CLINICAL TRIAL PROTOCOL

A Phase II, Randomized, Sham Controlled Dose Finding Study of the RD-X19 Treatment Device in Individuals with Mild to Moderate COVID-19

Protocol Number: EB-P20-01 Version 5.0 (Amendment 4)

Investigational Countermeasure: EmitBio™ RD-X19

Specific Indication: Treatment of Mild to Moderate COVID-19

Target Respiratory Disease Pathogen(s): SARS-CoV-2

Phase: Phase II

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GCP Statement: This trial will be performed in compliance with (c)GCP.

Signatures of the following individuals indicate that all agree this version is final.

Nate Stasko, PhD Chief Science Officer EmitBio Inc	Date
John McNeil, MD Chief Medical Officer EmitBio Inc	Date

1 INSTITUTIONAL STATEMENT OF COMPLIANCE

Each institution engaged in this research will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP), and/or will be guided by the review and deliberations of an Institutional Review Board (IRB)/Independent or Institutional Ethics Committee (IEC) that must be registered with OHRP as applicable to the research.

The study will be carried out in accordance with the following as applicable:

- United States (US) Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (IRBs), 21 CFR Part 11, and 21 CFR 812 (Investigational Device Exemptions)
- The International Council for Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice (GCP), and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Any additional applicable Federal, State, and Local Regulations and Guidance

2 INVESTIGATOR'S AGREEMENT

This signature provides the necessary assurance that this study will be conducted according to all stipulations of the protocol, including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) GCP guidelines.

Principal Investigator Signature:

Signed: _____ Date: _____

3 TABLE OF CONTENTS

4 PROTOCOL SUMMARY

4.1 Executive Summary

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown origin. Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) was shortly thereafter identified as the etiological agent for Coronavirus Disease 2019 (COVID-19). Recent reports demonstrate that viral load strongly correlates with disease severity, progression, and mortality in SARS-CoV-2 infected humans.[1-3]A higher number of health risk factors equates to a higher saliva viral load, with saliva viral load being superior to nasopharyngeal viral load as a predictor of mortality.[2] Indeed, many of the tissues and glands in the oral cavity have been documented to have high levels of ACE2 expression, highlighting the importance of the oral cavity in understanding both disease progression and oral-lung transmission via aspiration.[4-5]

There are currently no FDA cleared or approved therapies that directly target early (i.e., within 3 days of symptom appearance) mild to moderate COVID-19 without risk factors for progression to severe disease nor are there treatments directed locally to the high SARS-CoV-2 viral loads observed in the upper respiratory tract or oral cavity. Systemically administered antibody therapies and convalescent plasma have recently shown clinical evidence of nasopharyngeal viral load reductions and improved clinical outcomes in non-hospitalized populations.[6-8] However, subsequent emergency use authorizations have restricted these therapies only to populations with risk factors for progression to severe disease and hospitalization and all require infusions in a clinical setting. The diversity of genetic variants of concern is increasing and demonstrate enhanced transmissibility and are more resistant to existing antibody therapies and vaccines.[9-11] The extreme magnitude of transmission in India and Brazil will give rise to a plethora of new variants some of which will almost certainly be of significant concern for the effectiveness of antibody therapies and vaccines that depend on neutralizing antibodies to exert their effect. These existing limitations underscore the need for innovative therapeutic countermeasures that can be made widely available in an equitable fashion and directly address the issue of emerging variants.

The Mechanisms of Action (MOA) of RD-X19 are through both direct and indirect antiviral effects. RD-X19 inactivates cell-free SARS-CoV-2 by as much as 99.99% and inhibits cell-associated replication of the virus by 99.9% when measured at 24 hours after a single treatment *in vitro*. Cell-free SARS-CoV-2 is inactivated directly by 425nm visible blue light and indirectly, during and after light therapy through photobiomodulation of human tissue. One of the putative antiviral mechanisms may involve upregulation of nitric oxide (NO) in epithelial cells via RD-X19-induced increased nitric oxide synthases (NOSs) and stimulation of the instantaneous release of the body's bound stores of NO. It is hypothesized that photoimmunomodulation of the respiratory epithelium signals additional effector cells of the innate immune system. The innate immune effectors include natural killer (NK) cells, monocytes, additional macrophages, and dendritic cells (professional antigen presenting cells) that rapidly proliferate and swarm the infecting virus. The innate immune response is our most ancient form of immunity and through pathogen-only protein pattern

recognition attack the pathogen at the site(s) of infection and end-organ pathology. The technology utilized by RD-X19 has been repeatedly demonstrated to provide high-level viral inactivation in multiple, consistent, expert-laboratory *in vitro* studies. The direct cell-free inactivation of virus by visible blue light presents a transformational opportunity for therapy that is not antigen-directed or antigen-specific, unlike adaptive immunity induced or provided by vaccines and monoclonal antibodies.

Herein we report in vivo clinical proof of concept from our phase I/II Randomized, Sham-controlled, Double-blind Safety, Tolerability and Bioeffect Study (RCT) - EB-P12-01 (ClinicalTrials.gov Identifier NCT04662671). In summary, a total of 31 study subjects were randomized 2:1 into this RCT evaluating the RD-X19 device vs. Sham control. The protocol was open to individuals diagnosed positive by an FDA-authorized SARS-CoV-2 antigen test performed within 24 hours of enrollment with the presence of two or more COVID-19 signs and symptoms of ≥ moderate severity (using guidance applied to severity grading of Treatment Emergent Adverse Events (TEAEs)) with initial symptoms no longer than 3 days prior to study enrollment. The listing of inclusion and exclusion criteria can be found in the ClinicalTrials.gov reference above.

Primary safety analyses returned the following results: no SAEs, no medically attended or device-related TEAEs (all TEAEs captured were the appearance or worsening of COVID-19 related signs or symptoms). All TEAEs were attributed to COVID-19, and, notably, there were no local site reactions including no changes within the oral cavity indicative of pathology reflecting clinically meaningful potential changes to the oral microbiome. The device was completely safe and exceptionally well-tolerated in this study.

