A Phase III, Randomized, Double-Blind, Placebo Controlled Trial to Evaluate the Efficacy and Safety ofNitazoxanide in the Treatment of Uncomplicated Influenza

Protocol No. RM08-3004

Study Sponsor:

The Romark Institute for Medical Research

[redacted]

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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 docmnents will be available for review by the Sponsor or their designated representative.

Principal Investigator Signature:

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PROTOCOL SYNOPSIS

Title:	A Phase III, Randomized, Double-Blind, Placebo Controlled Trial to Evaluate the Efficacy and Safety of Nitazoxanide in the Treatment of Uncomplicated Influenza
Study Number:	RM08-3004
IND Number:	107,316
Indication:	Treatment of uncomplicated influenza
Design:	Multicenter, randomized, double-blind, placebo controlled trial to evaluate efficacy and safety of nitazoxanide (NTZ) in the treatment of uncomplicated influenza
Number of Subjects:	At least 600 (up to maximum of 700) with laboratory-confirmed influenza; estimated to require approximately 800-1200 subjects in total
Population:	Males and females ≥ 12 years of age with uncomplicated influenza
Randomization:	1:1
Study Dose and Administration:	Group 1 (NTZ): Two NTZ 300 mg tablets orally twice daily (b.i.d.) for 5 days. Group 2 (Placebo): Two placebo tablets orally b.i.d. for 5 days.
Objective:	Evaluate the effect of NTZ administered 600 mg orally b.i.d. for 5 days in reducing the duration of symptoms compared to that of a placebo.
Primary Efficacy Parameter:	Time from first dose to Symptom Response over 21 days of follow up based upon the FLU-PRO© instrument
Key Secondary Efficacy Parameter:	Time from first dose to Ability to Perform All Normal Activities
Other Secondary Efficacy Parameters:	(i) Proportions of subjects experiencing one or more complications of influenza including pneumonia, otitis media, bronchitis, sinusitis, worsening of pre-existing health conditions, systemic antibiotic use for infections secondary to influenza infection, hospitalization due to influenza or complications of influenza, and death (ii) Time to Symptom Response excluding the FLU-PRO Gastrointestinal and Eye domains
Safety Parameters:	Adverse events
Biological Samples:	Blood samples will be collected for all subjects at baseline, day 7 and day 22. Urine samples will be collected at baseline and day 7. Nasopharyngeal swabs will be collected at baseline, days 2, 3, 7 and 22 for all subjects. A blood sample will be collected on day 3 for pharmacokinetics.
Study Centers:	Multicenter
Trial Duration:	December 2017 – April 2019

1 BACKGROUND

1.1 Influenza

Influenza, a contagious respiratory illness caused by influenza A, B or C viruses, is of global concern with an annual attack rate estimated at 5% to 10% in adults and 20% to 30% in children. Infection with influenza results in about 3-5 million cases of severe disease and 250,000-500,000 deaths annually worldwide.[1] In the United States, seasonal influenza has been responsible for between 9.2 million and 35.6 million illnesses, 140,000 and 710,000 hospitalizations, and 12,000 and 56,000 deaths annually since 2010. [2]

Pandemics caused by new influenza strains have typically occurred every 10 to 50 years throughout recorded history and are recognized as a global threat. The pandemic of 1918 was particularly severe, resulting in approximately 40 million deaths worldwide.[3]

The genome of influenza A viruses consists of eight single-stranded RNA segments that encode 11 proteins, including the main surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), of which 16 HA (H1–H16) and nine NA (NA1–NA9) subtypes have been identified so far.[4] Influenza virus infection involves a series of steps: the virus attaches to host sialylated glycoproteins via the viral HA and enters the cell by endocytosis, followed by pH-dependent fusion and release of viral genomic ribonucleo-protein complexes in the cytoplasm. Ribonucleoproteins then translocate to the nucleus where transcription and replication of viral RNA occurs. During the replication cycle, some viral proteins translocate to the nucleus for progeny ribonucleoprotein formation, whereas the viral HA, NA, and M2 proteins reach the plasma membrane via the secretory pathway, an event that is essential for viral particle formation and budding from host cells.[5] In humans, influenza A virus replicates throughout the respiratory tract, where the viral antigen is found predominantly in the epithelial cells. The typical course of influenza is self-limiting and lasts for about a week; however, clinical outcomes range from mild disease to fatal viral pneumonia.[6,7] Although the mechanisms underlying the expression of symptoms and the development of secondary complications that may result in respiratory failure are still not well understood, excessive inflammation caused by overabundant production of pro-inflammatory cytokines and lung inflammatory infiltrates, driven in part by ongoing viral replication, is considered an important factor in disease pathogenesis.[8-10]

HA and NA glycoproteins, which are the main targets of the protective immune response, vary continuously as a result of antigenic drift and less often antigenic shift. Major changes from antigenic shift are caused by different HA and NA subtypes derived from viruses circulating in birds and other animals that create a reservoir of influenza A genes available for genetic reassortment with the circulating human viruses.[11] The lack of protective immunity in the human population against new HA with or without new NA proteins can result in rapid global spread of the virus. In recent history, the emergence of high pathogenicity avian influenza viruses in domestic poultry and the increasing number of cases of direct transmission of avian influenza viruses to humans represent a major risk, as indicated by the ongoing outbreak of high pathogenicity avian influenza H5N1 viruses in the bird population and by an approximate 50% case fatality rate among the people infected.[12,13] In addition, the highly contagious pandemic 2009 A(H1N1) virus derived from swine recently emerged in Mexico and rapidly spread worldwide causing an estimated 201,200 respiratory deaths (range 105,700-395,600) and an additional 83,300 cardiovascular deaths (46,000-179,900), 80% of which were in people younger than 65 years in its first year of circulation.[14] Novel antiviral drugs effective against different strains of influenza viruses are therefore greatly needed.

1.2 Nitazoxanide (NTZ)

NTZ is a thiazolide anti-infective with *in vitro* activity against parasites, anaerobic bacteria, and viruses.[15]

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.[16]

1.2.1 Activity of NTZ Against Influenza Virus Replication

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.[17-19] (Romark Laboratories, data on file)

A study of the susceptibility of 210 circulating seasonal influenza viruses to tizoxanide demonstrated median EC_{50} 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.[20]

Studies in cell cultures have shown that combinations of nitazoxanide and oseltamivir or nitazoxanide and zanamivir act synergistically in inhibiting replication of the influenza viruses. Strains used in these studies included A/Puerto Rico/8/1934 (H1N1), A/WSN/1933 and the avian A/chicken/Italy/9097/1997 (H5N9) strains.[21] A confirmatory study showed synergistic activity with oseltamivir using A/California/07/2009 (pH1N1), A/Victoria/361/2011 (H3N2), A/North Carolina/39/2009 oseltamivir-resistant (pH1N1), and B/Nevada/3/2011 strains. (Romark Laboratories, data on file)

Mechanism studies demonstrate that tizoxanide inhibits the replication of H1N1 and other strains of influenza A virus by a novel mechanism.[17] It acts at the post-translational level by selectively blocking the maturation of the viral hemagglutinin at a stage preceding resistance to endoglycosidase H digestion, thus impairing hemagglutinin intracellular trafficking and insertion into the host plasma membrane, a key step for correct assembly and exit of the virus from the host cell.[17] Whether the alteration of hemagglutinin maturation is caused by direct binding of tizoxanide to the viral glycoprotein or is due to a cell-mediated effect remains to be established.[17] Tizoxanide has been shown to possess antiviral activity in cell culture against a broad range of other viruses including parainfluenza (Sendai) virus, respiratory syncytial virus (RSV) A-2, canine coronavirus S-378, 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).[22] The wide spectrum of antiviral activity suggests a cell-mediated effect rather than a specific viral target.

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

1.2.2 Pharmacokinetics of NTZ in Humans

NTZ is not detectable in the plasma following oral administration of the drug. The main metabolites of NTZ in humans are tizoxanide and tizoxanide glucuronide. Tizoxanide is highly bound to plasma proteins (>99%). The absorption of NTZ in immediate release tablets is significantly enhanced (C_{max} and AUC of tizoxanide and tizoxanide glucuronide in plasma are more than doubled) when it is administered with food. In fasted human volunteers receiving a single 500 mg dose of ^{14}C NTZ, approximately one-third of the dose was excreted in urine as tizoxanide and tizoxanide glucuronide, and two-thirds was excreted in feces as tizoxanide. No other significant metabolites were detected. (Investigators Brochure for NTZ 300 mg Tablets, November 2017)

The pharmacokinetics of tizoxanide and tizoxanide glucuronide during repeated oral dosing of nitazoxanide (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:

Summary of Tizoxanide and Tizoxanide Glucuronide Pharmacokinetics Parameters

PK Parameter (unit)	Tizoxanide		Tizoxanide Glucuronide	
	Day 1 N=12	Day 7 N=12	Day 1 N=12	Day 7 N=12
C_{max} (µg/mL)	5.23 ± 2.71	8.16 ± 4.16	4.88 ± 1.72	8.96 ± 3.48
t_{max} (h)	6.00 (4.00-9.00)	5.00 (3.00-8.00)	6.00 (5.00-11.00)	5.50 (0.00-7.02)
t_{lag} (h)	0.00 (0.00-2.00)	0.00 (0.00-0.00)	0.50 (0.00-2.00)	0.00 (0.00-0.00)
AUC_{0-t} (µg.h/mL)	26.9 ± 16.1	52.5 ± 33.7	29.5 ± 12.1	75.0 ± 37.8
AUC_{0-T} (µg h/mL)	28.6 ± 16.3[a]	48.3 ± 31.9[b]	30.5 ± 12.2[c]	75.2 ± 37.9
C_T (µg/mL)	0.709 ± 0.987	1.72 ± 2.04	1.39 ± 0.846	3.89 ± 2.88
$AUC_{0-\infty}$ (µg h/mL)	27.8 ± 17.8[b]	52.3 ± 35.6[b]	35.3 ± 16.5[d]	62.1 ± 24.2[e]
$t_{1/2}$ (h)	1.66 ± 0.408[b]	2.19 ± 0.485[b]	2.70 ± 0.848[c]	4.99 ± 5.20
λ_z (1/h)	0.441 ± 0.106[b]	0.331 ± 0.0733[b]	0.282 ± 0.0902[c]	0.201 ± 0.0813
C_{avg} (µg/mL)	NA	4.02 ± 2.66[b]	NA	6.27 ± 3.16
C_{min} (µg/mL)	NA	1.50 ± 1.83	NA	3.63 ± 3.00
PTF (%)	NA	193 ± 39.1[b]	NA	101 ± 40.7
Swing (%)	NA	1039 ± 656	NA	268 ± 194

Values are arithmetic mean ± SD, except median (range) for t_{max} and t_{lag}
N = number of subjects with data; NA = not applicable
[a] N=10; [b] N=11; [c] N=11; [d] N=8; [e] N=7

Summary of Tizoxanide and Tizoxanide Glucuronide Trough Plasma Concentrations

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

1.2.3 Phase 2 Clinical Trials of NTZ in Subjects with Influenza-like Illness: Studies RM02-2022 and RM01-2021

Two randomized, double-blind, placebo controlled clinical trials were conducted in subjects with symptoms of viral respiratory infection (VRI) in Cajamarca, Peru.

Study RM02-2022: One-hundred (100) children aged 12 months through 11 years of age with fever, at least one respiratory symptom (cough, nasal discharge or congestion, sneezing or sore throat) and at least one constitutional symptom (myalgia, malaise, fatigue, headache, chills/sweat) of less than 72 hours duration were randomized to receive NTZ 100 mg/5 mL suspension or a matching placebo suspension b.i.d. for 5 days. The dose of the suspension was 5 mL for children aged 12 through 47 months and 10 mL for children aged 48 months through 11 years. A nasopharyngeal swab was obtained at baseline and subjected to rapid direct immunofluorescence assay for respiratory syncytial virus (RSV), influenza A, influenza B, parainfluenza 1, 2 and 3, and adenovirus. Physical examinations were performed at baseline and on study day 7. Subjects or their parents or guardians maintained a daily diary to record administration of study medication and adverse events and to grade each of their symptoms on a 4 point scale: 0= absent, 1= mild, 2= moderate, 3= severe. A study nurse visited each subject daily during the treatment period to ensure compliance with the study and to collect plastic zipper storage bags containing tissue used during the preceding day. The primary endpoint of the study was time from first dose to alleviation of symptoms (all symptoms absent or mild) compared using a survival analysis (log rank test). The median times from first

dose to alleviation of symptoms were 4 days (IQR 2-7) for the NTZ treatment group and >7 days (IQR 3- >7) for the placebo group (P<0.001, log rank test). This analysis was supported by secondary analyses. Subjects randomized to the placebo treatment group were more likely to have at least one illness-related physical exam abnormality at day 7 follow up (81% vs. 28%, P<0.0001), and they were more likely to require antibiotic treatment at the day 7 follow up (64% vs. 9%, P<0.0001) than subjects treated with NTZ. The most common illness-related physical exam findings at the day 7 follow-up visit were erythematous oropharynx (72% vs. 20%, P<0.0001), hypertrophic tonsils (74% vs. 17%, P<0.0001), nasal congestion (49% vs. 9%, P<0.0001), ronchi (40% vs. 7%, P=0.0006) and adenomegaly (26% vs. 7%, P=0.02). Treatment with NTZ was associated with a significant decline in weight of daily tissue collections during the treatment period (P=0.0347). By rapid direct immunofluorescence assay, respiratory viruses were identified in 17% of the subjects, 12 subjects with adenovirus, 2 with influenza A, 2 with parainfluenza 1, and 1 with RSV. The small number of subjects with identified VRI did not allow for analyses for subsets with specific VRIs. There were no serious adverse events. All adverse events were mild to moderate in severity. The nature and frequency of adverse events reported by subjects in the active and placebo groups were similar, the only exception being a higher incidence of chromaturia (yellow discoloration of urine), which was reported by 64% of subjects in the NTZ group and 28% of subjects in the placebo group (P=0.0006).

