 16.1	52.5 ± 33.7	29.5 ± 12.1	75.0 ± 37.8
AUC0- 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
AUC0-∞ (µg.h/mL)	27.8 ± 17.8[b]	52.3 ± 35.6[b]	35.3 ± 16.5[d]	62.1 ± 24.2[e]
t1/2 (h)	1.66 ± 0.408[b]	2.19 ± 0.485[b]	2.70 ± 0.848[c]	4.99 ± 5.20
λz (1/h)	0.441 ± 0.106[b]	0.331 ± 0.0733[b]	0.282 ± 0.0902[c]	0.201 ± 0.0813
Cavg (µg/mL)	NA	4.02 ± 2.66b	NA	6.27 ± 3.16
Cmin (µg/mL)	NA	1.50 ± 1.83	NA	3.63 ± 3.00
PTF (%)	NA	193 ± 39.1b	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 (µg/mL) by Study Day

Analyte	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Tizoxanide	0.709 (139)	1.55 (100)	2.36 (101)	3.24 (100)	3.80 (146)	3.26 (119)	3.02 (99)
Tizoxanide Glucuronide	1.39 (61)	3.68 (72)	4.38 (73)	5.35 (77)	5.83 (99)	5.94 (91)	5.65 (69)

2.2.3. Overview of Clinical Experience with NTZ

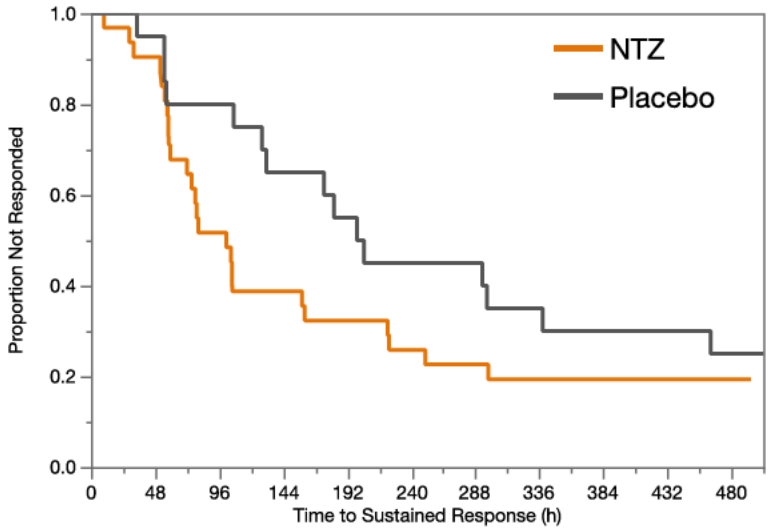
NTZ has been marketed for diarrheal disease caused by *Giardia* or *Cryptosporidium* in the United States since 2003 and in Latin America since 1996. It is estimated that more than 350 million patients have been exposed to NTZ worldwide. No drug-related serious adverse events have been reported during 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, 2,659 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 (NT-300 Investigators Brochure-COVID/VRI).

2.2.4. Clinical Experience with NTZ in Treatment of Coronaviruses

Fifty-two (52) coronavirus-infected subjects meeting the criteria proposed by this protocol were enrolled in study RM08-3004, a study of NTZ in the treatment of influenza. The FLU-PRO instrument was administered daily for 21 days. The NTZ group experienced a treatment benefit of 101 hours at the median in Time to Sustained Response [Median (IQR): 101.3 (58-250) for the NTZ group and 201.8 (117->504) for the placebo group, p=0.0932]. See Figure 1 for Kaplan-Meier curves of Time to Sustained Response for this population.

Figure 1: Time to Sustained Response for Coronavirus-Infected Subjects Enrolled in Study RM08-3004



2.3. Rationale for the Study

There is an important need for a treatment for outpatient COVID-19 that can reduce duration of illness and prevent hospitalizations, as well as mitigate economic and lifestyle impact during the present outbreak.

NTZ has demonstrated antiviral activity *in vitro* against SARS-CoV-2 and has a well-characterized favorable safety profile in extensive human clinical trials. This study will evaluate the safety and efficacy of NTZ in the treatment of COVID-19 in outpatient subjects.

3. STUDY OBJECTIVES

Primary Objective: To evaluate the effect of NTZ in reducing the time to Sustained Response compared to placebo in subjects with mild or moderate COVID-19

Secondary Objective: To evaluate the effect of NTZ in reducing the rate of progression to Severe COVID-19 Illness compared to placebo

Exploratory Objectives: To evaluate:

i. The proportion of subjects positive for SARS-CoV-2 by Aptima® SARS-CoV-2 Assay at each of Days 4 and 10

ii. The change from baseline in quantitative SARS-CoV-2 RNA measured by RT-PCR at each of Days 4 and 10

iii. The effect of NTZ in reducing the rate of hospitalization compared to placebo

iv. The effect of NTZ in reducing the rate of mortality compared to placebo

Safety Objectives: Safety will be assessed by analysis of adverse events.

4. STUDY DESIGN

4.1. Study Design Overview

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 five days compared to a placebo for the treatment of mild or moderate COVID-19.

Subjects will be stratified according to the following criteria:

Severity of COVID-19 Illness:

- Mild illness defined as baseline assessments of (1) at least one respiratory domain* with a baseline score ≥2 and (2) resting pulse <90 beats per minute and (3) resting respiratory rate <20 breaths per minute.
- Moderate illness defined as baseline assessments of (1) at least one respiratory domain* with a baseline score ≥2 and either (2) resting pulse ≥90 beats per minute or (3) resting respiratory rate ≥20 breaths per minute.

* For this purpose, respiratory domains shall include the following 5 FLU-PRO domains/subdomains: chest, cough, nose, throat and head.

Time from onset of symptoms to randomization: <36 hours/≥36 hours

Risk of severe illness (per CDC):

- At Increased Risk: Subjects with COPD, Type 2 diabetes mellitus, obesity (BMI ≥30), chronic kidney disease, sickle cell disease, serious heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies), asthma (moderate or severe), cerebrovascular disease, cystic fibrosis, hypertension or high blood pressure, immunocompromised state (due to immune deficiencies, HIV, use of corticosteroids, or use of other immune-weakening medications), neurologic conditions (e.g., dementia), liver disease, pulmonary fibrosis, past or present history of smoking, thalassemia, or type 1 diabetes mellitus. Subjects who are ≥65 years of age.
- Not At Increased Risk: Subjects with none of the above conditions

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

- Group 1 (NTZ): Two NTZ 300 mg tablets b.i.d. for 5 days

- Group 2 (Placebo): Two placebo tablets b.i.d. for 5 days

The study is expected to take place from July 2020 through January 2021.

We expect that a large number of subjects enrolled will be positive for Enterovirus/Rhinovirus (EV/RV). Efficacy and safety data for subjects who are positive for EV/RV at Baseline will be analyzed as part of concurrently enrolling study RM08-3009.

