CLINICAL PROTOCOL NCTO4811339

A 3 day open label, Pilot study followed by an-up to 21 day double-blind study to assess stool frequency of COVID + patients treated with oral bismuth subsalicylate (Pepto-Bismol): SABER-C

(Specific Administration of Bismuth for Early Recovery of COVID-19)

PROTOCOL DATE:	13JAN2021
DEVELOPMENT PHASE:	IV
PRODUCTS:	*Chewable Pepto-bismol (bismuth subsalicylate tablets) and matched placebo*
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Table of Contents

List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
AEMG	Adverse event management group
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
BSS	*Bismuth subsalicylate*
BID	Twice daily
FCALP	Fecal calprotectin
CFR	Code of Federal Regulations
COX	Cyclo-oxygenase
CQA	Clinical Quality Assurance
CRP	C-reactive protein
CT	Computed axial tomography
COV+	COVID+ patient
eCRF	Electronic case report form
ER	Emergency room
ERES	Electronic Records/Electronic Signatures
ESR	Erythrocyte sedimentation rate
FCALP	Fecal calprotectin
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GSS	Global symptom score
HIV	Human immunodeficiency virus
HQUANT	Hemoquant assay
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgA	Immunoglobulin A

IL	Interleukin
IM	Intramuscular
IRAE	Immediately reportable adverse event
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
LF	Lactoferrin
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
NO	Nitric oxide
NSAID	Nonsteroidal anti-inflammatory drug
PMNs	Polymorphonuclear elastase
PO	Oral
POC	Proof of concept
SOC	Standard of Care
TEAE	Treatment-emergent adverse event
TD	Traveller's diarrhea
US	United States
WBC	White blood cell count

Clinical Protocol Body

1. Study Rationale/Background

The CDC and WHO have deemed the COVID-19 virus a global pandemic of unprecedented severity in modern times. In 2019, this novel Coronavirus (COVID-19) emerged from the Asian continent and has now caused upwards of 360,000 deaths and over 6 million infections globally. Its impacts economically and socially are massive, with an estimated global economic impact of over 5 Trillion dollars.

Understanding the host response to pathogens, specifically the cellular and humoral responses, has played an important role in new non-antibiotic therapies.

Scientific understanding of immune characteristics of virus susceptibility have opened the door to the development of diagnostic and therapeutic agents to identify and treat patients at risk of acquiring COV+, and treating patients at risk of developing persistently positive (by QRT-PCR) COV+ disease or mild COV+ disease.

An extensive epidemiologic study of the mechanism of transmission of the Coronavirus SARS is available on-line. Fauci's textbook, Harrison's Principles and Practise of Infectious disease (2013) outlined the potential of an intestinal nidus of Coronavirus. Viral shedding of Coronavirus was detected up to 2 months following the resolution of respiratory infection in some individuals. This further emphasizes the gut involvement of this class of viruses and the interest in determining the causative and treatment opportunities afforded by a gut-focused strategy to decreasing viral load and shedding. Further, GI symptoms have been found in a significant number of patients with COVID-19, although the incidence of these symptoms vary immensely by region studied.

An IND is not needed for this study as we are primarily looking at stool frequency.

Bismuth subsalicylate (Pepto-Bismol) has a potential role in the clearance and/or recurrence of non-COV+ enteric viral infections.

