# Statistical Analysis Plan (SAP)

## A Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Nitazoxanide (NTZ) for Pre- and Post-exposure Prophylaxis of COVID-19 and Other Viral Respiratory Illnesses (VRI) in Healthcare Workers and Others at Increased Risk of SARS-CoV-2 Infection

**Study No.: RM08-3007**

**Version 1.3**
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**The Romark Institute for Medical Research**

[redacted]

## Approval Page

I agree to the format and content of this document.

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## Revision History

Version 1.2 to 1.3

1. Updated planned software from SAS to Python and related statistical packages (section 2.6).
2. Updated document ownership from [redacted] to Romark Institute for Medical Research.

Version 1.1 to 1.2

1. Changed the author and internal reviewer.
2. Added terms to list of abbreviations.
3. Added methods to handle missing data in the primary analysis.
4. Added further details to the interim analysis description.
5. Updated the demographic and baseline characteristic variables in Section 3.0.
6. Clarified the definition of an ARI to include the Suspected ARI Visit requirements.
7. Modified the primary analysis description to compute the common relative risk in place of the risk difference.
8. Renamed Table 14.2.1.9, added Table 14.2.1.10, and renumbered subsequent 14.2.1.x tables.
9. The following updates were made to align with Protocol Version 3.0, dated 27 August 2020:
    a. Study title
    b. Added 'social activities' as a stratum for most likely location of exposure
    c. Changed the nasopharyngeal swab sample details
    d. Changed description of Week 3 and 8 Evaluations to state that subjects will attend in-clinic visits
    e. Modified sample size description to account for 6 strata
10. The following updates were made to align with Protocol Version 4.0, dated 28 September 2020:
    a. Updated the strata so that 'social activities' stratum is now divided into social activities (3-5 per week) and social activities (> 5 per week), resulting in a total of 7 strata in the study.
11. The following updates were made to align with Protocol Version 5.0, dated 26 October 2020:
    a. Modified sample size justification to reflect an event-drive approach

Version 1.0 to 1.1

1. Risk differences added to primary efficacy endpoint.
2. Section 2.2.2 Sex, Age, and Race subgroup analyses for primary efficacy endpoint added.
3. Sensitivity analyses added for missing values of primary efficacy variables.

## Table of Contents

## Abbreviations and acronyms

| Term | Definition |
|---|---|
| AE | Adverse Event |
| ARI | Acute Respiratory Illness |
| ATC | Anatomic Therapeutic Chemical |
| CDER | Center for Drug Evaluation and Research |
| CFB | Change from baseline |
| CMH | Cochran-Mantel-Haenszel Chi-square Test |
| COVID-19 | Corona Virus Disease, 2019 |
| CS | Clinically significant |
| FDA | US Food and Drug Administration |
| IAP | Interim Analysis Plan |
| IDMC | Independent Data Monitoring Committee |
| ITT | Intention-to-treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCS | Not clinically significant |
| NTZ | Nitazoxanide |
| PE | Physical exam |
| PI | Principal Investigator |
| RT-PCR | Reverse-Transcriptase Polymerase Chain Reaction |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome-Corona Virus 2 (the pathogen responsible for COVID-19) |
| SOC | System organ class |
| TE(S)AE | Treatment Emergent (Serious) Adverse Event |
| VRI | Viral Respiratory Illness |
| WHO | World Health Organization |

# 1.0 Synopsis of Study Design Procedures

## 1.1 Design and Treatment

This is a multi-center, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of Nitazoxanide (NTZ) for post-exposure prophylaxis of COVID-19, the viral respiratory disease caused by the novel coronavirus SARS-CoV-2 and other viral respiratory illnesses (VRIs) in healthcare workers and others at high risk of contracting SARS-CoV-2 infection. The study is a stratified two-arm study. The most likely location of exposure is being used as a proxy for SARS-CoV-2 exposure. The seven strata are:

- Emergency Department
- Intensive Care Unit
- COVID-specific Care Unit
- Walk-in Clinic
- Paramedics and First Responders
- Social Activities (3-5 per week)
- Social Activities (> 5 per week)

Participants will be randomized within strata (1:1) to one of

- Group I (NTZ)—Two 300 mg NTZ tablets orally b.i.d. (twice daily) for six weeks.
- Group II (Placebo)—Two placebo tablets b.i.d. (twice daily) for six weeks.

