Official Title:

Statistical Analysis Plan

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study on the Safety and Efficacy of Niclosamide in Patients with COVID-19 with Gastrointestinal Infection

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AzurRx BioPharma, Inc.

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A 2-Part, 2-Arm, Phase 2, Randomized, Double-Blind, Placebo-Controlled Study on the Safety and Efficacy of Niclosamide in Patients with COVID-19 with Gastrointestinal Infection

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Final Statistical Analysis Plan

Version *1.0*

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List of Abbreviations

AE	Adverse event
BMI	Body mass index
CI	Confidence interval
CMH	Cochran mantel-Haenszel
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
DMC	Data Monitoring Committee
eCRF	Electronic case report form
FAS	Full analysis set
GI	Gastrointestinal
ICU	Intensive care unit
IMP	Investigational medical product
IWRS	Interactive web randomization system
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per-protocol (analysis set)
PT	Preferred term
RT-qPCR	Reverse transcriptase-quantitative polymerase chain reaction
SAE	Serious adverse event
SAF	Safety (analysis set)
SaO2	Blood oxygen saturation by pulse oximetry
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SE	Standard error
SoC	Standard of care
SOC	System organ class
TEAE	Treatment-emergent adverse event
TID	3 times per day (ter in die)
WHO	World Health Organization

1. Introduction

The coronavirus disease (COVID-19 2019) is a public health emergency of international concern caused by the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) virus. An increasing volume of convergent evidence indicates that gastrointestinal (GI) infection and fecal oral transmission of SARS-CoV-2 are important factors in the clinical presentation, virology, and epidemiology of COVID-19. There are currently no approved or investigational treatments with demonstrated clinical efficacy for control of the intestinal SARS-CoV-2 viral shedding and fecal positivity. The evaluation of a safe and effective antiviral agent that is able to potently block SARS-CoV-2 replication in the intestine would address serious unmet medical and epidemiological needs.

To address this unmet need, AzurRx BioPharma Inc. is developing a drug product containing micronized niclosamide in an immediate-release tablet formulation as treatment for SARS-CoV-2 intestinal infection in patients presenting with GI symptoms of COVID-19 disease. Evidence of niclosamide's antiviral properties is sufficient to expect a clinical pharmacodynamic response against viral replication and clinical benefit, justifying the proposed clinical study in COVID-19 patients and favorable benefit-risk assessment.

This statistical analysis plan (SAP) is based upon Section 12 (Statistical Analysis Plan and Statistical Analysis) of the clinical study protocol (version 3.0, dated 30July2021), and is prepared in compliance with International Conference on Harmonisation (ICH) E9. Furthermore, this SAP contains definitions for analysis sets, derived variables, and statistical methods and data presentations for the analysis of efficacy and safety endpoints.

2. Objectives

2.1. Primary Objective

The primary objective for Part 1 of the study is to evaluate the safety of niclosamide administered to subjects with COVID-19.

The primary objective for Part 2 of the study is to evaluate the effect of niclosamide in addition to standard of care (SoC) compared to placebo in addition to SoC on fecal clearance of SARS-CoV-2 RNA.

2.2. Secondary Objective

The secondary objective of the study is to evaluate the clinical efficacy, safety, and tolerability of oral niclosamide in addition to SoC compared to placebo in addition to SoC.

2.3. Exploratory Objective

The exploratory objectives include characterization of the effect of niclosamide on disease progression and severity 4 and 6 months after starting treatment, and possible genotypic resistance analysis using the nasopharyngeal swabs, and/or stool samples.

3. Investigational Plan

3.1. Overall Study Design and Plan

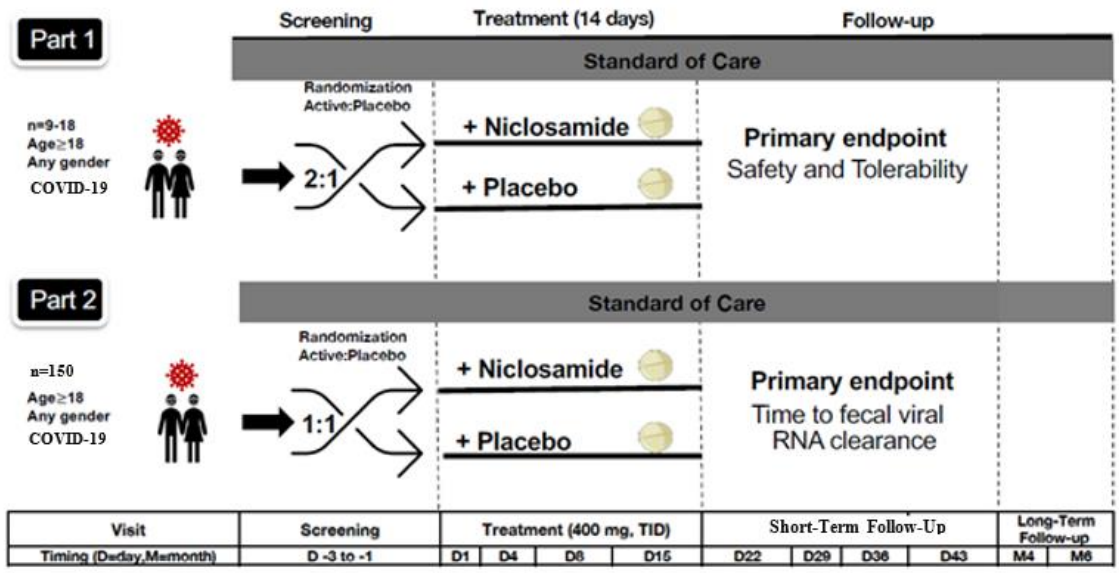
This a 2-part, 2-arm, Phase 2, multicenter, randomized, double-blind, placebo-controlled study in adults with COVID-19. Subjects will be recruited and randomized to niclosamide oral formulation plus SoC or placebo matching niclosamide tablets plus SoC. The study will initiate with Part 1 and, upon safety review, the study may proceed to Part 2.

Part 1 will enroll approximately 9 subjects. After treatment is concluded for all 9 subjects, a DMC will review the safety data and determine if the study may proceed to Part 2 or if additional subjects are needed to assess tolerability of the study drug. If additional subjects are needed, approximately 9 more subjects will be enrolled in Part 1, and then the DMC will meet again after all subjects are treated to determine if the study may proceed to Part 2.

Part 2 will enroll up to approximately 150 subjects receiving at least 1 dose of study treatment.

Each part will include 2 study arms with randomized enrollment. Randomization of subjects in Part 2 will be stratified by age and sex. An overview of the study design is shown in Figure 1 and the Schedule of Assessments for the study is detailed in Appendix 16.1.

Figure 1: Study Design



3.2. Study Endpoints

3.2.1. Primary Endpoint

The primary endpoint of Part 1 is summarization of safety (AEs, clinical laboratory results, and vital signs) from Day 1 (first dose) to Day 43 comparing the niclosamide arm to placebo arm.

The primary endpoint of Part 2 is time to fecal viral RNA clearance for subjects with a positive Day 1 stool test assessed by RT-qPCR from Day 1 (first dose) to Day 43 in the niclosamide arm compared to the placebo arm.

