Statistical Analysis Plan (SAP)

A Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Nitazoxanide (NTZ) for Post-exposure Prophylaxis of COVID-19 and Other Viral Respiratory Illnesses (VRI) in Elderly Residents of Long-term Care Facilities (LTCF)

Study No.: RM08-3006

Version 1.2
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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 1.1 to 1.2

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 1.0 to 1.1

1. Wording of futility analysis purpose in Section 2.4 clarified.
2. Risk differences added to primary efficacy endpoint.
3. Section 2.2.2 Sex, Age, and Race subgroup analyses for primary efficacy endpoint added.
4. Sensitivity analyses added for missing values of primary efficacy variable.

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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

1.1 Design and Treatment

This is a multi-center, randomized, double-blind, placebo-controlled trial 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 (VRI) in residents of long-term care facilities (LTCF) aged 65 years and over.

Participants will be randomized (1:1) within LTCF (i.e., within strata) 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 -90 to Study Day 1. After giving informed consent, the subject will be assigned a subject number and complete the following procedures:

1. Complete medical history.
2. Physical examination including body weight and vital signs (blood pressure, pulse, respiratory rate and body temperature).
3. Collection of demographic information and smoking history.
4. Evaluation according to eligibility (inclusion and exclusion) criteria.

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

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 two nasopharyngeal swabs (one from each nostril) using nylon flocked dry swabs for RT-PCR.
2. Collection of blood sample for laboratory safety tests and anti-SARS-CoV-2 antibodies.

3. Collection of a urine sample for routine urinalysis (appearance, glucose, protein and blood).
4. Review and recording of any concomitant medications.
5. Completion of baseline electronic symptom diary entries.
6. Randomization and dispensing of study medication (medication assigned in sequential order). Subjects will be considered enrolled in the study upon the randomized assignment to a treatment group.
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 1, 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)

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

If the subject reports (i) at least one of the Lower Respiratory Symptoms presented in 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] • Sore throat (sore or painful throat)[2]	• Cough (coughing, chest congestion, chest tightness, dry or hacking cough, wet or loose cough)[2] • Dyspnea (shortness of breath)[2] • Sputum (coughing up sputum or phlegm)[2] • Wheezing	• Myalgias or arthralgias (body aches or pains)[2] • Fatigue (weak or tired, sleeping more than usual)[2] • Headache • Decreased appetite (lack of appetite, did not feel like eating)[2] • Feverishness (felt hot, chills or shivering, felt cold, sweating)[2]

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

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 two nasopharyngeal swabs using nylon flocked dry swabs for RT-PCR at the Suspected ARI Visit.
4. Collect two nasopharyngeal swabs 24 to 36 hours later, and then again 4 to 5 days later.

5. The subject will complete a FLU-PRO© symptom diary daily until he/she responds "yes" to the FLU-PRO© question, "Have you returned to your usual health?" for 3 consecutive days or until the Week 6 Visit, whichever occurs first. The daily FLU-PRO© diary will be completed between 4:00 pm and 8:00 pm. A caregiver may assist the subject with completing the diary if necessary.
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 1, Week 3 and Week 6 Evaluations (± 2 days)

Study personnel (physician, nurse, or other study personnel) will visit each subject at Week 3 and Week 6 and performing 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)

Study personnel (physician, nurse, or other study personnel) will visit each subject at Week 3 and Week 6 and performing 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 two nasopharyngeal swabs using nylon flocked dry swabs for RT-PCR.
4. Collection of blood sample for laboratory safety tests.
5. Collection of urine sample for routine urinalysis.
6. Review of compliance with study medication.
7. Review and recording of concomitant medications.
8. Review and recording of adverse events/side effects.

1.3 Sample Size

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

For purposes of calculating sample size, we assume that the proportion of subjects experiencing COVID-19 over a 6-week period is 5%, the proportion of subjects experiencing any VRI is 10%, and that effective prophylaxis will reduce the rate of COVID-19 and other VRIs by 80%.