Study RM01-2021: In a second clinical trial, 86 adults and adolescents ≥12 years of age with fever, at least one respiratory symptom (cough, nasal discharge or congestion, sneezing or sore throat) and at least one constitutional symptom (myalgia, malaise, fatigue, headache, chills/sweat) of less than 72 hours duration were randomized to receive NTZ 500 mg tablets or a placebo b.i.d. for 5 days. A nasopharyngeal swab was obtained at baseline and subjected to rapid direct immunofluorescence assay for respiratory syncytial virus (RSV), influenza A, influenza B, parainfluenza 1, 2 and 3, and adenovirus. Physical examinations were performed at baseline and on study day 7. Subjects maintained a daily diary to record administration of study medication and adverse events and to grade each of their symptoms on a 4 point scale: 0= absent, 1= mild, 2= moderate, 3= severe. A study nurse visited each subject daily during the treatment period to ensure compliance with the study and to collect plastic zipper storage bags containing tissue used during the preceding day. The primary endpoint of the study was time from first dose to alleviation of symptoms (all symptoms absent or mild) compared using a survival analysis (log rank test). The median time from first dose to alleviation of VRI symptoms was 4 days (IQR 3-5) for the NTZ treatment group and 7 days (IQR 3- >7) for the placebo group (P=0.0365, log rank test). This analysis was supported by secondary efficacy analyses. Subjects randomized to the placebo treatment group were more likely to have at least one illness-related physical exam abnormality at the day 7 follow up (71% vs. 37%, P=0.0032), and they were more likely to require antibiotic treatment at the day 7 follow up (36% vs. 18%, P=0.132) than subjects treated with NTZ. The most common illness-related physical exam findings at the day 7 follow up visit were erythematous oropharynx (69% vs. 26%, P<0.001) and hypertrophic tonsils (50% vs. 21%, P=0.01). The mean weight of tissue collected over the treatment period was also higher for subjects in the placebo group than for subjects treated with NTZ (14.23 grams vs. 10.58 grams, P=0.20), with the difference arising primarily during the first two to three days of the study. By rapid direct immunofluorescence assay, respiratory viruses were identified in 12% of the subjects, 4 subjects with adenovirus, 5 with RSV and 1 with influenza A. There were no serious adverse events. All adverse events were mild to moderate in severity. The nature and frequency of adverse events reported by subjects in the active and placebo groups were similar, the only exception being a higher incidence of chromaturia (yellow discoloration of urine), which was reported by 60% of subjects in the NTZ group and 19% of subjects in the placebo group (P=0.0001).

1.2.4 Phase 2b/3 Clinical Trial of NTZ in Uncomplicated Influenza: Study RM08-3001

A randomized, double-blind, placebo controlled dose-range finding study was conducted to compare the efficacy of 300 mg NTZ twice daily for 5 days, 600 mg NTZ twice daily for 5 days or a placebo for the treatment of uncomplicated influenza in subjects 12 to 65 years of age. The study was conducted in 74 outpatient primary care centers located throughout the United States during the 2010-2011 flu season. 624 subjects were enrolled in the study within 48 hours of symptom onset. Subjects were enrolled based upon symptoms and the presence of influenza in the community. Upon enrollment, subjects were randomized to one of the three treatment groups. Nasopharyngeal swabs were collected at baseline for identification of 19

different viral respiratory infections by RT-PCR. Subjects maintained diaries to record time of medication intake, oral temperature, the severity of each of 9 symptoms (cough, sore throat, nasal congestion, runny nose, headache, muscle aches, tiredness/fatigue, feverish, sweats or chills graded as absent, mild, moderate or severe), ability to perform normal activities (scale of 0-10), time lost from work or school, concomitant medications and adverse events. Diary data was recorded twice daily through study day 7 or, if longer, until the subject no longer had any moderate or severe influenza symptoms. Subjects returned to the clinic for follow-up on day 7 and day 28. Blood and urine samples were collected at baseline and day 7 for laboratory safety tests, and blood samples were collected at baseline and day 28 for influenza antibody titer. A subset of subjects from approximately 20% of the study sites were visited by the study team to collect nasopharyngeal swabs on days 2, 3, 4 and 5 for quantitative influenza viral titer determination. Nasopharyngeal swabs were collected from all subjects at day 7 for identification of viruses and for quantitative influenza viral titer. The primary efficacy endpoint was time from first dose to alleviation of symptoms (all symptoms absent or mild and remained so for at least 24 hours).

257 subjects (41%) enrolled in this study were infected with influenza A or influenza B based upon RT-PCR and viral cultures performed on nasopharyngeal swabs collected at baseline. 17% were infected with influenza A subtype 2009 H1N1, 8% with influenza A H3N2, 4% with influenza A subtype undetermined, and 12% with influenza B. 22% were infected with other viruses, the most common being rhinovirus (14% of all subjects enrolled) followed by coronaviruses (3% of all subjects enrolled). While RT-PCR was used to identify viruses in the baseline nasopharyngeal sample, no cause of illness was identified for 37% of subjects enrolled in the study.

Time from first dose to alleviation of symptoms was significantly lower (P=0.0084, Wilcoxon test) for influenza-infected subjects randomized to the 600 mg NTZ treatment group (median 95.5 hours, IQR: 71-126) than for subjects randomized to the placebo treatment group (median 116.7 hours, IQR: 91-144). Time from first dose to alleviation of symptoms for the 300 mg NTZ treatment group (median 109.1 hours, IQR: 82-152) was lower than for the placebo group, but the difference was not statistically significant (P=0.5208). Sensitivity analyses confirmed the effect in the 600 mg NTZ dose group compared to the placebo regardless of (i) acetaminophen use, (ii) exclusion of subjects that failed to complete the study or had major protocol deviations, or (iii) treating subjects with missing data as having resolved symptoms at day 28. Analysis of all subjects treated (regardless of cause of illness) also showed a statistically significant reduction (P=0.0026) of times from first dose to alleviation of symptoms for the 600 mg NTZ treatment group (median 94.9 hours, IQR: 62-126) compared to the placebo group (median 108.2 hours, IQR: 82-152).

Further virology testing using an updated RT-PCR method was undertaken to investigate the cause of illness for those patients with no virus identified at baseline, and patients were re-classified into new analysis populations based on positive RT-PCR or culture results at any time during the treatment period (baseline through day 7). In these new analysis populations, 46% were infected with influenza A or B, 28% were infected with other viruses, and 26% had no cause of illness identified.

In the retrospective analysis of patients with laboratory-confirmed influenza from samples collected between baseline and day 7, times from first dose to resolution of symptoms were significantly lower (P=0.0006) for influenza-infected patients randomized to the 600 mg NTZ treatment group (median 95.5 hrs, IQR: 65-124) than for patients randomized to the placebo treatment group (median 117.3 hrs, IQR: 93-152). Times from first dose to resolution of symptoms for the 300 mg NTZ treatment group (median 108.6 hrs, IQR: 81-144) were lower than for the placebo group, but the difference was not statistically significant (P=0.1930).

Analyses of daily $TCID_{50}$ viral titers of subjects with daily nasopharyngeal swab collections showed statistically significant reductions of viral titer for the 600 mg NTZ treatment group compared to the placebo treatment group (P=0.0006). Reductions of viral titer compared to the placebo were observed at the first nasopharyngeal swab collection following initiation of treatment (~24 hours after initiating treatment) and were maintained until day 5, by which time the viral titers for subjects in the placebo treatment group had declined to levels approximating those of subjects in the NTZ treatment groups. As observed in the analysis of time to resolution of symptoms, treatment with 300 mg NTZ twice daily for 5 days was associated with an

intermediate viral titer response between that of the 600 mg NTZ treatment group and the placebo group. Differences in viral titers between this low dose treatment group and the placebo treatment group were not statistically significant (*P*=0.1553).

Treatment with NTZ did not impair the normal humoral antibody response to infection. There were no significant differences between the treatment groups in antibody titer increases from baseline to study day 28.

Adverse events were similar to those reported by subjects receiving placebo, with the exception of a greater frequency of diarrhea in the 600 mg NTZ treatment group (17/211, 8.1%) compared to the placebo group (7/212, 3.3%) (*P*=0.0373). None of these adverse events resulted in interruption or discontinuation of therapy.[23]

1.2.5 Randomized 2x2 Factorial Trial of NTZ and OST in Treating Uncomplicated Influenza: Study RM08-3002

A randomized, double-blind, factorial trial of NTZ and OST was conducted in 130 outpatient primary care clinics in the United States, Canada, Belgium, Australia and New Zealand between March 2013 and April 2015. 1,941 subjects 13 to 65 years of age were enrolled based upon symptoms and the presence of influenza in the community. Subjects were enrolled within 48 hours of symptom onset and randomized to receive NTZ 600 mg, OST 75 mg, NTZ 600 mg plus OST 75 mg or placebo twice daily for five days. Nasopharyngeal swabs were collected at baseline for identification of 19 different viral respiratory infections by RT-PCR. Subjects maintained diaries to record time of medication intake, oral temperature, the severity of each of 7 symptoms (cough, nasal obstruction, sore throat, fatigue, headache, myalgia or feverishness graded as absent, mild, moderate or severe), ability to perform normal activities (scale of 0-10), time lost from work or school, concomitant medications and adverse events. Diary data was recorded twice daily through study day 14 or, if longer, until the subject no longer had any moderate or severe influenza symptoms. Subjects returned to the clinic for follow-up on day 7, day 14 and day 28. Blood and urine samples were collected at baseline and day 7 for laboratory safety tests, and blood samples were collected at baseline and day 28 for influenza antibody titer. A subset of subjects from selected study sites (approximately 33% of the subjects enrolled) were visited by the study team to collect nasopharyngeal swabs on days 2, 3, 4 and 5 for quantitative influenza viral titer determination. For the subjects, blood samples were also collected on days 3 and 5 for population pharmacokinetics. Nasopharyngeal swabs were collected from all subjects at days 7 and 14 for identification of viruses and for quantitative influenza viral titer. The primary efficacy endpoint was time from first dose to alleviation of symptoms (all 7 symptoms absent or mild and remained so for at least 24 hours). There were two primary efficacy analyses: (1) comparison of time to symptom alleviation for the NTZ treatment group and the placebo, and (2) comparison of time to symptom alleviation for the NTZ+OST treatment group to each of the other treatment groups.

737 subjects (38%) enrolled in this study were infected with influenza A or influenza B based upon RT-PCR and viral cultures performed on nasopharyngeal swabs collected at baseline. 25% were infected with influenza A subtype 2009 H1N1, 8% with influenza A H3N2, 1% with influenza A subtype undetermined, and 4% with influenza B. 23% were infected with other viruses, the most common being rhinovirus (12% of all subjects enrolled) followed by coronaviruses (6% of all subjects enrolled). No cause of illness was identified for 39% of subjects enrolled in the study.

In the primary analysis, times from first dose to alleviation of 7 symptoms were not significantly different for any of the treatment groups. Each of the three active treatment groups showed improvement in time to alleviation of a composite endpoint made up of fever, feverishness and myalgia (acute febrile illness) compared to the placebo (nominal $p<0.05$), and each of the three active treatment groups showed meaningful (up to approximately 2 days) improvement in time from first dose until subjects were able to perform all of their normal activities compared to the placebo (NS). No significant differences (i.e., nominal p-value <0.05) in time to alleviation of the respiratory symptoms were observed between groups.

Under these experimental conditions, the positive control, OST, did not show the expected effect on time to alleviation of 7 symptoms. The inability to detect treatment effect in the primary analysis was attributed to methodology used to collect patient-reported outcome/symptom data.

Treatment with NTZ as monotherapy or in combination with OST did not impair the normal humoral antibody response to infection. There were no significant differences between the treatment groups in antibody titer increases from baseline to study day 28.

Treatment with NTZ 600 mg twice daily for five days as monotherapy or in combination with OST was well tolerated by subjects. The most commonly reported adverse events (reported by ≥2% of subjects in any treatment group) regardless of causality were:

Adverse event (≥2%)	NTZ (%)	OST (%)	NTZ+OST (%)	Placebo (%)
Nausea	3.9	4.4	6.4	5.3
Vomiting	2.5	4.2	6.4	2.7
Diarrhoea	6.2	2.5	3.9	4.9
Abdominal pain upper	2.1	0.8	2.3	1.2
Chromaturia	5.2	-	5.5	0.4
Dizziness	2.5	3.1	3.1	1.0

There were no serious adverse events related to any of the treatments.