All participants will receive a B-complex vitamin ([redacted]) twice daily to mask potential chromaturia that may be associated with NTZ.

## 1.2 Study Procedures

**Screening**
Patients will be screened from Study Day -30 to Study Day 1. After giving informed consent, the subject will be assigned a subject number and complete the following procedures:

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

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

**Baseline**

At Baseline (Study Day 1, which may be the same day as the screening evaluation) the subject will be randomized to Group I or Group II and complete the following procedures:

1. Collection of a nasopharyngeal swab sample using a single nylon flocked dry swab inserted into both nostrils for RT-PCR.
2. Collection of blood sample for laboratory safety tests and anti-SARS-CoV-2 antibodies.
3. Collection of a urine sample for routine urinalysis (appearance, glucose, protein, and blood).
4. Review and recording of any concomitant medications.
5. Provision of an electronic symptom diary to subject and subject completion of baseline electronic diary under supervision and instruction of study site personnel.
6. Randomization and dispensing of study medication (medication assigned in sequential order). Subjects are enrolled in the study at this point.
7. Administration of the first dose of study medication with food (< 1 hour after food intake) and a B complex vitamin ([redacted]) under observation of Investigator or a member of Investigator's staff, and entry in the medication administration record.
8. The subject will be instructed regarding the administration of study medication, completion of the electronic subject diary, use of birth control, follow-up visits at weeks 3, 6, 8, and on seeking emergency medical care or contacting the study physician or nurse under specific conditions.

   CONTACT STUDY PHYSICIAN, IF:

   - Trouble breathing including shortness of breath.
   - Severe headache, stiff neck, confusion or excessive somnolence.
   - If fever (≥99°F or ≥37.2°C) returns after being absent for 24 hours.
   - Increased difficulty breathing.
   - Wheezing develops.
   - New pain develops or pain localizes to one area, such as an ear, the throat, the chest, or the sinuses.
   - Symptoms become more severe or frequent.

- Symptoms recur or any difficulty breathing following 5-10 days resolution of illness.
- An allergic-like reaction occurs or is suspected.
- Abnormal behavior.

**Study Weeks 1 through 6 (Daily)**

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

If the subject reports (i) at least one of the Lower Respiratory Symptoms presented in Text Table 1 below or (ii) at least one symptom from each of the Upper Respiratory Symptoms and Systemic Symptoms categories presented in Text Table 1 below, the subject will then contact the study physician to complete a "Suspected ARI Visit" with the procedures provided below.

**Table 1: Clinical Illness Required for Diagnosis of ARI[1] (adapted from Yu et al. 2020)**

| Upper Respiratory Symptoms | Lower Respiratory Symptoms | Systemic Symptoms |
|---|---|---|
| • Nasal congestion/rhinorrhea (runny or dripping nose, congested or stuffy nose, head congestion, sinus pressure)[2]<br>• Sore throat (sore or painful throat)[2] | • Cough (coughing, chest congestion, chest tightness, dry or hacking cough, wet or loose cough)[2]<br>• Dyspnea (shortness of breath)[2]<br>• Sputum (coughing up sputum or phlegm)[2]<br>• Wheezing | • Myalgias or arthralgias (body aches or pains)[2]<br>• Fatigue (weak or tired, sleeping more than usual)[2]<br>• Headache<br>• Decreased appetite (lack of appetite, did not feel like eating)[2]<br>• Feverishness (felt hot, chills or shivering, felt cold, sweating)[2] |

[1] Suspected ARI requires self-reporting of any Lower Respiratory Symptom, or at least one Upper Respiratory Symptom together with one Systemic Symptom.
[2] Lay language used in the FLU-PRO© questionnaire is presented in parentheses.