4.2. Rationale for Important Issues in the Study Design

4.2.1. Choice of NTZ Dose and Duration of Treatment

The dose of NTZ used for this clinical trial (600 mg b.i.d. for 5 days) has been associated with reductions in durations of illness in subjects infected with influenza, *Enterovirus/Rhinovirus*, and coronavirus. Dose-range-finding study RM08-3001 in subjects with influenza infection demonstrated a dose-dependent efficacy response with a 300 mg b.i.d. group demonstrating a non-significant improvement over placebo.

In clinical trials involving 2,659 subjects, adverse events reported by subjects receiving 600 mg NTZ b.i.d. for 5 days were similar to those of subjects receiving the placebo, with the exception of a higher rate of chromaturia (10.8% compared to 0.8% for the placebo). Studies of NTZ at higher doses have shown dose-dependent increases in the frequency of reported diarrhea and other gastrointestinal side effects, therefore no higher dose is planned for this study.

SARS-CoV-2 virus titer is believed to peak between the onset of symptoms and symptomatic day 4 and is not able to be cultured after seven days of symptoms (Wölfel et al. 2020). Antiviral treatment will have a reduced magnitude of treatment benefit when the host immune response is effectively decreasing the infectious viral load. Further, a study of remdesivir comparing 5- and 10-day courses of treatment found no difference between the two in patients with severe COVID-19 (Goldman et al. 2020). Therefore, it is unlikely that a course of treatment beyond five days will confer any significant additional benefit.

4.2.2. Choice of Duration of Follow Up

A 28-day (+3 days) study duration is proposed, including five days on treatment and approximately 23 days of safety and symptom follow-up. As previously described, SARS-CoV-2 virus titer is believed to peak between the onset of symptoms and symptomatic day 4 and is not able to be cultured after seven days of symptoms (Wölfel et al. 2020). Further, onset of Acute Respiratory Distress Syndrome (ARDS) in patients infected with SARS-CoV-2 is approximately 8-12 days (Li and Ma 2020). Therefore, 28 days is expected to be a sufficient period of time to capture resolution of viral shedding and any hospitalizations or severe complications of illness. Any adverse events ongoing at the time of the Day 28 visit will be followed to resolution.

4.2.3. Choice of Control Group

A placebo control is appropriate for the study due to lack of any approved active control.

4.2.4. Choice of Patient Population

The population to be studied includes adults and adolescents with mild or moderate illness consistent with SARS-CoV-2 infection. Because there are no approved antivirals for the treatment

of mild or moderate COVID-19 in outpatients, 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. Discussion of specific eligibility criteria is presented below.

4.2.4.1. Choice of Signs and Symptoms Required for Inclusion

Data from studies RM08-3004 and RM08-3005 indicate that, in subjects infected with influenza, *EV/RV* or seasonal coronavirus, subjects with low symptom scores for the head, throat, nose, chest and cough symptom domains in the absence of elevated pulse or respiratory rate, illness may be expected to resolve quickly. These subjects have less opportunity to benefit from antiviral treatment. Further, subjects who indicate that symptoms are already improving are also unlikely to benefit from treatment. Therefore, subjects will be required to have a score of ≥2 for two respiratory symptom domains (head, throat, nose, chest, or cough) or a score of ≥2 for one respiratory symptom domain in the presence of elevated vital signs (pulse ≥90 beats per minute or respiratory rate ≥16 breaths per minute). Subjects will be excluded if they report having no symptoms (global assessment), being at their usual health, that their symptoms do not interfere with their usual activities, or that their symptoms have improved since yesterday. Subjects presenting with signs or symptoms consistent with severe COVID-19 (resting shortness of breath, resting pulse ≥125, resting respiratory rate ≥30) will also be excluded from the study.

4.2.4.2. Inclusion of Subjects At Least 12 Years of Age (No Upper Age Limit)

The population to be studied includes adults and adolescents at least 12 years of age with mild or moderate COVID-19. This is a population similar to those selected for studies RM08-3001, RM08-3002, RM08-3003, RM08-3004 and RM08-3005 of the NTZ 300 mg extended release tablets in more than 5,000 subjects with colds or influenza-like illness. No safety concerns have been identified from these clinical trials. Data from pharmacokinetics studies in healthy volunteers 12 to 17 years of age or 18 to 65 years of age indicate that the pharmacokinetics of the major NTZ metabolites, tizoxanide and tizoxanide glucuronide, following oral administration of a NTZ 500 mg tablet are similar for these age groups. Safety data is also similar for these age groups. Therefore, the adult dose is deemed appropriate for pediatric patients down to 12 years of age. Informed consent will be required for subject participation in this study (see Section 8.1.1). A signed assent form will be required for any minors enrolled (≤ 18 years of age or as local regulations apply) as well as signed parental/legal guardian consent by their parent/legal guardian allowing for the minor's participation.

4.2.4.3. Inclusion of Subjects with Underlying Conditions

For the present study, some subjects (e.g., subjects >65 years of age, underlying asthma or COPD, diabetes mellitus, underlying cardiovascular disease, etc. – see Inclusion/Exclusion criteria) who are at higher risk of complications or exacerbations of underlying conditions will be allowed to participate if, in the judgment of the investigator, they are able to comply with protocol requirements and are not expected to require hospitalization. There is no approved antiviral for mild or moderate COVID-19, and subjects will not be prevented from being prescribed rescue medication for complications. Therefore, participation in the study will not pose unreasonable risk to any eligible subject.

The pharmacokinetics of the proposed dose of NTZ have been studied in subjects with renal and hepatic impairment and no dose adjustment is recommended in these populations. A thorough QTc study of NTZ at doses of 675 mg and 2700 mg found no prolongation of the QTc interval.

CYP450 inhibition assays indicate that tizoxanide inhibits CYP2C8 with an IC50 of 4.3µM, but a mechanistic static model used for potential drug-drug interactions indicated that a clinical interaction stemming from CYP2C8 inhibition by tizoxanide is unlikely.

While tizoxanide is more than 99.9% bound to plasma proteins, an *in vivo* drug-drug interaction study found no interaction between NTZ and warfarin. Tizoxanide inhibits the BCRP transporter and therefore may affect the pharmacokinetics of BCRP substrates, such as rosuvastatin. Co-administration of NTZ and rosuvastatin for seven days led to a 40% increase in the C_{max} of rosuvastatin and 80% and 70% increases of rosuvastatin AUC_{0-t} and $AUC_{0-\infty}$, respectively. However, the short duration of treatment in this study is not anticipated to cause adverse effects related to co-administration of NTZ and rosuvastatin.

For more detailed information, refer to the NT-300 Investigator's Brochure-COVID/VRI.

4.2.4.4. Exclusion of Subjects with Significant Immunodeficiency

Individuals with significant immunodeficiency, such as patients undergoing chemotherapy, transplant recipients receiving immunosuppressive therapy, and HIV patients with very low CD4 counts are more susceptible to longer durations of illness and more likely to experience complications due to viral respiratory infections. This is an important population in which to study antiviral drugs for the treatment of viral respiratory infections. Nonetheless, these subjects will be excluded from the present study due to (1) the likelihood of longer viral shedding necessitating longer courses or higher doses of treatment than what is proposed in this study, and (2) the likelihood that symptoms of illness may present differently in immunocompromised persons compared to immunocompetent persons due to reduced ability to produce the immune response that results in symptoms (van der Vries et al. 2013, St. Jude Children's Research Hospital).