3.2.2. Secondary Endpoints

The secondary endpoints will all compare the niclosamide arm to the placebo arm. These secondary endpoints will be assessed for both Part 1 and Part 2 from Day 1 (first dose) to Day 43, as applicable.

- **Gastrointestinal Efficacy Secondary Endpoints**

a) Part 1: Time to fecal viral RNA clearance for subjects with a positive Day stool test for SARS-CoV-2 assessed by RT-qPCR.
b) Time from the first dose of study treatment to the first formed stool (this formed stool must have been followed by a non-watery stool) in subjects with loose or watery stool (Bristol Stool Scale Types 6-7) on Day 1.
c) Time from the first dose of study treatment to the last loose or watery stool in subjects with loose or watery stool (Bristol Stool Scale Types 6-7) on Day 1.
d) Proportion of subjects administered any anti-diarrheal agent from the first dose of study treatment to Day 8, first dose of study treatment to Day 15 and from Day 16 to 29.
e) Time from the first dose of study treatment to improvement of abdominal symptoms in subjects with adnominal symptoms on Day 1.
f) Proportion of patients with a negative Day 1 stool test for SARS-CoV-2 who acquire SARS-CoV-2 in stool through Day 43.

- **Systemic and Respiratory Efficacy Secondary Endpoints**

g) Proportion of subjects with each clinical severity score as recommended by the WHO for COVID-19 studies by study visit.
h) Total duration, type of administration (e.g., mean increased room oxygen, nasal tubes, ventilator, or ECMO), and quantity of supplemental oxygen treatment, whenever possible.
i) Body temperature and proportion of subjects with normal body temperature by study visit. Criteria for normalization was temperature: $\leq 36.9^{o}$ C axillary, $\leq 37.4^{o}$ C oral, $\leq 37.8^{o}$ C rectal, and $\leq 37.5^{o}$ C tympanic (Geneva et al., 2019).
j) Proportion of subjects with normal blood oxygen saturation by pulse oximeter (SaO2) >90% on room air by study visit.
k) Proportion of subjects admitted to the intensive care unit (ICU) and length of ICU stay.
l) Time to nasopharyngeal viral clearance assessed by RT-PCR.
m) Proportion of subjects requiring hospitalization and duration of hospitalization.

- **Safety and Tolerability Secondary Endpoints**

n) All-cause mortality 6 weeks after randomization.
o) Proportion of subjects with treatment-emergent adverse events (TEAEs) leading to study drug discontinuation.
p) Serious adverse events (SAEs) coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).
q) Clinically significant changes in laboratory measurements.
r) Clinically significant changes in vital sign measurements.

3.2.3. Exploratory Endpoints

s) All-cause mortality 4 months and 6 months after randomization.
t) Proportion of subjects with recurrence of COVID-19 symptoms after Day 43 at 4 months and 6 months after randomization.
u) Proportion of subjects with persistence of COVID-19 symptoms beyond Day 43 at 4 months and 6 months after randomization.
v) Proportion of subjects with new hospitalization or rehospitalization due to COVID-19 at 4 months and 6 months after randomization.
w) Summarization of genotypic resistance analysis data.

3.3. Treatments

The chemical name of niclosamide is 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide. The IMPs are in the form of white yellowish oval 400-mg uncoated immediate-release (IR) tablets containing the active ingredient micronized niclosamide or a matched placebo.

Subjects who are able to comply with the oral treatment must take, for each administration, 1 tablet (400-mg niclosamide or placebo) TID for 14 days. Treatment may begin at any time of day; if only 1 or 2 doses are administered on Day 1, the planned total number of doses should be administered (42 total doses) and the final doses may be administered on Day 15. The total study duration for a subject will not be extended if the final dose occurs on Day 15 for this reason.

4. General Statistical Considerations

Continuous data will be described using descriptive statistics (i.e., number of subjects, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum). Unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation (SD) and standard error (SE) will be displayed to two levels of precision greater than the data collected. If the precision of the values being summarized are too large (e.g., 3 or more decimal places), then limit the precision to two decimal places and follow the rules previously stated above. If n=0, then display n and leave all other statistics blank. If n=1, then display “N/A” for SD and SE.

Categorical data will be described using the subject count and percentage in each category. When count data are presented, the percentage will be suppressed when the count is zero. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values where applicable. The denominator for all percentages will be

the number of subjects in that treatment within the analysis set of interest, unless otherwise specified. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places.

All subject data collected at scheduled and unscheduled visits, excluding data collected in the daily diary, will be presented in individual subject data listings. Dates will be shown in subject listings as they have been recorded. Data listings will be sorted by treatment group, subject identification number, date/time and visit where applicable. The treatment group (randomized) as well as subject's sex and age will be stated on each listing where applicable. Unless otherwise stated, data listings will be based on all subjects randomized. When no data are available for a table or listing, an empty page with the title will be produced with suitable text (e.g., "There are no records for this table/listing.").

Unless otherwise specified, baseline will be defined as the last non-missing assessment prior to or on the date that the first dose of treatment is taken. For subjects who are randomized, but not treated, the baseline will be defined as the last non-missing assessment prior to or on the date of randomization. Assessments from both scheduled and unscheduled visits will be used to determine baseline. The date of first and last dose will be collected on the End of Treatment eCRF.

Study day will be calculated relative to the first dose date:

- Day 1 is defined as the first dose date
- Assessments before the first dose date: Study Day = Assessment Date – First Dose Date
- Assessments after the first dose date: Study Day = Assessment Date – First Dose Date +1

Summaries or analyses by study visit will be based on data collected at scheduled visits (i.e., nominal visits as collected on eCRF) and data from unscheduled visits will not be included. Efficacy analyses for time to viral clearance or clinical improvement will include data from both scheduled and unscheduled visits. Laboratory treatment emergent summaries will also include data from both scheduled and unscheduled visits.

A two-sided hypothesis test will be used at a significance level of 0.05 for comparison between the niclosamide and the placebo group for the primary efficacy analysis. All other statistical analyses will also be performed using a two-sided hypothesis test at a nominal significance level of 0.05. No adjustment for Type I error will be made for multiple comparisons. Models will include stratification factors, age (<65 years or ≥65 years) and sex (female or male), unless an insufficient amount of data exists where convergence or the analysis cannot be performed.

Confidence intervals will be presented as two-sided 95% CI for the primary efficacy analysis secondary efficacy analyses. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999." For analyses where convergence or the analysis cannot be performed, "NC" (not calculable) will be presented.

For all Tables, Listings, and Figures, treatment group will be labelled as follows: "Niclosamide + SoC" and "Placebo + SoC". All analyses will be conducted using SAS Version 9.4 or higher.

4.1. Sample Size

The sample size for Part 1 of the study was selected empirically for an initial evaluation of safety in subjects with COVID-19.

The sample size for Part 2 of the study was determined by simulations based on the following assumptions:

- The time to fecal viral clearance has an exponential distribution for each treatment arm.
- The median time to fecal viral clearance is anticipated to be approximately 21 days for placebo arm and 10 days for niclosamide arm.
- Fecal viral clearance assessments are performed at Day 3, 7, 14, 28, 42 after first dose.
- Log-rank test (2-sided) is conducted to compare treatment difference.