Readily available over-the-counter (OTC) medication for symptomatic relief and appropriate oral hydration can be health saving measures of great convenience for those affected by enteric bacterial and viral infections. BSS is a non-proprietary monograph product that is available in the USA and abroad, over-the-counter (OTC). Of all OTC medications for TD, bismuth subsalicylate (BSS) has the greatest antimicrobial activity against pathogenic bacteria. A study by Gump et al. (1992) first demonstrated the ability of BSS to decrease the invasiveness of enteropathic bacteria in gastrointestinal epithelial cells. Electron-dense deposits of bismuth were found in *Yersinia enterocolitica* cells exposed to BSS, indicating that the antibacterial effect of BSS was mediated by its ability to increase permeability of the bacterial cell wall and increase bismuth concentrations in bacterial cells. Other studies had indicated that the exposure of bacteria to BSS resulted in a loss of membrane integrity and, possibly, inactivation of cellular ATP synthesis leading to death of the organism. More recently, Pitz et al. (2015) verified *in vitro* the antimicrobial effects of BSS and bismuth oxychloride (BiOCl) on key pathogens, such as *Escherichia coli* O104:H21 (surrogate to 2011 German outbreak strain), *Salmonella*, and norovirus (NoV). These authors showed that bismuth reduced bacterial growth significantly, resulting in less than 10cfu/ml within 24hrs. *C. difficile* was the most susceptible pathogen to the bismuth challenges in the antibacterial assays. BSS also exhibited significant inhibition on viral invasion of host cells and viral efficacy. Both BSS and bismuth oxychloride (BiOCl, which is formed in the stomach after ingestion of BSS) at low concentration (0.004-0.13mg/mL) significantly reduced NoV RNA levels, suggesting an *in vivo* antiviral mechanism. BSS has also been shown to have antiviral activity since it

inhibited replication of 4 strains of rotavirus in tissue culture cells and caused a dose-dependent reduction in the growth of several enteric viruses.

Historically, BSS has been indicated and effectively used for the treatment of TD or enteric infection, mainly when vomiting occurs. Although the safety and efficacy of BSS is well known, some of the research done with BSS resides within the industry and have not been published. I have recently completed an extensive meta-analysis using unpublished clinical studies regarding BSS safety and efficacy. Meta-analyses of randomized controlled clinical trials were performed with studies specifically designed to capture prevention of manifestation and relief of diarrhea.

The first meta-analysis specifically assessed the diarrhea preventive effects of BSS in generally healthy adults who had no diarrhea at the time of randomization. Five P&G-sponsored studies were identified for consideration. Out of the five studies, 3 were designed for prevention of TD, and 2 involved induced diarrhea through viral inoculation (Norwalk agent or Norovirus) or chemical irritation (castor oil consumption) induced diarrhea. Although BSS had shown efficacy in these 2 chemical irritation studies, in order to maintain relevance to populations at risk for TD, only the 3 naturally occurring diarrhea studies were considered for meta-analysis. All 3 studies (n=404 subjects, age between 16 to 70 years old) followed a similar parallel-group, placebo-controlled design in diarrhea-free individuals embarking on a trip to tropical countries (Mexico and African destinations) known for elevated incidence of TD. All subjects initiated a 21-day prophylactic BSS dosing regimen (one study used BSS tablets QID to a total of 2.1g/day, the second study used oral suspension of 1050 mg QID to a total dose of 4.2 g/day and the third study used tablets BID to total dose of 2.1g/day) starting from 1 day before departure or 2 days after arrival at the trip destination.

The meta-analysis efficacy endpoint was self-assessed diarrhea (presence/absence) during the 21-day treatment period. Meta-analysis results are reported in terms of odds ratios and 95% confidence intervals with larger values indicative of greater efficacy for BSS relative to placebo. The data indicate that subjects who dosed BSS had 3.5 times greater odds of not developing TD than subjects who dosed placebo (95% CI: 2.1, 5.9; $p < 0.001$, $I^2 = 27\%$).

Several studies have identified gastrointestinal symptoms associated with COVID-19. Up to 60% of patients in some studies had upper or lower gastrointestinal symptoms, including diarrhea.

Two specific papers have supported the use of Bismuth as a treatment option for COV+. Dr Nan Yang (Hong Kong) found that Bismuth was effective in inhibiting the SARS Corona virus helicase. Of note, this potential efficacy was noted by the Jinyintan Hospital during the current COV-19 pandemic. After several of their staff were infected, they used bismuth compounds prophylactically and noted no further infections.

These data point to the efficacy of preventing viral enteritis and low risk-profile for patients treated with BSS. Clearly, BSS may be part of a strategy for COV+ treatment given its low therapeutic risk profile and documented gut-virus clinical efficacy.