### Suspected ARI Visit

Subjects reporting any lower respiratory symptom or at least one upper respiratory symptom and one systemic symptom are considered to have a suspected acute respiratory illness (ARI) and will complete the following procedures at an unscheduled Suspected ARI Visit.

1. Physical examination as warranted by the Investigator for any change from baseline.
2. Body weight and collection of vital signs to include blood pressure, pulse, respiratory rate, and body temperature.
3. Collect a nasopharyngeal swab sample using a single nylon flocked dry swab inserted into both nostrils for RT-PCR at the Suspected ARI Visit, 24 to 36 hours later, and then again 4 to 5 days later.
4. Collect a fecal specimen for RT-PCR at the Suspected ARI Visit, 24 to 36 hours later, and then again 4 to 5 days later.
5. The subject will complete a FLU-PRO© symptom diary daily until he/she responds "yes" to the FLU-PRO© question, "Have you returned to your usual health?" for 3 consecutive days or until the Week 6 Visit, whichever occurs first. The daily FLU-PRO© diary will be completed between 7:00 pm and 11:00 pm.
6. Review and recording of concomitant medications.
7. Review and recording of adverse events/side effects.
8. Laboratory investigations for safety may be performed as warranted based upon the Investigator's judgment.
9. Subjects testing positive for a respiratory virus by RT-PCR may receive standard of care as clinically warranted by the Investigator.

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

### Week 3 (± 7 days) and Week 6 (± 2 days) Evaluations

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

1. Physical Examination as warranted by the Investigator for any change from baseline.
2. Body weight and collection of vital signs to include blood pressure, pulse, respiratory rate, and body temperature.
3. Collection of blood sample for laboratory safety tests, pharmacokinetics (pre-dose) and anti-SARs-CoV-2 antibodies (antibody testing at Week 6 visit only).
4. Collection of urine sample for routine urinalysis.

5. Review of compliance with study medication, collection of medication bottle with any unused medications (Week 6 visit only), and completion of the pill count log form.
6. Review and recording of concomitant medications.
7. Review and recording of adverse events/side effects and complications. Note that all adverse events and complications must be followed until their resolution or stabilization even beyond the 8-week study period.

**Week 8 Evaluation (± 7 days)**

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

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

**Other Unscheduled Visits**

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

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

### 1.3 Sample Size

For purposes of calculating sample size, it is assumed that the proportion of subjects experiencing COVID-19 disease over a 6-week period is 1% and that the proportion of subjects experiencing any VRI is 2%. At the time protocol Version 5.0 was finalized, current illness rates in the trial based upon blinded pooled data were approximately 1.2% for COVID-19 and 2.8% for VRIs. It is further assumed that effective prophylaxis will result in 80% reduction of the illness rate. Influenza prophylaxis studies of oseltamivir have resulted in approximately 80% reduction of influenza illness (see Tamiflu® prescribing information).

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

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

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

## 2.0 Data Analysis Considerations

### 2.1 Types of Analyses

Data analyses will consist of analyzing patient characteristics, safety, and efficacy data.

## 2.2 Analysis Populations

### 2.2.1 Population Definitions

Subjects will be considered enrolled in the study upon completion of the baseline procedures. The following analysis populations will be used in the study.

- **Safety Population** – the safety population includes all patients who are enrolled in the study and that have received at least one dose of the assigned treatment arm (NTZ or placebo).
- **Intention-to-Treat Population** (ITT) – the ITT population includes all patients in the safety population who did not have a laboratory detected respiratory virus infection at the baseline visit.

The safety population will be used for all safety analyses. The ITT population will be the primary population for all efficacy analyses.

A data listing displaying the patients excluded from the ITT population will be created, as shown in the Table Requirements Document. This listing will be relative to all patients in the safety population.

### 2.2.2 Subgroup Definitions

Certain efficacy analyses will be conducted on the various study strata. Efficacy analyses for the primary endpoints will be performed by sex (male/female), race (white/non-white), and age group (18- 34 years, 35- 64 years, and 65 year or older). Safety analyses will be grouped by treatment received.