4.2.5. Use of Vitamin B Complex Supplement

All subjects will receive a vitamin B complex supplement (Super B-Complex™, Igennus Healthcare Nutrition, Cambridge, UK) 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.

4.2.6. Choice of Patient-Reported Outcome Instrument

This clinical trial will use the InFLUenza Patient-Reported Outcome Questionnaire (FLU-PRO©).

FLU-PRO© was developed with the support of the U.S. Department of Health and Human Services through the National Cancer Institute and the National Institutes of Allergy and Infectious Diseases, National Institutes of Health, in response to the need for improved metrics to evaluate

treatment effect in clinical trials of drugs for the treatment of influenza and other respiratory tract viral diseases. It was developed and validated in accordance with FDA's guidance, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims." It has also been validated for use on an electronic device as part of an electronic diary ("eDiary") that can time stamp diary entries to ensure timely recording, thereby mitigating risks of recall bias. We will use an electronic diary for this clinical trial. FLU-PRO© was separately validated for use in a population with non-influenza like illness and also has recently been used in vaccine studies with older adults for the prevention of RSV (Powers et al. 2018, Yu et al. 2020). Data from Romark studies RM08-3004 and RM08-3005 also indicates validity and ability to detect change in patients infected with *Enterovirus/Rhinovirus* or seasonal coronavirus.

4.2.7. Choice of Primary Endpoint

The primary endpoint was developed using data collected from 1,467 subjects infected with influenza, *Enterovirus/Rhinovirus* or seasonal coronaviruses during Romark studies RM08-3004 and RM08-3005. The endpoint defines a level of symptom improvement that constitutes a meaningful within-patient change in health status. The determination of meaningfulness was based on empiric evidence derived from the use of anchor questions. The endpoint requires (1) oral temperature <100.4 ºF, (2) reduction of total symptom severity score from the previous day, (3) the patient to provide confirmation that symptoms are at least somewhat better, and (4) no symptom domain increase except below background levels for the remainder of the study (sustained response). These background levels were derived based on symptom scores reported by patients at the time they also reported being at usual health.

5. STUDY POPULATION

5.1. Inclusion Criteria

1. Male or female outpatients at least 12 years of age
2. [*Criterion removed in protocol amendment 2. See Appendix 1 for revision history.*]
3. Presence of clinical signs and/or symptoms consistent with worsening or stable mild or moderate COVID-19 (one of the following is required):
   a. Presence of at least two respiratory symptom domains (head, throat, nose, chest, cough) with a score of ≥2 as determined by Screening FLU-PRO OR
   b. Presence of at least one respiratory symptom domain (head, throat, nose, chest, cough) with a score of ≥2 as determined by Screening FLU-PRO with pulse rate ≥90 OR
   c. Presence of at least one respiratory symptom domain (head, throat, nose, chest, cough) with a score of ≥2 as determined by Screening FLU-PRO with respiratory rate ≥16

   AND patient reported assessment that symptoms are present, the symptoms are not consistent with the subject's usual health, the symptoms interfere with daily activities, and the symptoms have worsened or remained the same relative to the previous day, as confirmed by responses to questions in the Screening FLU-PRO.

4. Onset of symptoms no more than 72 hours before enrollment in the trial. Onset of symptoms is defined as the earlier of the first time at which the subject experienced subjective fever or any respiratory symptom (head, throat, nose, chest, or cough symptoms).
5. Willing and able to provide written informed consent (including assent by legal guardian if under 18 years of age) and comply with the requirements of the protocol, including completion of the subject diary and all protocol procedures.

5.2. Exclusion Criteria

1. Persons with any clinical sign or symptoms suggestive of severe systemic illness with COVID-19, including the following:
   a. shortness of breath at rest,
   b. resting pulse ≥125 beats per minute,
   c. resting respiratory rate ≥30 breaths per minute, or
   d. $SpO_2 \leq 93\%$ on room air at sea level.
2. Subjects who experienced a previous episode of acute upper respiratory tract infection, otitis, bronchitis or sinusitis or received antibiotics for these conditions within two weeks prior to and including study day 1.
3. Severely immunodeficient persons including:
   a. Subjects with immunologic disorders or receiving immunosuppressive therapy (e.g., for organ or bone marrow transplants, immunomodulatory therapies for certain autoimmune diseases)
   b. Subjects with untreated HIV infection or treated HIV infection with a CD4 count below 350 cells/mm^3 in the last six months
   c. Subjects actively undergoing systemic chemotherapy or radiotherapy treatment for malignancy
   d. Subjects using steroids as maintenance therapy for chronic conditions
4. Subjects with active respiratory allergies or subjects expected to require anti-allergy medications during the study period for respiratory allergies.
5. Females of childbearing potential who are either pregnant or sexually active without the use of birth control. Female subjects of child-bearing potential that are sexually active must have a negative baseline pregnancy test and must agree to continue an acceptable method of birth control for the duration of the study and for 1 month post-treatment. A double barrier method, oral birth control pills administered for at least 2 monthly cycles prior to study drug administration, an IUD, or medroxyprogesterone acetate administered intramuscularly for a minimum of one month prior to study drug administration are acceptable methods of birth control for inclusion into the study. Female subjects are considered of childbearing potential unless they are postmenopausal (absence of menstrual bleeding for 1 year - or 6 months if laboratory confirmation of hormonal status), or have had a hysterectomy, bilateral tubular ligation or bilateral oophorectomy.
6. Subjects with a history of COVID-19 or known to have developed anti-SARS-CoV-2 antibodies.
7. Subjects residing in the same household with another subject participating in the study.

8. Treatment with any investigational drug or vaccine therapy within 30 days prior to screening and willing to avoid them during the course of the study.
9. Receipt of any dose of NTZ within seven days prior to screening.
10. Known sensitivity to NTZ or any of the excipients comprising the study medication.
11. Subjects unable to swallow oral tablets or capsules.
12. Subjects with known severe heart, lung, neurological or other systemic disease that the Investigator believes could preclude safe participation.
13. Subjects likely or expected to require hospitalization unrelated to COVID-19 during the study period.
14. Subjects taking medications considered to be major CYP2C8 substrates. Refer to Table 5 in Section 6.5.
15. Subjects who, in the judgment of the Investigator, will be unlikely to comply with the requirements of this protocol including completion of the subject diary.

5.3. Study Population Diversity

The Sponsor will select clinical sites to support recruitment of a diverse and representative population, including older individuals and racial and ethnic minorities.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administration

6.1.1. Study Intervention Description

NTZ 300 mg extended release tablets for use in this study are yellow, round, convex, film-coated, bi-layer tablets for oral administration, each tablet contains 300 mg of NTZ and the inactive ingredients.

Placebo tablets will have the same appearance and inactive ingredients as the active NTZ 300 mg extended release tablet.

The vitamin B complex supplement is Super B-Complex™ manufactured by Igennus Healthcare Nutrition, Cambridge, UK. 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%.