2. Study Objectives

The objectives of this pilot study are: To evaluate the tolerance and efficacy of BSS and SOC in mild/moderate severity COV+ population as defined by QRT-PCR of saliva or nasal swab samples compared to SOC and placebo and compare this efficacy to patients treated with SOC (placebo) alone. This will first be tested in 10 open-label patients, then in 2 groups of 25 patients as follows: Group one with mild/moderate disease and Group 2, patients with mild/moderate disease and persistently positive

for the SARS-Cov-2 virus by QRT-PCR testing for 14 days or more. This study is to assess the potential for BSS to influence the gut as a reservoir of infection by the SARS-Cov-2 virus and to determine the primary effect objective of change in stool frequency of patients treated with BSS compared to placebo treated patients.

Primary efficacy objective:

To determine whether treatment with BSS of Mild/Moderate COV+ decreases mean daily stool frequency compared to placebo-controlled patients

Secondary efficacy objectives:

- Duration of hospitalization in BSS compared to PBO treated groups.
- Weight gain (and BMI) relative to baseline at Week 1, and through Week 2.
- Stool microbiota at baseline and Week 1, and through Week 2 (to be analysed at a later date).
- To determine whether treatment with BSS of Mild/Moderate COV+ decreases the time to viral clearance (negative test by daily saliva testing) and persistently COV+ testing patients (over 14 days of COV+ testing) with Mild/Moderate disease, time until negative test by daily Saliva test.

3. Investigational Plan

3.1 Study Design

This will be a 3 week, randomized, single-center, double-blind, proof-of-concept (POC) pilot study to evaluate the efficacy of patients with mild-moderate COVID-19+ infection. There will be an initial 10-pateint open-label study to assess patient tolerance to the active treatment arm of the study. The first 10 open-label patients will be treated with BSS 2 tablets PO (to chew) up to 4 times daily for 3 days (72 hours). The second 2 groups of patients will be mild (at home) or moderate (hospitalized, not on a ventilator) COV+ testing or with persistently + COVID testing for 14 days or more.

Patients will be allowed to receive a SOC treatment regimen at baseline (Appendix 2)

- Standard of care (which includes any non-excluded SOC medications).

This pilot study will be conducted in the US in 1 center. A total of 60 patients are expected to be enrolled into the 3 arms of the study. Study one will consist of 10 open label COV+ patients with mild/moderate disease, the second and third studies will be double-blind placebo controlled studies of 25 patients each, the first with Mild/Moderate disease upon diagnosis by QRT-PCR+ testing and the third will consist of patients who are COV+, mild to moderate in severity with documented COV+ status by QRT-PCR testing for 14 days or more.

Screening will occur at the time patients are diagnosed via QRT-PCR testing. This may occur at one of several locations and/or time points of diagnosis:

- emergency room [ER]
- physician's office on the U of L campus.
- University of Louisville hospitals (ULH Main and Jewish facilities).
- Selected parking lot on UL campus.

- Campus Health (patients/students may be recruited via Practitioners or by approved recruitment flyers

Patients with initial COV+ confirmed by QRT-PCR testing will be approached to provide informed consent for the study. A third group of patients will be recruited with persistently + QRT-PCR testing for 14 days or more (see table 2).

Randomization will occur during SOC treatment.
Visits will occur at Baseline (Day 1) when patients will receive their first dose of study drug (BSS or PBO), and daily during the study until the patient tests COV- by saliva test or 21 days, whichever comes first.

The study design is depicted in Appendix 2.

3.2 Selection of Study Population

3.2.1 Inclusion Criteria

To be eligible to participate in the study, patients must meet the following criteria:

- Ability to provide written or remote informed consent (telephone and DocuSign)
- Ability to comply with study requirements,
- Men or women 18 to 85 years of age, inclusive
- Current diagnosis of an initial occurrence of non-severe, non-complicated COV+ infection as defined by:
    - Presence COVID-19 in the saliva or nasal cavity using POC QRT- PCR assay or, in study #3, documented COV+ status for 14 days or more.
    - Management in an outpatient (i.e., non-hospital) or inpatient setting NOT on a ventilator.
    - Alert and awake
    - Able to chew the study drug completely.
    - Women should fulfill one of the following criteria:
    - Answer in the affirmative that "they are not or could not be pregnant"
    - Post-menopausal; either amenorrhea ≥12 months or follicle stimulating hormone >20 mIU/mL
    - Surgically sterile; hysterectomy, bilateral oophorectomy, or tubal ligation.
    - Women of childbearing potential participating in heterosexual sexual relations must be willing to use adequate contraception from Screening through the 21 Day visit, per Section 10.2.