## 2.3 Missing Data Conventions

Date variables with missing items will be imputed as shown in Table 2 below.

**Table 2. Imputation rules for missing dates.**

| Data | Handling Convention |
|---|---|
| Adverse event onset date | If onset date is completely missing, impute with the date of first dose.<br><br>If year is missing, impute with the year of enrollment.<br><br>If only year or if year and day are present:<br>• If year = year of first dose, then set month and day to the date of the first dose.<br>• If year < year of first dose, then set month and day to December 31.<br>• If year > year of first dose, then set month and day to January 1.<br><br>If month and year are present, but day is missing:<br>• If year = year of first dose and<br>o If month = month of first dose, then set day to day of first dose. |

| Data | Handling Convention |
|---|---|
| | ○ If month < month of first dose, then set day to the last day of the month.<br>○ If month > month of first dose, then set day to the first day of the month.<br>• If year < year of first dose, then set day to the last day of the month.<br>• If year > year of first dose, then set day to the first day of the month.<br>• For all other cases, set onset date to the date of first dose. |
| Adverse event end date | If the end date is partially or completely missing, set to the last date the subject was known to be in the study. |
| Concomitant medications start date | If start date is completely missing, it will not be imputed.<br><br>If only year or if year and day are present, set the month and day to January 1.<br><br>If year and month are present and day is missing, set day to the first day of the month. |
| Concomitant medications end date | If end date is missing, frequency is "1X" and the medication is not listed as "ONGOING", then end date should be set to equal the start date.<br><br>If end date is completely missing, it will not be imputed.<br><br>If only year or if year and day are present, set the month and day to December 31.<br><br>If year and month are present and day is missing, set day to the last day of the month. |

While every effort will be made to compile the data in accordance with intent-to-treat, it is likely that some subjects will have missing endpoints. Subjects with a completely missing baseline FLU-PRO© will have their symptoms imputed with a score of 0. Additionally, subjects who only partially complete a FLU-PRO© at any visit will have their missing scores imputed with a 0. Note that completely missing FLU-PRO© questionnaires at post-baseline visits will not be imputed.

After taking into account the imputation of missing FLU-PRO© scores as described above, subjects with missing primary endpoints will be imputed as uninfected. That is, subjects in both treatment arms will have their missing primary endpoint data imputed as absence of symptomatic COVID-19 disease and absence of symptomatic VRI.

Sensitivity analyses will be performed to assess the influence missing primary endpoints may have on the study's conclusions. The first analysis will be a best-case analysis, assigning infected status to all missing COVID-19 disease and VRI status in the placebo arm and non-infected status to these variables in the NTZ arm. The second sensitivity analysis will be a worst-case analysis. This analysis will assign infected status for COVID-19 disease and VRI to missing values in the NTZ arm and non-infected status to the missing values in the placebo arm. Finally, a tipping point analysis will use multiple imputation methods to determine the allocation of infected and non-infected status to missing values in the NTZ arm which changes the study conclusions.

### 2.4 Interim Analyses

Two interim data reviews and analyses will be scheduled and held promptly after the pertinent milestone has been reached. The first analysis will occur when 25% of the subjects have completed week 3. The first interim analysis will be a blinded analysis for drug safety only.

The second analysis will occur when 50% of the planned 24 COVID-19 cases have been reported (i.e., after 12 COVID-19 cases are reported). The second interim analysis will be for safety and potentially stopping the trial for futility. The Interim Data Review Plan will be included in the Independent Data Monitoring Committee (IDMC) charter.

Futility will be assessed via the efficacy of NTZ for the COVID-19 endpoint. The IDMC will recommend stopping for futility if the CMH test statistic for comparing the treatment groups on the COVID-19 endpoint is less than 0.179 (i.e., a *p*-value greater than 0.3278). The CMH test will be conducted for the sole purpose of evaluating futility; there will be no early stopping for efficacy. This bound was set using O'Brien-Fleming bounds for futility with overall ⇨ = 0.049.