Bioeffects (efficacy) included evaluation of reductions in mean $\log_{10}$ salivary viral load from baseline through study day 8 via RT-qPCR and time to sustained clearance of COVID-19 signs and symptoms, defined as all COVID-19 signs or symptoms graded as 0 (absent) or 1(mild) with no reoccurrence of any sign or symptom of severity score >1 after clearance was achieved.

The EmitBio RD-X19 is safe, reduces salivary viral load 100-fold after 4 days of treatment at study day 5 and 1000-fold (99.9%) at study day 8 – a full 72 hours after completion of treatment. This represents a profound reduction in salivary viral load which is highly correlated with clinical improvement of COVID-19. In our study, signs and symptoms of COVID-19 resolved 57 hours faster in the RD-X19 treated group than in the sham control group; a result that is both clinically meaningful and statistically significant. No study volunteer required medical intervention other than self-medication with OTC remedies. There were no study subjects that discontinued participation.

EmitBio will continue efforts to understand the detailed mechanisms of action that inactivate SARS-CoV-2 and inhibit its replication during and after application of RD-X19. This technology presents an unprecedented opportunity for protection that is NOT antigen-directed or antigen-specific, with a high likelihood of mitigating the threat posed by current SARS-CoV-2 variants as

well as novel pre-emergent coronavirus strains. RD-X19 results in inactivation of all variants of SARS-CoV-2 tested to date, including B.1.1.7, B.1.351, and additional variant strains obtained from California and New York. (unpublished results)

4.1.1 Study Goals

This is a randomized, sham controlled, dose finding study of the EmitBio RD-X19 device in individuals with symptomatic COVID-19 in the outpatient setting. Study subjects will self-administer treatment twice daily for 7 days with a one week follow-up period at Day 14 (+/- 2 days) and will not be aware of which treatment group to which they have been randomized. Clinical outcomes will be assessed via patient reported outcomes (disease assessment and diary cards) and virologic outcomes will be assessed post baseline on Days 3, 5, 8, and 14 via biospecimen collection.

The primary goal of the study is to evaluate multiple doses of the RD-X19 treatment device and establish evidence for safety and efficacy for a single selected RD-X19 dose compared to sham in SARS-CoV-2 infected individuals with outpatient COVID-19. The primary efficacy outcomes are: (i) time to sustained symptom resolution in all patients (mild or moderate disease at baseline); and (ii) time to sustained symptom resolution in patients with mild disease at baseline. Other clinical and microbiological outcomes will also be assessed.

Safety and tolerability (local reactogenicity) will be assessed actively and study subject diary card data recorded at each clinic visit by review of potential treatment emergent adverse events (TEAEs) and targeted oral and physical examinations. Volunteers will be instructed to contact designated clinical trial staff for AEs of a medically-urgent nature as soon as is practically possible and to seek immediate medical care, if needed. On study days 2 and 4 between clinic visits, study personnel will contact each subject by phone for additional safety monitoring. Study subjects who experience progression of disease to a grade 3 severity score (e.g $SpO_2 \leq 93\%$,or respiratory rate ≥30/ minute on room air) will be instructed to urgently seek medical care at their nearest Urgent Care or Emergency Department. Study subjects who progress to severe acute respiratory distress syndrome with substantial risk for mortality without immediate medical intervention will be referred directly by site staff to their closest hospital. All study subjects who are hospitalized will be tracked to assess time to hospital discharge or death; the time and date of these events will be captured as part of the trial data.

Metabolic, liver, kidney and hematological laboratory evaluations will be performed at baseline and at Day 14 or early termination (and potentially during unscheduled) clinic visits. Methemoglobin assessments will be performed at baseline and Day 14.

4.1.2 Study Design

Subjects will provide written informed consent prior to initiating any screening procedures. Subjects meeting all screening criteria will be eligible for enrollment and randomization into the study. Subjects with COVID-19 disease with signs and symptoms reported > 72 hours from onset will be given instructions to see their primary care physician or be advised to seek potential treatment (if eligible) at a local antibody infusion center.

This Phase II, dose finding portion of the trial is targeting to enroll a minimum of 60 volunteers with 30 in each of at least two dosing cohorts (20 assigned to RD-X19 and 10 assigned to sham per cohort, 2:1 randomization).

Cohort A will begin with 24 J/cm^2 per treatment, administered 2X/Day for duration of 7 days. Once 80% of subjects (n=24) in Cohort A complete the Day 8 visit and no predefined safety signals as outlined in the study pausing/stopping criteria have been observed, Cohort B, 32 J/cm^2 per treatment will start enrollment. In the event device-related serious adverse events or patterns of device-related adverse events, including application site reactions, are observed in Cohort A, and based on the review and recommendation of the external safety monitoring committee (SMC) of unblinded data, the study may proceed with enrollment and dosing in Cohort C, 16 J/cm^2 per treatment in keeping with SMC recommendations. An illustration of the ascending (or descending) dose finding design is provided below.

Cohort A: RD-X19 24 J/cm^2 vs. Sham

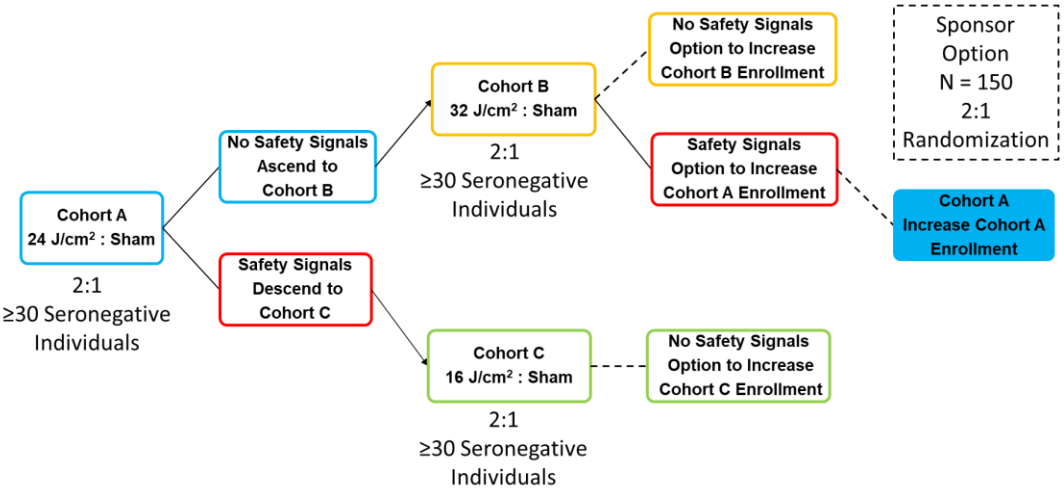
(5 minute treatment, 2X/Day for a duration of 7 days)