Using a 1:1 randomization ratio, a sample size of 30 patients per treatment arm (60 patients total with a positive stool test for SARS-CoV-2 on Day 1) provides 74% power to detect a significant treatment difference for alpha=0.05 and 83% power for alpha=0.10. It is expected that approximately 40% of COVID-19 patients will be positive for SARS-CoV-2 in the stool sample. Therefore, approximately 150 patients with COVID-19 are needed to be enrolled/randomized to ensure 60 patients have a positive stool test for SARS-CoV-2 on Day 1.

To assess the sensitivity analysis of the above power calculation, additional scenarios of assumptions of stool positivity rate and longer time to fecal viral clearance for niclosamide arm (i.e. less treatment effect) are also evaluated in the below table.

Total Sample Size for Enrollment	Stool Positivity Rate	**Niclosamide:** Median Time to Fecal Clearance in Days	**Placebo:** Median Time to Fecal Clearance in Days	2-sided Significance Level (Alpha)	Statistical Power (%)
150	0.3	10	21	0.05	61
150	**0.4**	**10**	**21**	**0.05**	**74**
150	0.5	10	21	0.05	84
150	0.3	12	21	0.05	40
150	0.4	12	21	0.05	49
150	0.5	12	21	0.05	61

4.2. Randomization, Stratification, and Blinding

Subjects will be randomized to the niclosamide plus SoC or placebo plus SoC arms using a computer-generated randomization list generated by the PPD unblinded randomization team and using an IWRS. The treatment assignment is performed by pre-assigning the subject's number to the treatment kits corresponding to the randomization list.

Subjects will be randomized for Part 1 of the study in a 2:1 ratio to niclosamide plus SoC or placebo plus SoC. Subjects will be randomized for Part 2 of the study in a 1:1 ratio to

niclosamide plus SoC or placebo plus SoC and balanced and stratified by age (<65 years, ≥65 years) and sex (Female, Male).

This study will be double-blinded, meaning that the subjects, investigators, and site staff will be blinded to the subject treatment assignments until the completion of the long-term follow-up at Month 6. Any member of the study team involved in study conduct or participation in data handling decisions will also be blinded to the subject treatment assignments, but only until the completion of the short-term follow-up at Day 43.

At the initiation of the study, the study site will be given instructions on the method for breaking the blind. The method for breaking the blind will use the IWRS process. Unblinding of individual subject treatment by the Investigator should be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, the Investigator must first attempt to contact the PPD Medical Monitor to discuss and agree to the need for unblinding. In situations which the Investigator has attempted and failed to contact the PPD Medical Monitor and/or the urgency of the case requires immediate action, investigators should use their best judgment, based on the nature and urgency of the clinical situation, and proceed with unblinding.

Once a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the PPD Medical Monitor should be notified within 24 hours of unblinding of the treatment. Information relating to unblinding (e.g., the reason, date) should be clearly recorded in the subject's study file.

4.3. Analysis Sets

4.3.1. Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all randomized subjects who received at least one dose of study drug. The FAS will be used for systemic and respiratory efficacy secondary endpoints as well as exploratory endpoints and will be analyzed according to the study treatment as randomized.

4.3.2. Efficacy Evaluable (EE) Set

The efficacy evaluable (EE) set will consist of all randomized subjects who received at least one dose of study drug, had a positive stool test for SARS-CoV-2 on Day 1 assessed by RT-PCR, and did not test positive for bacteria or parasites in the screening stool analysis by the local laboratory. The EE set will be used for the primary efficacy endpoint and relevant gastrointestinal efficacy secondary endpoints and will be analyzed according to the study treatment as randomized.

4.3.3. Per Protocol (PP) Set

The per-protocol (PP) set will consist of subjects in the evaluable efficacy set who had at least 80% exposure of study drug (i.e., at least 12 days with any dose administered) and do not have major protocol deviations that may affect the primary efficacy endpoint (time to fecal viral RNA

clearance). The PP set will be used as a supportive analysis set for gastrointestinal efficacy analyses and will be analyzed according to the study treatment as randomized.

4.3.4. Safety (SAF) Set

The safety (SAF) set will include all randomized subjects who received at least one dose of study drug. The SAF set will be used for safety summaries and will be analyzed according to the study treatment actually received.

5. Subject Disposition

Subject disposition will be presented separately for Part 1 and Part 2 of the study.

5.1. Disposition

Subject disposition will be summarized by treatment group and overall for all subjects who provided informed consent and were screened. The subject disposition summary includes the number and percentage of subjects for the following categories: screened, randomized, treated, completed study treatment and discontinued study treatment, completed Day 43 follow-up visit and discontinued before Day 43 follow-up visit. The reasons for discontinuation of study treatment and discontinuation before Day 43 follow-up visit will be summarized in this table. In addition, reasons for screen failures will also be summarized overall. All percentages will be based on the number of subjects randomized, except for screen failures.

For subjects who completed Day 43 follow-up visit, a separate disposition summary will be provided to present the number and percentages of subjects who completed the long-term follow-up and subjects who discontinued from the long-term follow-up and reasons for discontinuation.

Study drug completion data will be collected on the End of Treatment eCRF. Disposition data for randomized subjects will be collected on the End of Study Day 43 and the End of Long Term Follow Up eCRFs. For screen failures, reasons will be collected on the Inclusion Exclusion eCRF or End of Study Day 43 eCRF.

Additionally, a summary of the analysis sets will be provided to include the number and percentage of subjects in each analysis set (FAS, EE, PP, and SAF) by treatment group and overall. The number and percentage of subjects excluded from each analysis set and the reasons for exclusion will also be presented. All percentages will be based on the number of subjects randomized.

Subject disposition and exclusions from analysis sets will also be presented in a listing.

5.2. Protocol Deviations

All protocol deviations will be entered and tracked within the PPD Clinical Trial Management System (CTMS) by the study team throughout the conduct of the study in accordance with PPD's Study Deviation Rules Document. A significant deviation is any deviation that may affect primary efficacy and safety assessments (as applicable), the safety or mental integrity of a

subject, or the scientific value of the trial. A significant deviation does not necessarily affect the primary endpoint and be excluded from the PP set.

Data will be reviewed by the study team prior to unblinding and official database lock for final analysis at Day 43 to ensure all significant deviations are captured and properly categorized. Particularly, a final list of significant protocol deviations leading to exclusion from the PP set (also referred to as major protocol deviations) will also be determined by the study team and flagged in the final CTMS deviation data file.

Major protocol deviations are defined as significant deviations that might directly or indirectly impact the primary efficacy endpoint (time to fecal viral RNA clearance) and may include (but are not limited to) the following:

- Did not meet the key inclusion or exclusion criteria
- Had poor compliance with study treatment (< 80%)
- Received prohibited concomitant medications through the Day 43 follow-up visit
- Had a randomization error
- Received incorrect study drug

Significant protocol deviations will be summarized by treatment group and overall. A listing will also be provided for significant protocol deviations with a flag indicating major protocol deviations. Non-significant protocol deviations will be just listed. Summaries will be conducted on all subjects that were randomized.