6.1.2. Dosing and Administration

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 (Super B-Complex™, Igennus Healthcare Nutrition, Cambridge, UK) b.i.d. for 5 days

Group 2 (Placebo): Subjects will receive two placebo tablets b.i.d. with food (< 1 hour after food intake) and a B complex vitamin (Super B-Complex™, Igennus Healthcare Nutrition, Cambridge, UK) b.i.d. for 5 days

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.

6.2. Preparation, Handling, Storage and Accountability

6.2.1. Acquisition and Accountability

Study medication will be provided by the Sponsor to the Investigational Site for dispensing.

Drug accountability will be tracked using an IWRS/IRT system as described in the study-specific Data Management Plan. Unused supplies must be returned to the Sponsor or destroyed in accordance with institutional procedures in effect at the study Site.

6.2.2. Packaging and Labeling

NTZ or placebo tablets will be packaged in white 30 cc HDPE bottles, each containing 20 tablets. The kits will be stored at room temperature and will bear labels with the following information:

Table 4: Study Medication Label

20 Tablets	Study No. RM08-3008	Treatment No: XXXX
Lot No: 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]

6.3. Randomization and Blinding

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. Unmasking procedures will be detailed in the Medical Monitoring Plan and Investigators will be provided instructions for unmasking.

6.4. Study Intervention Compliance

Subject compliance with study medication will be checked by site staff daily during the treatment period. Subjects will return the treatment kit with any unused medication to the clinic at the Day 10 visit. Subjects will be considered non-compliant (major protocol deviation) if they have missed more than two doses of the study medication during the first three days of the study. Non-compliance will not be cause for discontinuation of subject participation in the study.

6.5. Concomitant Therapy

The following medications will not be allowed during the study: topical or systemic decongestants, nasal corticosteroids, and any prescription or non-prescription medications classified as (i) expectorants and cough preparations, (ii) analgesics and antipyretics, (iii) antihistamines (American Hospital Formulary Service (AHFS) classification) or (iv) medications considered major CYP2C8 substrates (see Table 5 below). As an exception to this rule, subjects will be allowed to use acetaminophen and/or dextromethorphan as necessary for disabling symptoms.

Table 5: 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, remdesivir, azithromycin or lopinavir/ritonavir during the study except as standard-of-care rescue medication.

Medications for pre-existing conditions that are not excluded (see exclusion criteria) should be continued as prescribed. Standard-of-care rescue medication is permitted for complications of COVID-19 illness. The use of such medication will be recorded in the EDC system.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT 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 medication 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.

Subjects will be encouraged to complete all protocol-specified follow-up visits even if study drug is withdrawn.

8. STUDY PROCEDURES

8.1. Visit Procedures

Study procedures to be completed at each visit are indicated in the Schedule of Assessments. Descriptions of selected procedures are outlined in the following sections.

8.1.1. 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. 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.

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

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

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

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

8.1.2. Medical History

All relevant medical history should be entered in the EDC system at the Screening visit. Relevant medical history includes:

1. Any disease, condition or surgery active at the time of the Screening visit;
2. Any disease, condition or surgery ending within two months of the Screening visit; or
3. Any other disease, condition or surgery relevant to the subject's infection or clinical management.

8.1.3. Physical Examination

Physical examinations will include assessment of each body system including skin, head (eye, ear and nose), neck, mouth/throat, lymph nodes, cardiovascular, respiratory, gastrointestinal, neurological, and musculoskeletal systems as well as general appearance for abnormalities.

The Investigator will complete a full physical examination at the Screening visit. Physical examinations should occur at follow-up and unscheduled visits as required by symptoms or adverse changes from baseline.

8.1.4. Body Measurements and Resting Vital Signs

Body measurements and resting vital signs will include assessment of the following:

1. Height (Screening visit only)
2. Weight
3. Oral temperature
4. Blood pressure
5. Pulse rate
6. Respiratory rate
7. Oxygen saturation

8.1.5. Screening FLU-PRO

The FLU-PRO questionnaire will be administered during the Screening visit to confirm symptoms required for eligibility.

8.1.6. Randomization and Dispensing Study Medication

Randomization and study medication kit assignment will be accomplished using an Interactive Randomization Tool (IRT) feature in the EDC system after all screening procedures have been completed and the subject has been determined to be eligible for the study. Site staff will witness the subject take the first dose of study medication in the clinic as soon as possible following randomization and record the date and time of medication intake in the EDC system.

8.1.7. Subject Instructions

At each subject contact, site staff will instruct the subject regarding:

1. *Administration of study medication.* Subjects will be instructed to take the study medication (two tablets) twice daily with the morning and evening meals, approximately every 12 hours (< 1 hour after food intake, preferably a high-fat meal but at a minimum a cereal bar) and a B complex vitamin (Super B-Complex™, Igennus Healthcare Nutrition, Cambridge, UK).
2. *Completion of subject diary.* Subjects will be reminded to complete the electronic diary and any questions will be answered.
3. *Use of birth control.* Female subjects of childbearing potential, if sexually active, will be instructed to continue an acceptable method of birth control for the duration of the study and for 1 month post-treatment. Acceptable methods of birth control include a double barrier method, oral birth control pills, an IUD, or medroxyprogesterone acetate administered intramuscularly.
4. *Follow-up visits.* Subjects will be reminded of the study schedule and of the next scheduled visit.
5. *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 at any point during the study.

   <u>CONTACT STUDY PHYSICIAN IF YOU HAVE:</u>

   - 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

8.1.8. Day 2-7 Subject Contact

Site staff will contact each subject by telephone on study Days 2-7 to verify:

1. Did the subject take all expected doses of study medication?
2. Did the subject complete all expected electronic diaries?
3. Does the subject have worsening symptoms or adverse events that warrant an unscheduled visit?
4. Does the subject have shortness of breath at rest? *If yes, instruct the subject to come to the clinic for an unscheduled visit to screen for progression of illness or refer to hospital as warranted. If the subject is referred to the hospital or emergency department, the Investigator will attempt to obtain hospital records indicating SpO_2 or PaO_2/FiO_2 from the subject for the purposes of defining progression to severe COVID-19 illness. The SpO_2 or PaO_2/FiO_2 obtained from hospital records will be entered on an Unscheduled Visit eCRF.*

If the subject has missed medication or electronic diaries, the site staff will re-train the subject on the importance of medication and diary compliance.

This contact may occur at the Day 4 or unscheduled visit in lieu of telephone contact.

8.1.9. Day 28 Subject Contact

Site staff will contact each subject by telephone on study Day 28 to determine if the subject has experienced any new adverse events, developed severe COVID-19 illness, or required hospitalization for any reason.

If warranted, the Day 28 subject contact may also occur in-person at the clinic or another location as agreed upon by the site and subject.

8.2. Laboratory Assessments

8.2.1. Assessments in the Clinic

A urine pregnancy test will be performed in the clinic only for women of childbearing potential (post-menarche, pre-menopause, not surgically sterile) at the Screening visit.

8.2.2. Central Laboratory Assessments

A central laboratory will be used for safety, diagnostic virology, and serology testing. A laboratory manual will be provided to each clinical site with sample collection and handling details.