The IDMC will conduct the meetings in accordance with the IDMC charter. No efficacy analysis is planned and no allocation of ⇨ to the interim analysis is necessary.

### 2.5 Study Center Considerations in the Data Analysis

A study center is defined as a treatment administration site or group of treatment administration sites under the control and supervision of the same Principal Investigator (PI). There will be no selective pooling of study centers – all sites will be pooled. The study is planned to be conducted at multiple sites.

### 2.6 Documentation and Other Considerations

The data analyses will be conducted using Python and supported statistical packages.

## 3.0 Analysis of Baseline Patient Characteristics

Baseline and demographic characteristics of the safety population will be summarized. Continuous variables (age and baseline weight) will be summarized via mean, standard deviation, minimum, median, maximum, and number of non-missing responses. Categorical variables (gender, race ethnicity, and tobacco use (by product type)) will be summarized via counts and percentages.

A detailed listing of baseline data for each patient in the safety population will also be provided as shown in Appendix B.

# 4.0 Analysis of Efficacy

## 4.1 Efficacy Variables

All the efficacy variables are categorical in nature: the presence or absence of any VRI, ARI, or COVID-19 during the study period. Similarly, hospitalization (and its cause) and death (and its cause) are categorical.

**Primary Efficacy Variables**
There are two primary efficacy variables:

1. The presence or absence of symptomatic COVID-19 disease identified after the start of treatment and before the end of the 6-week treatment period.
2. The presence or absence of symptomatic VRI (including COVID-19) identified after the start of treatment and before the end of the 6-week treatment period.

Symptomatic COVID-19 is defined as an ARI after start of treatment and before the end of the 6-week treatment period associated with detection of SARS-CoV-2 by RT-PCR assay of nasopharyngeal swab.

Symptomatic VRI is defined as an ARI after start of treatment and before the end of the 6-week treatment period associated with detection of any respiratory virus by RT-PCR assay of nasopharyngeal swab.

A subject will be considered to have met the criteria for an ARI if:

1. The subject meets the criteria that trigger the Suspected ARI Visit (see Section 1.2);

   AND

2. The subject satisfies the following ARI definition: ARI is defined as ≥0.5 increase from baseline in mean symptom score for the FLU-PRO© chest/respiratory domain alone; or a $\geq$ 0.5 increase from baseline in mean symptom score for at least two of the following FLU-PRO© domains: body/systemic, nose, throat.

**Secondary Efficacy Variables**
The secondary efficacy variables are:

1. Mortality due to COVID-19 or complications thereof.
2. The presence or absence of anti-SARS-CoV-2 antibodies at either of the Week 6 or Week 8 visits.

**Exploratory Efficacy Variables**
The exploratory efficacy variables are:

1. Hospitalization due to VRI or complications thereof.
2. Mortality due to VRI or complications thereof.
3. Presence or absence of an ARI.
4. Hospitalization due to ARI or complications thereof.
5. Mortality due to ARI or complications thereof.

## 4.2 Efficacy Analysis

### 4.2.1 Primary Efficacy Variables

This study has two primary endpoints: symptomatic COVID-19 disease and symptomatic VRI. The study-wise Type I error rate is 0.05, allocated ⇨ = 0.049 to COVID-19 disease and ⇨ = 0.001 to all VRI. In each case the hypotheses to be tested are

$$\mathrm{H}_0: p_1 = p_2$$
$$\mathrm{H}_1: p_1 \neq p_2,$$

where $p_1$ represents the COVID-19 disease rate (or VRI rate) in the NTZ arm and $p_2$ represents the COVID-19 disease rate (or VRI rate) in the placebo arm.

**Primary Analysis**
The proportion of subjects experiencing symptomatic COVID-19 disease in the NTZ treatment group will be compared to the similar proportion in the placebo group using a two-sided CMH test with continuity correction at ⇨=0.049. The contingency tables will be provided with rates relative to the treatment margins. The common relative risk and the odds ratio between the treatment groups and 95% confidence intervals for these parameters will be provided. The analysis will be repeated by sex of subject (female or male), age group of subjects (18- 34 years, 35- 64 years, 65 years and older), and race of subject (white or non-white).