Cohort B: RD-X19 32 J/cm^2 vs. Sham

(5 minute treatment, 2X/Day for a duration of 7 days)

Cohort C: RD-X19 16 J/cm^2 vs. Sham

(5 minute treatment, 2X/Day for a duration of 7 days)



In the final Cohort to be investigated, once 80% of the subjects complete the Day 8 visit without observation of safety signals meeting the definition of predefined pausing/stopping criteria, a blinded review of available safety data for Cohort A and Cohort B will be conducted along with a blinded assessment of the proportion of 'success' events on the first primary endpoint of sustained symptom resolution for the subjects within each Cohort. At the sponsors option the final cohort enrollment may be increased in sample size (targeting up to an additional 150 subjects, 2:1 randomization). This option to increase overall enrollment is intended to provide better resolution of the point estimate between a safe, well tolerated dose and sham treatment in a broader population, including subjects who are SARS-CoV-2 Anti-Spike IgG antibody positive at Baseline, either through natural infection or immunization, in preparation for future trials. In the event safety signals are observed during the conduct of Cohort B (32 J/cm^2), based on the review and recommendation of the SMC, the sponsor may elect to proceed with the optional additional enrollment and dosing in the initial Cohort A, 24 J/cm^2 per treatment. As such, the Final Cohort is defined as the cohort including the final randomized subject.

Subjects meeting all inclusion criteria and none of the exclusion criteria will be randomized in a 2:1 ratio within each dosing cohort. Light will be administered locally to the mouth and throat only, aiming to eliminate SARS-CoV-2 viral load in these targeted portions and surrounding tissues of the upper respiratory tract. Assessments of safety, and clinical outcomes will occur as outlined in Table 1 below. Clinic vists will occur post-baseline (Day 1) on study days 3, 5, 8, and 14 (+/-2, inclusive). Telephonic outreach by study personnel will occur on days 2 and 4 for additional safety monitoring and to enhance compliance with at-home study procedures. Study subjects requiring hospitalization will be tracked until discharge or death and the time and date of these events captured.

Study Subject safety will be monitored throughout the study by the Site Investigators, supported by regular review by the Sponsor's Chief Medical Officer and the CRO medical monitor with strict stopping criteria identified for discontinuation of dosing within a treatment arm.

Table 1: Objectives and Outcome Measures

OBJECTIVES	**ENDPOINTS (OUTCOME MEASURES)**
Safety Assessments	
• Serious Adverse Events (SAEs) and Treatment Emergent Adverse Events (TEAEs) characterized by Medical Dictionary for Regulatory Affairs (MedDRA) System Order Classified (SOC) Preferred Terms (PTs), including application site local reactions and device-related TEAEs	• Collection and summary of all TEAEs reported from study subjects' daily diary cards or in office visits and via monitoring for application site reactions during clinic visits by investigators' examination of intraoral pathology. MedDRA SOC PT-

	defined TEAEs will be established and evaluated individually and collectively for severity and attribution and presented in tables and listings.
Primary Outcome Assessments	
• Sustained resolution of COVID-19 signs and symptoms in all subjects (with mild or moderate disease at baseline)	• Time to sustained resolution of COVID-19 signs and symptoms as measured by the time (in hours) when cough, sore throat, nasal congestion, headache, chills and or sweats, myalgia, fatigue, and nausea (with or without vomiting) have been assessed by the subject as none (0) or mild (1) and all symptoms remain at or below 1 until study Day 14. *Subjects reporting a persistent fever (100.5 degrees for 36 hours or more) and/or SpO_2 levels <96% with any shortness of breath fail to meet the success criterion on that day even if all other symptoms are reported as none (0) or mild (1).
• Sustained resolution of COVID-19 signs and symptoms in subjects with Mild disease at baseline	• Time to sustained resolution of COVID-19 signs and symptoms as measured by the time (in hours) when cough, sore throat, nasal congestion, headache, chills and or sweats, myalgia, fatigue, and nausea (with or without vomiting) have been assessed by the subject as none (0) or mild (1) and all symptoms remain at or below 1 until study Day 14. *Subjects reporting a persistent fever (100.5 degrees for 36 hours or more)

	and/or SpO_2 levels <96% with any shortness of breath fail to meet the success criterion on that day even if all other symptoms are reported as none (0) or mild (1).
Secondary Clinical Outcome Assessments	
• Day 8 Composite Resolution	• Proportion of study subjects who achieve 'Day 8 Composite Resolution' defined as both a negative SARS-CoV-2 antigen test within the window for Visit 4 and all symptoms assessed by the subject as none (0) or mild (1), absence of fever and SpO2 ≥96% without shortness of breath on study day 8.
• Worsening of Disease	• Number and percentage of study subjects who experience progression of COVID-19 as defined by an increase of the composite COVID-19 severity score greater than baseline at any point in the study on or after day 3.
• Return to Pre-COVID Health	• Numbers and percentages of study subjects on day 8 and day 14 who answer yes to the following patient-reported global impression assessments, a) return to usual health and b) return to usual activities. a) In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)? Yes or No b) In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)? Yes or No • Numbers and percentages of study subjects who:

• Severe Clinical Outcomes	1) who require medical attention or intervention attributed to COVID-19; 2) who progress to severe disease with respiratory rate >30/minute and/or O2 saturation ≤93% on room air or FiO2 ≥300% with any respiratory distress; 3) who require hospitalization for severe COVID-19; 4) who require endotracheal ventilation or ECMO with or without the use of solumedrol; and 5) who die.
Secondary Virologic Outcome Assessments	
• Change in Nasopharyngeal VL • Clearance of viral shedding (undetectable SARS-CoV-2 VL)	• Mean change in nasopharyngeal VL from baseline on days 3, 5, 8, and 14. • Tabulated geometric mean nasopharyngeal VL at baseline and on Days 3, 5, 8 and 14. • Proportion of subjects demonstrating clearance of viral infection, defined as a negative nasopharyngeal swab via RT-qPCR as assessed on each of Days 3, 5, 8 and 14.
Exploratory Assessments	
• Change in oral microbiome	• Change in α and β diversity in microbial flora from baseline on day 8 and day 14 as analyzed by 16S rRNA subunit analysis from frozen saliva

• Change in Saliva VL	samples. • Mean change in saliva VL on days 3, 5, 8, and 14. • Tabulated geometric mean saliva VL at baseline and on days 3, 5, 8 and 14.