8.2.2.1. Laboratory Safety Assessments

Blood tests for safety monitoring 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.

8.2.2.2. Diagnostic Virology Testing

Diagnostic virology testing will be performed using nasopharyngeal swab samples collected at the Baseline, Day 4 and Day 10. The nasopharyngeal sample for virology testing will be collected using a single nasopharyngeal swab inserted into both nostrils in accordance with procedures detailed in the study-specific laboratory manual.

The ePlex® Respiratory Pathogen Panel ("ePlex RPP", GenMark, Carlsbad, CA) will be used 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 detect SARS-CoV-2.

All Baseline nasopharyngeal swabs will be tested by the ePlex RPP and Aptima® SARS-CoV-2 assays. If the Baseline nasopharyngeal swab is positive for SARS-CoV-2, the Day 4 and 10 nasopharyngeal swabs will be tested for SARS-CoV-2. If the Baseline nasopharyngeal swab is positive for EV/RV, the Day 4 and 10 nasopharyngeal swabs will be tested using the ePlex RPP.

8.2.2.3. Quantitative Virology Testing

Nasopharyngeal swab samples testing positive for SARS-CoV-2 will be subjected to quantitative RT-PCR for analysis of quantitative changes in viral RNA.

8.2.2.4. Serology Testing

Baseline and Day 22 blood samples will be tested for quantitative anti-SARS-CoV-2 antibodies.

8.2.3. Pharmacokinetics Assessments

Blood samples for pharmacokinetics analysis will be sent to the central laboratory by the site and shipped to a referral laboratory for analysis. Sample collection and handling details will be included in the central laboratory manual.

8.2.4. Plan for Monitoring Viral Resistance

If any Day 10 nasopharyngeal swab sample is positive for SARS-CoV-2 by the SARS-CoV-2 assay or for EV/RV by the ePlex RPP, the Baseline and Day 10 nasopharyngeal swab samples for the subject will be tested for post-treatment reduced susceptibility to tizoxanide.

8.3. Subject Diary

The subject diary will be used to generate primary efficacy data. Therefore, diary compliance is of critical importance.

8.3.1. Subject Diary Completion

Subjects will complete a diary including:

- Oral temperature taken using the study thermometer twice daily (morning and evening), and

- The FLU-PRO© symptoms questionnaire daily in the evening.

The diary will be completed using the subject's smartphone or provisioned device.

Site staff will ensure subject access and ability to complete the diary during the Baseline visit. Subjects will complete the first post-Screening diary at home on the evening of study Day 1.

Subjects will receive electronic reminders to complete the diary daily to ensure compliance.

8.3.2. Subject Diary Compliance Monitoring

It is the responsibility of the clinical site to ensure that subjects are completing the diary as directed. E-mail notifications will be sent to the site daily with a list of subjects who missed the previous day's diary in order to direct follow-up contact with the subject to re-train on the importance of the diary. Site staff may also view a diary completion report at any time within the EDC system.

8.4. Adverse Events and Serious Adverse Events

8.4.1. Definitions

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

1. Adverse Event: 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 viral respiratory infections (VRIs) (cough, sore, throat, nasal obstruction, fatigue, headache, myalgia, or feverishness) will not be reported as adverse events.
2. 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.
3. Unexpected Adverse Event: Any adverse experience that is not identified in nature, severity, or frequency in the Investigator's Brochure for NTZ.
4. Severity of adverse events will be assessed as mild, moderate, severe or potentially life-threatening by the Investigator using the Toxicity Grading Scale Tables provided in Appendix 4 (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).
5. 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.

8.4.2. Recording and Follow Up of Adverse Events

At the time of each visit, the subject will be questioned regarding the occurrence and nature of any adverse events and all events will be recorded in the subject's 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 adverse events must be followed until their resolution or stabilization even beyond the planned study period.

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.

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.

8.4.3. Reporting Requirement

The Principal Investigator is required to notify The Romark Institute for Medical Research (Sponsor) immediately (within 24 hours of the initial report) 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 as required by the IRB procedures. Adverse events should be reported to:

The Romark Institute for Medical Research
Medical Affairs
[redacted]
Tel: [redacted] Fax: [redacted]
[redacted]

8.4.4. Management of Subjects Requiring Hospitalization

Subjects requiring hospitalization for any reason during the course of the study will receive local standard of care under the supervision of the hospital's attending physicians. The Investigator will attempt to follow up on the subject to obtain complete data for a narrative of the Serious Adverse Event and complete safety follow up procedures for the study as feasible.

8.4.5. 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.

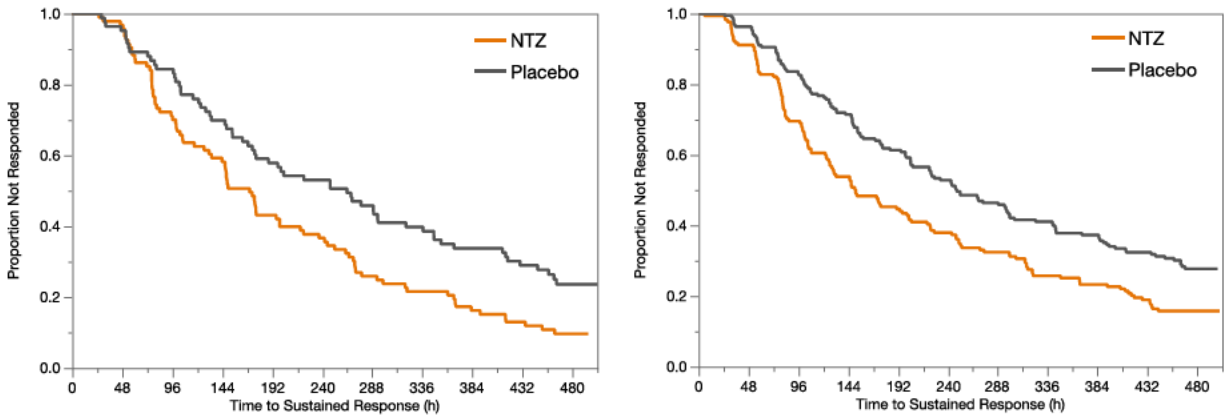
9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

The primary efficacy parameter is the time from first dose to Sustained Response based on the FLU-PRO Patient Reported Outcomes instrument (see Section 9.3). This response definition was applied to Romark studies RM08-3004 and RM08-3005 in the treatment of influenza and colds caused by *EV/RV*, respectively. Kaplan-Meier curves for the studies are shown below.

Figure 2: Kaplan-Meier Curves Forming the Basis for Sample Size Calculations

RM08-3004 Influenza *RM08-3005 EV/RV*



Based upon the influenza data, a sample size of 288 subjects (144 per group) would provide 90% power to detect a statistically significant difference in the survival distributions between the NTZ and placebo groups (two-sided alpha=0.05). Using the *EV/RV* data yields a sample size of 312 subjects (156 per group). These calculations were performed for the Gehan rank test using SAS PROC POWER (SAS 9.4) with the curves shown above (proportion not responded by the end of each day was used as input) and censoring at day 21. In order to ensure a robust dataset, we have selected a sample size of at least 350 SARS-CoV-2-infected subjects based upon the EV/RV data and adding an allowance for approximately 10% of subjects to discontinue early or otherwise have missing data. If the pace of enrollment is high, we will enroll up to 400 SARS-CoV-2-infected subjects.