1.2.6 Randomized Double-Blind Placebo Controlled Trial of NTZ in Treating Uncomplicated Influenza: Study RM08-3003

A Phase 3 randomized, double-blind, placebo controlled trial was conducted in 25 outpatient primary care clinics in the United States, Puerto Rico and Australia between December 2015 and August 2016. Three hundred twenty-four subjects 12 to 65 years of age were enrolled based upon symptoms and the presence of influenza in the community. Subjects were enrolled within 40 hours of symptom onset and randomized to receive NTZ 600 mg or placebo twice daily for five days. Nasopharyngeal swabs were collected at baseline for identification of respiratory pathogens by RT-PCR. All subjects either returned to the clinic or were visited daily by the study team to collect nasopharyngeal swabs on days 2, 3, 4 and 5 for quantitative influenza viral titer determination. Blood samples were collected on days 3 and 5 for population pharmacokinetics. Subjects maintained diaries to record time of medication intake, oral temperature, the severity of each of 7 symptoms (cough, nasal obstruction, sore throat, fatigue, headache, myalgia or feverishness graded as absent, mild, moderate or severe), ability to perform normal activities (scale of 0-10), time lost from work or school, concomitant medications and adverse events. Diary data was recorded twice daily through study day 14 or, if longer, until the subject no longer had any moderate or severe influenza symptoms. Subjects returned to the clinic for follow-up on day 7, day 14 and day 28. Blood and urine samples were collected at baseline and day 7 for lab safety tests, and blood samples were collected at baseline and day 28 for influenza antibody titer. Nasopharyngeal swabs were collected from all subjects at days 7 and 14 for identification of viruses and for quantitative influenza viral titer. The primary efficacy endpoint was time from first dose to alleviation of symptoms (all 7 symptoms absent or mild and remained so for at least 21.5 hours). The primary efficacy analysis was a comparison of times from first dose to symptom alleviation for subjects in the NTZ and placebo treatment groups with laboratory-confirmed influenza at baseline, day 2 or day 3. The analysis was performed using a Prentice Wilcoxon test with an alpha of 0.05.

Two hundred sixty-three (263) of the 324 subjects enrolled in the study had laboratory-confirmed influenza A or influenza B identified in a nasopharyngeal swab sample collected at baseline, day 2 or day 3. 38% were infected with influenza A subtype 2009 H1N1, 17% with influenza A H3N2, 43% with influenza B, and 2% were infected with two influenza viruses.

In the primary analysis, times to alleviation of 7 symptoms were not statistically different for the NTZ treatment group compared to the placebo. Median times from first dose to alleviation of all symptoms were 101 hours [IQR 68-153] for the NTZ-treated group compared to 102.5 hours [IQR 69-155] for the placebo group, p=0.6132. Nevertheless, the NTZ treatment group did show improvement in time to alleviation of a composite endpoint made up of fever, feverishness and myalgia (acute febrile illness) compared to the placebo (nominal p=0.004), and it showed median improvement of 42 hours in time from first dose until subjects were able to perform all of their normal activities compared to the placebo (NS). No significant differences (i.e., nominal p-value < 0.05) in time to alleviation of the respiratory symptoms were observed between groups.

Times to alleviation of the 7 symptoms, especially the respiratory symptoms, were very short during this particular season. In the subset subjects infected with influenza A/H3N2, the duration of symptoms was somewhat longer, and in this subset, treatment with NTZ was associated with a reduction of time to alleviation of all symptoms (difference at median -23.3 hrs [IQR -21, -16], NS).

Treatment with NTZ did not impair the normal humoral antibody response to infection. No resistance was observed. Adverse events were similar to those reported by subjects receiving placebo, with the exception of a greater frequency of mild chromaturia in the 600 mg NTZ treatment group (12.9%) compared to the placebo group (0%). None of these adverse events resulted in interruption or discontinuation of therapy.

Data from these studies as well as historical clinical trials of the approved neuraminidase inhibitors point to the need for improved methodology to measure treatment benefit for studies of influenza antivirals.

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

NTZ has been marketed in the United States since 2003 and in Latin America since 1996. It is estimated that more than 250 million patients have been exposed to NTZ post-marketing worldwide. No drug-related serious adverse events have been reported during post-marketing experience with NTZ.

Phase 2 and 3 clinical studies have been conducted in approximately 5,600 subjects to evaluate the safety and efficacy of NTZ in treating parasitic, bacterial and viral infections. During these studies, no drug-related serious adverse events have been observed. The side effects have been usually of a mild transient nature, and less than 1% of subjects have discontinued therapy because of an adverse event. The most common adverse events reported in clinical trials include abdominal pain, chromaturia, diarrhea, dizziness, headache, nausea and vomiting and did not differ significantly from those of placebo except for chromaturia which was reported by 4 to 5% of subjects and is attributed to urinary excretion of NTZ metabolites. Clinical chemistry and hematology obtained before and after treatment have not revealed any abnormalities attributable to the test drug.[15]

1.3 Rationale for the Study

There is an important need for new treatments of influenza that may offer novel mechanisms of action, improved efficacy and safety profiles or reduced risks of resistance. There is also an important need for improvement in the methodology used to evaluate the effectiveness of influenza antiviral drugs. Notably, the patient-reported outcomes instruments used for historical clinical trials have not been validated according to current FDA standards.

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 in the treatment of uncomplicated influenza. The study will employ a new patient-reported outcome questionnaire, FLU-PRO©, that has been developed and validated according to current FDA standards. All subjects will complete the questionnaire daily for 21 days using an electronic diary for accountability.

2 STUDY OBJECTIVES

The primary objective of this study is to evaluate the effect of NTZ administered orally 600 mg b.i.d. for 5 days in reducing the duration of symptoms of influenza compared to that of a placebo during 21 days of follow up based upon the FLU-PRO© patient-reported outcome instrument.

A key secondary efficacy objective is to evaluate the effect of NTZ compared to placebo on time to return to ability to perform all normal activities.

Another secondary efficacy objective is to evaluate the effect of NTZ compared to placebo on the proportion of subjects experiencing one or more complications of influenza including pneumonia, otitis media, bronchitis, sinusitis, worsening of pre-existing health conditions, systemic antibiotic use for infections secondary to influenza infection, hospitalization due to complications of influenza, and death.

Exploratory efficacy objectives include evaluating the effect of treatment with NTZ on the time to response for each FLU-PRO symptom, time to response for each FLU-PRO domain, time to resolution of febrile illness, time to return to usual health, and changes in viral titers from baseline to each of days 2, 3 and 7.

Other important objectives include evaluation of the safety of NTZ by analysis of adverse events and evaluation of the effect of nitazoxanide on influenza antibody response and evaluation of relationships between pharmacokinetics and clinical or virologic responses.

3 STUDY DESIGN

The study will be a multicenter, randomized, double-blind trial to evaluate the efficacy of NTZ compared to placebo in treating uncomplicated influenza. Subjects will be selected according to the inclusion and exclusion criteria listed below. The study is designed to enroll at least 600 subjects (up to 700 maximum) with laboratory-confirmed influenza. Total enrollment required to achieve this number is expected to be approximately 800 to 1200 subjects. Prior to screening for inclusion in the study, informed consent will be obtained.

Immediately after completion of informed consent, screening, and enrollment in the study, two baseline nasopharyngeal swabs will be collected for viral culture and RT-PCR. A blood sample will be collected for laboratory safety tests and anti-influenza antibodies, and a urine sample will be collected for laboratory safety tests. Subjects will receive instruction on completion of their electronic diaries, concomitant medications and attending follow-up visits.

Then 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 medication will be taken twice daily with food (preferably a high-fat meal, but at minimum a cereal bar). The first dose will be taken with food in the physician's office under the observation of the Principal Investigator or a member of the Investigator's staff. The second dose will be taken by the subject as close as possible to 12 hours after the first dose.

A nurse or other study personnel will visit each subject (or the subject will return to the clinic) on study days 2 and 3 to collect two nasopharyngeal swabs, to review patient diaries, and to review symptoms and screen for influenza-related complications including sinusitis, otitis, bronchitis, pneumonia and central nervous system disease. Subjects will be referred for immediate care as needed based on the screening. A blood sample for pharmacokinetics will also be collected on study day 3. These day 2 and 3 visits will occur at approximately

the same time of day that the subject took his/her first dose of study medication (roughly 24 and 48 hours post-first dose). On day 3, the blood sample for pharmacokinetics will be collected before the dose. The nasopharyngeal swabs will be used to evaluate quantitative changes in viral shedding. The blood samples will be used to evaluate relationships between pharmacokinetics and virologic or clinical response. Study sites or subjects may opt out of the day 2 and day 3 visits due to site staffing, patient availability or other practical considerations or preferences; nevertheless, at least 75% of subjects enrolled in the trial are expected to complete the day 2 and day 3 visits and related procedures (for viral kinetics and pharmacokinetics).

A study physician, nurse or other site personnel will make daily telephone calls to subjects for the first five days of dosing to review symptoms and screen for influenza-related complications including sinusitis, otitis, bronchitis, pneumonia and central nervous system disease. Subjects will be referred for immediate care as needed based on the screening. [Note: In lieu of a telephone call, this information may be obtained during the day 2 or 3 office or home visits (see the preceding paragraph).] The study sites and subjects will be blinded from virology laboratory data until after study day 22 or, if earlier, until the subject is discontinued from the study. During the study period, each subject will be presumed to have influenza infection, and any worsening of symptoms or complications will be presumed to be influenza-related.

Subjects will return to the clinic on days 7 and 22 for post-treatment follow-up, including two nasopharyngeal swabs, drug accountability, reporting of adverse events and complications of influenza. Blood and urine samples for laboratory safety tests will be collected at day 7, and a blood sample for anti-influenza antibodies will be collected on day 22. A nurse or other study personnel will review the electronic patient diary entries daily (synchronized to a web-based data system) to ensure contemporaneous and complete recording of diary data. Subjects will maintain the electronic patient diaries until study day 22. Any visits that do not occur on the prescribed date, or within 1 day of that date in the case of the day 7 visit or within 3 days after that date in the case of the day 22 visit, will be recorded as protocol deviations.

A central laboratory will be used for laboratory safety tests, anti-influenza antibodies and virology testing. Laboratory safety tests will include hemoglobin, hematocrit, complete blood count (total and differential), platelet count, random blood sugar, total cholesterol, HDL, LDL, triglycerides, albumin, AST, ALT, GGT, alkaline phosphatase, bilirubin (total/direct), BUN, creatinine, sodium, potassium, chloride and routine urinalysis (glucose, protein and blood). Virology testing will include RT-PCR assay ePlex® Respiratory Pathogen Panel (GenMark, Carlsbad, CA) to identify influenza A (non-specific as to subtype); influenza A H1, H1N1 (2009) and H3 subtypes; influenza B; respiratory syncytial virus A and B (RSV); parainfluenza 1, 2, 3 and 4; human metapneumovirus (hMPV); adenovirus (A-F); human rhinovirus/enterovirus; coronavirus NL63, HKU1, 229E and OC43; *Chlamydophila pneumoniae*; and *Mycoplasma pneumoniae* (baseline and day 7 nasopharyngeal swabs), culture (baseline and day 7 nasopharyngeal swabs), and quantitation of influenza viruses by $TCID_{50}$ (baseline and days 2, 3 and 7 nasopharyngeal swabs). Follow-up samples (days 2, 3, 7 and 22) collected from subjects who do not test positive for influenza A or influenza B at baseline will not be analyzed for quantitative influenza viral titer.

This study is expected to run from December 2017 through April 2019.

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

- *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) was selected based upon results of a Phase 2b/3 dose-range finding clinical trial (Study RM08-3001) conducted in the United States during the 2010-2011 flu season. In that study, treatment with 600 mg NTZ b.i.d. for 5 days was associated with a statistically significant reduction in time from first dose to alleviation of symptoms compared to the placebo. A 300 mg NTZ dose group also experienced a reduction of time to alleviation of symptoms compared to the placebo, but the difference was not statistically significant. The 600 mg NTZ dose was well tolerated. Adverse events reported for subjects receiving the

600 mg dose were similar to those of subjects receiving the placebo, with the exception of a higher rate of diarrhea (8.1% compared to 3.3% for the placebo).

- *Choice of control groups.* According to FDA Guidance, a placebo-controlled rather than non-inferiority design should be used for trials evaluating treatment of uncomplicated influenza because the risks of receiving a placebo are low, and the efficacy of available treatment is modest, variable and cannot be predicted well enough to support an adequate inferiority margin.[24]

- *Choice of patient population.* The population to be studied includes adults and adolescents at least 12 years of age with uncomplicated influenza. This is a population similar to those selected for studies RM08-3001, RM08-3002, and RM08-3003 of the NTZ 300 mg extended release tablets. No safety concerns have been identified from these clinical trials.