The study SAP will outline all study analytical tables and listings, by treatment assignment and whether analysis population is Safety/FAS, mFAS or PP.

4.2 Inclusion and Exclusion Criteria

A subject must meet all the following criteria to be eligible for **inclusion** in this study:

1. Positive for SARS-CoV-2 as detected using an FDA authorized SARS-CoV-2 antigen test at or within 24 hours of the screening visit.
2. COVID-19 signs and symptoms within 72 hours from symptom onset, including at least two moderate* or greater symptoms from: cough, sore throat, nasal congestion, headache, unexplained chills and/or sweats, myalgia, fatigue, nausea (with or without vomiting).
    - Subjects with the presence of at least one moderate symptom and either a) a fever with an oral temperature of at least 100.5 °F or b) shortness of breath/difficulty breathing on exertion (e.g., walking, going up and down stairs) are also eligible for enrollment.
3. BMI <40
4. Provides written informed consent prior to initiation of any study procedures.
5. Be able to understand and agrees to comply with planned study procedures and be available for all study visits.
6. Agrees to the collection of saliva, nasopharyngeal, and venous blood specimens per protocol.
7. Males or females, 18 to 65 years of age, inclusive.
8. No uncontrolled disease process(es) based on patient reported medical history (chronic or acute), other than direct COVID-19 signs and symptoms.
9. No physical or mental conditions or attributes at the time of screening, which in the opinion

of the PI, will prevent full adherence to, and completion of, the protocol.

*Symptom scoring is independent from the classification of COVID-19 disease severity at baseline. Guidance to study subjects for grading of signs and symptoms will be based on definitions used for the grading of TEAEs:

- None (Grade 0): Not present
- Mild (Grade 1): Symptoms that are usually transient and may require only minimal or no palliative or specific therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.
- Moderate (Grade 2): Symptoms that are usually alleviated with palliative or specific therapeutic intervention. The symptoms interfere with usual activities of daily living causing discomfort but pose no significant or permanent risk of harm to the study subject.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly effect clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

A subject who meets any of the following criteria will be **excluded** from participation in this study:

1. Positive urine pregnancy test at screening or females who intend to become pregnant during the study.
2. COVID-19 signs associated with severe respiratory distress or imminent serious medical outcomes.^^

   ^^Potential Study Subjects Presenting with any of the following should be referred for immediate medical care and are not eligible for the study

   - Fever > 104° F
   - Cough with sputum production
   - Rales and/or rhonchi
   - Difficulty breathing with respiratory distress defined by a respiratory rate ≥30 per minute, heart rate ≥125 per minute, SpO2 ≤93% on room air at sea level or PaO2/FiO2 <300.
   - Persistent pain or pressure in the chest
   - Confusion
3. Any medical disease or condition that, in the opinion of the site Principal Investigator (PI) or appropriate sub-investigator, precludes study participation.
5. Reports a recent positive test result (within the past 6 months) for hepatitis A, hepatitis B or,

hepatitis C virus antibody, or HIV-1 antibodies at screening.

6. Has a history of alcohol abuse or other recreational drug (excluding cannabis) use within 1 month of Study Day 1.
7. Currently enrolled in or plans to participate in another clinical trial with a therapeutic investigational agent (e.g., monoclonal antibody, oral protease inhibitor) that will be received during the study period.
8. History of systemic antiviral therapies (e.g., remdesivir) within the past 30 days.
9. History of oral or parenteral corticosteroid use within the past 30 days. Active use of nasal or inhalable steroids is also exclusionary. Topical steroids are not exclusionary.
10. Has a history of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticaria, angioedema, other significant reaction) to sun exposure.
11. Currently undergoing photodynamic therapy (PDT) or photochemotherapy (PUVA) for an unrelated disease or condition that utilizes photosensitizing drugs including but not limited to 5-aminolevulinic acid, Methyl-5-aminolevulinic acid, porfimer sodium, methoxsalen (8-methoxypsoralen), 5-methoxypsoralen, trioxsalen.
12. Has any oral abnormality including ulcer, oral candidiasis, oral mucositis, gingivitis, burning mouth syndrome, dry mouth syndrome, a disease that can result in xerostomia (e.g. Sjogren's syndrome), or other oral disorder that in the opinion of the investigator would interfere with device use and evaluation.
13. Any intra-oral body piercings that cannot be removed and remain removed for the duration of the study. Metal orthodontia is permitted as braces will be covered by the device mouthpiece.
14. Any individual without teeth or with a dental malformation that precludes directed use of the device as intended.

4.3 Study Schedule of Activities

Study Procedures	Screening, Enrollment & Randomization	Follow-up Period (Visit Window)					
@ Each Study Day	1	2	3	4	5 (-1 to +1)	8 (-1 to +1)	14/ET (-2 to +2)
Informed Consent	X						
COVID-19 Testing - SARS-CoV-2 Rapid Antigen Test*	X					X	X
Medical History & Physical Examination	X		Changes since last visit only		Changes since last visit only	X	X
Oropharyngeal Assessment	X**		Changes since last visit only		Changes since last visit only	X	X
Urine Pregnancy Test	X						
Concomitant Medication History/New	Baseline		Changes since last visit only		Changes since last visit only	Changes since last visit only	Changes since last visit only
Blood Draw (CMP, CBC, SARS-COV-2 antibody)	X						X
Methemoglobin	X						X
Vital Signs	X		X		X	X	X
Adverse Event Assessment / Reactogenicity	Baseline		X		X	X	X
Demographics, Inclusion / Exclusion Review	X						
Diary Dispensation (Diary Card Training) / Collection	X					X	X
Dispense RD-X19 Device / Treatment at Site***	X		X		X		
SARS-CoV-2 Biospecimen collection for viral assays (2 specimens – saliva and nasopharyngeal swab)****	X		X		X	X	X
Extra saliva specimen collection for exploratory oral microbiome assessment	X					X	X
COVID-19 Disease Assessment	X					X	X
Telephone Call for Safety Monitoring and Compliance		X		X			
Collect RD-X19 Device						X	

* Subjects presenting at the time of screening that have tested positive via a SARS-CoV-2 rapid antigen test at or within the past 24 hours of the screening visit and can provide documentation confirming proper identification, the date of the test and testing location, positivity of the result, and name/identity of the assay used to generate the result, are also eligible for enrollment and the rapid antigen test does not have to be repeated at the site.