6. Demographics and Baseline Characteristics

All summaries will be based on the safety set and presented separately for Part 1 and Part 2 of the study.

6.1. Demographics

A summary of demographics and baseline information will be presented by treatment group and overall. The demographic characteristics consist of age, sex, race, and ethnicity. The baseline characteristics consist of the WHO severity score as reported in Appendix 16.2, loose or watery stool on Day 1, abdominal symptom(s) on Day 1, stool test for SARS-CoV-2 by RT-qPCR on Day 1, stool test for bacteria or parasites at Screening (local laboratory) and COVID-19 vaccination(s) prior to Screening.

Age (years) will be summarized using descriptive statistics. The number and percentage of subjects will be presented for each of the following variables and its associated categories:

- Age (<65, ≥65)
- Sex (Male, Female)
- Race (White, African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino),
- WHO severity score (ordinal categorical scores of 1 to 7)

- Loose or watery stool on Day 1 (Yes, No) as collected on the Diarrhea Clinical Assessment at Randomization eCRF
- Abdominal symptom(s) on Day 1 (Yes, No)
- Stool test for SARS-CoV-2 by RT-qPCR on Day 1 (Positive, Negative)
- Stool test for bacteria or parasites at Screening (Positive, Negative)
- COVID-19 vaccination(s) prior to Screening (Yes, No)

Subject demographic and baseline characteristics will also be presented in a listing.

6.2. Medical History

6.2.1. General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0. The number and percentage of subjects with any medical history will be summarized overall and for each system organ class and preferred term by treatment group and overall. Percentages will be calculated based on number of subjects in the safety set.

Subject medical history data including specific details, will also be presented in a listing.

7. Treatments and Medications

All summaries will be based on the safety set and presented separately for Part 1 and Part 2 of the study.

7.1. Prior and Concomitant Medications

All medications taken during the study, from screening visit to short-term follow-up (Day 43), will be collected. All medications will be coded according to the World Health Organization (WHO) drug dictionary (WHODrug Global B3 2021 MAR or higher version). Details for imputing missing or partial start and/or stop dates of medications are described in Appendix 16.3.

A prior medication is defined as any medication with a start date prior to the first dose of study drug. A concomitant medication is defined as any medication that has a start date that is on or after the first dose of study drug or any medication with a start date prior to the first dose and a stop date after the first dose of study drug. Furthermore, a medication could be labeled as both a prior and concomitant medication if it was started prior to the first dose of study drug and continued after the first dose of study drug.

The number and percentages of subjects with at least one prior medication will be summarized by treatment group and overall. The number and percentages of all prior medications will be summarized by treatment group and overall and listed by Anatomical Therapeutic Chemical (ATC) level 2 and preferred term.

The number and percentages of subjects with at least one concomitant medication will be summarized by treatment group and overall. The number and percentages of all concomitant

medications will be summarized by treatment group and overall and listed by Anatomical Therapeutic Chemical (ATC) level 2 and preferred term.

Prior and concomitant medications, including prohibited medication, will also be presented in a listing.

7.2. Study Treatments

7.2.1. Extent of Exposure

Duration of study drug in days will be calculated as: last dose date – first dose date + 1 day, regardless of study drug interruption (i.e., missed dose). Study drug exposure will be summarized by treatment group and overall using the safety set.

A summary of each subject's exposure will also be presented in a listing.

7.2.2. Treatment Compliance

The study drug compliance will be calculated as: 100 * [1 – (total number of days with any missed dose / duration of study drug in days)]. Days of missed dose (full or partial dose) will be based on the Missed Dose eCRF.

Study drug compliance will be summarized for all subjects in the safety set with descriptive statics by treatment group and overall. Additionally, the number and percentages of subjects in each compliance category (<80% and ≥80%) will be also presented by treatment group and overall.

A summary of each subject's compliance will also be presented in a listing.

8. Efficacy Analysis

Primary and secondary efficacy analyses will be conducted on efficacy data collected through the Day 43 follow-up visit for all randomized subjects and will be included as part of the Day 43 Final Analysis for the main clinical study report (CSR).

All efficacy analyses will be performed using the FAS or EE set and will be presented separately for Part 1 and Part 2 of the study unless otherwise specified. For Part 1, due to the small sample, only descriptive summary statistics will be provided by treatment group and no inferential statistical tests will be performed. For Part 2, all efficacy data will be summarized descriptively and also analyzed using appropriate inferential statistical tests as applicable. Relevant subject data listings will also be provided to support all efficacy analyses and will be presented separately for Part 1 and Part 2 of the study unless otherwise specified.

Missing data will not be imputed.

8.1. Primary Efficacy Endpoint

The primary endpoint for Part 2 of the study is the time to fecal viral RNA clearance for subjects with a positive stool test for SARS-CoV-2 on Day 1 assessed by RT-qPCR in the niclosamide arm compared to the placebo arm.

Time to fecal viral RNA clearance is defined as the time (days) from the first dose of study treatment to the first stool RT-qPCR sample negative for SARS-CoV-2, after which all stool samples (if any) are negative. A stool sample is considered negative for SARS-CoV-2 if the test result is reported as "Not Detected"; otherwise, the stool sample is positive if the test result is reported as "Detected". Furthermore, an "Inconclusive" test result is considered positive if it is followed directly by a positive test result; an "Inconclusive" test result is considered negative if it is followed directly by a negative test result. Subjects without fecal viral RNA clearance will be censored as follows:

- In the case of death of any cause, the subject will be considered to have the worst outcome with censoring at the planned Day 43 follow-up visit.
- In the case of hospitalization for any reason and withdrawal of consent, the subject will be considered to have the worse outcome with censoring at the planned Day 43 follow-up visit.
- In the case of study discontinuation prior to Day 43 follow-up visit due to any other reasons, the subject will be censored at the last available visit.
- In the case of study completion for Day 43, the subject will be censored at the date of the actual Day 43 follow-up visit.

8.1.1. Primary Analysis

The analysis of the primary efficacy endpoint, time to fecal viral RNA clearance, will be conducted on the EE set.

The number and percentages of subjects achieving and not achieving the first fecal viral RNA clearance will be summarized up to each post-first dose study visit (Days 4, 8, 15, 22, 29, 36, and 43) by treatment group. For each study visit, only subjects with available assessment at the visit or having a negative stool test before the visit will be included in the summary and counted in the denominator for the percentages.

A stratified log-rank test will be used to compare time to fecal viral RNA clearance between niclosamide and placebo treatment groups adjusting for stratification factors, age (<65 years or ≥65 years) and sex (female or male). The two-sided p-value will be reported. The estimate of the hazard ratio (niclosamide vs. placebo) and the associated 95% confidence interval (CI) will be obtained from a Cox Proportional Hazards model adjusting for stratification factors and will also be reported.

Kaplan-Meier curves with 95% CIs will be generated for the total population by treatment group. Summary statistics obtained from Kaplan-Meier estimates, including the median time to fecal viral clearance with corresponding 95% CI and the proportion of subjects achieving fecal viral clearance at 3, 7, 14, 21, 28, 35, and 42 days post first dose (Day 1), will be summarized by treatment group.