A Cochran-Mantel-Haenszel (CMH) chi-square test stratifying by 20 LTCFs will have 87.1% statistical power to detect the difference between 5% and 1% rates of occurrence of COVID-19 across all strata at a two-sided alpha of 0.047 with a total sample size of 800, allocated equally to strata (LTCFs) and treatment groups within strata. The statistical

power remains >87% when the number of LTCFs is 5, 10, 16 or 20. The CMH chi-square test has 91% power to detect the difference between 10% and 2% rates of occurrence of VRIs over all strata at a two-sided alpha of 0.001 with 800 subjects allocated equally to 20 LTCFs. Both tests are insensitive to stratum size. Varying the number of subjects per stratum (LTCF) between a minimum of 8 to a maximum of 80 while holding both the effect size and total sample constant results in changes in the third significant figure of the test's power.

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

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.

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

2.2.2 Subgroup Definitions

Safety analyses will be grouped by treatment received. The primary efficacy analysis will be grouped by sex (male/female), age (65 to 79 years, 80 years and over), and race (white/non-white).

2.3 Missing Data Conventions

Date variables with missing items will be imputed as shown in Text 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. 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 o If month = month of first dose, then set day to day of first dose. o If month < month of first dose, then set day to the last day of the month. o 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, 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. 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.

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. 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

A first review for safety will be conducted by the Independent Data Monitoring Committee (IDMC) when 20% of the planned number of subjects have completed three weeks of treatment. This review will examine the available data for safety signals contained in the AE, vital sign, and clinical laboratory data.

An unblinded analysis may be performed under circumstances defined in the IDMC charter, which relate to the rate of COVID-19 illnesses and the rate of occurrence of diarrhea as an adverse event.

If conditions required for unblinding are satisfied, futility will be assessed using a conditional power approach assessing the efficacy of NTZ for the COVID-19 endpoint. The IDMC will recommend stopping for futility if the conditional power of the study at that stage is less than 30%. The conditional power will be calculated according to Chow and Chang (2007):

$$\text{Conditional Power} = 1 - \Phi\left(\sqrt{z_{1-\alpha_2}^2 - z_{1-p_1}^2} - \frac{\delta}{\sigma}\sqrt{n_2}\right).$$

In the above, $z_{⇨}$ refers to the ⇨-th quantile of the Standard Normal distribution, $⇨_2$ is the planned final significance level of the study, $p_1 > ⇨_2$ is the p-value at the first interim analysis, ⇦ is the observed study effect size (i.e., the difference in observed rates in the two groups), ▽ is the observed standard error of the difference in rates at the interim, and n_2 is the number of subjects remaining to be enrolled in the study.

A second review for safety and futility will be conducted by the IDMC when 50% of the planned number of subjects have completed 6 weeks of treatment. An unblinded analysis will be conducted under circumstances defined in the IDMC charter, which relate to the rate of COVID-19 illnesses, the rate of occurrence of diarrhea as an adverse event and other safety considerations. Futility will be concluded 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). This bound was set using O'Brien-Fleming bounds for futility with overall ⇨ = 0.049.

An interim analysis of effectiveness will be performed when there are at least 25 laboratory-confirmed COVID-19 cases observed among the study participants. If the assumptions made in the power calculations are correct (COVID-19 rate is 0.05 in the placebo group and 0.01 in the NTZ group) we expect to observe only 24 events during the entire study. If this milestone is reached early, it indicates that the assumptions were

conservative and merit review given the high rate of mortality observed from COVID-19 illness in this population. This review will be conducted by the IDMC in accordance with its charter and will encompass both a safety and efficacy determination. In the event that the timing of the interim analysis of effectiveness is near that of the second review for safety and futility, analyses of safety, futility and effectiveness may be performed simultaneously.

O'Brien-Fleming bounds are used to set the Type I error rates for the third interim and final analyses. The interim efficacy review will be performed with ⇨ = 0.0052 (overall), allocated 0.005 to the COVID-19 endpoint and 0.0002 to the VRI endpoint. The final data analysis (if the efficacy hypotheses are not rejected at the interim review) will be performed with ⇨ = 0.048, allocated 0.047 to the COVID-19 endpoint and 0.001 to the VRI endpoint. Power at the interim analysis is 31% for the COVID-19 endpoint. If the interim review for efficacy does not occur (i.e., the event count of 25 is not reached or reached too late in the study for the interim review to be useful), the alpha levels for the final analysis will be 0.049 for the COVID-19 endpoint and 0.001 for the VRI endpoint.

