Statistical Analysis Plan (SAP)

Phase 3, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Nitazoxanide (NTZ) in the Treatment of Mild or Moderate COVID-19

Study No.: RM08-3008

Version 1.2
February 24, 2021

Prepared for The Romark Institute for Medical Research

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Prepared by

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Approval Page

By entering into this Statistical Analysis Plan (SAP), the parties acknowledge and agree that this SAP shall be incorporated into and subject to the terms of the Master Services Agreement (MSA). Any changes requested by Client to this SAP shall be subject to Section I.C of the MSA requiring a mutually agreed upon "Change Order" prior to any modification of the procedures set forth herein.

I agree to the format and content of this document.

Approved by:

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24 Feb 2021
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Revision History

Version 1.1 to 1.2

- Updated the imputation rule for adverse event end dates to take into account the adverse event outcome in Section 2.3.
- Added serology to Section 2.4.1.

Version 1.0 to 1.1

- Removed $TCID_{50}$ and replaced it with either Aptima® SARS-CoV-2 Assay or quantitative RT-PCR, as appropriate.
- Added Section 2.4.1 to describe the process for running a subset of the final TLFs prior to receiving final data from quantitative RT-PCR and/or PK testing.
- Changed the units of the primary efficacy endpoint from hours to days. Updates include edits to the text in Section 4.1.1 and Section 4.2.1.3.
- Added subgroup analyses of the primary efficacy endpoint. Updates include edits to the text in Section 2.2.2 and Section 4.2.1 and an additional table and figures in Section 8.0.
- Added a sensitivity analysis of the primary efficacy endpoint using the log-rank test. Updates include the addition of Section 4.2.1.1 (previous Section 4.2.1.1 and 4.2.1.2 renumbered accordingly) and an additional table in Section 8.0.

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Abbreviations and Acronyms

AE	Adverse Event
ARI	Acute Respiratory Illness
ATC	Anatomic Therapeutic Chemical
CDER	Center for Drug Evaluation and Research
COVID-19	Novel Corona Virus Infectious Disease, 2019
CMH	Cochran-Mantel-Haenszel Chi-square Test
FDA	US Food and Drug Administration
IAP	Interim Analysis Plan
LTCF	Long Term Care Facility
NTZ	Nitazoxanide
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome-Corona Virus 2, the pathogen causing COVID-19
TEAE	Treatment Emergent Adverse Event
VRI	Viral Respiratory Illness
WHO	World Health Organization

1.0 Synopsis of Study Design Procedures

This study is a multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate efficacy and safety of NTZ 600 mg administered orally twice daily for five days compared to a placebo for the treatment of mild or moderate COVID-19.

The objectives of the study are:

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

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

Exploratory Objectives: To evaluate:

i. The proportion of subjects positive for SARS-CoV-2 by Aptima® SARS-CoV-2 Assay at each of Days 4 and 10
ii. The change from baseline in quantitative SARS-CoV-2 RNA measured by RT-PCR at each of Days 4 and 10
iii. The effect of NTZ in reducing the rate of hospitalization compared to placebo
iv. The effect of NTZ in reducing the rate of mortality compared to placebo

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

1.1 Design and Treatment

Subjects will be stratified according to the following criteria:

- Severity of COVID-19 illness: mild, moderate
- Time from onset of symptoms to randomization: < 36 hours, at least 36 hours
- Risk of severe illness (per CDC): at increased risk, not at increased risk

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

- Group 1 (NTZ): Two 300 mg NTZ tablets b.i.d. (twice daily) for 5 days;
- Group 2 (Placebo): Two placebo tablets b.i.d. for 5 days.