8.1.2. Sensitivity Analysis

The analysis of the primary efficacy endpoint, time to fecal viral RNA clearance assessed by RT-qPCR, will also be conducted on the PP set.

8.1.3. Subgroup Analysis

The primary efficacy endpoint, time to fecal viral RNA clearance assessed by RT-qPCR, will be analyzed in the same manner as the primary analysis for age group (<65 years, ≥65 years) and gender. For the subgroup analysis of age group, the primary endpoint will be analyzed by the log-rank test and Cox Proportional Hazards model adjusting only for gender. For the subgroup analysis of gender, the primary endpoint will be analyzed by the log-rank test and Cox Proportional Hazards model adjusting only for age group.

8.2. Gastrointestinal Secondary Efficacy Endpoints

The analysis of the gastrointestinal secondary efficacy endpoints will be conducted on the EE set unless otherwise specified.

8.2.1. Time to fecal viral RNA clearance assessed by RT-qPCR (Part 1)

The number of subjects with and without fecal viral RNA clearance assessed by RT-qPCR (as defined in Section 8.1.) will be summarized up to each post-first dose study visit (Days 4, 8, 15, 22, 29, 36, and 43) by treatment group. For each study visit, only subjects with available assessment at the visit or having a negative stool test before the visit will be included in the summary and counted in the denominator for the percentages.

8.2.2. Time from the first dose of study treatment to the first formed stool

Only subjects with loose or watery stool (Bristol Stool Scale Types 6-7) on Day 1 will be included in this analysis. This data was collected on the Diarrhea Clinical Assessment at Randomization eCRF.

Date of the earliest formed stool (followed by a non-watery stool) between study visits will be collected on the Diarrhea Clinical Assessment eCRF. A summary table will include the number and percentage of subjects achieving and not achieving the first formed stool (followed by a non-watery stool) up to each post-first dose study visit (Days 4, 8, 15, 22, 29, 36, and 43) by treatment group. For each study visit, only subjects with available assessment at the visit or having a formed stool test before the visit will be included in the summary and counted in the denominator for the percentages.

Time to the first formed stool is defined as the time in days from the first dose of study treatment to the first formed stool (followed by a non-watery stool). If subjects experienced a formed stool on the first day of treatment, time to first formed stool will be imputed as 0.5 days. Subjects without a first formed stool will be censored using the same rules as described for the primary efficacy endpoint in Section 8.1. Time to the first formed stool (followed by a non-watery stool) will be analyzed using the same time to event methods described for the analysis of the primary endpoint in Section 8.1.1.

8.2.3. Time from the first dose of study treatment to the last watery stool

Only subjects with loose or watery stool (Bristol Stool Scale Types 6-7) on Day 1 will be included in this analysis. This data was collected on the Diarrhea Clinical Assessment at Randomization eCRF.

Date of the last watery stool between study visits will be collected on the Diarrhea Clinical Assessment eCRF. A summary table of events will include the number and percentage of subjects achieving and not achieving the last watery stool (followed by all formed stools) up to each post-first dose study visit (Days 4, 8, 15, 22, 29, 36, and 43) by treatment group. For each study visit, only subjects with available assessment at the visit or having the last watery stool before the visit will be included in the summary and counted in the denominator for the percentages.

Time to the last watery stool is defined as the time in days from the first dose of study treatment to the last watery stool (followed by all formed stools). Only subjects with baseline and at least one non-missing post-baseline will be included. Time to the last loose/watery stool during the course of the study will utilize the last visit at which a subject had watery stool. If a subject did not experience watery stool at any timepoint post-baseline, we impute time as 0.5 days. Subjects will not be censored because relapse cases of watery stool will be included in the analysis (i.e. subject experienced watery stool again after formed stool) and in such cases, the last visit at which relapse occurred is considered to be the last visit at which watery stool is experienced. Time to the last watery stool will be analyzed using the same time to event methods described for the analysis of the primary endpoint in Section 8.1.1.

8.2.4. Proportion of subjects administered any anti-diarrheal agent during designated time periods

A summary table of anti-diarrheal agent administration will include the number and percentage (proportion) of subjects administered any anti-diarrheal agent during the following time periods by treatment group: first dose (Day 1) to Day 43 (inclusive), first dose (Day 1) to Day 8 (inclusive), first dose (Day 1) to Day 15 (inclusive), Day 16 to Day 29 (inclusive), and Day 30 to Day 43 (inclusive).A time period is defined if at least one visit unique to the time period exists. An anti-diarrheal agent will be considered administered during a specific time period if the calculation of days between the date of the first dose of study treatment and the start date of the anti-diarrheal agent falls within the specific time period. The use of anti-diarrheal agents along with start and end dates will be recorded on the Concomitant Medications eCRF at all study visits up to Day 43.

A Cochran Mantel-Haenszel (CMH) test will be used to compare the proportion of subjects administered any anti-diarrheal agent during each specified time period [first dose to Day 8 (inclusive), first dose to Day 15 (inclusive), and Day 16 to Day 29 (inclusive)] between niclosamide and placebo treatment groups adjusting for stratification factors, age (<65 years or ≥65 years) and sex (female or male). The two-sided p-value will be reported. The adjusted difference in proportions between the 2 treatment groups (niclosamide vs. placebo) will be computed as a weighted average of the treatment differences across strata using the Mantel-

Haenszel weights, and the associated 95% CI will also be provided using the Sato variance estimator (Sato, 1989).

8.2.5. Time from first dose of study treatment to improvement of abdominal symptoms

Only subjects with abdominal symptom(s) on Day 1 will be included in this analysis.

The overall severity of abdominal symptoms and the date of assessment will be collected on the Diarrhea Clinical Assessment. A summary table of severity will include the number of subjects with an assessment available and the number and percentage of subjects within each severity category at each study visit (Baseline, Days 4, 8, 15, 22, 29, 36, and 43) by treatment group. The proportion of subjects with any improvement from baseline of abdominal symptoms will also be provided in the summary table by treatment group. Improvement of abdominal symptoms is defined as any severity reduction from baseline by at least one level (i.e., mild to normal, moderate to mild or normal, or severe to moderate or mild or normal).

Time to the first improvement of abdominal symptoms is defined as the time in days from the first dose of study treatment to the first improvement of abdominal symptoms. Subjects without improvement of abdominal symptoms will be censored using the same rules as described for the primary efficacy endpoint in Section 8.1. Time to improvement of abdominal symptoms will be analyzed using the same time to event methods as described for the analysis of the primary endpoint in Section 8.1.1.

8.2.6. Proportion of subjects with a negative stool test for SARS-CoV-2 on Day 1 who acquire SARS-CoV-2 in stool through Day 43

This analysis will be conducted on the FAS and include only all subjects with a negative stool test for SAS2-CoV-2 on Day 1.

A summary table will include the number and percentage (proportion) of subjects acquiring SARS-CoV-2 by treatment group first overall after Day 1 through Day 43 visit, then for each post-first dose study visit (Days 4, 8, 15, 22, 29, 36, and 43). For each study visit, only subjects with available assessment at the visit or having a positive stool test before the visit will be included in the summary and counted in the denominator for the percentages.