3.2.2 Exclusion Criteria

Patients with any of the following will be excluded from admission into the study:

- Existence of an intra-abdominal abscess, enteric fistula, or symptomatic bowel obstruction
- History of allergy to salicylates.
- History of short gut syndrome, active ulcer or recent history of GI bleeding or melena.
- Systemic chemotherapy for the treatment of cancer during the 60 days prior to consent or planned during the study

- Presence of ileostomy or colostomy, or history of prior gastric resection or significant colon resection
- Intra-abdominal surgery within the past 60 days
- Current use of drugs that control diarrhea or affect peristalsis (e.g., loperamide. Opiates can be used in hospitalized patients and with outpatients if they are prescribed to a patient), or any anticipated use during the study
- Active drug, chemical, or alcohol dependency as determined by Investigator through history or urine toxicology screen
- Enrollment in any other investigational drug or device study known to interfere with Pepto bismol (bismuth subsalicylate) within the GI tract, within 30 days prior to Randomization (Day 1) or within 5 half-lives of the last dose of the previous investigational compound, whichever is longer. Vaccines are not exclusionary as they do not interfere with the mechanism of the study drug.
- Severe acute illness unrelated to COVID-19
- Pregnant, breast-feeding, or considering becoming pregnant during the study
- Planned hospitalization or surgery during the study
- Any medical, psychiatric, social, or other circumstances that may interfere with study compliance, completion, or accurate assessment of study outcomes

Standard therapy that is used for treatment of COVID-19 infection does not constitute an exclusion from this study.

3.3 Removal of Patients from the Study

During the study, patients will be withdrawn if any of the following applies:

- Patient's request;
- Complicated COVID-19 infection that requires intubation;
- The Investigator determines that continued participation may cause harm. The Investigator always has the right to withdraw patients in the event of adverse events (AEs), intercurrent illnesses, protocol violations, laboratory abnormalities, treatment failure, or for administrative or other reasons;
- The patient becomes pregnant the treatment code will be revealed and the patient will be referred to an obstetrician and followed throughout the remainder of the study period

When possible, any patient who is withdrawn from the study during the treatment period will undergo all end-of-treatment (Day 21) procedures at the time of withdrawal, regardless of the length of treatment s/he received. Patients withdrawn from the study for medical reasons will remain under medical supervision until the Investigator deems the condition to be resolved or stabilized.

3.4. Study Procedures

3.4.1 Schedule of Events

The schedule of events is displayed in tabular form in Appendix 2.

3.4.1.1 Screening Visit (Days -1 to 0)

Screening will occur at the time the diagnosis of COV+ is confirmed for the first study. For the second study, screening will occur at 2 weeks or more of documented COV+ status. During the screening visit

enrolled patients will be provided with a stool collection kit. Two patient groups will be studied: The following will be obtained to determine patient eligibility:

a. Written or remote informed consent; (telephone and DocuSign)
b. Demographic data;
c. Medication history for the previous 30 days;
d. Medical history including daily stool frequency;
e. Social history (alcohol, tobacco, drugs);
f. Height and Weight (which can be self-reported);
g. Vital signs (temperature, pulse, blood oxygen saturation, blood pressure within 1 week of screening visit);
h. Verbal affirmation that to the best of their knowledge they are not pregnant;
i. Collection of serious, procedure-related non-treatment emergent AEs;
j. Reminder for patients to avoid the use of protocol excluded medications for the duration of the study

All screening laboratory test results must be reviewed, signed, and dated by an Investigator when they are received (see list in Appendix 2).