** On Day 1 to be evaluated 30 minutes after first illumination at site.

*** **For scheduling purposes, the recommended interval between treatment is not < 6 hours.**

Only one treatment of the twice daily regimen will be done on site on Days 1, 3 and 5, the second treatment will be done at home. For Day 1, the subject will be instructed to complete two treatments regardless of time of enrollment (e.g. 4 pm and 10 pm).

**** At Baseline and days 3, 5, 8, and 14, subjects will provide one saliva specimen and one nasopharyngeal swab for virology endpoint assessments. Biospecimens will be collected, preserved, and shipped to a central lab for assessment of SARS-CoV-2 mRNA via RT-qPCR. Optionally, the sponsor may perform additional genetic sequencing on one or both baseline specimens to obtain incidence of CDC classified variants of concern in the study population.

5 INTRODUCTION

5.1 Background and Study Rationale

In laboratory studies, the LED technology employed in the RD-X19 device has demonstrated the ability through both direct and intermediate mechanisms, to kill cell-free virus by as much as 99.99% and inhibit cell-associated replication of multiple coronaviruses by 99.9% when measured at 24 hours after a single light treatment in vitro. The technology utilized by RD-X19 has been repeatedly demonstrated to provide dose-dependent antiviral activity in multiple, laboratory in vitro modelss. The mechanism of action, direct cell-free killing of virus by 425nm visible blue light and an augmented innate immune response presents an breakthrough opportunity for therapy that is not specific pathogen-directed or dependent on antigen-specific adaptive immunity.

5.2 Risk/Benefit Assessment

5.2.1 Known Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn and mild, transient, local reactions as measured in EB-P10-01, a Phase I Open Label, Acute Safety Study of the EmitBio RD-X19 Device in healthy adults. There were no SAEs, TEAEs (including local reactions) attributed in EB-P12-01, a Phase I/II randomized, sham controlled, double-blinded trial in indivuals with mild to moderate COVID-19. See the Clinical Investigators Brochure for more detail.

Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the subject lie down and elevate his/her legs. Bruising at the blood draw site may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken.

Extensive evaluation of the RD-X19 and similar energy-based devices routinely used for oral and skin care purposes resulted in the Sponsor, after careful consideration, making the determination that RD-X19 ia a “Not Significant Risk” (NSR) device per FDA guidelines. This was affirmed twice by protocol Institutional Review Boards (IRBs).

CAUTION - The light emitted may be harmful to the eyes. Do not stare at the light. Photobiological eye safety testing has classified this device as Risk Group 2 - Moderate risk. The blue light emitted does not pose an immediate hazard due to aversion response to very bright light sources or due to thermal discomfort of prolonged exposures. However, direct illumination of unprotected eyes should be avoided. Study staff must ensure volunteers understand to never point the RD-X19 device toward their or anyone else's eyes.

A summary of the known and potential risks of the RD-X19 are as follows:

- Depth of insertion beyond recommended depth has the potential to result in pharyngeal gag reflex for some study subjects.

- Exposure to blue light may be harmful to the eyes when the device is used incorrectly.
- Overexposure of tissues to blue light can cause mild, transient pharyngeal discomfort and erythema.
- Extended blue light exposure to eyes may result in worsened headache pain associated with chronic migraines and other cerebral vascular disorders associated with headache.
- Shining the end of the RD-X19 illumination device directly onto skin, approximately 1 cm away has the potential to induce mild erythema.
- Elimination of oral microflora with blue light has the potential to lead to oral candidiasis and/or disruption of the oral microbiome.

Risks to Privacy

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subject's PHI. All study records will be kept in a locked file cabinet or maintained in a locked room at the participating clinical trial site(s). Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publications from this trial will not use information that will identify subjects by name.

Organizations that may inspect and/or copy research records maintained at the participating clinical trial site(s) for quality assurance (QA) and data analysis include groups such as the IRB and the FDA.

A description of this clinical trial will be posted on http://www.ClinicalTrials.gov. This web site does not include information that can identify subjects.

There may be other risks, discomforts or side effects that are entirely unknown at this time.

5.2.2 Known Potential Benefits

There is no guaranteed benefit to study participants; however, based on EB-P12-01, we expect to observe benefits including substantially decreased SARS-CoV-2 virus in the upper respiratory tract and quicker resolution of COVID-19 signs and symptoms. Use of EmitBio™ RD-X19 is intended to reduce SARS-CoV-2 viral load and alleviate the clinical signs and symptoms associated with COVID-19. There is also the potential for benefit to society resulting from insights gained from participation in this, and other similar studies

6 STUDY DESIGN

The study population is individuals confirmed infected with an FDA-authorized SARS-CoV-2 antigen test who have mild to moderate COVID-19. Study subjects must be symptomatic for 72 hours or less and have a positive COVID-19 antigen test within the past 24 hours of screening.

The targeted number of subjects randomized per Cohort in the dose finding portion of the study is 30 individuals seronegative for SARS-CoV-2 Spike IgG antibodies (minimum 60 subjects total, with sponsors option to increase enrollment by an additional 150 total subjects to include all serostatuses after a dose has been selected based on safety for the final cohort). Based on findings in the EB-P12-01 and the hazard ratio observed for the median time to sustained symptom resolution in the proof of concept trial, the increased sample size with an anticipated roughly equal number of antibody positive to negative individuals in the final cohort has at least 90% power in the modified full analysis set population to detect clinically meaningful changes in SARS-CoV-2 symptom resolution (Hazard ratio of 0.4 between active RD-X19 and Sham observed in EB-P12-01).