  For the present study, some subjects (e.g., subjects >65 years of age, mild asthma, stage I or II COPD, diabetes mellitus if not poorly controlled, etc. – see Inclusion/Exclusion criteria in Sections 4.1 and 4.2) who are at higher risk of influenza complications according to CDC criteria will be allowed to participate if, in the judgment of the investigator, they are able to comply with protocol requirements and do not have a pre-existing illness or condition that would place them at an unreasonably increased risk. Inclusion of these patients in the study will improve recruitment efforts and will provide important data related to the effectiveness and safety of the NTZ 300 mg extended release tablets in this population. Notably, there is limited evidence to support the effectiveness of existing influenza antivirals in subjects at higher risk of influenza complications.

  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 Protocol Section 15). A signed assent form will be required for any minors enrolled (≤ 18 years of age or as local regulations apply) as well as a signed parental/legal guardian consent by their parent/legal guardian allowing for the minor's participation.

  According to FDA Guidance, antiviral drug efficacy in children cannot be extrapolated from data generated from trials in adults because: (1) prior exposure and immunity typically present in adults may affect influenza illness and response to treatment differently than in children; and (2) viral shedding may differ in pediatric and adult age groups.[24] Study of the efficacy and safety of the product in children is, therefore, required in order to have the product licensed for use in pediatric patients. Separate subset analyses of safety, pharmacokinetics and efficacy data for pediatric patients will be performed to evaluate the safety and efficacy of NTZ in this population.

- *Choice of Patient-Reported Outcome Instrument.* This clinical trial will use a new, recently released patient-reported outcome questionnaire, 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 treatment of influenza. 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 is designed to comprehensively assess the presence and severity of influenza symptoms across body systems. The questionnaire has addressed issues that limit interpretation of historical influenza studies by including extensive input from influenza-infected patients to ensure that (1) all symptoms of influenza are assessed (content validity), and (2) the questions are asked in a manner and with response options that patients understand (context validity) and that distinguish between known groups. The resulting instrument assesses 32 symptoms of influenza across six domains (nose, throat, eyes, chest/respiratory, gastrointestinal, body/systemic). Each question provides 5 response options instead of 4 used in traditional PRO instruments.[25, 26]

- *Choice of Endpoints*. The primary efficacy endpoint for this study will be Time to Symptom Response based upon the FLU-PRO© instrument. This is directed to the way the patient "feels" as measured by his/her symptoms. A Symptom Response definition will be developed based upon a blinded review of FLU-PRO symptom scores (pooled for all subjects without regard to treatment group assignment so as to maintain blinding) and correlation of those scores to the time at which subjects report that they have returned to their usual state of health (a "yes" or "no" question incorporated into the daily Questionnaire). The Time to Symptom Response used for evaluating the primary endpoint will be calculated based upon this response definition and programmed prior to database unblinding for the primary analysis. This anchor-based approach to defining responders ensures that the symptom response definition is valid and meaningful for the subjects participating in each given clinical trial – a point that may be particularly important in the case of an illness like influenza that is not uniform from year to year.

  The key secondary endpoint will be Time to Ability to Perform All Normal Activities. This endpoint will provide important information with respect to the way a patient "functions." Each of the previous clinical trials of NTZ in subjects with influenza have indicated improvement in this endpoint while data collection from those studies has typically not extended out long enough to fully characterize the benefit.

  Another secondary endpoint will be proportions of subjects experiencing complications of influenza. We do not expect to see enough complications of influenza in this population to demonstrate differences between treatment groups, and therefore, this endpoint is lesser in priority compared to Time to Ability to Perform All Normal Activities. All other efficacy endpoints will be considered exploratory.

4 PATIENT SELECTION

The criteria for inclusion and exclusion are defined below:

4.1 Inclusion Criteria

1) Male and female subjects at least 12 years of age

2) Presence of clinical signs and/or symptoms consistent with an acute illness compatible with influenza infection (each of the following is required):
   a) oral temperature of ≥99.4°F or ≥37.4°C (obtained in office or self-measured within 12 hours prior to screening – if self-measured, subject must also have taken an antipyretic within 4 hours prior to screening), AND
   b) at least one of the following respiratory symptoms (cough, sore throat, nasal obstruction), AND
   c) at least one of the following constitutional symptoms (fatigue, headache, myalgia, feverishness).

3) Confirmation of influenza A or B infection in the local community by one of the following means: (a) the institution's local laboratory, (b) the local public health system, (c) the national public health system, or (d) a laboratory of a recognized national or multinational influenza surveillance scheme

4) Onset of illness no more than 40 hours before enrollment in the trial
   Note: Time of onset of illness is defined as the earlier of:
   a) the time when the temperature was first measured as elevated, OR
   b) the time when the subject experienced the presence of at least one respiratory symptom AND the presence of at least one constitutional symptom.

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 patient diary

4.2 Exclusion Criteria

1) Severity of illness requiring or anticipated to require in-hospital care

2) Moderate or severe asthma (Global Initiative for Asthma (GINA) 2017 classification)

3) Cystic fibrosis

4) Stage II, III or IV chronic obstructive pulmonary disease (COPD) (Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) 2017 classification)

5) NYHA Class III or IV congestive heart failure (at least marked limitation of physical activity in which minimal ordinary activity results in fatigue, palpitation, dyspnea, or angina pain)

6) Cardiac arrhythmia

7) Immunologic disorders or receiving immunosuppressive therapy (e.g., for organ or bone marrow transplants, immunomodulatory therapies for certain autoimmune diseases)

8) Untreated HIV infection or treated HIV infection with a CD4 count below 350 cells/mm^3 in the last 6 months

9) Persons with sickle cell anemia or other hemoglobinopathies

10) Poorly controlled insulin-dependent diabetes mellitus (HbA1C >8.0%)

11) Residents of any age of nursing homes or other long-term care institutions

12) Concurrent infection at the screening examination that requires systemic antimicrobial therapy

13) Females of childbearing potential who are either pregnant, breast-feeding or are 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.

14) Receipt of any dose of NTZ, oseltamivir, zanamivir, peramivir, laninamivir, baloxavir, amantadine or rimantadine within 3 days prior to screening

15) Prior treatment with any investigational drug therapy within 30 days prior to screening

16) Subjects with active respiratory allergies or subjects expected to require anti-allergy medications during the study period for respiratory allergies

17) Known sensitivity to NTZ or any of the excipients comprising the NTZ tablets

18) Subjects unable to take oral medications

19) Presence of any pre-existing illness or condition that, in the opinion of the Investigator, would place the subject at an unreasonably increased risk through participation in this study

20) Subjects who, in the judgment of the Investigator, will be unlikely to comply with the requirements of this protocol

5 STUDY PROCEDURES

5.1 Screening Evaluation (day 1)

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

1) Complete medical history;

2) Full physical examination including body weight and vital signs (blood pressure, pulse, respiratory rate and oral temperature using standard electronic oral thermometer provided by Sponsor);

3) Collection of demographic information and smoking history;

4) Urine pregnancy test for all females of childbearing potential;

5) Recording of symptoms and time of onset; and

6) Evaluation according to eligibility (inclusion and exclusion) criteria.

While not required by this study protocol, local influenza diagnostic testing may have been conducted prior to the screening visit in accordance with local standards of care. Results of any such local influenza diagnostic tests will not impact subject selection. Subjects will be selected solely on the basis of the eligibility criteria set forth in the protocol irrespective of the result of any local influenza diagnostic test that may have been performed.

5.2 Baseline (day 1, same day as screening evaluation)

At baseline, the following procedures will be carried out:

1) Collection of two nasopharyngeal swabs (one from each nostril) using nylon flocked dry swabs (Copan Diagnostics) for RT-PCR and culture;

2) Collection of blood sample for anti-influenza antibodies;

3) Collection of blood sample for laboratory safety tests including 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;

4) Collection of a urine sample for routine urinalysis (glucose, protein and blood);

5) Review and recording of any concomitant medications;

6) Provision of an electronic diary to subject via his/her own smartphone or a provisioned device, and subject completion of baseline electronic diary under supervision and instruction of study site personnel;

7) Randomization and dispensing of study medication (medication assigned in sequential order);

8) Administration of the first dose of study medication with food (< 1 hour after food intake) under observation of Investigator or a member of Investigator's staff, and entry in diary; and

9) Instruct subject regarding:

a. *Administration of study medication*. Subjects will be instructed to take the study medication (two tablets) twice daily with food (< 1 hour after food intake). The patient should take his/her second dose as close as possible to 12 hours after the first dose. Then he/she will take the study medication every 12 hours for the remaining 4 days.

b. *Concomitant medications*. Subjects will be instructed that they may take acetaminophen for fever if their oral temperature is ≥100.4°F (38°C). No other symptom relief medication should be used.

c. *Completion of patient diary*. Subjects will be instructed on completion of the electronic diary.

d. *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.

e. *Follow-up visits*: Patients will be instructed to return to the clinic for follow-up on day 7 and day 22.

f. *Seeking emergency care or contacting the study physician or nurse*: Subjects must be informed to seek emergency medical care or contact the study physician or nurse if they develop any of the following symptoms listed below during the full 22 day study and follow-up period.

CALL 911 (United States) OR LOCAL EMERGENCY SERVICES (outside of United States) OR HOSPITAL OR CONTACT STUDY PHYSICIAN, IF:

- Trouble breathing including shortness of breath.
- Severe headache, stiff neck, confusion or excessive somnolence.

CALL STUDY NURSE OR PHYSICIAN, IF:

- Extremely high fever >104°F (40°C).

- Fever (≥100.4°F or ≥38°C) lasts for longer than 3 days.
- 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.
- Fever (≥100.4°F or ≥38°C) returns after being absent for 24 hours.
- Symptoms recur or any difficulty breathing following 5-10 days resolution of influenza.
- An allergic-like reaction occurs or is suspected
- Abnormal behavior

10) Review and record adverse events.

5.3 Day 2 – Day 22

A study physician, nurse or other site personnel will review each subject's electronic diary entries daily to ensure compliance with collection of diary data. If a subject has not completed his/her diary or if errors are suspected, the study personnel will contact the subject to implement appropriate corrective actions.

5.4 Day 2-5 Telephone Monitoring

A study physician, nurse or other site personnel will make daily telephone calls to subjects on each of days 2, 3, 4 and 5 of dosing to review compliance with study medication, review symptoms, screen for influenza-related complications including sinusitis, otitis, bronchitis, pneumonia, central nervous system disease and worsening of pre-existing health conditions, and review adverse events. Subjects will be referred for immediate care as needed based on the screening. All information gained from telephone monitoring will be included in the case report forms for each subject. [Note: In lieu of a telephone call, this information may be obtained during the day 2 and 3 home or office visits (see below).]

5.5 Day 2 and 3 Evaluations

A study physician, nurse or other study personnel will visit each subject at home (or at the clinic or another location as agreed with the subject) on each of days 2 and 3 to (i) collect two nasopharyngeal swabs for detecting (RT-PCR) and quantifying ($TCID_{50}$) influenza virus, and (ii) review symptoms and screen for influenza-related complications including sinusitis, otitis, bronchitis, pneumonia, central nervous system disease and worsening of pre-existing health conditions as well as adverse events. Subjects will be referred for immediate care as needed based on the screening. All information gained from these visits will be included in the case report forms for each subject. In addition, a blood sample for pharmacokinetics will be collected on day 3. The day 2 and day 3 visits will occur at approximately the same time of day that the patient took his/her first dose of study medication (approximately 24 and 48 hours after the first dose). On day 3, the blood sample for pharmacokinetics will be collected before the first dose of that day.

Study sites or subjects may opt out of these day 2 and day 3 visits due to site staffing, patient availability or other practical considerations or preferences; nevertheless at least 75% of subjects enrolled in the trial are expected to complete the day 2 and day 3 visits and related procedures (for viral kinetics and pharmacokinetics).

5.6 Day 7 Follow-up (+/- 1 day)

Subjects will return to the clinic on day 7, and the following procedures will be performed:

1) Physical examination. Brief physical examination (body weight and vital signs with nursing physical assessment) including symptom directed physician physical examination as required by patient symptoms. Vital signs will include blood pressure, pulse, respiratory rate and oral temperature (use standard electronic oral thermometer provided by Sponsor);

2) Collection of two nasopharyngeal swabs using nylon flocked dry swabs (Copan Diagnostics) for RT-PCR and culture;

3) Collection of blood sample for laboratory safety tests including 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;

4) Collection of urine sample for routine urinalysis (glucose, protein and blood);

5) Review of compliance with study medication, collection of medication bottle with any unused medications, and completion of the pill count log form;

6) Review and recording of concomitant medications; and

7) Review and recording of adverse events/side effects.

5.7 Day 22 Follow-up (+ 3 days)

Subjects will return to the clinic on day 22, and the following procedures will be performed:

1) Physical examination. Brief physical examination (body weight and vital signs with nursing physical assessment) including symptom directed physician physical examination as required by patient symptoms. Vital signs will include blood pressure, pulse, respiratory rate and oral temperature (use standard electronic oral thermometer provided by Sponsor);

2) Collection of two nasopharyngeal swabs using nylon flocked dry swabs (Copan Diagnostics) for RT-PCR and culture (to be tested for presence of virus only if the sample collected at the preceding time point had detectable virus);

3) Collection of blood sample for anti-influenza antibodies;

4) Review and recording of concomitant medications; and

5) Review and recording of adverse events/side effects. Note that all adverse events must be followed until their resolution or stabilization even beyond the 22-day study period.