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

1.2 Study Procedures

Screening

Subjects will be screened on Study Day 1. After giving informed consent, the subject will be assigned a subject number and complete the following procedures:

1. Collection of relevant medical history.
2. Physical examination including body measurements and resting vital signs (blood pressure, pulse rate, respiratory rate, oxygen saturation, and oral temperature).
3. Collection of demographic information and smoking history.
4. Completion of the FLU-PRO questionnaire to confirm presence of symptoms required for eligibility.
5. 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, the same day as the screening evaluation) the subject will be randomized and complete the following procedures:

1. Collection of a nasopharyngeal swab sample for virology testing.
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. Randomization and dispensing of study medication. Subjects will be considered enrolled in the study upon the randomized assignment to a treatment group.
6. Administration of the first dose of study medication with food (< 1 hour after food intake) and a B complex vitamin (Super B-Complex™, Igennus Healthcare Nutrition, Cambridge, UK) under observation of Investigator or a member of Investigator's staff, and entry in the medication administration record.
7. Review/record adverse events.
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 Study Days 4, 10, and 22, and on seeking emergency medical care or contacting the study physician or nurse under specific conditions, as listed in the protocol.

Treatment Period: Study Days 2 through 7 (Daily)

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

1. Completed all expected doses of study medications.
2. Completed all expected electronic diaries.
3. Worsening symptoms or adverse events warranting an unscheduled visit.
4. Presence of shortness of breath at rest.

Follow-up Visits

Follow-up visits will occur on Day 4 ± 1, Day 10 ± 3, and Day 22 ± 3. On Days 4 and 10 the following assessments will be performed:

1. Physical Examination, completed as necessary.
2. Body weight and resting vital signs.
3. Collect nasopharyngeal swab samples.
4. Collect blood sample for pharmacokinetic analysis (Day 4 only).
5. Record concomitant medications.
6. Review and record adverse events.
7. Review instructions re: dosing of study medication, concomitant medications, diary completion, follow-up visits, and emergency care.

On Day 22 the following assessments will be performed:

1. Physical Examination, completed as necessary.
2. Body weight and resting vital signs.
3. Collect blood sample for lab safety tests.
4. Collect blood sample for antibody tests.
5. Collect urine sample for routine urinalysis.
6. Record concomitant medications.
7. Review and record adverse events.
8. Review instructions re: dosing of study medication, concomitant medications, diary completion, follow-up visits, and emergency care.

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 blood sample for laboratory safety tests.
4. Collection of urine sample for routine urinalysis.
5. Review and recording of concomitant medications.
6. Review and recording of adverse events.

1.3 Sample Size

The response definition planned for this study, the time from first dose to Sustained Response, was applied to data collected in Romark Institute for Medical Research studies RM08-3004 and RM08-3005, which evaluated the use of NTZ in the treatment of influenza (RM08-3004) and colds caused by Enterovirus/Rhinovirus (EV/RV) (RM08-3005), respectively.

For purposes of calculating sample size, we assume that the time to sustained response for SARS-CoV-2 infection is similar to influenza or colds caused by EV/RV. Based upon the influenza data, a sample of size 288 (144 per treatment group) would provide 90% power with α = 0.05 using the Gehan-Wilcoxon rank test. Based upon the EV/RV survival curves and the same testing parameters results in a required sample size of 312 subjects (156 per treatment group) to obtain 90% power. In order to ensure a robust dataset, a sample size of 350 subjects (175 per treatment group) was chosen including an allowance for approximately 10% of subjects to discontinue early or otherwise have missing data. If the pace of enrollment is high, the Sponsor will enroll up to 400 SARS-CoV-2 infected subjects.

The Sponsor anticipates a SARS-CoV-2 positive rate between 50% and 75%, and hence enrolling 350-400 SARS-CoV-2 positive subjects may require enrolling 450 to 800 subjects.

2.0 Data Analysis Considerations

2.1 Types of Analyses

Data analyses will consist of analyzing subject characteristics and 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.

- **Intent-to-Treat (ITT) Population** – the ITT population includes all subjects who are enrolled in the study and have received at least one dose of study medication (NTZ or placebo).
- **Intent-to-Treat Infected (ITTI) Population** – the ITTI population includes all ITT subjects who are positive for SARS-CoV-2 by Aptima® SARS-CoV-2 assay at Baseline.
- **Per Protocol (PP) Population** – the subset of the ITTI population with no major protocol deviations that may affect the integrity of the data or evaluation of effectiveness. Exclusion from the PP will be done before database lock.

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

Data listings displaying the subjects excluded from each population will be created. These listings will be relative to all subjects enrolled in the study.