8.3. Systemic and Respiratory Secondary Efficacy Endpoints

The analysis of the systemic and respiratory secondary efficacy endpoints will be conducted on the FAS.

8.3.1. Proportion of subjects with each WHO severity score by study visit

The WHO severity score and the date of assessment will be collected on the WHO Ordinal Scale for Clinical Improvement eCRF. A summary table severity will include the number of subjects with an assessment available and the number and percentage (proportion) of subjects with each WHO severity score at each study visit (Baseline, Days 4, 8, 15, 22, 29, 36, and 43) by treatment

group. The proportion of subjects with any clinical improvement or clinical worsening of illness severity from baseline will also be provided in the summary table by treatment group. Clinical improvement of illness severity is defined as a 1-point or greater reduction from baseline in WHO severity score. Clinical worsening of illness severity is defined as a 1-point or greater increase from baseline in WHO severity score.

Time to first clinical improvement of illness severity is defined as the time in days from the first dose of study treatment to the first clinical improvement of illness severity. Subjects without clinical improvement of illness severity will be censored using the same rules as described for the primary efficacy endpoint in Section 8.1. As a supportive analysis, time to clinical improvement of illness severity will be analyzed using the same time to event methods as described for the primary endpoint in Section 8.1.1.

8.3.2. Total duration, method of administration, and quantity of supplemental oxygen treatment

A summary table by treatment group will include the following:

- Number and percentage of subjects who require supplemental oxygen
- Number and percentage of subjects with each method of oxygen administration
- Descriptive statistics for the total number of days requiring supplemental oxygen

A subject will be considered as requiring supplemental oxygen if the subject is administered any supplemental oxygen from first dose through Day 43. The total number of days requiring supplemental oxygen will be calculated by taking the sum of the duration (stop date – start date +1) for each supplemental oxygen treatment. The start and stop date of supplemental oxygen treatment, oxygen type, method of oxygen supplementation, oxygen flow rate and FiO2 will be collected on the Supplemental Oxygen Treatment eCRF at all study visits up to Day 43.

8.3.3. Proportion of subjects with normal body temperature by study visit

A summary table will include the number of subjects with an assessment available and the number and percentage of subjects with normal body temperature at each study visit (Baseline, Days 4, 8, 15, 22, 29, 36, and 43) by treatment group. Normal body temperature is defined for each method of measurement as follows: $\leq 36.9^{o}$ C axillary, $\leq 37.4^{o}$ C oral, $\leq 37.8^{o}$ C rectal, and $\leq 37.5^{o}$ C tympanic (Geneva et al., 2019).

8.3.4. Proportion of subjects with normal blood oxygen saturation by pulse oximetry (SpO2) on room air by study visit

A summary table will include the number of subjects with an assessment available and the number and percentage (proportion) of subjects with normal SpO2 on room air, defined as SpO2 >90%, at each study visit (Baseline, Days 4, 8, 15, 22, 29, 36, and 43) by treatment group. The oxygen saturation (%) on room air will be collected on the Vital Sign eCRF.

8.3.5. Proportion of subjects admitted to the intensive care unit (ICU) and length of ICU stay

A summary table containing the proportion of subjects admitted to the ICU from the first dose through Day 43 and the length of ICU stay for each treatment group will be presented. The length of ICU stay in days will be calculated by taking the sum of the duration (discharge date – admission date + 1) for each ICU admission. ICU admissions and dates of stay will be captured on the Hospitalizations eCRF.

8.3.6. Time to nasopharyngeal viral clearance assessed by RT-PCR

Only subjects with positive test on Day 1 will be included in this analysis.

Time to nasopharyngeal viral clearance is defined as the time in days from the first dose of study treatment to the first nasopharyngeal RT-PCR sample negative for SARS-CoV-2. Subjects without nasopharyngeal clearance will be censored using the same rules as described for the primary efficacy endpoint in Section 8.1.

A summary table will include the number and percentage of subjects achieving and not achieving the first nasopharyngeal viral clearance up to each post-first dose study visit (Days 4, 8, 15, 22, 29, 36, and 43) by treatment group. For each study visit, only subjects with available assessment at the visit or having a negative nasopharyngeal test before the visit will be included in the summary and counted in the denominator for the percentages.

Time to nasopharyngeal viral clearance will be analyzed using the same time to event methods as described for the analysis of the primary endpoint in Section 8.1.1..

8.3.7. Proportion of subjects requiring hospitalization and duration of hospitalization from first dose through Day 43

Hospital admissions and dates of stay will be captured on the Hospitalizations eCRF.

Summary table containing the proportion of subjects requiring any hospitalization and the duration of hospitalization will be presented for each treatment group. A subject will be considered as requiring hospitalization if the subject has at least one hospital admission with an admission date between the first dose date and the Day 43 follow-up visit date (inclusive). The duration of hospitalization in days will be calculated by taking the sum of the duration (discharge date – admission date + 1) for each hospitalization.

9. Safety Analysis

Safety analyses will be conducted on safety data collected through the Day 43 follow-up visit for all randomized subjects and will be included as part of the Day 43 Final Analysis for the main CSR. All safety analyses will be performed using the SAF set and will be presented separately for Part 1 and Part 2 of the study unless otherwise specified.

9.1. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 and classified by system organ class (SOC) and preferred term (PT) for all summaries.

The period of observation for AEs extends from the time the subject gives informed consent until the subject completes the Day 43 follow-up visit. AEs will be classified as pre-treatment AEs and treatment emergent adverse events (TEAEs) and are defined as follows:

- A pre-treatment event is any event that meets the criteria for an AE/SAE and occurs after the subject signs the informed consent form but before receiving the first administration of study drug.
- A TEAE is defined as an AE occurring or worsening on or after the date of first dose of study drug.

A treatment-related AE will be defined as related if causality is definitely, probably, or possibly related. AEs where the causality is missing will be assumed to be related in table summaries.

TEAEs leading to study drug discontinuation will be identified as TEAEs with a study drug action taken of "Drug Withdrawn". TEAEs leading to death will be identified as TEAEs with an outcome of "Death Related to Adverse Event".

The severity of AEs (serious and non-serious) will be graded in accordance with the investigator's clinical judgement as follows:

- Mild: The AE dose not interfere in a significant manner with normal functioning but may be an annoyance.
- Moderate: The AE produces some impairment of functioning but is not hazardous to health but is uncomfortable and/or an embarrassment. These events are usually ameliorated by simple therapeutic measures.
- Severe: The AE produces significant impairment of functioning or incapacitation and is a hazard.

AEs with missing severity will be assumed to be severe in table summaries.

Details for imputing missing or partial start and/or stop dates of AEs are described in Appendix 16.3.