The target population in the full analysis set (FAS) for the Final Cohort will reflect the underlying communities largely impacted by COVID-19, possessing both seropositive and seronegative individuals from a mixture of vaccinated and unvaccinated subjects, and with a high prevalence of circulating variants. Nasopharyngeal and saliva biospecimens collected at baseline may be analyzed to obtain genetic sequencing and characterize the incidence of SARS-CoV-2 variants in the study population.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician, licensed to make medical diagnoses.

6.1 Inclusion Criteria

A subject must meet all the following criteria to be eligible for **inclusion** in this study:

1. Positive for SARS-CoV-2 as detected using an FDA authorized SARS-CoV-2 antigen test at or within 24 hours of the screening visit.
2. COVID-19 signs and symptoms within 72 hours from symptom onset, including at least two moderate* or greater symptoms from: cough, sore throat, nasal congestion, headache, unexplained chills and/or sweats, myalgia, fatigue, nausea (with or without vomiting).
    - Subjects with the presence of at least one moderate symptom and either a) a fever with an oral temperature of at least 100.5 °F or b) shortness of breath/difficulty breathing on exertion (e.g., walking, going up and down stairs) are also eligible for enrollment.
3. BMI <40
4. Provides written informed consent prior to initiation of any study procedures.

5. Be able to understand and agrees to comply with planned study procedures and be available for all study visits.
6. Agrees to the collection of saliva, nasopharyngeal, and venous blood specimens per protocol.
7. Males or females, 18 to 65 years of age, inclusive.
8. No uncontrolled disease process(es) based on patient reported medical history (chronic or acute), other than direct COVID-19 signs and symptoms.
9. No physical or mental conditions or attributes at the time ofscreening, which in the opinion of the PI, will prevent full adherence to, and completion of, the protocol.

*Symptom scoring is independent from the classification of COVID-19 disease severity at baseline. Guidance to study subjects for grading of signs and symptoms will be based on definitions used for the grading of TEAEs:

- None (Grade 0): Not present
- Mild (Grade 1): Symptoms that are usually transient and may require only minimal or no palliative or specific therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.
- Moderate (Grade 2): Symptoms that are usually alleviated with palliative or specific therapeutic intervention. The symptoms interfere with usual activities of daily living causing discomfort but pose no significant or permanent risk of harm to the study subject.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly effect clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

6.2 Exclusion Criteria

A subject who meets any of the following criteria will be **excluded** from participation in this study:

1. Positive urine pregnancy test at screening or females who intend to become pregnant during the study.
2. COVID-19 signs associated with severe respiratory distress or imminent serious medical outcomes.^^

   ^^Potential Study Subjects Presenting with any of the following should be referred for immediate medical care and are not eligible for the study:

   - Fever > 104° F
   - Cough with sputum production

- Rales and/or rhonchi
- Difficulty breathing with respiratory distress defined by a respiratory rate ≥30 per minute, heart rate ≥125 per minute, SpO2 ≤93% on room air at sea level or PaO2/FiO2 <300.
- Persistent pain or pressure in the chest
- Confusion

3. Any medical disease or condition that, in the opinion of the site Principal Investigator (PI) or appropriate sub-investigator, precludes study participation.
5. Reports a recent positive test result (within the past 6 months) for hepatitis A, hepatitis B or, hepatitis C virus antibody, or HIV-1 antibodies at screening.
6. Has a history of alcohol abuse or other recreational drug (excluding cannabis) use within 1 month of Study Day 1.
7. Currently enrolled in or plans to participate in another clinical trial with a therapeutic investigational agent (e.g., monoclonal antibody, oral protease inhibitor) that will be received during the study period.
8. History of systemic antiviral therapies (e.g., remdesivir) within the past 30 days.
9. History of oral or parenteral corticosteroid use within the past 30 days. Active use of nasal or inhalable steroids is also exclusionary. Topical steroids are not exclusionary.
10. Has a history of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticaria, angioedema, other significant reaction) to sun exposure.
11. Currently undergoing photodynamic therapy (PDT) or photochemotherapy (PUVA) for an unrelated disease or condition that utilizes photosensitizing drugs including but not limited to 5-aminolevulinic acid, methyl-5-aminolevulinic acid, porfimer sodium, methoxsalen (8-methoxypsoralen), 5-methoxypsoralen, trioxsalen.
12. Has any oral abnormality including ulcer, oral candidiasis, oral mucositis, gingivitis, burning mouth syndrome, a disease that can result in xerostomia (e.g. Sjogren's syndrome), or other oral disorder that in the opinion of the investigator would interfere with device use and evaluation.
13. Any intra-oral body piercings that cannot be removed and remain removed for the duration of the study. Metal orthodontia is permitted as braces will be covered by the device mouthpiece.
14. Any individual without teeth or with a dental malformation that precludes directed use of the device as intended.

6.3 Overall Design

Volunteers will provide written informed consent prior to initiating any screening procedures. Those meeting all screening criteria will be eligible for enrollment into the study. Study subjects

will be randomized in a 2:1 ratio within each Cohort, targeting to complete two cohorts in ascending or descending fashion based on safety/tolerability of Cohort A as follows:

Cohort A: RD-X19 24 J/cm^2 vs. Sham

(5 minute treatment, 2X/Day for a duration of 7 days)

Cohort B: RD-X19 32 J/cm^2 vs. Sham

(5 minute treatment, 2X/Day for a duration of 7 days)

Cohort C: RD-X19 16 J/cm^2 vs. Sham

(5 minute treatment, 2X/Day for a duration of 7 days)

Volunteers meeting all inclusion criteria and none of the exclusion criteria will be randomized in a 2:1 ratio within each cohort (30 per cohort). Assessments of study subjects will occur on study days 1, 3, 5, 8, with the final assessment visit on Day 14. Individuals who are hospitalized will be tracked until discharge or death and the date and time of these events will be captured in the study data.