3.4.1.2 Baseline Visit/Dosing (Day 1)

The baseline visit should occur within 2 days after the screening assessment. The following procedures will be performed at this visit:

a. Medical and medication history update to include any changes or new medications since screening if applicable, and to ensure there is no change in medical condition that, in the Investigator's opinion, would interfere with study participation;
b. Weight (which can be self reported);
c. Recording of vital signs (temperature, pulse, blood oxygen saturation);
d. Patient daily testing by saliva sample for COVID-19; Note: These data will not be reconciled with clinical data collected during the study. Saliva collection protocol:
    a. The patient should not consume food or drink within 30 mins of sample collection
    b. ID number placed on 15 ml collection tube and source docs so all samples/data can be reconciled.
    c. Provide patient with sterile 15 ml falcon tube, ethanol wipe, and paper-covered straw.
    d. The patient uses the straw to funnel spit into the collection tube. At least 1 ml of saliva should be collected. NOTE: saliva can be foamy, the foam does not count towards the 1 ml. Saliva collection may be undertaken inside the car with the window up.
    e. Patient screws lid onto the tube, wipes down outside with ethanol wipe, and places into biohazard bag held by site personnel. The patient keeps straw and wipe and disposes of in the trash.
e. Stool sample for bacterial speciation, metabolomics (at a later date). Collection kits will be provided at initial screening.
f. Collection of serious, study procedure-related, nontreatment-emergent AEs;
g. Review dosing instructions with the patient and stress the importance of compliance;
h. Schedule all daily study visits.
i. Recording of daily stool frequency and symptom questionnaire.

3.4.1.3 Daily Visits (1+/-21 Days)

The visits may occur daily up to Day 21(whichever comes first), or until the patient tests COVID- by saliva test. The following procedures will be performed at this visit:

a. Medication history updated to include any changes or new medications since baseline;
b. Recording of daily stool frequency and symptom questionnaire;
c. Patient daily testing by saliva sample for COVID-19
d. Assessment of AEs;
e. Stool specimen collection at Day 7, Day 14 and Day 21. Collection kits to be given to patient 1 day prior if in an outpatient setting.

3.4.2 Efficacy Assessments

- Mean daily stool frequency and aggregate weekly stool frequency of treated versus placebo treated patients
- Time to negative test of subjects experiencing clinical cure (negative test of saliva-confirmed COV+infection).
- Incidence of Adverse Events (AEs)

3.4.3 Safety Assessments

Safety assessments will include the collection of AEs reported by the patient or observed by the investigator or study site personnel and will be reviewed by the Principal Investigator. Patients should be asked whether, since the time of the last observation or visit, they had any of the following:

- experienced any changes in well-being,
- used any new prohibited medications,
- changed medication regimens (both prescription and over-the-counter), or
- been hospitalized on a ventilator.

Questions should be of a general nature and should not suggest symptoms.

When an AE is suspected, all relevant evaluations will be carried out and appropriate treatment provided. Additional follow-up will be performed as necessary, recorded in the patient's source documents, with the results provided to the Sponsor. Patients who experience any clinically significant AE will remain under medical supervision until the Investigator deems the AE to be resolved, stabilized, or no longer serious enough to warrant follow-up. Laboratory values that are abnormal and not assessed as AEs may be followed at the discretion of the Investigator Monitor until resolved or stabilized.

Symptoms will not be considered AEs unless the symptom meets the International Conference on Harmonization (ICH) definition of a serious AE or the patient withdraws from the study due to the symptom. Symptoms meeting either of these 2 conditions will be recorded on the AE log page so that the event can be assessed for immediate reportability.

3.4.1 Sample Collections

Salivary samples and stool samples for clinical laboratory tests will be obtained according to the schedule of events table (Appendix 2). The list of clinical laboratory tests is in Appendix 3.

Scientific advances in metabonomics indicate that it may be possible to identify biomarkers that will allow a better understanding of the pathogenesis, diagnostics and treatments of COV+, and that are predictive of drug efficacy and toxicity for available therapies

3.5 Treatments

3.5.1 Method of Assigning Patients to Treatment Groups

All patients will be assigned to the treatment group for the first 10 patients treated with open label BSS. The Subsequent 50 patients (two groups of 25) will be randomized to either placebo or BSS. The patients will be assigned by coin-toss, heads to placebo and tails to active treatment (or other suitable randomization event) by a member of the research team not directly involved in the clinical trial.

3.5.2 Treatments Administered

BSS&PBO group:
During the first visit, patients will receive BSS according to manufacturers' instructions in addition to SOC (Chew tablets completely). BSS and PBO will be provided by Procter and Gamble, and are FDA approved.