We anticipate a SARS-CoV-2-positive rate between 50% and 75%. Therefore, we estimate that enrollment of 350-400 SARS-CoV-2 subjects may require enrollment of 450-800 subjects.

9.2. Efficacy Variables

Primary Efficacy Parameter:	Time from first dose to Sustained Response based on the FLU-PRO Patient Reported Outcomes Instrument.
Secondary Efficacy Parameter:	Proportion of subjects progressing to severe COVID-19 illness.
Exploratory Efficacy Parameters:	i. Proportion of subjects positive for SARS-CoV-2 by Aptima® SARS-CoV-2 Assay at Days 4 and 10. ii. Mean changes from baseline in quantitative SARS-CoV-2 RNA measured by RT-PCR . iii. Proportion of subjects hospitalized due to COVID-19 or complications thereof. iv. Proportion of subjects with mortality due to COVID-19 or complications thereof.

9.3. Response Definitions

Sustained Response: A decrease in total FLU-PRO score from the previous diary with patient assessment that symptoms are at least "somewhat better than yesterday", no oral temperature ≥100.4°F in the prior 24 hours, and no future increase in any of the FLU-PRO domains except within the following levels:

FLU-PRO Domain*	Background Level
Body/Systemic	0.56
Throat	0.67
Eyes	0.67
Gastrointestinal	2.00
Head	2.00
Nose	Score at time of response or 0.75, whichever is greater
Chest	Score at time of response or 0.00, whichever is greater
Cough	Score at time of response or 1.75, whichever is greater

* A diagram of the FLU-PRO domain/subdomain structure is attached as Appendix 5.

Time of Sustained Response: The time of the first diary at which all Sustained Response criteria are met.

Time to Sustained Response: The time (hours) from the first dose of study medication and the Time of Sustained Response.

Severe COVID-19 Illness: Subject must have (1) shortness of breath at rest and (2) $SpO_2 \leq 93\%$ on room air or $PaO_2/FiO_2 < 300$.

9.4. Statistical Methodology

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

9.4.1. Efficacy Analyses

Efficacy analyses will be based on a population consisting of all subjects randomized who receive at least one dose of study medication and are positive for SARS-CoV-2 by Aptima® SARS-CoV-2 Assay at Baseline. For time-to-event analyses, a test of significance (as described in the following) will be performed with descriptive statistics provided, including the use of Kaplan-Meier figures.

There will be one primary efficacy analysis:

- Time to Sustained Response for the NTZ treatment group will be compared to that of the placebo treatment group using a stratified Gehan-Wilcoxon test (α=0.05) where stratification will follow that used for randomization. Subjects without a Sustained Response recorded will be treated as censored as of the last diary without a documented Sustained Response, except for subjects who are hospitalized or die during the study, who will be censored at Day 21 (hour 504).

Sensitivity analyses for the primary efficacy analysis will be described in the Statistical Analysis Plan.

If the primary analysis is significant at the 0.05 level, the key secondary efficacy analysis will be formally evaluated at the 0.05 level as follows:

- Proportions of subjects progressing to Severe COVID-19 Illness will be compared between the treatment groups using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata.

Exploratory analyses will be performed as follows:

- Proportions of subjects positive for SARS-CoV-2 by Aptima® SARS-CoV-2 Assay at study Day 4 and Day 10 will be compared between the treatment groups using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata.
- Mean changes from baseline in quantitative SARS-CoV-2 RNA measured by RT-PCR at Day 4 and Day 10 will be compared using a t-test.
- Proportions of subjects hospitalized due to COVID-19 or complications thereof will be compared across the treatment groups using a CMH test stratified by the randomization strata.
- Proportions of subjects with mortality related to COVID-19 or complications thereof will be compared across the treatment groups using a CMH test stratified by the randomization strata.

9.4.2. Population Pharmacokinetics Analysis

On Day 4, plasma samples will be collected before the morning dose (at the trough) for determination of drug concentration. 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 NTZ-treated subjects except those positive for EV/RV at Baseline. 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.

Pharmacokinetics data for subjects positive for EV/RV at Baseline will be analyzed as part of concurrently enrolling study RM08-3009.

9.4.3. Safety Analyses

All randomized subjects who receive at least one dose of study medication except those positive for EV/RV at Baseline will be evaluated for drug safety. Safety analyses will be done descriptively.

Safety data for subjects positive for EV/RV at Baseline will be analyzed as part of concurrently enrolling study RM08-3009.

10. OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical and Study Oversight Considerations

10.1.1. 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).

Informed consent will be obtained from each subject as described in Section 8.1.1.

Prior written approval of the study protocol and of the informed consent form will be obtained by the Sponsor from the appropriate central or local IRB.

Prior to study initiation, the Investigator will provide the IRB with required documents for review and approval. See Appendix 3: List of Essential Documents for designation of documents that may be required by the IRB prior to study initiation or during the course of study conduct. No site will screen subjects until the IRB has given full approval of required documents and the data approval letter identifying the IRB and the documents approved is delivered to the study Sponsor.

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.

10.1.2. 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.

10.1.3. Quality Assurance and Quality Control

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 (see Section 10.1.6). Written instructions will be provided for collection, preparation and shipment of biological samples.

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.

Quality oversight of study management will be accomplished according to the study-specific Integrated Quality and Risk Management Plan.

10.1.4. Safety Oversight

The Sponsor and Medical Monitor will be responsible for safety oversight of the study. Procedures for safety oversight are described in the study-specific Medical Monitoring Plan.

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

10.1.5. Data Handling and Record Keeping

10.1.5.1. Data Collection and Management Responsibilities

Sponsor Data management will be responsible for oversight of data collection, cleaning and locking according to the study-specific Data Management Plan.

Data will be collected on site-specific source data forms and transcribed into an electronic data capture (EDC) system by site staff. The responsible study monitor(s) will verify data according to the Clinical Monitoring Plan, either remotely or at the clinical study site. The Investigator will ensure that the data recorded are accurate and complete.

Queries emerging during data cleaning will be generated within the EDC system by monitors or data management personnel. The Investigator and/or designee will answer the queries and update the source data, as needed.

10.1.5.2. Study Records Retention

The Investigator/institution will maintain all CRFs, 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, and all study documents as specified by the applicable regulatory requirements for the duration required by applicable regulatory authorities or until the Sponsor informs the Investigator/institution that 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 will be responsible for maintaining the Trial Master File which is a clear documentation of the course of the study.

10.1.6. Clinical Monitoring

Clinical monitoring will be conducted by the Sponsor and/or a contract research organization (CRO) according to the study-specific 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.

10.1.7. 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.

10.1.8. Study Discontinuation and Closure

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 4).

   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 efficacy data will be submitted to the FDA in a timely manner.