2.2.2 Stratum and Subgroup Definitions

Subjects will be stratified on the basis of Severity of COVID-19 illness (Mild or Moderate), Time from onset of symptoms to randomization (less than 36 hours or at least 36 hours), and Risk of severe illness per CDC guidelines (At increased risk or not at increased risk). There will be a total of 8 strata.

The primary efficacy variable of the Time to Sustained Response will also be summarized by the following subgroups:

- Risk of severe COVID-19 illness per CDC guidelines (At increased risk or not at increased risk)
- Age (12-17, 18-64, ≥ 65)
- Sex
- Race (White/Non-white)

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. If year is missing, impute with the year of enrollment.

Data	Handling Convention
	If only year or if year and day are present: • If year = year of first dose, then set month and day to the date of the first dose. • If year < year of first dose, then set month and day to December 31. • If year > year of first dose, then set month and day to January 1. If month and year are present, but day is missing: • If year = year of first dose and ○ If month = month of first dose, then set day to day of first dose. ○ If month < month of first dose, then set day to the last day of the month. ○ If month > month of first dose, then set day to the first day of the month. • If year < year of first dose, then set day to the last day of the month. • If year > year of first dose, then set day to the first day of the month. • 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 and AE outcome is not one of the following: RECOVERING/RESOLVING, NOT RECOVERED/NOT RESOLVED, UNKNOWN, or missing, then set to the last date the subject was known to be in the study. Otherwise, if AE outcome is one of the following: RECOVERING/RESOLVING, NOT RECOVERED/NOT RESOLVED, UNKNOWN, or missing, then set the end date to missing.
Concomitant medications start date	If start date is completely missing, it will not be imputed. If only year or if year and day are present, set the month and day to January 1. 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. If end date is completely missing, it will not be imputed. If only year or if year and day are present, set the month and day to December 31. If year and month are present and day is missing, set day to the last day of the month.

2.4 Interim Analyses

No interim analyses are planned.

2.4.1 Analysis Timing Considerations

It is anticipated that central lab data for the serology, quantitative SARS-CoV-2 RNA measured by RT-PCR, and the pharmacokinetics (PK) analysis of blood samples may be delayed at the end of the study, due to sample processing timelines. These lab data will be transferred outside of the clinical database and will not impact the timing of database lock. Further, these data have no impact on the primary and secondary efficacy

objectives of the study.

At the Sponsor's discretion, the final unblinded tables, listings, and figures (TLFs) using the locked database may be generated and shared with the Sponsor prior to completion of the serology, RT-PCR, and PK sample testing. The central lab responsible for processing the serology, RT-PCR, and PK data will have no knowledge of the subjects' treatment information nor any knowledge of the study outcomes while samples are being processed. At the completion of sample processing, the central lab will transfer the serology, RT-PCR, and PK data directly to SCS to incorporate into the final study datasets. The SAS programs used to generate the final study datasets will be re-run to include these new data files, and the final set of all TLFs will be generated. This re-run of final TLFs will be conducted for the sole purpose of including the new central lab data; the TLFs generated prior to completion of serology, RT-PCR, and PK sample testing will remain unchanged.

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 SAS® Software, version 9.4 or later.

3.0 Analysis of Baseline Subject Characteristics

Baseline and demographic characteristics of the ITT and ITTI populations will be summarized. Continuous variables (age, baseline height, baseline weight) will be summarized via mean, standard deviation, minimum, median, maximum, interquartile range, and number of non-missing responses. Categorical variables (gender, race, and ethnicity) will be summarized via counts and percentages.

A detailed listing of baseline data for each subject in the ITT population will also be provided.

4.0 Analysis of Efficacy

4.1 Efficacy Variables

4.1.1 Primary Efficacy Variable

The primary efficacy variable is the Time to Sustained Response. This is defined as the time in days from the first dose of study medication to the time of the first diary entry meeting all the criteria for a sustained response (i.e., Time of Sustained Response).