All summaries of AEs will be based on treatment-emergent adverse events (TEAEs) in the safety set. The following summaries of TEAEs will be provided by treatment group:

- An overall summary of TEAEs including the number of TEAEs and the number and percentage of subjects with any of the following: TEAEs, study drug related TEAEs, TEAEs by maximum severity, TEAEs leading to study drug discontinuation, TEAEs leading to death, serious TEAEs, and study drug related serious TEAEs.
- TEAEs (by SOC and PT)
- Study Drug-Related TEAEs - by SOC and PT
- TEAEs by Maximum Severity – by SOC and PT

- TEAEs leading to study drug discontinuation – by SOC and PT
- AEs leading to death – by SOC and PT
- Serious TEAEs – by SOC and PT
- Study Drug-Related Serious TEAEs – by SOC and PT

For the above summaries by SOC and PT, each subject is counted once within each unique category. For the summary by maximum severity, subjects who experience the same event several times, with different severity levels, will only be counted with the maximum severity. AEs will be sorted in descending order of frequency of SOC based on the total of all treatment groups. Within each SOC, AEs will be sorted in alphabetical order of preferred terms.

All AEs, including pre-treatment AEs and TEAEs, will also be presented in a listing.

9.2. Clinical Laboratory Evaluations

Safety laboratory tests include chemistry and hematology on Days 1, 8, 15, 29, and 43 and will performed by a central laboratory. All summaries will be based on the units provided by the central laboratory; no conversion will be made.

Summary tables displaying observed values and changes from baseline will be presented for numeric clinical laboratory tests by treatment group for subjects in the Safety set. Changes from baseline to each scheduled post-baseline visit (Days 8, 15, 29, and 43) will be presented. Box-and-whisker plots will also be displayed for each laboratory test at baseline and each scheduled post-baseline visit by treatment group.

All safety laboratory data will be included in separate listings and all test values outside the normal range will be flagged.

9.2.1 Hematology

The following laboratory tests will be included: complete blood count (CBC).

9.2.2 Chemistry

The following laboratory tests will be included: blood urea nitrogen (BUN), blood sugar, electrolytes (sodium, chloride, and bicarbonate [HCO3]), alkaline phosphatase, AST, ALT, lactate dehydrogenase (LDH), total bilirubin, serum creatinine, C-reactive protein, and fecal calprotectin.

9.3 Vital Signs

Vital signs will be measured on Days 1, 4, 8, 15, 22, 29, 36, and 43. Vital signs include systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), blood oxygen saturation SpO2, and temperature (^{o} C) with method of measurement (axillary, oral, rectal, or tympanic).

Summary tables displaying observed values and changes from baseline will be presented for numeric vital sign data by treatment group for subjects in the Safety set. Changes from baseline to each scheduled post-baseline visit (Days 4, 8, 15, 22, 29, 36, and 43) will be presented.

All vital sign data will also be presented in a listing.

10. Exploratory Analysis

Exploratory analyses will be conducted on exploratory data collected at the Month 4 and Month 6 visits during the long term follow-up and will be included as the End of Study Final Analysis in an addendum to the main CSR.

All exploratory analyses will be performed using the FAS and will be presented separately for Part 1 and Part 2 of the study unless otherwise specified. Due the exploratory nature of these analyses, only descriptive summary statistics will be provided by treatment group and no inferential statistical tests will be performed.

All exploratory data including deaths will also be presented in separate listings.

10.1. Proportion of subjects with recurrence of COVID-19 symptoms during long term follow-up

A summary table will include the number and percentage (proportion) of subjects with any recurrent COVID-19 symptoms during the entire long term follow-up, after Day 43 visit to Month 4 visit and after Month 4 visit to Month 6 visit by treatment group. Only subjects who continued into the long term follow-up will be included in the summary and counted as the denominator for proportion. Additionally, the summary table will also include the number and percentage of subjects reporting each individual recurrent COVID-19 symptom by treatment group.

10.2. Proportion of subjects with persistence of COVID-19 symptoms during long term follow-up

A summary table will include the number and percentage (proportion) of subjects with any persistent COVID-19 symptoms during the entire long term follow-up, beyond Day 43 visit to Month 4 visit and beyond Month 4 visit to Month 6 visit by treatment group. Only subjects who continued into the long term follow-up will be included in the summary and counted as the denominator for proportion. Additionally, the summary table will also include the number and percentage of subjects reporting each individual persistent COVID-19 symptom by treatment group.

10.3. Proportion of subjects with new hospitalization or rehospitalization during long-term follow-up

A summary table will include the number and percentage (proportion) of subjects with any new hospitalization or rehospitalization during the entire long term follow-up, after Day 43 visit to Month 4 visit and after Month 4 visit to Month 6 visit by treatment group. Only subjects who

continued into the long term follow-up will be included in the summary and counted as the denominator for proportion. A subject will be considered as having a new hospitalization or rehospitalization if the subject has at least one hospitalization with an admission date after the Day 43 follow-up visit. Hospital admissions and dates of stay are collected on the Hospitalizations eCRF.

10.4. Summarization of genotypic resistance analysis data

Nasopharyngeal swabs and stool samples will be collected and stored for possible genotypic resistance analysis. The summary results will be provided when data become available.

11. Interim Safety Analysis

The interim safety data review for Part 1 and 2 of the study will be performed by the DMC (see Section 12. below). Data to be reviewed includes subject disposition, demographics, medical history, concomitant medications, study drug Exposure and compliance, adverse Events, safety clinical laboratory and vital signs. The DMC will be unblinded to study data and will operate under a DMC charter. Blinded and unblinded PPD Biostatisticians will produce and provide tables, listings, and figures requested by the DMC.

Part 1 will enroll approximately 9 hospitalized subjects. After treatment is concluded for all 9 subjects, the DMC will review the safety data and determine if the study may proceed to Part 2 or if additional subjects are needed to assess tolerability of the study drug. If additional subjects are needed, approximately 9 more subjects will be enrolled in Part 1, and then the DMC will meet again after all subjects are treated to determine if the study may proceed to Part 2. Due to the relatively small number of subjects in Part 1, the decision for DMC review of Part 1 will be based on medical judgment of niclosamide tolerability compared to placebo and will not require specific statistics.

For Part 2, the planned interim safety data review will occur when 50 subjects have been randomized and completed the 2-week treatment period. The outcome from the DMC to be delivered to the sponsor will be: (1) continue as planned; (2) pause enrollment and undertake further evaluation of safety; or (3) recommend that the study be terminated due to safety concerns. No rigid statistical stopping rules will be used to make these decisions. While the DMC statistician may perform statistical analyses to examine adverse trends in safety, such as excess deaths and SAEs in the active arm, the decision to recommend a pause in enrollment or termination of the study will be reached by clinical consensus of the DMC.

No formal interim analysis for efficacy is planned to stop the study early for benefit or futility.

12. Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be established to review the safety data throughout the study to ensure the safety of study subjects, the ethical continuation of the study, and provide recommendations regarding continuation or termination of the study or protocol modifications. The DMC will be headed by a DMC Chair and will consist of 2 clinicians and 1 biostatistician, who, collectively, have experience in the management of patients with infectious

diseases and in the conduct and monitoring of randomized clinical trials. The DMC will consist of experts independent from the Sponsor.

The roles, responsibilities and rules governing operation of the DMC are discussed in full in the DMC charter, which will be finalized prior to the administration of investigational product. The DMC charter will define the primary responsibilities of the DMC; guide its activities, its relationship with other study components, its membership, and the purpose and timings of its meetings. It will provide the procedures for ensuring confidentiality, formal communication, and outline of the content of reports that will be provided by the DMC.