The treatment regimen is summarized below:

Treatment Group	Dose Regimen	Route of Administration
BSS open label 2 chewable tablets 4 times per day COV+ (N=10)	2 chewable tablets up to 4 times PO per day, manufacturer's instructions	PO
Mild/Moderate COV+, newly diagnosed (N=25)	Double blind BSS or placebo (20 BSS and 5 placebo) for up to 21 days or until COV- by QRT-PCR. 2 chewable tablets up to 4 times po per day, manufacturer's instructions	PO
Mild/Moderate COV+, diagnosed at least 14 days prior, still COV+ (N=25)	Double blind BSS or placebo (20 BSS and 5 placebo) for up to 21 days or until COV- by QRT-PCR. 2 chewable tablets up to 4 times po per day, manufacturer's instructions	PO

3.5.3 Management of Clinical Supplies

Study medication should be securely stored as per manufacturers guidance until dispensed in accordance with the protocol.

Study medication will be dispensed at Baseline. Accurate, up-to-date records of all clinical supplies must be maintained. At the end of the study, the study site must be able to reconcile delivery records with those of received, dispensed, and returned study medication. Unused medication will be disposed in an environmentally responsible fashion. Written account of any discrepancies will be required.

3.5.4 Treatment Compliance

Patients should administer their study medication at approximately the same time each day. Patients will return all used and unused (if any) drug supplies at the end of the study.

3.5.5 Prior and Concomitant Therapy

Patients are restricted from taking any medications listed in the exclusion criteria or any other medications that, in the opinion of the Investigator or the Medical Monitor, may affect the safety profile of the study medication or interpretation of the results, except when such drugs are vital for the patient's welfare and/or no other drug is available. However, this may result in patient discontinuation from study participation (see Section 3.4, Removal of Patients from the Study).

Patients will be prohibited from taking the following medications during the study:

- Corticosteroids (including oral, IV, IM, or rectally administered) except those used in the treatment of COVID-19 infection
- Chemotherapy agents
- Anti-diarrheals and anti-spasmodics - Opiates can be used in hospitalized patients and with outpatients if they are prescribed to a patient
- Any investigational or marketed drugs that, in the opinion of the investigator, may interfere with the evaluation of the study medication.

3.6. Statistical Methods

3.6.1 Statistical Analysis Plan

Statistical Analysis Plan

Efficacy Analysis:

The primary efficacy analyses will be to compare the negative Saliva rates at Week 1, 2 and 3 between the SOC control group and the BSS + SOC treatment groups using the analysis of variance (ANOVA) with treatment group and baseline BMI as a covariate variable in the model. Clinical factors such as age, antibiotic use, number of recurrences, etc. will be examined for the impact on the treatment effect.

The analyses of the primary efficacy endpoint will be conducted to compare historical SOC control vs. BSS plus SOC groups. The ANOVA or a nonparametric method, whichever is appropriate, will be used to compare the rates of recurrence at each time point.

For categorical endpoints, chi-square test or a Fisher exact test (for 2x2 tables) will be used to assess treatment effect. For continuous endpoints, the ANOVA or a nonparametric method will be used, whichever is appropriate.

The comparability of patient's population at baseline will be assessed using either chi-square test (for categorical data) or t-test (for continuous variables).

Safety Analysis:

Intent-to-treat (ITT) patients who receive one dose of study drug will be included in the safety evaluation.

The number of AEs reported by patients, who participate in the study, as well as their causality and severity, will be summarized for each treatment group. Frequency tables for AEs by MedDRA terms will be presented. AEs will be assessed by age, sex, and race.

3.7. Data Quality Assurance

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Data management quality control checks
- Statistical quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final report

4. Investigator's Obligations

A summary of Investigator Obligations are in Appendix 4.

4.1 Institutional Review

The Investigator will not begin the study until the protocol and informed consent form have been approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB/IEC will also review and approve all advertisements.

4.2 Patient Consent

Each patient must personally sign and personally date a study-specific informed consent form (ICF) or each patient can be consented remotely if testing positive for Covid-19 to serve as a participant in the study. This ICF will comply with all applicable regulations governing the protection of human patients. The basic elements of informed consent are specified in the US Code of Federal Regulations (CFR) Title 21 parts 50.25, 50.27, and 50.55 and the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for good clinical practice (GCP).