The proportion of subjects experiencing symptomatic VRI infections in the NTZ treatment group will be compared to the similar proportion in the placebo group using a two-sided CMH Chi-square test with continuity correction at ⇨=0.001. The contingency tables will be provided with rates relative to the treatment margins. The common relative risk and the odds ratio between the treatment groups and 95% confidence intervals for these parameters will be provided. The analysis will be repeated by sex of subject (female or male), age group of subjects (18- 34 years, 35- 64 years, 65 years and older), and race of subject (white or non-white).

While every effort will be made to compile the data in accordance with intent-to-treat, it is likely that some subjects will have missing endpoints. Subjects with missing outcomes data will be included in the primary analysis. The primary analysis will impute missing data as uninfected in each treatment arm. Best-case and worst-case sensitivity analyses will be performed as outlined in Section 2.3 above. In addition, a tipping point analysis will

be performed, imputing various levels of COVID-19 and VRI infection rates to missing values in the NTZ arm to determine the infection rate at which the study conclusions change.

**Secondary Analysis**
Secondary analyses of the primary endpoints include the proportion of subjects experiencing symptomatic COVID-19 in the NTZ treatment group will be compared with the similar proportion in the placebo group for each stratum using a Pearson Chi-square test with continuity correction. A 95% Wilson confidence interval (with continuity correction) will be produced for the symptomatic COVID-19 infection in each group within each stratum. A 95% confidence interval for the odds-ratio of symptomatic COVID-19 infection rate in the NTZ vs placebo groups will be produced for each stratum. The contingency tables will be provided with rates relative to the treatment margins.

### 4.2.2 Secondary Efficacy Variables

Statistical tests for the secondary efficacy variables will be performed only if the primary analyses of primary efficacy variables both reject the null hypothesis. These tests act as gatekeepers to the secondary efficacy tests. No allocation of study-wise ⇨ to the secondary tests is necessary.

The mortality rates due to COVID-19 or complications will be compared by stratum with a Pearson Chi-square test. The overall mortality rate due to COVID-19 or complications in the two treatment groups will each be compared using a CMH Chi-square test with continuity correction at ⇨=0.05. A 95% confidence interval for the pooled odds-ratio will be provided.

The proportion of subjects testing positive for SARS-CoV-2 antibodies at either Week 6 or Week 8 will be compared using Pearson Chi-square tests with continuity correction in each stratum. The contingency tables will be provided with rates relative to the treatment margins. The overall positive rates in the treatments will be analyzed with a CMH Chi-square test.

### 4.2.3 Exploratory Efficacy Variables

Hospitalization due to VRI or complication thereof, mortality due to VRI or complications thereof, presence of an ARI, hospitalization due to ARI or complications thereof, and mortality due to ARI or complications thereof will each be summarized in a three-way contingency table (Stratum*Treatment*Variable) with counts and percentages relative to the table row margins. Pearson chi-square test results per stratum will be provided as will a CMH Chi-square test of treatment effects and a 95% confidence interval for the pooled odds ratio for the NTZ vs placebo group.

# 5.0 Analysis of Safety

## 5.1 Description of Safety Variables

The safety analysis variables are defined as follows:

- Adverse Events (AEs).
- Clinical Laboratory Values (Hematology, Blood Chemistry, and Urinalysis).
- Physical Exam.
- Vital Signs.

The following describes the safety analyses to be performed for the study. All safety analyses will be performed on the safety population.

## 5.2 Description of Safety Analyses

**Adverse Events**

Adverse events will be graded by the investigator according to the "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials" as adapted in the Study Protocol. The investigator will also assess causality (relationship to treatment) as *Definitely related, Probably related, Possibly related,* and *Unrelated*. AEs will also be coded using the Medical Dictionary for Regulatory Activities version 23 or higher (MedDRA®). Treatment-emergent AEs (TEAEs), defined as any AE that occurs after a patient receives the first dose of the assigned study treatment, will be summarized by the number and proportion of patients reporting at least one occurrence of the AE. Frequencies and rates of each TEAE will be summarized by MedDRA preferred term within system organ class (SOC), by severity grade, and relation to treatment for each treatment group The rate calculation will be based on the number of patients in the Safety population for the relevant treatment group.