2.5 Study Center Considerations in the Data Analysis

A study center is defined as a treatment administration site (i.e., LTCF) 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, baseline height, baseline weight) will be summarized via mean, standard deviation, minimum, median, maximum, 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 patient in the safety population will also be provided as shown in Appendix B.

4.0 Analysis of Efficacy

4.1 Efficacy Variables

The efficacy variables are categorical in nature: the presence or absence of ARI, VRI, or COVID-19 and sequelae during the study period or COVID-19 and sequelae (i.e., hospitalization and death) during the study 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.

ARI is defined as ≥ 0.5 increase from baseline in mean symptom score in the chest/respiratory domain of the FLU-PRO© instrument; or an increase of at least 0.5 in the mean symptom score of at least two of the following FLU-PRO© domains: body/systemic, nose, throat.

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.

Secondary Efficacy Variables
The secondary efficacy variables are:

1. Hospitalization due to COVID-19 or complications thereof.
2. Mortality due to COVID-19 or complications thereof.
3. 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

The study has two primary efficacy endpoints: reduction in symptomatic COVID-19 disease and reduction in all VRI. The study-wise ⇨ level is set at 0.05, allocated with 0.049 to the COVID-19 endpoint and 0.001 to the all VRI endpoint. See Section 2.4 for details on how the study- wise ⇨ level will be allocated to the interim and final analyses. For each endpoint, the following hypotheses will be tested

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

here, p_1 represents the probability of symptomatic disease (either COVID-19 or VRI) in the NTZ treatment group and p_2 represents the probability of symptomatic disease in the placebo group.

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 ⇨=0.047. The test will be stratified by LTCF. The contingency tables will be provided with rates relative to the treatment margins. A 95% confidence interval for the odds ratio of symptomatic COVID-19 infection in the NTZ group relative to the placebo group will be provided. The risk difference for the treatment groups and a 95% confidence interval for the difference will be provided.

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 test, stratified by LTCF with continuity correction at ⇨=0.001. The contingency tables will be provided with rates relative to the treatment margins. A 95% confidence interval for the odds ratio of symptomatic VRI in the NTZ group relative to the placebo group will be provided. The risk difference for the treatment groups and a 95% confidence interval for the difference will be provided.

CMH analyses of symptomatic COVID-19 disease and symptomatic VRI will be repeated with subjects divided by sex (female or male), age (65- to 79 years or 80 years and over), and race (white or non-white). Estimates and confidence intervals for the odds ratio and relative risk differences will be provided.

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.

4.2.2 Secondary Efficacy Variables

The proportion of subjects in the NTZ and placebo groups experiencing hospitalization due to COVID-19 or its complications will be analyzed using a CMH test stratified by LTCF

with appropriate continuity correction at an unadjusted ⇨=0.05. The contingency tables will be provided with rates relative to the treatment margins.

The mortality rate due to COVID-19 or complications in the two treatment groups will be compared using a CMH test stratified by LTCF with continuity correction at unadjusted ⇨=0.05. Contingency tables with rates computed relative to the treatment margins will be provided.

The proportion of subjects in the treatment groups testing positive for SARS-CoV-2 antibodies at either Week 6 or Week 8 will be compared using a CMH test stratified by LTCF. The contingency tables will be provided with rates computed relative to the treatment margins.

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 (i.e., treatment) margins. A CMH test stratifying by LTCF will be provided for each variable.

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” (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 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 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 performed:

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)”. Urinalysis appearance results will appear only in the shift table.

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

Physical Exam

Physical exams 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 will be summarized for the safety population with summary statistics (mean, standard deviation, n, minimum, median, maximum) by time point and study arm. 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 of subject completion status showing counts for each withdrawal reason. Tabulations will be performed overall for the safety population.

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

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. Medications will be coded using the most recent version of the WHO Drug Dictionary. A summary of frequencies for ATC Levels I and IV will be provided, as will a data listing of concomitant medications 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 a data listing for the safety population. History events will be coded using the current version of MedDRA.

7.0 References

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8.0 List of Analysis Tables, Figures and Listings

Table No.	Table Title
14.1.1.1	Subject Disposition Summary by Treatment and Overall (All Subjects)
14.1.2.1	Summary of Major Protocol Deviations (Safety Population)
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