5.8 Unscheduled Visit

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

1) Physical examination. Brief physical examination (body weight and vital signs with nursing physical assessment) including symptom directed physician physical examination as required by patient symptoms. Vital signs will include blood pressure, pulse, respiratory rate and oral temperature (use standard electronic oral thermometer provided by Sponsor);

2) Collection of two nasopharyngeal swabs using nylon flocked dry swabs (Copan Diagnostics) for RT-PCR and culture;

3) Collection of blood sample for laboratory safety tests including 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;

4) Collection of urine sample for routine urinalysis (glucose, protein and blood);

5) Review of compliance with study medication;

6) Review and recording of concomitant medications; and

7) Review and recording of adverse events/side effects.

5.9 Study Discontinuation

Rules for discontinuation of a patient or for discontinuing the study are provided in section 11.2. All subjects discontinued from the study before day 7 will be evaluated at study discontinuation using the procedures described above for day 7. All subjects discontinued from the study after day 7 will be evaluated at study discontinuation using the procedures described above for day 22.

5.10 Electronic Subject Diary

Electronic subject diaries will be completed twice daily through day 21. The electronic diaries will capture the following information:

1) Medication intake (twice daily at time of medication intake).

2) Oral temperature (twice daily at time of medication intake). Use standard electronic oral thermometer provided by Sponsor. Oral temperature should, preferably, be recorded prior to acetaminophen dosing or greater than 4 hours after acetaminophen dose.

3) Use of other medications taken (including acetaminophen) by the subject not previously captured in the subject's medication history. Document in detail including dose in milligrams or other applicable units, time of ingestion, and the reason for use of the medication (at time of medication intake).

4) FLU-PRO Questionnaire (once daily between 7 pm and 11 pm) to characterize symptoms of influenza.

5) Activity assessment using an 11-point visual analog scale (0= unable to perform normal activity, 10= fully able to perform normal activity) (once daily between 7 pm and 11 pm).

6) Adverse experiences (once daily between 7 pm and 11 pm).

5.11 Plan for Virology Testing and Monitoring Resistance

In an effort to monitor potential resistance to tizoxanide during study RM08-3004, the following procedures will be performed:

1) Collection of samples:
Two nasopharyngeal swabs will be collected from each patient at Baseline (day 1) and days 2, 3, 7 and

22.

2) Testing of biological samples
   a. Each Baseline sample will be subjected to: (1) culture to detect influenza A and B, (2) RT-PCR using the ePlex® Respiratory Pathogen Panel (GenMark, Carlsbad, CA) to detect influenza A (non-specific as to subtype); influenza A H1, H1N1 (2009), H3 subtypes; influenza B; respiratory syncytial virus A and B (RSV); parainfluenza 1, 2, 3 and 4; human metapneumovirus (hMPV); adenovirus (A-F); human rhinovirus/enterovirus; coronavirus NL63, HKU1, 229E and OC43; *Chlamydophila pneumoniae*; and *Mycoplasma pneumoniae*.
   b. If a subject's Baseline sample is negative for influenza by RT-PCR, his/her day 2 and day 3 samples will be subjected to RT-PCR using the ePlex® Respiratory Pathogen Panel to detect respiratory pathogens.
   c. If the Baseline sample or the day 2 or day 3 sample is positive for influenza A or influenza B, the Baseline sample and each of the day 2 and 3 samples will be subjected to $TCID_{50}$ to quantify viral shedding.
   d. Day 7 samples will be subjected to culture and RT-PCR using the ePlex® Respiratory Pathogen Panel. All samples positive for influenza A or influenza B will also be subjected to $TCID_{50}$ to quantify viral shedding.
   e. Day 22 samples will be subjected to culture and RT-PCR using the ePlex® Respiratory Pathogen Panel only if the sample collected at the preceding time point (day 7) had detectable influenza virus. All samples positive for influenza A or influenza B will also be subjected to $TCID_{50}$ to measure viral shedding.

3) Drug susceptibility testing
   a. If any day 7 or day 22 sample is positive for influenza A or influenza B by culture, the virus will be isolated and tested for susceptibility to tizoxanide ($TCID_{50}$).
   b. The Baseline isolate for subjects with virus cultured at day 7 or 22 will also be tested for susceptibility to tizoxanide, and the results will be compared to the results observed for the day 7 or 22 isolate.

4) Nucleotide sequencing
   a. All day 7 or 22 samples with reduced susceptibility (IC_{50} >2x IC_{50} at Baseline) or resistance (IC_{50} ≥10x IC_{50} at Baseline) to tizoxanide will be subjected to hemagglutinin and neuraminidase nucleotide sequencing. The corresponding Baseline sample will also be subjected to hemagglutinin and neuraminidase nucleotide sequencing. Initial genotypic assessments of resistance to tizoxanide will focus on isolates displaying the largest shifts in susceptibility.
   b. Sequencing data for day 7 or 22 isolates with reduced susceptibility or resistance to tizoxanide will be compared to sequence data for the Baseline sample to identify mutations that may confer resistance.

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

6) Clinical Virology Laboratory:

[redacted]

5.12 Pregnancy

Fertility and reproduction studies in animals have revealed no evidence of impaired fertility or harm to the fetus due to NTZ. There are, however, no adequate and well controlled studies of fertility or reproduction in humans. All pregnancies including those of partners of male subjects included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using a pregnancy reporting form.

6 RANDOMIZATION

An independent third party ([redacted] will prepare a master randomization list and maintain the masking of the study. Randomization will be performed using permuted block randomization. Blocks of masked study medication will be assigned to each Investigator. Each Investigator will then assi$_{gn}$ treatment numbers to subjects who qualify for the study using centralized randomization procedures strntified by time since symptom onset for each subject (≤24 hours, >24 - 36 hours, and >36 hours). 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, subjects and laboratory personnel. Unmasking for any individual patient will occur only if necessitated by emergency and knowledge of the medication being tk en will influence the medical management of the subject. Furthermore, if the event warrants submission of an IND Safety Report, then the subject will be unmasked for completion of the report.

7 DATA MANAGEMENT

7.1 Electr·onic Data Enh-y

[redacted]

- - - i s a source data collection solution that will allow the site staff to record subject data on ch-iven source forms by using tablets provided by - - - - - Its purpose is to eliminate the need for data transcription into a traditional electronic case to allow both real-tinle access to source data by authorized Sponsor personnel and real-time edit checks.

1111111111111111 is a mobile application for the capture of patient-repor1ed outcomes (PROs). Study owed to use [redacted] ca1 their own smartphones or a provisioned device provided by [redacted]. in order to record PROs, concomitant medications and adverse events (in the form of an electronic subject di$_{ary}$) and to receive personalized study-specific reminders and education.

- - - - is the - - web portal. It delivers real-time access to source data, and enables personn y review, clean and analyze study data.

The site staff will u s e - - - - - a s they meet with study subjects and perform study procedw-es. Computerized data clee 'used in addition to manual review including listings review, to check for discrepancies and to ensure consistency and completeness of the data.

The responsible study monitor(s) will verify data, which can be performed remotely or at the clinical study site. The Investigator will ensw-e that the data recorded are accw-ate and complete.

Queries emerging during data cleaning will be generated by data management or clinical research associates in - - - - . The Investigator or his/her desi$_{gn}$ee will answer the queries and update the sow-ce da .

Adverse events will be coded by data management using the latest version of the Medical Dictionaiy for Regulatory Activities (MedDRA); medications will be coded by data management using the latest version of the World Health Organization (WHO) DRUG dictionaiy.

After the Last Subject Last Visit (LSLV) has taken place, the database will be cleaned as necessary. As soon as the database is considered clean, it will be locked. The locked database will be used in the final statistical

analysis for study reporting. Measures will be undertaken to protect subject data handled during inspections against disclosure to unauthorized third parties. Subject confidentiality will be maintained at all times.

All listings, summaries and analyses will be produced using SAS Statistical Software (SAS Institute, Inc., Cary, NC).

7.2 Protocol Deviations

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

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

7.3 Data Quality Assurance

The accuracy and reliability of the study data will be assured by the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to the study, and by periodic monitoring visits by the Sponsor. Written instructions will be provided for collection, preparation, and shipment of samples.

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

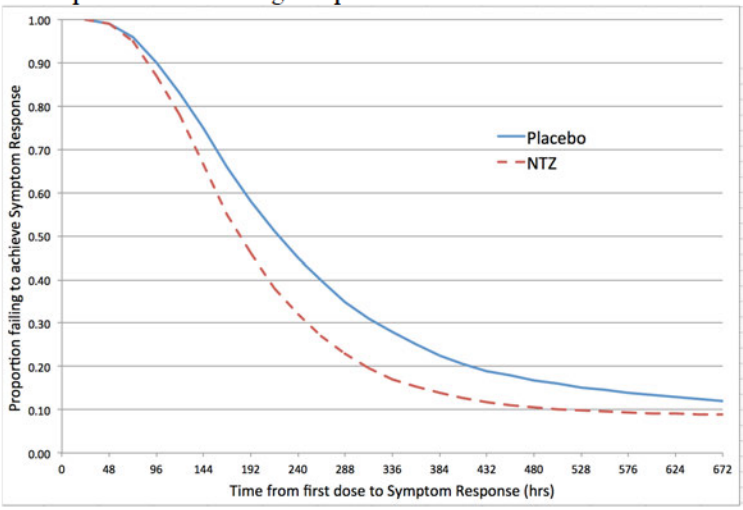
The Sponsor will be entitled to inspect and audit the facilities used in the clinical and laboratory parts of the study, as well as to make anonymized copies of all the data files pertaining to the study. Similar procedures may also be conducted by agents of any regulatory body, either as part of a national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

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Calculation

As described in section 7.3 below, the Symptom Response definition for this study will be derived from the subjects' FLU-PRO questionnaire responses. The FLU-PRO-derived endpoint is expected to track very closely to return to usual health status (a daily yes/no question in the FLU-PRO questionnaire). Patient-reported outcomes for time to return to usual health status have been shown to track very closely with time to ability to perform 100% of usual activities.[27,28,29] We assume, therefore, that the cumulative distributions of time to Symptom Response for the placebo treatment group will closely reflect historical data (Romark studies RM08-3002 and RM08-3003 and oseltamivir studies WV15670 and WV15671) for time from first dose until the subjects report that they are able to perform 100% of usual activities. Based upon data from Romark studies RM08-3001, RM08-3002 and RM08-3003, we assume that treatment with NTZ should result in reduction of at least 40 hours in median time to symptom response with differences being less at the first

quartile and greater at the third quartile. Based upon this historical data, the following curves have been developed for determining sample size.



Based upon these curves, a sample size of 552 subjects with laboratory-confirmed influenza (i.e. 276 for each of the 2 groups) will provide 90% power to detect a statistically significant difference in the survival distributions between NTZ and placebo groups (2-sided alpha of 0.05). This calculation was performed for the Gehan rank test using SAS PROC POWER (SAS 9.4) with the curves shown above (proportion not recovering by the end of each day was used as input) and censoring at day 21 (hour 504). Assuming that 8% of subjects will have incomplete data, we arrive at a sample size of 600 subjects in total, 300 per treatment group to yield at least approximately 550 with complete data (all 600 subjects will be included in the primary analysis with subjects with incomplete data censored as of their last entry).

Based upon these calculations, the study will enroll at least 600 subjects with laboratory-confirmed influenza up to a maximum of 700 subjects with laboratory-confirmed influenza. We estimate that this will require enrollment of 800 to 1,200 subjects in total assuming a flu-positive rate between 50% and 75%.