13. Final Analyses and Unblinding

13.1. Day 43 Final Analysis

This analysis will be carried out for the main clinical study report (CSR) when the last subject has completed the Day 43 follow-up visit. The main CSR will contain all efficacy (primary and secondary) and safety data through Day 43 as specified per protocol for all randomized patients. An official database lock with PI sign off will be implemented prior to this final analysis at Day 43.

13.2. End of Study Final Analysis

This analysis will be provided in an addendum to the main CSR. It will include only exploratory data collected at Month 4 and Month 6 long-term follow-up visits. Specifically, the exploratory data contains subject survival status, recurrence of COVID-19 symptoms and associated hospitalization(s) and treatments/therapies. A second official database lock with PI sign off will be performed but only for exploratory data prior to this final analysis at end of long-term follow-up.

13.3. Unblinding

At the time of the final analysis at Day 43, the randomization will be unblinded to the central study team after the official database lock. However, the investigators, other site study staff, and subjects will remain blinded to their treatment allocation(s) for as long as they are participating in the study.

14. Changes in the Planned Analysis

Bristol Stool Scale Types 5-7 has been updated to 6-7 for the secondary endpoint in section 3.2.2, section 8.2.2, and section 8.2.3 to be consistent with Appendix B of the protocol. Furthermore, for both analyses if the day of the formed stool/last watery stool was the same as the first day of treatment, then the time to event was imputed as 0.5 days. In the time to last watery stool analysis, there was no censoring necessary.

15. References

Geneva II, Cuzzo B, Fazili T, et al. Normal body temperature: a systematic review. Open Forum Infect Dis. 2019;6(4):ofz032.

He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020;26(5):672-5.

Sato, T. (1989). On the variance estimator for the Mantel-Haenszel risk difference, Biometrics 45, 1323-1324. Letter to the editor.

16. Appendices

16.1. Schedule of Assessments

Visit[1]	Screening[2]	Treatment				Follow-Up					
						Short-term				Long-term	
Timing (D=day, M=month)	**D -3 to -1**	**D1**	**D4**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**M4**	**M6**
Deviation vs randomization day			±1 day	±1 day	±2 days	±2 days	±2 days	±3 days	±3 days	±1 week	±1 week
Informed consent	X										
Eligibility (inclusion/exclusion criteria)	X	X									
Demography	X										
Medical history (or changes)	X	X	X	X	X	X	X	X	X		
Stool analysis	X										
Stool sample for SARS-CoV-2 RNA[3]	X	X	X	X	X	X	X	X	X		
Diarrhea clinical assessment	X	X	X	X	X	X	X	X	X		
Nasopharyngeal swab for SARS-CoV-2 RNA[3]	X	X	X	X	X	X	X	X	X		
Laboratory assessments[4] (L=local, C=central)	L	C		C	C		C		C		
Overall clinical assessment[5]	X	X	X	X	X	X	X	X	X		
Randomization		X									

Dosing study drug		Daily TID, with last dose on D14 or 15									
Daily diary		Daily									
Adverse events	X	X	X	X	X	X	X	X	X		
Concomitant medications		X	X	X	X	X	X	X	X		
Survival status										X	X
Persistence of COVID-19 symptoms										X	X
Recurrence of COVID-19 symptoms										X	X
(Re)Hospitalization due to COVID-19										X	X

1. Patients may be hospitalized, inpatient in a research unit, or seen in an outpatient clinic or in a home care setting.

2. Screening may occur on the same day as randomization, if all procedures may be completed. If they occur on the same day, procedures scheduled for both visits are not required to be duplicated.

3. At screening, eligibility can be determined by local SARS-CoV-2 viral RNA analysis on a nasopharyngeal swab. Only one screening sample is required and can be determined by local requirements. Eligibility can be determined at a local laboratory at screening; however, a central laboratory may be used at screening if needed. On Days 1 to 43, the nasopharyngeal swab and stool sample will be collected and sent to the central lab.

4. Local laboratory testing at screening should include at least AST, ALT, and serum creatinine to determine eligibility. Central laboratory testing will include CBC, BUN, blood sugar, electrolytes (sodium, chloride, potassium, and bicarbonate [HCO3]), alkaline phosphatase, AST, ALT, LDH, total bilirubin, serum creatinine, C-reactive protein, and fecal calprotectin. When only central testing is required, any other laboratory assessment may be conducted at the local laboratory for the physician's safety assessment according to the local practice and patient's clinical needs.

5. Including: mortality; hospital admission and discharge; ICU admission and discharge; WHO severity score and duration, type of administration, vital signs, and quantity of supplemental oxygen treatment. Vital signs should be completed on Days 1-8, 10, and 12 for Part 1 patients, but only need to be recorded in the CRF when the full Overall Clinical Assessment is due at the study visits above.

* Initial medical history will collect date of initial symptom onset. If date is uncertain, verbatim response from patient will be collected.

16.2. WHO Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virologic evidence of infection	0
Ambulatory	No limitation of activities	1
Ambulatory	Limitation of activities	2
Hospitalized, Mild Disease	Hospitalized, no oxygen therapy	3
Hospitalized, Mild Disease	Oxygen by mask or nasal prongs	4
Hospitalized, Severe Disease	Non-invasive ventilation or high-flow oxygen	5
Hospitalized, Severe Disease	Intubation and mechanical ventilation	6
Hospitalized, Severe Disease	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Dead	8

A special WHO (2020) committee arrived at the ordinal scale that measures illness severity over time.

16.3. Missing Date Imputation

Imputation rules for missing or partial AE start/end dates are defined as:

- Only Day of AE start date is missing:
  - If the AE start year and month are the same as that for the first dose date, then:
    - If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date.
  - Otherwise, impute the AE start day as 1.
- If Day and Month of AE start date are missing:
  - If AE start year = first dose year, then:
    - If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date.
  - Otherwise, impute the AE start MONTH as January and the DAY as 1.
- If Year of AE start date is missing:
  - If the year of AE start is missing or AE start date is completely missing, then query site and leave as missing.
- For missing and partial adverse event end dates, imputation will be performed as follows:
  - If only the day of the month is missing, the last day of the month will be used to replace the missing day.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.

Imputation rules for missing or partial medication start/stop dates are defined below:

- If only Day of CM start date is missing:
  - If the CM start year and month are the same as that for the first dose date, then:

        - If the full (or partial) CM end date is NOT before the first dose date or CM end date is missing, then impute the CM start day as the day of first dose date.
    - Otherwise, impute the CM start day as 1.
- If Day and Month of CM start date are missing:
    - If CM start year = first dose year, then:
        - If the full (or partial) CM end date is NOT before the first dose date or CM end date is missing, then impute the CM start Month and Day as the Month and Day of first dose date.
    - Otherwise, impute the CM start MONTH as January and the DAY as 1.
- If Year of CM start date is missing:
    - If the year of CM start is missing or CM start date is completely missing, then query site and leave as missing.
- For missing and partial CM end dates, imputation will be performed as follows:
    - If only the day of the month is missing, the last day of the month will be used to replace the missing day.

If the day and month are missing or a date is completely missing, it will be considered as missing.