Treatment emergent serious adverse events (TESAEs) will be summarized and displayed by frequency and rate by MedDRA preferred term within SOC.

A by-patient AE data listing of all adverse events including verbatim term, coded term, grade, and relation to study treatment will be provided.

**Laboratory Tests**

Clinical laboratory tests will be performed at the times prescribed in the protocol. The following clinical laboratory tests will be analyzed:

**Hematology:**

Hemoglobin, hematocrit, complete white blood count (total and differential), platelet count, random blood glucose, total cholesterol, HDL, LDL, and triglycerides.

**Clinical Chemistry:**

AST, ALT, GGT, alkaline phosphatase, bilirubin (total and direct), BUN, creatinine, sodium, potassium, and chloride.

**Urinalysis:**

Appearance, glucose, protein, and blood.

Clinical laboratory results and the change from baseline (CFB, baseline defined as the value at the baseline visit) will be summarized for the Safety population with summary statistics (mean, standard deviation, n, minimum, median, maximum) by time point for each treatment group. Clinical laboratory results will be classified as "Normal", or "Abnormal"; "Abnormal" results will be further classified by the PI as "Clinically significant" (CS) or "Not clinically significant" (NCS). Clinical laboratory results will be summarized by a shift table from baseline with categories "Normal", "Abnormal (NCS)", and "Abnormal (CS)".

All clinically significant abnormal laboratory findings will be reported as AEs. All AEs recorded will be listed.

**Physical Exam**

Physical exams (PEs) will be performed as outlined in the protocol. All clinically significant abnormal PE findings will be recorded as AEs. All physical exam data will be listed as shown in Appendix B.

**Vital Signs**

Vitals signs will include weight, heart rate, respiratory rate, blood pressure (diastolic and systolic), and temperature. Vital signs will be taken as outlined in the protocol. The baseline visit vital signs will be used for baseline for changes at the Week 3 and Week 6 follow-up visits. If repeat vital signs are taken at a given time point, then the last measurement will be used for the analysis tables.

Vital signs and CFB will be summarized for the safety population with summary statistics (mean, standard deviation, n, minimum, median, maximum) by time point and treatment group. All vital signs will be listed.

## 6.0 Other Relevant Data Analyses/Summaries

### 6.1 Patient Completion

A table will be constructed with counts and percentages by treatment assignment of subjects' disposition status, including the reason for withdrawal for all subjects who

withdrew. Percentages will be computed relative to the number of subjects randomized to each treatment.

### 6.2 Prior and Concomitant Medications

All prior/concomitant medications taken by or administered to a patient will be collected from the 30 days prior to treatment through the completion of the follow-up visit. Concomitant medications will be coded using the most recent version of the WHO Drug Dictionary. A data listing for concomitant medications including ATC Levels I and IV will be provided.

### 6.3 Death Report

The number and percentage of deaths from all causes will be computed by treatment group for the safety population. All death report data will be listed.

### 6.4 Additional Baseline Data

Medical history will be presented in data listings for the safety population. History events will be coded using the current version of MedDRA (version 23 or higher).

### 6.5 Protocol Deviations

Tables will be constructed to summarize major and minor protocol deviations by treatment group for the safety population. All protocol deviations will be listed.

### 6.6 Treatment Compliance and Administration

Treatment compliance data will be summarized by treatment group for the safety population. All treatment compliance and administration data will be listed.

## 7.0 References

FDA/CDER Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. US Department of Health and Human Services. September 2007. (Retrieved 28April2020 from https://www.fda.gov/media/73679/download).

Yu J, Powers JH, Vallo D, Falloon J. Evaluation of efficacy endpoints for a phase IIb study of a respiratory syncytial virus vaccine in older adults using patient-reported outcomes with laboratory confirmation. *Value Health* 2020; 23:227-35.

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