8.2 Efficacy Variables

Primary Efficacy Parameter: Time from first dose until Symptom Response

Secondary Efficacy Parameters:

i. Time from first dose until subjects are able to perform 100% of normal activities (i.e., a score of 10 on the scale of 0-10)

ii. Proportions of subjects experiencing one or more complications of influenza including pneumonia, otitis media, bronchitis, sinusitis, worsening of pre-existing health conditions, systemic antibiotic use for infections secondary to influenza infection, hospitalization due to influenza or complications of influenza and death

iii. Time to Symptom Response excluding the FLU-PRO Gastrointestinal and Eye domains

Exploratory Efficacy Parameters:

i. Time to Individual Symptom Response
ii. Time to FLU-PRO Domain Response
iii. Time to Resolution of Acute Febrile Illness
iv. Time to Return to Usual Health

v. Change in influenza virus titer ($TCID_{50}$) from baseline to day 2 and from baseline to day 3
vi. Proportions of subjects with virus detected in nasopharyngeal swabs collected at each of days 2, 3 and 7 by culture and by RT-PCR

8.3 Response Definitions

Symptom Response:	To be defined based upon a blinded review of symptom scores (pooled for all influenza-infected subjects without regard to treatment group assignment) that correlate to the time at which subjects report that they return to usual health (a daily global assessment question). Methodology for the correlation will be defined in the Statistical Analysis Plan. Symptom scores must be maintained at the defined level for at least 2 daily diary periods without any symptom relief medication during those 2 daily diary periods.
Time of Symptom Response:	The start of the first daily diary period in which Symptom Response is achieved and is maintained for at least 2 daily diary periods without any symptom relief medication during those 2 daily diary periods.
Time to Symptom Response:	Time (hours) from first dose to the Time of Symptom Response.
Ability to Perform All Normal Activities:	Subject reports a score of 10 on the 0-10 scale for ability to perform normal activities, which is maintained for at least 2 daily diary periods without symptom relief medication during those 2 daily diary periods
Time of Ability to Perform All Normal Activities:	The time of the first daily diary entry in which the subject reports a score of 10 on the 0-10 scale for ability to perform normal activities, which is maintained for at least 2 daily diary periods without symptom relief medication during those 2 daily diary periods
Time to Ability to Perform All Normal Activities:	Time (hours) from first dose to the Time of Ability to Perform All Normal Activities
Individual Symptom Response:	For each individual symptom (n=32), a score of $\leq$ the maximum response value specified in the Symptom Response definition maintained for at least 2 daily diary periods without symptom relief medication during those 2 daily diary periods
Time of Individual Symptom Response:	The start of the first daily diary period in which the Individual Symptom Response is achieved and is maintained for at least 2 daily diary periods without symptom relief medication during those 2 daily diary periods
Time to Individual Symptom Response:	Time (hours) from first dose to Time of Individual Symptom Response
FLU-PRO Domain Response:	For each individual domain (n=6), each item scored $\leq$ the maximum response value specified in the Symptom Response definition

	maintained for at least 2 daily diary periods without symptom relief medication during those 2 daily diary periods
Time of FLU-PRO Domain Response:	For each domain, the start of the first daily diary period in which the FLU-PRO Domain Response is achieved and is maintained for at least 2 daily diary periods without symptom relief medication during those 2 daily diary periods
Time to FLU-PRO Domain Response:	Time (hours) from first dose to FLU-PRO Domain Response for each domain
Resolution of Acute Febrile Illness:	Oral temperature is recorded by the patient as <100.4°F (<38 °C) and symptom scores for each of "body aches or pains", "chills or shivering", "felt cold", "felt hot" and "sweating" are 0 or 1 and remain so throughout 2 daily diary periods without symptom relief medication during those 2 daily diary periods
Time to Resolution of Acute Febrile Illness:	Time (hours) from first dose to resolution of acute febrile illness.
Return to Usual Health:	"Yes" response to the daily FLU-PRO global assessment question, "Have you returned to your usual health today?" maintained for at least 2 daily diary periods without symptom relief medication during those 2 daily diary periods
Time of Return to Usual Health:	The time of the first daily diary entry in which Usual Health is achieved and is maintained for at least 2 daily diary periods without symptom relief medication during those 2 daily diary periods
Time to Return to Usual Health:	Time (hours) from first dose to Time of Return to Usual Health

8.4 Statistical Methodology

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

8.4.1 Efficacy Analyses

Efficacy analyses will be based on a population consisting of all subjects that received at least one dose of study drug and had laboratory-documented influenza infection (infected intent-to-treat or ITTI population). Laboratory-documented influenza infection is defined by identification of influenza virus in nasopharyngeal secretions by RT-PCR or viral culture at baseline, day 2 or day 3.

There will be one primary efficacy analysis:

- Time to Symptom 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) stratified by (1) time since symptom onset for each subject at enrollment (≥24 hours, >24 – 36 hours, >36 hours) and (2) whether the subject received seasonal influenza vaccination after August 1, 2018. Subjects without a Symptom Response being recorded will be treated as censored as of their last diary without a documented Symptom Response.

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

- Time to Ability to Perform All Normal Activities for the two treatment groups will be compared using a stratified Gehan-Wilcoxon test (α =0.05) stratified by (1) time since symptom onset for each subject at enrollment (≥24 hours, >24 – 36 hours, >36 hours) and (2) whether the subject received seasonal influenza vaccination after August 1, 2018. Subjects without an Ability to Perform All Normal Activities response being recorded will be treated as censored as of their last diary without a documented Ability to Perform All Normal Activities response.

If both the primary analysis and the key secondary efficacy analysis are significant at the 0.05 level, another secondary efficacy analysis will be formally evaluated at the 0.05 level as follows:

- Proportions of subjects experiencing one or more complications of influenza including pneumonia, otitis media, bronchitis, sinusitis, worsening of pre-existing health conditions, systemic antibiotic use for infections secondary to influenza infection, hospitalization due to influenza or complications of influenza and death will be compared between the treatment groups using a Fisher's exact test (α =0.05).

A third secondary analysis will be performed as follows:

- The primary efficacy analysis will be repeated using only items from the four FLU-PRO domains (Body/Systemic, Throat, Chest/Respiratory and Nose) that correspond to the seven symptoms included in the traditional PRO instrument (feverishness, myalgia, headache, fatigue, sore throat, nasal obstruction and cough). For this secondary analysis, we will derive the Symptom Response definition in the same manner as for deriving the Symptom Response definition used in the primary analysis (after removing the Eye and Gastrointestinal symptoms).

Exploratory analyses will be performed as follows:

- For each of the 32 individual FLU-PRO symptoms, Time to Individual Symptom Response for the NTZ and placebo treatment groups will be compared using the Gehan-Wilcoxon test.

- For each of the 6 FLU-PRO domains, Time to FLU-PRO Domain Response for the NTZ and placebo treatment groups will be compared using the Gehan-Wilcoxon test.

- Time to Resolution of Acute Febrile Illness for the NTZ and placebo treatment groups will be compared using the Gehan-Wilcoxon test.

- Time to Return to Usual Health for the NTZ and placebo treatment groups will be compared using the Gehan-Wilcoxon test.

- Changes in influenza $TCID_{50}$ viral titers from baseline to day 2 and from baseline to day 3 for the NTZ and placebo treatment groups will be compared using a t-test.

- For subjects with laboratory-confirmed influenza, the proportions of subjects with influenza virus detected by culture in nasopharyngeal swabs collected at each of days 2, 3 and 7 will be compared for the two treatment groups using a Fisher's exact test.

Sensitivity analyses for the primary endpoint will include:

- Repeat the primary efficacy analysis, assigning a Time to Symptom Response of 21 days for subjects that discontinue prior to day 21 without achieving Symptom Response.

- Repeat the primary efficacy analysis for a "per protocol" subset.

8.4.2 Influenza Antibody Titer Analysis

For subjects with laboratory-confirmed influenza at baseline by culture or RT-PCR, changes in influenza antibody titers from baseline to day 22 will be analyzed by comparison of means as well as proportions of subjects seroprotected (day 22 antibody titer ≥40) and seroconverted (day 22 antibody titer >4x baseline titer) at day 22. Means will be compared using a t-test, and proportions will be compared using a Fisher's exact test.

8.4.3 Population Pharmacokinetics Analysis

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

Day 3 trough plasma concentrations of tizoxanide and tizoxanide glucuronide will be summarized descriptively for each of the treatment groups. Exploratory analyses will be conducted to evaluate relationships between plasma concentrations and age, race, gender, body weight, body mass index, concomitant medications, changes in viral titer over time, time from first dose to Symptom Response and adverse events.

8.4.4 Safety Analyses

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

9 INVESTIGATIONAL PRODUCTS

9.1 Drug Regimens, Administration and Duration

Group 1 (NTZ):	Subjects will receive two NTZ 300 mg tablets b.i.d. with food (< 1 hour after food intake) for 5 days.
Group 2 (Placebo):	Subjects will receive two placebo tablets b.i.d. with food (< 1 hour after food intake) for 5 days.

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

9.2 Identity of Investigational Products

NTZ 300 mg and placebo tablets were manufactured for Romark Laboratories, L.C. by [redacted] in the United States. The active formulation for this study is a yellow, film-coated tablet that contains 300 mg NTZ plus standard excipients. The placebo tablet will have the same appearance and inactive ingredients as the active tablet.

9.3 Packaging and Labeling

NTZ or placebo tablets will be packaged for each patient in a white HDPE bottle, each containing 20 tablets. The subjects will take two tablets at each dosing time point. The bottles will be stored at room temperature and will bear a label with the following information:

20 Tablets	Study N RM08-3004 Treatment N : XXXX
Lot:	**Principal Investigator:**

Take 2 Tablets by Mouth with Food Twice Daily
Caution: New Drug-Limited by Federal Law to Investigational Use
STORE AT ROOM TEMPERATURE • DO NOT USE BEYOND END OF STUDY
KEEP OUT OF REACH OF CHILDREN
Study Sponsor: The Romark Institute for Medical Research
[redacted]

9.4 Drug Accountability

Medication will be dispensed at baseline. Medication compliance will be reviewed with each subject during the Day 2-5 Telephone Monitoring. At the day 7 visit, subjects will be asked to return the bottle in which the medication was dispensed along with any unused medication.

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

9.5 Subject Compliance

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

Subjects will be considered non-compliant (major protocol violation) if they have missed more than two doses of the study medication during the first three days of the study or if they take any prohibited/disallowed medication. Non-compliance will not be cause for discontinuation of subject participation in the study.

9.6 Disallowed Medication

The following medications will not be allowed during the study: any antiviral medication for flu or any prescription or non-prescription medications classified as (i) expectorants and cough preparations, (ii) analgesics and antipyretics or (iii) antihistamines (American Hospital Formulary Service (AHFS) classification). As an exception to this rule, subjects will be allowed to use acetaminophen as necessary for fever if oral temperature is ≥100.4°F (38°C).

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

10 ADVERSE EVENTS

The term "adverse event" is defined for purposes of this study as any unwanted physical, psychological or behavioral change experienced by a subject during the course of the study and after taking the first dose of study medication regardless of its severity or relation to the study. Adverse events may include symptoms, signs, unexpected worsening of pre-existing conditions, clinically significant changes in laboratory values, diseases and syndromes, and significant and unexpected failures of pharmacological action of other medications. Symptoms of influenza (i.e., those captured in the FLU-PRO Questionnaire) and complications of influenza (e.g., pneumonia, otitis media, bronchitis, sinusitis) shall not be reported as adverse events unless

there is a causal relationship between the study medication and the event. These symptoms and complications will be analyzed separately from adverse events as they are study endpoints.

Bacterial pneumonia, acute bacterial otitis media and acute bacterial sinusitis will be reported as complications of influenza only if the following criteria are satisfied:

Bacterial pneumonia:

1. At least two of the following symptoms: difficulty breathing, cough, production of purulent sputum, chest pain
2. At least two of the following vital sign abnormalities: fever, hypotension, tachycardia, tachypnea
3. At least one of the following findings: hypoxemia, clinical evidence of pulmonary consolidation, elevated white blood cell count or leukopenia
4. Chest radiograph findings of new infiltrates in a lobar or multilobar distribution.
5. Microbiologic criteria: appropriate sputum specimen with fewer than 10 squamous epithelial cells and more than 25 polymorphonuclear cells per low power field

Acute bacterial otitis media:

1. Symptoms of ear pain or earache, ear fullness or decreased hearing
2. One or more of the following otoscopic findings performed by a clinician experienced in otoscopy:
   - Bulging or fullness of the tympanic membrane (convexity of the plane of the eardrum), with loss of anatomic landmarks on visualization,
   - Opacification of the tympanic membrane regardless of color,
   - Erythema of the tympanic membrane, or
   - Abnormal tympanic membrane mobility on biphasic pneumatic otoscopy; a tympanic membrane in the neutral position or retracted is not sufficient evidence of acute bacterial otitis media because these findings are not specific enough to distinguish the disease from otitis media with effusion

Bacterial sinusitis:

1. At least two of the following symptoms:
   - Maxillary tooth pain (unilateral findings can be more specific)
   - Facial pain (unilateral findings can be more specific)
   - Frontal headache
   - Purulent nasal discharge (unilateral findings can be more specific)
   - New onset fetor oris (bad breath)
   - Morning cough
   - Nasal obstruction
2. At least one of the following signs:
   - Purulent secretions from sinus ostia on examination
   - Abnormal sinus transillumination
   - Pain on palpation over sinuses
   - Facial swelling
3. Radiographic findings consistent with acute sinusitis

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

10.1 Definitions

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

1) Serious Adverse Event: Any adverse experience occurring at any dose that is fatal or life threatening; requires in-patient hospitalization or prolongation of an existing hospitalization; is a persistent significant disability/incapacity; is a congenital anomaly or birth defect; or is an important medical event that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

2) Unexpected Adverse Event: Any adverse experience that is not identified in nature, severity, or frequency in the Investigator's Brochure for NTZ.

3) Severity of adverse events will be assessed by the Investigator using the Toxicity Grading Scale Tables provided in Appendix II (derived and adapted from "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", US Dept. of HHS, FDA, CDER, September 2007 and the National Institutes of Health, National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0).

4) Causality (relationship to treatment) will be assessed as follows:

- *Definitely Related:* The adverse event is clearly related to the investigational agent(s) or research intervention: the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known pattern of response, and no alternative cause is present.

- *Probably Related:* The adverse event is likely related to the investigational agent(s) or intervention: the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known or suspected pattern of response, but an alternative cause may be present.

- *Possibly Related:* There is a reasonable possibility that the event may have been caused by or is linked in a significant way to the research; the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a suspected pattern of response, but an alternative cause is present.

- *Unrelated (or Not Related):* The adverse event is clearly NOT related to the investigational agent(s) or intervention: the adverse event has no temporal relationship to the administration of the investigational agent(s) or research intervention, follows no known or suspected pattern of response, and an alternative cause is present.