Sustained response to treatment is defined as a decrease in the total FLU-PRO score from the previous, subject assessment that symptoms are at least "somewhat better than yesterday", no oral temperature $\geq$ 100.4 F in the preceding 24 hours, and no future increase in any of the FLU-PRO domains except within the following levels:

FLU-PRO Domain	Background Level
Body/Systemic	0.56
Throat	0.67
Eyes	0.67
Gastrointestinal	2.00
Head	2.00
Nose	Larger of score at time of response or 0.75
Chest	Score at time of response
Cough	Larger of score at time of response or 1.75

Subjects must have at least one diary following the time of sustained response in which there is no relapse, meaning that a subject cannot achieve sustained response at the last diary entry.

Situation	Censoring rule
Has Time of Sustained Response	Not censored.
Hospitalized due to COVID-19	Censored at Day 21 (i.e., hour 504).
Died (any cause)	Censored at Day 21 (i.e., hour 504).
No Time of Sustained Response	Censored at time of last diary entry without sustained response.

4.1.2 Key Secondary and Exploratory Efficacy Variables

The key secondary efficacy variable is Progression to Severe COVID-19 Illness. Any subject meeting both of the following criteria has advanced to Severe COVID-19 Illness:

1. Shortness of breath at rest.
2. $SpO_2 \leq 93\%$ on room air, or $PaO_2/FiO_2 < 300$.

The exploratory efficacy variables are:

1. Proportion of subjects positive for SARS-CoV-2 by Aptima® SARS-CoV-2 assay at Days 4 and 10.
2. Change from baseline of quantitative SARS-CoV-2 RNA measured by RT-PCR at Days 4 and 10.
3. Hospitalization due to COVID-19 or complications thereof.
4. Mortality due to COVID-19 or complications thereof.

4.2 Efficacy Analysis

4.2.1 Primary Efficacy Analysis

The Time to Sustained Response will be summarized with descriptive statistics (n, mean, standard deviation, minimum, maximum, median, and interquartile range) with censored values excluded from the descriptive statistics.

The Time to Sustained Response will be tested for differences between the treatment groups using a stratified Gehan-Wilcoxon test at α = 0.05 using the stratification at randomization. Kaplan-Meier curves will be provided. The hypotheses being tested are

H_0: The survival curves of the NTZ Group and the Placebo Group are identical.
H_1: The survival curves of the NTZ Group and the Placebo Group are different.

The analysis table will include the Kaplan-Meier estimates of the mean and median for each treatment group.

Subgroup analyses will be conducted on the subgroups specified in Section 2.2.2. Descriptive statistics and Kaplan-Meier estimates of the mean and median Time to Sustained Response will be provided by subgroup, but there will be no hypotheses tested in these subgroups.

4.2.1.1 Sensitivity Analysis Using Log-rank Test

The primary efficacy analysis will be repeated using a stratified log-rank test at α = 0.05 using the stratification at randomization.

4.2.1.2 Sensitivity Analysis for Major Protocol Deviations

The primary efficacy analysis will be repeated for the PP population to assess the impact of subjects with major protocol deviations.

4.2.1.3 Sensitivity Analyses for Missing Data

Our assumptions for missing data and subject discontinuation rates are based on observations from the approximately 2,800 subjects enrolled in studies RM08-3004 and RM08-3005. These studies enrolled a similar population to the one planned for this study, had a similar study design, and used the same diary requirements and strategies to minimize missing diary data.

The majority of missing diary entries in RM08-3004 and RM08-3005 occurred after patient-reported return to usual health, which is consistent with findings in the validation study of FLU-PRO (Powers et al. 2018). Therefore, we expect that most missing data will not be informative regarding symptom course. Subjects missing a single diary entry after the time of Sustained Response had similar responses at the diary entries immediately before and after the missing entry.

A sensitivity analysis will be performed assuming symptom worsening during all periods of potentially meaningful missing data.

Situation	Rule
Subject discontinued study or was lost to follow up prior to achieving Sustained Response	Censored at Day 21 (i.e., hour 504)
Subject discontinued study or was lost to follow up after achieving Sustained Response	Censored at Day 21 (i.e., hour 504)
Subject missed at least two consecutive diary entries after achieving Sustained Response	Assign the Time of Sustained Response to the next non-missing diary after the two consecutive missed diary entries

4.2.2 Key Secondary and Exploratory Efficacy Analysis

All key secondary and exploratory efficacy analyses will be performed for the ITTI population.