5. Appendices

Appendix 1: Schedule of Study Procedures

Procedures	Screening (Days -1 to 0)	Treatment Period							Unscheduled Visits including primary SOC failure
		Baseline/ Dosing (Day 1)	Day 2-21 (optional)	Day 7 collection	Day 14 collection	Day 21 collection			
Written informed consent or remote via telephone and DocuSign	X								
Demographic data	X								
Medical/medication/social history	X	X[f]		X[f]	X[f]				
Height and Weight (which can be self-reported)	X	X		X	X				X
Vital signs[b]	X	X							
Daily stool frequency	X	X	X	X	X				X
Stool sample (metabolomics), stool speciation. Collect on ice for -70C storage by the lab of Dr Collins.		X		X	X	X			X
Saliva for QRT-PCR for COVID-19.		X	X	X	X				X
Assessment of AEs[e]	X	X	X	X	X				X
Study medications and compliance		X	X	X	X	X			X

[a] Weight (which can be self-reported) at baseline, Week 1 & 2 and unscheduled visits only;
[b] Includes temperature, pulse, blood oxygen saturation;

[e] Before dosing, only serious, study-procedure related AEs will be collected;
[f] Medication update only;
WD = withdrawal

Appendix 2: Clinical Laboratory Tests

Fecal Exam

- **For microbial speciation and metabolomics (later date)**

Other

Saliva for Sars_CoV-2

Appendix 3: Investigator Obligations

It is the responsibility of the Investigator to:

- Ensure that he/she has sufficient time to conduct and complete the study, has adequate staff and appropriate facilities which are available for the duration of the study, and ensure that other studies do not divert essential patients, facilities, or personnel away from the study.
- Submit an up-to-date curriculum vitae and other credentials for key study personnel to the Sponsor and, where required, to relevant authorities.
- Agree to and sign the protocol with the Sponsor and confirm in writing that he/she has read, understands, and will work according to the protocol and Good Clinical Practice, accepting the oversight of the monitor and control procedures.
- Identify a local study coordinator to assist with administration of the study.
- Maintain a list of appropriately qualified persons to whom the Investigator has delegated significant trial-related duties. For example, causality assessments must be carried out by the investigator or by a physician delegate.
- Obtain the name and address of your IRB/IEC and a statement from them that states they are organized and operate according to GCP and the applicable laws and regulations.
- Submit notification/application of intent to conduct a clinical study and annual updates to relevant bodies, including local hospital management, and to the IRB/IEC, jointly with the Sponsor, where appropriate.
- Provide information to all staff members involved with the study or with other elements of the patients' management.
- Obtain written informed consent or remote informed consent via telephone and DocuSign from study patients, prior to inclusion in the study; provide each with a copy of the signed informed consent form; and document the method of obtaining informed consent.
- Collect, record, report, and correct data in a timely and proper manner in the source documents and patient case report form.
- Maintain source and study documents [protocol and amendments, source documentation corresponding to all information contained in the eCRFs, signed informed consent forms, relevant correspondence, test results (COVID-19 tests), and all other supporting documentation] for the required period of time
- Notify (with documentation), when applicable, the IRB/IEC (and relevant authorities, when required) immediately in the case of potentially serious AEs.
- Notify patients of any information that may affect their willingness to continue in the study.
- Make all data available to the IRB for verification/ audit/inspection purposes.
- Sign and provide the study data (e.g., case report forms, analyses, and reports
- Ensure that all proprietary information is kept confidential.
- Observe the following points related to patient care:

- If appropriate, fully functional resuscitation equipment should be immediately available in case of emergency.
- The Investigator is medically responsible for those patients who are under his/her care for the duration of the study.

- Ensure it is noted in the medical records that the patient is participating in a clinical trial.
- Be aware of the need for records to be maintained and the minimum time they are to be kept. This also includes procedures to transfer record custody in the event the Investigator retires, relocates, etc. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigation product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements, the hospital, institution, private practice, or by an agreement with the Sponsor.
- The Study Site or Principal Investigator will obtain written IRB/IEC approval/favorable opinion for patient recruitment advertising copy.