This is a randomized, adaptive dose-finding study. The primary goal of the study is to evaluate multiple doses of the RD-X19 treatment device and establish evidence for safety and efficacy for a single selected RD-X19 dose~~s~~ compared to sham in SARS-CoV-2 infected individuals with outpatient COVID-19.

The primary efficacy outcomes are: (i) time to sustained symptom resolution in all patients (mild or moderate disease at baseline); and (ii) time to sustained symptom resolution in patients with mild disease at baseline. Other clinical and microbiological outcomes will also be assessed.

Since CMP and CBC results may not be available until study day 3, all volunteers who have significant clinical abnormalities will be immediately contacted and advised of the abnormality, discontinued from active participation in the protocol and advised regarding appropriate medical follow-up outside the study. All such study subjects will be replaced with a new volunteer.

Subjects who test positive for SARS-CoV-2 antibodies from blood draws at baseline will continue treatment for the duration of the study, undergo all assessments, and be excluded from the modified full analysis set (mFAS). For each subject testing positive for SARS-CoV-2 antibodies at baseline, one additional subject will be enrolled and randomized into the study for each of Cohorts A and B (*does not apply to optional enrollment period once the dose has been selected for the additional 150 subjects).

Safety and tolerability (local reactogenicity) will be assessed actively on each clinic visit by review of study subjects' daily diary cards for potential TEAEs, and oral cavity examination and targeted physical examination, as required.

Metabolic, liver, kidney and hematological laboratory evaluations will be performed at screening and at Day 14 or early termination (and potentially during unscheduled) clinic visits.

Subjects will be instructed to fill out diary cards twice daily to assess their symptoms associated with disease progression and record the number of treatments completed. Each of the eight symptoms will be rated on a 4-point scale from none (0) to severe (3) and a summary severity average will be calculated. Twice daily oral temperatures and oxygen saturation levels (SpO2) will also be recorded on the diary from readings taken by at-home devices dispensed to each subject. Reminders will be sent to each subject twice daily via an appropriate communication platform (e.g. text messaging).

Study Subject safety will be monitored throughout the study by the Investigator and supported by regular review by the Medical Monitor and a Chartered Safety Monitoring Committee.

6.4 Objectives and Outcome Measures

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Safety Assessments	
• Serious Adverse Events (SAEs) and Treatment Emergent Adverse Events (TEAEs) characterized by Medical Dictionary for Regulatory Affairs (MedDRA) System Order Classified (SOC) Preferred Terms (PTs), including application site local reactions and device-related TEAEs	• Collection and summary of all TEAEs reported from study subjects' daily diary cards or in office visits and via monitoring for application site reactions during clinic visits by investigators' examination of intraoral pathology. MedDRA SOC PT-defined TEAEs will be established and evaluated individually and collectively for severity and attribution and presented in tables and listings.
Primary Outcome Assessments	
• Sustained resolution of COVID-19 signs and symptoms in all subjects (with mild or moderate disease at baseline)	• Time to sustained resolution of COVID-19 signs and symptoms as measured by the time (in hours) when cough, sore throat, nasal congestion, headache, chills and or sweats, myalgia, fatigue, and nausea (with or without vomiting) have been assessed by the subject as none (0) or mild (1) and all symptoms remain at or below 1 until study Day 14.

	*Subjects reporting a persistent fever (100.5 degrees for 36 hours or more) and/or SpO_2 levels <96% with any shortness of breath fail to meet the success criterion on that day even if all other symptoms are reported as none (0) or mild (1).
• Sustained resolution of COVID-19 signs and symptoms in subjects with Mild disease at baseline	• Time to sustained resolution of COVID-19 signs and symptoms as measured by the time (in hours) when cough, sore throat, nasal congestion, headache, chills and or sweats, myalgia, fatigue, and nausea (with or without vomiting) have been assessed by the subject as none (0) or mild (1) and all symptoms remain at or below 1 until study Day 14. *Subjects reporting a persistent fever (100.5 degrees for 36 hours or more) and/or SpO_2 levels <96% with any shortness of breath fail to meet the success criterion on that day even if all other symptoms are reported as none (0) or mild (1).
Secondary Clinical Outcome Assessments	
• Day 8 Composite Resolution	• Proportion of study subjects who achieve 'Day 8 Composite Resolution' is defined as both a negative SARS-CoV-2 antigen test within the window for Visit 4 and all symptoms assessed by the subject as none (0) or mild (1), absence of fever and SpO2 ≥96% without shortness of breath on study day 8.

• Worsening of Disease	• Number and percentage of study subjects who experience progression of COVID-19 as defined by an increase of the composite COVID-19 severity score greater than baseline at any point in the study on or after day 3.
• Return to Pre-COVID Health	• Numbers and percentages of study subjects on day 8 and day 14 who answer Yes to the following patient-reported global impression assessments, a) return to usual health and b) return to usual activities. a) In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)? Yes or No b) In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)? Yes or No
• Severe Clinical Outcomes	• Numbers and percentages of study subjects who: 1) who require medical attention or intervention attributed to COVID-19; 2) who progress to severe disease with respiratory rate >30/minute and/or O2 saturation <94% on room air or FiO2 ≥300% with any respiratory distress; 3) who require hospitalization for severe COVID-19; 4) who require endotracheal ventilation or ECMO with or without the use of solumedrol; and 5) who die.
Secondary Virologic Outcome Assessments	
• Change in Nasopharyngeal VL	• Mean change in nasopharyngeal VL from baseline on days 3, 5, 8, and 14. • Tabulated geometric mean

• Clearance of viral shedding (undetectable SARS-CoV-2 VL)	nasopharyngeal VL at baseline and on Days 3, 5, 8 and 14. • Proportion of subjects demonstrating clearance of viral infection, defined as a negative nasopharyngeal swab via RT-qPCR as assessed on each of Days 3, 5, 8 and 14.
Exploratory Assessments	
• Change in oral microbiome • Change in saliva VL	• Change in α and β diversity in microbial flora from baseline on day 8 and day 14 as analyzed by 16S rRNA subunit analysis from frozen saliva samples. • Mean change in saliva VL on days 3, 5, 8, and 14. • Tabulated geometric mean saliva VL at baseline and on days 3, 5, 8 and 14.