4.2.2.1 Key Secondary Efficacy Analysis: Proportion of Subjects Progressing to Severe COVID-19 Illness

The cross-tabulation (i.e., two-way table) of Progression to Severe COVID-19 illness versus treatment group will be provided, with conditional rates of progression for each treatment group.

If the primary efficacy analysis is statistically significant at α=0.05, the key secondary efficacy variable (Progression to Severe COVID-19 Illness) will be analyzed. The proportion of subjects in the NTZ and placebo groups experiencing progression to severe

COVID-19 illness will be analyzed using a CMH test stratified by randomization stratum with appropriate continuity correction at an unadjusted α=0.05. The hypotheses tested are

$$H_0: p_{NTZ} = p_{Ctl}$$
$$H_1: p_{NTZ} \neq p_{Ctl},$$

where p_{NTZ} and p_{Ctl} respectively represent the rate at which NTZ subjects and placebo subjects progress to severe COVID-19 illness. The overall odds ratio and a 95% confidence interval for the odds ratio will be provided.

4.2.2.2 Exploratory Analysis: Proportion of subjects Positive for SARS-CoV-2 by Aptima® SARS-CoV-2 Assay at Days 4 and 10

Nasopharyngeal swabs for virology testing are scheduled to be taken on the Day 4 and Day 10 visits. The rates at which subject nasopharyngeal swabs test positive for SARS-CoV-2 in the NTZ and placebo groups will be analyzed using a CMH test stratified by the randomization stratum with the appropriate continuity correction at an unadjusted α of 0.05. The hypotheses tested are

$$H_0: p_{NTZ} = p_{Ctl}$$
$$H_1: p_{NTZ} \neq p_{Ctl},$$

where p_{NTZ} and p_{Ctl} respectively represent the rate at which NTZ subjects and placebo subjects test positive by the Aptima® SARS-CoV-2 assay. The overall odds ratio and a 95% confidence interval for the odds ratio will be provided. The cross-tabulation of SARS-CoV-2 status versus treatment group will be provided, with conditional rates for each treatment group. Day 4 and Day 10 data will be analyzed separately.

4.2.2.3 Exploratory Analysis: Changes from Baseline in Quantitative SARS-CoV-2 RNA Measured by RT-PCR

Viral RNA levels will be determined for the Day 4 and Day 10 nasopharyngeal swabs by quantitative RT-PCR. The reported value will be transformed by $\log_{10}(X+1)$, where X is the reported number of RNA copies/µL. The transformed values will be summarized with descriptive statistics (number of observations, mean, standard deviation, minimum, maximum, median) by treatment group. A Satterthwaite T-test will be used to test the hypotheses

$$H_0: \mu_{NTZ} = \mu_{Ctl}$$
$$H_1: \mu_{NTZ} \neq \mu_{Ctl},$$

where μ_{NTZ} and μ_{Ctl} respectively represent the mean $\log_{10}$(RNA copies/µL) concentrations for the NTZ and placebo groups. A 95% confidence interval for the difference in means will be provided.

4.2.2.4 Exploratory Analysis: Proportion of Subjects Hospitalized Due to COVID-19 or Complications Thereof

The cross-tabulation of Hospitalization due to COVID-19 illness or complications thereof versus treatment group will be provided, with conditional rates for each treatment group.

Hospitalization due to COVID-19 or complications thereof will be analyzed using a CMH test stratified by the randomization stratum with the appropriate continuity correction at an unadjusted α of 0.05. The hypotheses tested are

$$H_0: p_{NTZ} = p_{Ctl}$$
$$H_1: p_{NTZ} \neq p_{Ctl},$$

where p_{NTZ} and p_{Ctl} respectively represent the rate at which NTZ subjects and placebo subjects are hospitalized due to COVID-19 illness or its consequences. The overall odds ratio and a 95% confidence interval for the odds ratio will be provided.

4.2.2.5 Exploratory Analysis: Proportion of Subjects with Mortality Due to COVID-19 or Complications Thereof

The cross-tabulation of Mortality due to COVID-19 illness or complications thereof versus treatment group will be provided, with conditional rates for each treatment group.