10.1.9. Data and Report Requirements

See Appendix 3: List of Essential Documents for designation of documents required from the Investigator by the Sponsor prior to approval and initiation of the study and before the study can be considered complete and terminated.

10.1.10. Confidentiality and Privacy

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 will 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 will 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. All reports and communications relating to the study subjects will identify subjects only by initials and subject identification number.

Data generated for the study will 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.

10.1.11. Publication and Data Sharing

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.

10.1.12. Key Roles and Study Governance

See Appendix 2 for a list of key personnel and contact information.

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APPENDIX 1. PROTOCOL REVISION HISTORY

Table 6: Protocol Revision History

Summary of Changes	
Initial Protocol: Version 1.0, effective July 14, 2020	
Purpose:	New protocol
Amendment 1: Version 2.0, effective July 23, 2020	
Purpose:	To address FDA comments on study design. To correct the definition of "Mild COVID-19 Illness" for purposes of stratification
Change 1:	Pages 6 & 14, *Exploratory Objectives* Added *"The effect of NTZ in reducing the rate of hospitalization compared to placebo"*
Change 2:	Pages 8, 20 & 21 *Exclusion Criteria* Added exclusion criterion 3d: *"Subjects using steroids as maintenance therapy for a chronic condition"* and exclusion criterion 14: *"Subjects taking medications considered to be major CYP2C8 substrates. Refer to Table 5 in Section 6.5."*
Change 3:	Page 15, *Study Design Overview* • Corrected definition of "Moderate illness" from *"[...]baseline assessments of (1) at least two respiratory domains with a baseline score ≥2 [...]"* to *"[...]baseline assessments of (1) at least one respiratory domain with a baseline score ≥2 [...]"*. • Removed stratification by age group and added *"Subjects ≥65 years of age"* to the list of criteria for subjects "At Increased Risk" of severe illness. • Combined "At Increased Risk" and "May Be At Increased Risk" groups into one "At Increased Risk" group.
Change 4:	Page 32, *Concomitant Therapy* • Added *"or (iv) medications considered major CYP2C8 substrates (see Table 5 below)."* • Added table of major CYP2C8 substrates. • Added *"Subjects are also prohibited from taking hydroxychloroquine, chloroquine, remdesivir, azithromycin or lopinavir/ritonavir during the study except as standard-of-care rescue medication."* • Added *"Standard-of-care rescue medication is permitted for complications of COVID-19 illness."*

Summary of Changes	
Change 5:	Page 25, Randomization and Dispensing Study Medication Updated *"Site staff will witness the subject take the first dose of study medication in the clinic and record the date and time of medication intake in the EDC system"* to *"Site staff will witness the subject take the first dose of study medication in the clinic as soon as possible following randomization and record the date and time of medication intake in the EDC system."*
Change 6:	Page 27, *Day 2-7 Contact* Updated *"4. Does the subject have shortness of breath at rest? If yes, instruct the subject to come to the clinic for an unscheduled visit to screen for progression of illness including determination of PaO_2/FiO_2."* to *"4. Does the subject have shortness of breath at rest? If yes, instruct the subject to come to the clinic for an unscheduled visit to screen for progression of illness or refer to hospital as warranted. If the subject is referred to the hospital or emergency department, the Investigator will attempt to obtain hospital records indicating SpO_2 or PaO_2/FiO_2 from the subject for the purposes of defining progression to severe COVID-19 illness. The SpO_2 or PaO_2/FiO_2 obtained from hospital records will be entered on an Unscheduled Visit eCRF.*
Change 7:	Page 27, *Diagnostic Virology Testing* Added: *"The nasopharyngeal sample for virology testing will be collected using a single nasopharyngeal swab inserted into both nostrils in accordance with procedures detailed in the study-specific laboratory manual."* Replaced *"Panther Fusion"* with "*Aptima®*" Replaced: *"Post-baseline samples (Days 4 and 10) will only be tested by the SARS-CoV-2 assay and will only be tested if the sample from the preceding timepoint was positive for SARS-CoV-2. For example, a subject who is positive for SARS-CoV-2 at Baseline will have the Day 4 sample tested by the SARS-CoV-2 assay. If the subjects' Day 4 sample is negative for SARS-CoV-2, the Day 10 sample will not be tested."* With: *"If the Baseline nasopharyngeal swab is positive for SARS-CoV-2, the Day 4 and 10 nasopharyngeal swabs will be tested for SARS-CoV-2."*
Change 8:	Page 30: *Management of Subjects Requiring Hospitalization* Added: *8.4.4 Management of Subjects Requiring Hospitalization* *Subjects requiring hospitalization for any reason during the course of the study will receive local standard of care under the supervision of the hospital's attending physicians. The Investigator will attempt to follow up on the subject to obtain complete data for a narrative of the Serious Adverse Event and complete safety follow up procedures for the study as feasible.*

Summary of Changes	
Change 9:	Page 32, *Exploratory Efficacy Parameters* Added *"iii. Proportion of subjects hospitalized due to COVID-19 or complications thereof."*
Change 10:	Page 33, *Response Definitions* Updated definition of Severe COVID-19 Illness from *"Subject must have (1) shortness of breath at rest and (2) PaO_2/FiO_2 <300."* to *"Subject must have (1) shortness of breath at rest and (2) $SpO_2 \leq 93\%$ on room air or PaO_2/FiO_2 <300."*
Change 11:	Page 33, *Efficacy Analyses* • Added: *", except for subjects who are hospitalized or die during the study, who will be censored at Day 21 (hour 504)."* • Added: *"Sensitivity analyses for the primary efficacy analysis will be described in the Statistical Analysis Plan."*
Change 12:	Page 39, *References* Added: *"Backman JT, Filppula AM, Niemi M, Neuvonen PJ. Role of cytochrome P450 2C8 in drug metabolism and interactions. Pharmacol Rev 2016; 68:168-241."*
Change 13:	Page 55, *FLU-PRO Domain/Subdomain Structure* Updated to add Additional COVID-19-specific Questions, "Loss of Taste" and "Loss of Smell".
Amendment 2: Version 3.0, effective September 16, 2020	
Purpose:	To remove inclusion criterion #2 and add a Day 28 subject contact per FDA recommendations. To correct the Day 22 visit window. To specify that efficacy and safety data for subjects who are positive for Enterovirus/Rhinovirus at Baseline will be analyzed as part of concurrently enrolling study RM08-3009.
Change 1:	Page 7, *Synopsis* & Page 19, *5.1 Inclusion Criteria* Removed Inclusion Criterion #2, "Patient-reported subjective fever within the last 12 hours or oral temperature in-office of at least 99.4°F" Page 32, *Sample Size Determination* Removed: "*Because febrile viral respiratory infections such as influenza typically are not circulating during the studied time frame (July – October 2020) and this study requires that eligible subjects have fever,*"