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

10.2 Clinical Adverse Events

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

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

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

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

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

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

10.3 Reporting Requirement

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

The Romark Institute for Medical Research
Medical Affairs
[redacted]

10.4 Medication Modification/Withdrawal Due to an Adverse Event

No dose adjustment is permitted during the 5-day treatment period. If a severe adverse reaction develops during therapy, the study medication should be discontinued, and the subject should be withdrawn from the study.

10.5 Medication Errors

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

11 DISCONTINUATION

11.1 Study Discontinuation:

The study may be discontinued under the following circumstances:

1) The Sponsor reserves the right to discontinue the study at any time.

2) Adverse event listings will be produced for safety monitoring at least once every two weeks during recruitment. The data will be tested to determine if there are greater than 5% of the subjects who have had ≥ grade 3 adverse events considered by the Investigator to be possibly, probably or definitely related to the study drug (defined by the Toxicity Grading Scale Tables provided in Appendix II).

   If greater than 5% 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 Antiviral Drug Products will be notified. All safety and activity data will be submitted to the FDA in a timely manner.

11.2 Subject Discontinuation:

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

1) An allergic-like reaction occurs or is suspected.

2) Medical conditions that may require study discontinuation in the Investigator's judgment.

3) Subject desire to discontinue participation.

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

12 ELECTRONIC DATA COLLECTION (EDC) SYSTEM

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

All electronic source forms are to be completely filled out by the examining site staff and reviewed and signed off on by the Investigator(s). Electronic diaries will be completed by the study subjects and reviewed by study personnel and authorized Sponsor representatives.

13 RETENTION OF RECORDS

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

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

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

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

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

14 MONITORING THE STUDY

Monitoring will be conducted by the Sponsor and/or a contract research organization (CRO) according to the Sponsor's standard operating procedures. Site visits will be conducted by the Sponsor at regular intervals to conduct inspections.

Any data transcribed into the EDC system will be 100% source verified.

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.

Given the short duration of this study, the large clinical experience with NTZ, and the population being studied, the data from this study will not be monitored by an independent data monitoring committee.

15 INFORMED CONSENT

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The informed consent form (ICF) must be signed before performance of any study-related activity. The ICF must be approved by both the Sponsor and by the reviewing IRB. It should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the Investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care he/she will receive. Finally, they will be told that the Investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized Sponsor staff without violating the

confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, and agrees to allow his or her study physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

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

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

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

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

16 ETHICS

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

16.1 Study-Specific Design Considerations

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

16.2 Investigator Responsibilities

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

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

16.3 Institutional Review Board (IRB)

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

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

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

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

- protocol amendments;
- revision(s) to ICF and any other written materials to be provided to subjects;
- if applicable, new or revised subject recruiting materials approved by the Sponsor;
- revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable;
- Investigator's Brochure addenda or new edition(s);
- summaries of the status of the study at intervals stipulated in guidelines of the IRB (at least annually);
- reports of AEs that are serious, unlisted, and associated with the investigational drug;
- new information that may adversely affect the safety of the subjects or the conduct of the study;
- deviations from or changes to the protocol to eliminate immediate hazards to the subjects;
- report of deaths of subjects under the Investigator's care;
- notification if a new Investigator is responsible for the study at the site;
- Annual IND Update Report, Short Term Study Specific Safety Summary and Line Listings, where applicable;
- any other requirements of the IRB.

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

implemented deviation or change, the reasons for it, and, if appropriate, the protocol amendment should be submitted to the IRB as soon as possible.

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

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

16.4 Privacy of Personal Data

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

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

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

17 DATA CONFIDENTIALITY/DISCLOSURE OF DATA/PUBLICATION

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

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

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

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

18 DATA/REPORT REQUIREMENTS

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

1) *Curriculum vitae* of the Principal Investigator and all Co-Investigators.

2) Copy of the IRB-approved Informed Consent and patient information forms.

3) Copy of the IRB approval for the conduct of the study.

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

1) Pre- and post-treatment history, physical examination and patient evaluations.

2) Pre- as well as interim and post-treatment laboratory findings and all special test results.

3) EDC forms properly completed and signed by the Principal Investigator.

4) Drug Inventory Logs indicating drug dispensed and return of the unused supplies to the Sponsor or destruction by study site.

5) Signed Informed Consent/Assent from each subject.

19 CONTACT INFORMATION

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

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21 APPENDICES

Appendix I: Study Schedule

Appendix II: Toxicity Grading for Adult Adverse Events

Appendix III: List of Essential Documents for the Investigative Site

Appendix IV: Protocol Revision History

Appendix V: Declaration of Helsinki

21.1 Appendix I. Study Schedule

	Screening (Day 1)	Baseline (Day 1)	Days 2-22	Days 2-5	Days 2,3	Day 7 ±1	Day 22+3	Unscheduled visit
Signed informed consent	X							
Complete medical history	X							
Physical examination/weight/vital signs	X					X[1]	X[1]	X
Demographics/smoking history	X							
Urine pregnancy test	X							
Record oral temperature	X					X	X	X
Record symptoms and time of onset	X							
Evaluate according to inclusion/exclusion criteria	X							
Collect nasopharyngeal swabs		X			X[2]	X	X[3]	X
Blood sample for pharmacokinetics					X[4]			
Blood sample for anti-influenza antibodies		X					X	
Blood sample for laboratory safety tests[5]		X				X		X
Urine sample for routine urinalysis[5]		X				X		X
Record concomitant medications		X				X	X	X
Complete baseline symptoms in diary and dispense diary		X						
Randomization/dispense study medication		X						
First dose in office and enter in diary		X						
Instructions re: dosing, concomitant medications, patient diary, birth control, follow-up visits and seeking emergency care		X		X		X		X
Review/record adverse events		X		X	X	X	X	X
Review electronic patient diary entries			X[6]					X[6]
Screen for influenza-related complications				X	X			
Review compliance with study medication, collect container with unused medication, complete pill count log form					X	X		X[7]

[1] Day 7 and 22 physical exam is a brief physical exam (vital signs and nursing physical assessment) including symptom directed physician physical examination as required by patient symptoms. Vital signs include blood pressure, pulse, respiratory rate and oral temperature.

[2] Nasopharyngeal swabs on days 2 and 3 will be collected at the patient's home (or clinic or another location as agreed with the patient).

[3] Nasopharyngeal swabs collected on day 22 will only be tested for the presence of virus if the sample from day 7 had detectable virus.

[4] Blood sample collected pre-dose on day 3.

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

[6] All subjects will maintain an electronic diary until day 22 (+3). Site staff will contact subjects as needed during study to ensure timely completion of electronic diary.

[7] Collection of unused IMP and completion of pill count log form will be performed at unscheduled visit if applicable.

21.2 Appendix II. Toxicity Grading for Adve1·se Events

[Dei ved and adapted from "Guidance for hidustry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", US Dept. of HHS, FDA, CDER, September 2007]

Tables fo1· Clinical Abnormalities

Vital Signs*	Mild (Gnde 1)	Moderate (Grade 2)	Sevel·e (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C).. (OF)..	38.0- 38.4 100.4-101.l	38.5-38.9 101.2-102.0	39.0-40 102.l - 104	>40 > 104
Tachycardia - beats per minute	101-115	116 - 130	>130	ER visit or hospitalization for an·hythmia
Bradycardia - beats per minute***	50-54	45-49	<45	ER visit or hospitalization for an·hythmia
Hypertension (systolic)- mmHg	141 - 150	151 -155	> 155	ER v-isitor hospitalization for mali$_{g\,n\,a\,n}$t h$_{y\,p\,e}$ltension
Hypertension (diastolic)- lllll Hg	91-95	96 - 100	> 100	ER visit or hospitalization for mali$_{g\,n\,a\,n}$t h$_{y\,p\,e}$ltension
H$_{y\,p\,o}$tension (systolic) - mm Hg	85-89	80-84	<80	ER visit or hospitalization for h$_{y\,p\,o}$tensive shock
Respiratory Rate - breaths per minute	17-20	21-25	> 25	Intubation

- Subject should be at rest for all vital si$_{g\,n}$ measurements.

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

... When resting heart rate is between 60 - 100 beats per minute. Use clinical jud$_{g\,m}$ent when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Appendix II. Toxicity Grading Scale Tables for Clinical Abnormalities (continued)

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 visitor 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 > 800gms/24 hours or requires outpatient IV hydration	ER visitor 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 visitor hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visitor hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

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

Appendix II. Toxicity Grading Scale Tables fo1· Labo1·ato1-y Abnormalities

The laboratory values provided in the tables below serve as guidelines and are d$_{e\ p}$endent upon institutional normal parameters.

Serum*	Mild (Grade 1)	Model'8te (G1·ade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium - Hyponatremia mEq/L	132-134	130-131	125 -129	< 125
Sodium - Hypematremia 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 - H$_{y\ p}$okalemia rnEq/L	3.5-3.6	3.3-3.4	3.1 - 3.2	< 3.1
Chloride -rnEq/L* o	Asymptomatic or mild symptoms; clinical or dia211ostic obs 1vations only; intervention not indicated	Moderate; mininial, local or noninvasive intervention indicated; limiting age-appropriate instmrnental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; lintiting self care ADL	Life-threatening consequences; urgent intervention indicated
Glucose - Hypoglycei^{n} a 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 h$_{y\ p\ e}$rosmolar coma
Blood Urea Nitrogen BUNmg/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
Calcilllll - h$_{y\ p}$oca lcem ia mg/dL	8.0-8.4	7.5 - 7.9	7.0 - 7.4	<7.0
Calcilllll - h$_{y\ p}$ercalcemia mg/dL	10.5 - 11.0	11.1-11.5	11.6- 12.0	> 12.0
MagnesiUlll - h$_{y\ p}$omagnesemia mg/dL	1.3 - 1.5	1.1 - 1.2	0.9 - 1.0	<0.9
Phosphorous - h$_{y\ p\ o}$phosphatem a mg/dL	2.3 -2.5	2.0-2.2	1.6 - 1.9	< 1.6
CPK-mg/dL	1.25 - 1.5 x ULN****	1.6-3.0xULN	3.1-10 x ULN	>lOxULN
Albumin - H$_{y\ p\ o}$albumi nemia g/dL	2.8-3.1	2.5-2.7	<2.5	-
Total Protein- Hypoproteinem.ia g/dL	***5.5-6.0***	***5.0-5.4***	< ***5.0***	—

* The laboratory values provided in the tables serve as guidelines and are d$_{e\ p\ e}$ndent upon institutional nonnal parameters. Institutional nom1al reference ranges should be provided to demonstrate that they are appropriate.

** The clinical si$_{g\ n\ s}$ or symptoms associated with laboratory abnonnalitics might result in characterization of the laboratory abno1malities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 para.meter (125-129 m E /) should be recorded as a grade 4 h$_{y\ p\ o}$natremia event if the subject had a new seiwre associated with the low sodium value.

*** Derived from the National Institutes of Health. National Cancer Institute Common Tenni..nology 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 tmdressing. feeding self, using the toilet, taking medications, and not bedridden.

**** "ULN" is the upper limit of the nonnal range.

Appendix II. Toxicity Grading Scale Tables fo1· Labo1·ato1-y Abnormalities (continued)

Serum*	Mild (Grade 1)	Mode1·ate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
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 - GOT*** 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
Bilimbin - when Liver Function Test is nonnal, 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	>500mg/dL
Triglycerides- mg/dL•••	150 mg/dL- 300 me/dL	>300 mg/dL- 500 me/dL	>500mg/dL- 1000 me/dL	>1000mg/dL
HDL-mg/dL***	Asymptomatic or mild symptoms; clinical or diaguostic observations only; intervention not **indicated**	**Moderate;** minimal, local or nominvas1ve intervention indicated; limiting age-appropriate **instnunental** ADL	**Severe** or **medically** significant but not immediately life threatening; hospitalization or prolongation of **existing** hospitalization indicated; disabling; lintiting self care ADL	**Life-threatening co11sequences;** urgent intervention indicated
LDL-mg!dL•••	Asymptomatic or mild symptoms; clinical or diaguostic obse1vations only; intervention not indicated	Moderate; minimal, local or **norunvas1vc intervention** indicated; limiting age-appropriate instnunental ADL	Severe or medically significant but not **immediately life** threatening; hospitalization or prolongation of existing hospitalization **indicated;** disabling; lintiting self care ADL	Life-threatening consequences; urgent **intervention** indicated

* The laboratory values provided in the tables serve as guidelines and arc d$_{e\ p\ e}$ndent upon institutional nonnal parameters. Institutional nomial reference ranges should be provided to demonstrate that they are appropriate.

** The clinical si$_{g\ n\ s}$ or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnonnalities as Potentially Life 11:ireatening (Grade 4). For example. a low sodirnn value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 h$_{y\ p\ o}$natremia event if the subject had a new seizure associated with the low sodillll1 value.

*** Derived from the National Institutes of Health. National Cancer Institute Common Tenninology 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.

•••• "ULN" is the upper limit of the noruial range.