Mortality due to COVID-19 or complications thereof will be analyzed using a CMH test stratified by the randomization stratum with the appropriate continuity correction at an unadjusted α of 0.05. The hypotheses tested are

$$H_0: p_{NTZ} = p_{Ctl}$$
$$H_1: p_{NTZ} \neq p_{Ctl},$$

where p_{NTZ} and p_{Ctl} respectively represent the rate at which NTZ subjects and placebo subjects die due to COVID-19 illness or its consequences. The overall odds ratio and a 95% confidence interval for the odds ratio will be provided.

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 ITT 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" (FDA/CDER, 2007) 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 be coded using the Medical Dictionary for Regulatory Activities version 23.0 or higher (MedDRA®).

Treatment-emergent AEs (TEAEs), defined as any AE that occurs after a subject receives the first dose of the assigned study treatment, will be summarized by the number and proportion of subjects reporting at least one occurrence of the AE. Frequencies and rates of each TEAE will be summarized by MedDRA system organ class (SOC) and by preferred term within SOC, by severity grade, and relation to treatment for each treatment group. The rate calculation will be based on the number of subjects in the ITT population for the relevant treatment group.

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

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

Laboratory Tests
Clinical laboratory tests will be performed at baseline and on Day 10. The following clinical laboratory tests will be performed:

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

Clinical Chemistry:
Albumin, 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 ITT population with summary

statistics (mean, standard deviation, n, minimum, median, maximum) by visit for each treatment group.

Clinical laboratory results will be classified according to the toxicity grading tables in the protocol Appendix 4 and will be summarized using a shift table from baseline according to these categories.

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 at baseline and at Days 4, 10 and 22 as needed due to symptoms or other changes from baseline. All clinically significant abnormal PE findings will be recorded as AEs. A shift table will be constructed to display changes in physical examination classification (Normal/Abnormal/Not Done) at each visit by body system for the ITT population. All physical exam data will be listed.

Vital Signs
Vital signs will include weight, heart rate, respiratory rate, blood pressure (diastolic and systolic), temperature and oxygen saturation. Vital signs will be taken at baseline, Day 4, Day 10, and Day 22. If repeat vital signs are taken at a given time point, then the last measurement will be used for the analysis tables.

Vital signs will be summarized for the ITT population with summary statistics (mean, standard deviation, n, minimum, median, maximum) by visit and treatment group for the raw and change from baseline values. All vital signs will be listed.

6.0 Other Relevant Data Analyses/Summaries

6.1 Subject Disposition

Tables will be constructed with counts and percentages of subjects who complete or discontinue from the study and the mean (SD), median (IQR), and minimum and maximum number of days in the study. The number of days in the study will be computed as the difference in the date of completion (or discontinuation) minus the date of randomization plus 1 day. Disposition will be summarized for the ITT and ITTI populations.

A data listing of all subjects' completion status with withdrawal reasons will also be constructed.

6.2 Protocol Deviations

Tables will be constructed with counts and percentages of subjects with protocol deviations by deviation classification (major or minor) and the common deviation term. Deviations will be summarized for the ITT and ITTI populations.

A data listing of all reported protocol deviations will also be constructed.

6.3 Medical History and Concomitant Diseases

Medical history and concomitant diseases will be presented in data listings for the ITT population. Medical history and concomitant disease terms will be coded using the current version of MedDRA and summarized separately for the ITT and ITTI populations.

6.4 Prior and Concomitant Medications

Prior and concomitant medications will be listed for the ITT population. Prior and concomitant medications will be coded using the current version of the WHO Drug Dictionary and summarized separately for the ITT and ITTI populations.

6.5 Population Pharmacokinetics Analysis

On Day 4, plasma samples will be collected before the morning dose (at the trough) for determination of drug concentration. These data will allow for analysis of relationships between trough plasma concentrations and clinical and virologic response.

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

6.6 Treatment Compliance

Treatment compliance tables will summarize the total number of days on therapy and number of tablets taken using descriptive statistics for the ITT and ITTI populations.

6.7 Anti-SARS-CoV-2 Antibodies

Descriptive statistics of Anti-SARS-CoV-2 IgG and IgM titers (mean, standard deviation, minimum, median, maximum, and interquartile range, raw values and change from baseline) will be presented.

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).

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