Summary of Changes	
Change 2:	Page 8, *Synopsis* Updated the following to reflect Day 28 contact: "*The safety of study drug administration will be monitored by assessment of adverse events from baseline through the Day 28 study exit, clinical laboratory testing at baseline and on Day 10, physical examinations and vital signs assessments at screening, Day 10 and Day 22 and telephone monitoring/at home visits during Day 2 through Day 7 and Day 28.*" Page 9, *Schedule of Assessments* Added subject contact at Day 28 (+3 days). Page 27, *8.1.9 Day 28 Subject Contact* Added section with text: "*Site staff will contact each subject by telephone on study Day 28 to determine if the subject has experienced any new adverse events, developed severe COVID-19 illness, or required hospitalization for any reason.* *If warranted, the Day 28 subject contact may also occur in-person at the clinic or another location as agreed upon by the site and subject.*"
Change 3:	Page 9, *Schedule of Assessments* Corrected Day 22 visit window from "±*3*" to "+*3*".
Change 4:	Page 16, *4.1 Study Design Overview* Added: "*We expect that a large number of subjects enrolled will be positive for Enterovirus/Rhinovirus (EV/RV). Efficacy and safety data for subjects who are positive for EV/RV at Baseline will be analyzed as part of concurrently enrolling study RM08-3009.*" Page 28, *8.2.2.2 Diagnostic Virology Testing* Added: "*If the Baseline nasopharyngeal swab is positive for EV/RV, the Day 4 and 10 nasopharyngeal swabs will be tested using the ePlex RPP."* Page 28, *8.2.4 Plan for Monitoring Viral Resistance* Added: "*or for EV/RV by the ePlex RPP*" Page 34, *9.4.2 Population Pharmacokinetics Analysis* Updated text, "*Trough plasma concentrations of tizoxanide and tizoxanide glucuronide will be summarized descriptively for NTZ-treated subjects*" to add "*except those positive for EV/RV at Baseline.*"

Summary of Changes	
	Added: "*Pharmacokinetics data for subjects positive for EV/RV at Baseline will be analyzed as part of concurrently enrolling study RM08-3009.*" Page 35, *9.4.3 Safety Analyses* Updated text, "*All randomized subjects who receive at least one dose of study medication will be evaluated for drug safety*" to add "*except those positive for EV/RV at Baseline".* Added: "*Safety data for subjects positive for EV/RV at Baseline will be analyzed as part of concurrently enrolling study RM08-3009.*"
Change 5:	Page 6, *Synopsis* & Page 16, *4.1 Study Design Overview* & Updated "*October"* to "*December*"
Amendment 3: Version 4.0, effective January 11, 2021	
Purpose:	To update the assay for quantitation of virus from $TCID_{50}$ to quantitative PCR based on central laboratory capabilities.
Change 1:	Page 6, *Synopsis*; Page 15, *3.0 Study Objectives*; Page 33, *9.2 Efficacy Variables* Updated: *i. The proportion of subjects positive for SARS-CoV-2 by culture at each of Days 4 and 10* *ii. The change from baseline in SARS-CoV-2 $TCID_{50}$ at each of Days 4 and 10* to: *i. The proportion of subjects positive for SARS-CoV-2 by Aptima® SARS-CoV-2 Assay at each of Days 4 and 10* *ii. The change from baseline in quantitative SARS-CoV-2 RNA measured by RT-PCR at each of Days 4 and 10*
Change 2:	Page 17, *4.2.2 Choice of Duration of Follow Up* Removed "*by $TCID_{50}$*"
Change 3:	Page 29, *8.2.2.3. Quantitative Virology Testing* Replaced "*$TCID_{50}$*" with "*quantitative RT-PCR*"

Summary of Changes	
Change 4:	Page 35, *9.4.1 Efficacy Analyses* Updated: • *Proportions of subjects positive for SARS-CoV-2 by $TCID_{50}$ at study Day 4 and Day 10 will be compared between the treatment groups using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata.* • *Mean changes from baseline in SARS-CoV-2 $TCID_{50}$ at Day 4 and Day 10 will be compared using a t-test.* To: • *Proportions of subjects positive for SARS-CoV-2 by Aptima® SARS-CoV-2 Assay at study Day 4 and Day 10 will be compared between the treatment groups using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata.* • *Mean changes from baseline in quantitative SARS-CoV-2 RNA measured by RT-PCR at Day 4 and Day 10 will be compared using a t-test.*
Change 5:	Page 6, *Synopsis* & Page 17, *Study Overview* Updated anticipated end of enrollment from December 2020 to January 2021
Change 6:	Page 7, *Synopsis* & Page 17, *Choice of Duration of Follow Up* Corrected study duration from 22 days to 28 days
Change 7:	Page 49, *Study Contact Information* Updated Sponsor Project Management and Central Laboratory contact information

APPENDIX 2. CONTACT INFORMATION

Table 7: Study Contact Information

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

APPENDIX 3. LIST OF ESSENTIAL DOCUMENTS FOR THE SITE

Table 8: List of Essential Documents

Document	Submitted to IRB	Required for Study Initiation	Required for Study Completion
1. Investigator's Brochure and Updates	X		
2. Signed protocol (all verisons) and amendments, if any, and sample CRF	X		
3. Information given to subjects: • Informed consent form (all versions) • Advertisement for subject recruitment (if used) • Any other written information	X		
4. Financial agreement between the Investigator/institution and the study Sponsor			
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 on the following: • Protocol and 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		X	
7. Institutional Review Board Composition			
8. Regulatory notice of Principal Investigator and sub-Investigator, FDA Form 1572			
9. Curriculum vitae and/or other relevant documents evidencing qualifications of Investigator and sub-Investigators	X	X	
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 validations (where required)			
12. Shipping records for investigational product(s) and trial-related materials			
13. Site initiation monitoring report			

Document	Submitted to IRB	Required for Study Initiation	Required for Study Completion
14. Relevant communications other than site visits: • Letters/emails • Meeting notes • Notes of telephone calls			
15. Signed informed consent forms			X
16. Source documents			X
17. Signed, dated and completed EDC forms including documentation of EDC form corrections			X
18. Notification by originating Investigator to Sponsor of serious adverse events and related reports			X
19. Notification by Investigator, where applicable, to IRB of unexpected serious adverse drug reactions and other safety information	X		
20. Notification by Sponsor to Investigator of safety information			
21. Interim or annual reports to IRB	X		
22. Subject Screening log			
23. Subject identification code list			
24. Subject enrollment log			
25. Investigational product accountability records (receipt, storage, dispensing, shipment)			X
26. Signature sheet			
27. Record of retained body fluids/tissue samples (if any)			
28. Final report by Investigator/institution to IRB	X		

APPENDIX 4. TOXICITY GRADING TABLES

[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 9: 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 10: 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 11: 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 12: 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
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

Table 12: Table for Laboratory Abnormalities: Serum (Continued)

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
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
Triglycerides – mg/dL**	150 mg/dL – 300 mg/dL	>300 mg/dL – 500 mg/dL	>500 mg/dL - 1000 mg/dL	>1000 mg/dL

Table 12: Table for Laboratory Abnormalities: Serum (Continued)

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
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 13: 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
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

Table 13: Table for Laboratory Abnormalities: Hematology (Continued)

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
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 14: 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.

APPENDIX 5. FLU-PRO DOMAIN/SUBDOMAIN STRUCTURE