Appendix II. Toxicity Grnding Scale Tables for Laboratory Abnormalities (continued)

Hematology *	1ild (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) chan2e from baseline value -2111/dL	AJ.1y 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	AJ.1y 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 inimediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent inte1-vention indicated
WBC Increase - cell/mn[1]	10,800 - 15,000	15,001 - 20,000	20,001- 25, 000	>25,000
WBC Decrease - cell/mm'	2,500 - 3,500	1,500- 2,499	1,000- 1,499	< 1,000
Lymphocytes Decrease - cell/llllll[3]	750-1,000	500-749	250-499	<250
Neutrophils Decrease - cell/= [3]	1,500 - 2,000	1,000- 1.499	500-999	< 500
Eosinophils - c e ll ! = '	650-1500	1501 - 5000	> 5000	$H_{y p c}$reosinophilic
Platelets Decreased - c e ll / =[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 - 15 x ULN	> l.5xULN
Fibrinogen increase - ml!'.ldL	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)

* Tl1e laboratory values provided in the tables serve as guideliues and are dependent upon institutional normal parameters. Institutional normal refereuce rauges 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 bed.ridden.

*** "ULN" is the upper limit of the nonnal rauge.

Appendix II. Toxicity Grading Scale Tables fo1· Labo1·ato1-y Abnormalities (continued)

Urine*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	I+	2+	Hospitalization or dialysis
Glucose	Trace	I+	2+	Hospitalization for hyperglycemia
Blood (microscopic)-red blood cells per high power field (rbc/hpf)	I - IO	1 1 - 5 0	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

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

21.3 Appendix III. List of Essential DocU1Dents for the Investigative Site

	Study No: RM0S-3004
	Title of Document
1.	Investigator's Brochme and U p d4es
2.	Signed protocol (all versions) and amendments, if any, and sample EDC fonns
3.	Information given to trial subject • Informed consent form (all versions), Any other written information, Advertisement for subject recruitment @j!Se including all al?plicable translations
4.	Financial agreement between the Investigator/institution and the Sponsor for the trial
5.	Signed agreement between involved parties • Financial Disclosure of Investigator/institution and Sponsor • Confidential Disclosm·e A~reement of Investigator/institution and Sponsor
6.	Dated, documented approval/favorable opinion ofIRB of the following: • Protocol and any amendments • Informed consent form and any revisions • Any other written info1mation to be provided to the subjects • Advertisement for subject recmitment (if t1Sed) • Subject compensation (if any) • Any other documents given approval • Continuing review of the trial
7.	Institutional Review Board composition
8.	Regulatory notice of Principal Investigator and sub-Investigators, FDA Fonn 1572
9.	Cuniculum vitae and/or other relevai1t documents evidencing qualifications of Investigator and sub-Investigators
10.	Normal values/ranges and updates for medical/laboratory/technical procedm·es and/or tests included in the protocol
11.	Medical/laboratory technical procedures/tests and updates: • certification or • accreditation or • established quality control and/or external quality assessment or • other validation (where required)
12.	Shipping records for investigational product(s) and trial-related materials
13.	Certificate(s) of Analysis of investigational product(s) shipped
14.	Unblinding procedure to docmnent how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects
15.	Site initiation monitoring report
16.	Relevant communications other than site visits: • Letters/ emails • Meeting notes • Notes of telephone calls
17.	Signed infonned consent forms
18.	Sow·ce docwnents
19.	Sig}!ed, dated, and completed EDC forms to include doctunentation ofEDC form cotTections
20.	Notification by origi!iating Investigator to Sponsor of serious adverse events and related rep011s
21.	Notification by Investigator, where applicable, to IRB of llllexpected serious adverse dmg

	reactions and of other safety information
22.	Notification by Sponsor to Investigator of safety information
23.	Interim or annual reports to IRB and authority/ies (if applicable)
24.	Subject Screening log
25.	Subject identification code list to permit identification of all subjects enrolled in the trial in case follow-up is required
26.	Subject enrollment log
27.	Investigational product accountability records (receipt, storage, dispensing, shipment, return or destruction)
28.	Signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on eCRFs
29.	Record of retained body fluids/tissue samples (if any)
30.	Final report by Investigator/institution to IRB
31.	Audit Certificate (if available)

21.4 Appendix IV. Protocol Revision History

Summary of Changes	
Initial Version	**Protocol version 1. 1 d 'ted December 14, 2017**
Pre-Enrollment l/i·date	
Purpose:	**Update the protocol to remove urine tests for ketones and pH that were inadvertently included in the previous version**
Effective Date:	**December 28, 2017**
Change 1:	**Page 15, Section 3,** *Sh1dy Design* **and page 20, Section 5.2,** *Baseline* **and page 22, Section 5.6,** *Day 7 Follow-up* **and page 23, Section 5.8,** *Unscheduled Visit* **and page 46, Section 21.1,** *Appendix I: Study Schedule* **Deleted** *"ketones, pH '* **from the list of w-inalysis tests**
Action:	**A revised protocol version 1.2 dated December 28, 201 7 was generated**
Amendment 1	
Pmpose:	**Update the protocol to update the inclusion criteria for oral temperature requirements and update contact information for medical monitor**
Effective Date:	**February 6, 2018**
Change 1:	**Page 17, Section 4.1,** *"Inclusion Criteria"* **Changed oral temperature criteria from** *"a) oral le11perat11re of?.99.4 °F or ?.37.4 °C obtained in office, AND"* **to** *"a) oral temperah1re of?.99.4 °F or ?.37.4 °C (obtained in office or self-measured within 12 hours prior to screening - if self-measured, subject 11lust also have taken an antipyrelic within 4 hours prior to screening), AND"*
Change 2:	**Page 42, Section 19,** *"CONTACT INFORMATION"* **Changed medical monitor name and e-mail address from** *"Name:* [redacted] **"to** *"Name:* [redacted] *"*
Action:	**A revised protocol version 1.3 dated Febrruuy 6, 2018 was generated**
Amendment2	
Pmpose:	**Administrative update to the protocol to (1) updated the expected trial dw-ation, (2) update the exclusion criteria for influenza season-specific vaccination dates, and (3) update the exclusion criteria to exclude use ofbaloxavir**
Effective Date:	**Jw1e 15, 2018**
Change 1:	**Page 5, Protocol Synopsis,** *Trial Duration* **and Page 15, Section 3,** *Study Design* **Changed trial dw-ation from** *"December 2017- October 2018"* **to** *"December 2017-April 2019"*
Change 2:	**Page 19, Section 4.2,** *Exclusion Criteria* **Changed exclusion crite1i on #14 from** *"Vaccination for seasonal influenza on or after August 1, 2017"* **to** *"Vaccination for seasonal influenza on or after (i) August 1, 2017 in the case of subjects enrolled during the 2017/2018 flu season in the Northern He11isphere, (ii) Februa,y 1, 2018 in the case of subjects enrolled during the 2018 flu season in the Southern Hemisphere, or (iii) August 1, 2018 in the case of subjects enrolled during the 2018/2019 flu season in the Northern Hemisphere."*

Summa1-y of Changes	
Change 3:	**Page 19, Section 4.2,** *Exclusion Criteria* **Changed exclusion criterion # 15 from** *"Receipt of any dose of NTZ, oseltamivir, zanamivir, peramivir, laninamivir, amantadine or rimantadine within 3 days prior to screening."* **to** *"Receipt of any dose of N1Z, oseltamivil; zanamivil; peramivir, laninamivir, baloxavir, amantadine or rimantadine within 3 days prior to screening."*
Action:	**A revised protocol version 1.4 dated June 15, 2018 was generated**
Amendment3	
Pmpose:	**Update the protocol (1) to remove the exclusion criterion for influenza vaccination in order to have the studied population more accurately reflect the population affected by influenza and to ensure robust patient enrolhnent, (2) to clarify endpoint response definitions in accordance with the way patient diary questions are phrased, and (3) to make additional administrative updates.**
Change 1:	**Page 19, Section 4.2,** *Exclusion Criteria* **Deleted exclusion criterion 4,** *"Vaccination for seasonal influenza on or after {i) August 1, 2017 in the case of subjects enrolled during the 2017/2018flu season in the Northern Hemisphere, {ii) Febmmy 1, 2018 in the case of subjects enrolled dwing the 2018flu season in the Southern Hemisphere, or (iii) Au ust 1, 2018 in the case of subjects enrolled durinf(the 2018/2019/lu season in the Northern Hemisphere."*
Change 2:	**Page 25, Section 7.1,** *Electronic Data Enhy* **Updated** *"Adverse events will be coded by data management using the Medical Dictionmy for Reg11lat01y Activities {MedDRA) version 15.1; medications will be coded by data management using the World Health Organization {WHO) DRUG dictiona1y."* **to** *"Adverse events will be coded by data management using the latest version of the Medical Dictionmy for Regulato,y Activities {MedDRA); medications will be coded by data management using the latest version of the World Health Organi::.ation {WHO) DRUG dicfionm)I."*
Change 3:	**Page 28, Section 8.3,** *Response Definitions* **Updated the definition of Tin1e of Ability to Pe1fo1m All Nom1al Activities from** *"Die start of the first daily dimy period in which the subject reports a score of 10 on the 0-10 scale for ability to pe1fo1111 normal activities, which is maintained for at least* **2** *daily dia1y periods without symptom reliefmedication dwing those* **2** *daily dia1y periods"* **to** *'The time of the first daily dia1y entry in which the subject reports a score of 10 on the 0-10 scale for ability to pe1fo1111 nonnal activities, which is maintained for at least* **2** *daily dia,y pe1iods without s mp tom reliefmedication durinf(those 2 daily diary periods".*
Change 4:	**Page 29, Section 8.3,** *Response Definitions* **Updated the definition of Time of Return to Usual Health from** *"The sta11 of the first daily dimy pe1iod in which Usual Health is achiered and is maintained for at least 2 dai y dia,y pe1iods without symptom reliefmedication during those 2 daily dia,y pe1iods"* **to** *"The time of the first daily dia1y enfly in which Usual Health is achiet·ed and is maintained for at least* **2** *daily dia1y periods without symptom reliefmedication dwing those* **2** *daily dia,y periods".*
Change 5:	**Page 29, Section 8.4.1,** *Efficacy Analyses* **Updated stratification specification for the primary and key secondary efficacy analyses from** *"where sh·atification will follow that used for randomization"* **to** *"sh·atified by (1) time since s mp tom onset for each subject at enrollment (?.24 hours, >24 - 36 hours, >36 hours) and (2) whether the subject recei ed seasonal influenza vaccination after August 1, 2018."*

Summa1-y of Changes	
Change 6:	**Page 32, Section 10,** *Adverse Events* **Updated** *"Symptoms of influenza (cough, sore throat, nasal obsh1.1ction, fatigue, headache, myalgia, fever is hness) and complications of influenza (pneumonia, ofitis media, bronchitis, sinusitis) shall not be reported as adverse events unless there is a causal relationship between the study medication and the event."* **to** *"Symptoms of influenza (i.e., those caph1red in the FLU-PRO Questionnaire) and complications of influenza (e.g., pneumonia, otitis media, bronchitis, sinusitis) shall not be reported as adverse events unless there is a causal relationship between the sh.1dy medication and the event."*
Change 7:	**Page 37, Section 15,** *Informed Consent* **Deleted** *"Electronic infonned consent systems and services will be used for this study ([redacted]). Prior to initiation, site staff and auth01ized Romark personnel will be trained lo use the system."* **and updated tle subsequent section text to update references to eICFs to ICFs (paper).**
Change 8:	**Page 42, Section 19,** *Contact Infonnation* **Updated Sponsor Project Management name and mobile phone number from** *"Name:* [redacted] *"* **to** *"Name:* [redacted] *"*
Change 9:	**Page 50, Appendix II,** *Toxicity Grading Scale Tables for Laborato1y Abno1111alities* **Updated grading categories for Cholesterol abnormalities from:** *Mild (Grade 1): 201-210 mg/dL* *Moderate (Grade 2): 211-225 mgldL* *Severe (Grade 3): >226 mg/dL* **to** *Mild (Grade 1): ULN - 300 mgldL* *Moderate (Grade 2): > 300-400 mgldL* *Severe (Grade 3): >400-500 mgldL* *Potentially Life-threatening: >500 mgldL* **and updated CTCAE version from 4.0 to 5.0 in table footnote.**
Change 10:	**Pages 53-54, Appendix** *ill, List of Essential Documents for the Investigative Site* **Updated per "ICH E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(Rl) Guidance for Inds try"**
Action:	**A revised protocol version 1.5 dated January 3, 2019 was generated**

21.5 Appendix V. Declaration of Helsinki

Special Communication

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

World Medical Association

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

Preamble

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

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

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

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care.·

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients. including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness. efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for alt human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination. privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical. legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical. legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientifJC education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

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

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

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

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

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

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

Vulnerable Groups and Individuals

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

    All vulnerable groups and individuals should receive specifically considered protection.

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

Scientific Requirements and Research Protocols

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

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

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

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

Research Ethics Committees

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

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

Privacy and Confidentiality

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

Informed Consent

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

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

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

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

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

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

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

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

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

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

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

Post-Trial Provisions

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

Research Registration and Publication and Dissemination of Results

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

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

Unproven Interventions in Clinical Practice

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

ARTICLE INFORMATION

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