The study SAP will outline all study analytical tables and listings, by treatment assignment and whether analysis population is Safety/FAS, mFAS or PP.

6.5 Scientific Rationale for the Study

The technology utilized by RD-X19 has been repeatedly demonstrated to provide dose dependent antiviral activity in multiple, consistent, expert-laboratory in vitro studies. The proof-of-concept clinical study EB-P12-01, established an effective dose (16 J/cm^2, BID) in subjects with mild-to-moderate COVID-19. The mechanism of action, including the potential to augment innate

immunity, presents an unprecedented opportunity for treatment that is not specifically antigen-directed or dependent with documented activity against SARS-CoV-2 variants which have shown increased speed of replication in human tissue. This dose range finding study is designed to select a single, safe and well-tolerated dose with the greatest likelihood of treatment benefit in a population with high prevalence of circulating SARS-CoV-2 variants.

6.5.1 Justification for Doses

In repeated laboratory experiments, including experiments conducted by external third parties with bench top LED arrays capable of delivering precise wavelengths and energy densities of light, it has been determined that the visible light emitted by the EmitBio RD-X19 device can provide potent antiviral activity against upper respiratory pathogens including SARS-CoV-2. Reduction in cell-free virus of ≥1000 fold and inhibition of viral replication of ≥99% have been observed in repeated experiments conducted by the sponsor and external expert laboratories. Dose dependent effects are observed ranging from as little as a single 7.5 J/cm^2 exposure up to complete antiviral activity at 30 J/cm^2 measured 24 hours and 48 hours after exposure. Multiple cell types including human respiratory epithelial cells and 3D epithelial tissue (oral and tracheal/bronchial tissues) in culture show high viability at single doses of visible blue light up to 120 Joules/cm^2 and after several days of repeat, twice daily dosing with 32 J/cm^2. These repeated experiments, conducted in multiple labs with multiple cell types, along with years of medical use of licensed devices with comparable wavelengths and energy, support the doses proposed in this protocol for dose finding to achieve optimal efficacy and safety for the doses tested.

As in the Phase I and Phase I/II studies of RD-X19, a primary dose and schedule of two treatments per day (separated by not less than 6 hours) will be evaluated. On Day 1, the subject will be instructed to complete two treatments regardless of time of enrollment.

In light of extant data, the current study beginning with a total energy per dose 50% increased over the previous study (EB-P12-01) will evaluate subjects over a 1 week treatment period with a follow up visit at day 14. Based on the observed safety and tolerability of Cohort A, ascending to Cohort B has been designed to deliver up to 100% increase in daily dose over the previous study and evaluate subjects over a 1 week treatment period with a follow up visit at day 14, consistent with the recommendation made by the external SMC in EB-P12-01. Cohort C, if dictated based on the safety tolerability of Cohort A, would evalute the same daily dose delivered in EB-P12-01. The dosing schedule, duration of treatment, and ascending/descending dose design has been selected to provide clinically meaningful reductions in viral load and symptomatic relief as rapidly as possible while still maintaining a well tolerated safety profile.

Strict safety oversight will provide rapid detection of significant device-related adverse events warranting pausing or halting the trial. See Section 8.5 for detailed description of study Pausing and Stopping Rules.

7 STUDY POPULATION

The study population is outpatients ages 18 to 65 confirmed to be infected with SARS-CoV-2 who have signs and symptoms consistent with mild to moderate COVID-19. Subjects presenting with severe disease at the time of screening are excluded. Study subjects must self-report symptom onset within 72 hours or less and separately have a positive COVID-19 antigen test at screening (or within the past 24 hours of screening).

Categorization of COVID-19 disease severity will be defined as follows:

Mild COVID-19

- Positive testing by an FDA authorized SARS-CoV-2 diagnostic test, and
- Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, headache, muscle or joint pain, unexplained chills or sweats, nausea (with or without vomiting) or other non-respiratory symptoms that may alter daily living (e.g. loss of taste or smell), and
- Do not have shortness of breath, dyspnea, abnormal chest imaging, or any other clinical signs indicative of Moderate or Severe COVID-19

Moderate COVID-19

- Positive testing by an FDA authorized SARS-CoV-2 diagnostic test, and
- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or dyspnea (shortness of breath) with exertion, and
- Clinical signs suggestive of lower airway involvement, such as resting respiratory rate ≥20 breaths per minute or imaging indicating lower airway disease , with an oxygen saturation (SpO2) ≥94% on room air at sea level.

Severe COVID-19

- Positive testing by an FDA authorized SARS-CoV-2 diagnostic test, and
- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, and
- Clinical signs indicative of severe systemic illness, such as resting respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, lung infiltrates > 50%, or SpO2 < 94% on room air at sea level or PaO2/FiO2 < 300 mm Hg.

The targeted number of subjects randomized per Cohort in the dose finding portion of the study is 30 individuals seronegative for SARS-CoV-2 Spike IgG antibodies (minimum 60 subjects total, with sponsors option to increase enrollment by an additional 150 total subjects to include all serostatuses after a dose has been selected based on safety for the final cohort). Based on findings in the EB-P12-01 and the hazard ratio observed for sustained symptom resolution in the proof of

concept trial, the increased sample size with an anticipated roughly equal number of antibody positive to negative individuals in the final cohort has at least 90% power in the modified full analysis set (mFAS) population to detect clinically meaningful changes in SARS-CoV-2 symptom resolution (Hazard ratio of 0.4 between active RD-X19 and Sham observed in EB-P12-01).

The target population in the full analysis set (FAS) for the Final Cohort is intended to reflect the communities largely impacted by COVID-19, possessing both seropositive and seronegative individuals from a mixture of vaccinated and unvaccinated subjects, and with a high prevalence of circulating variants. Nasopharyngeal and saliva biospecimens collected at basline may be analyzed to obtain genetic sequencing and characterize the incidence of SARS-CoV-2 variants in the study population.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician, licensed to make medical diagnoses.

7.1 Study Volunteer Selection, Retention & Compensation

7.1.1 Recruitment

Potential subjects may learn about the study via IRB-approved recruitment strategies, including direct mailing, recruitment from an IRB-approved trial registry, radio announcements, digital advertisements and local advertisements/flyers. Pre-screening may begin with a brief IRB-approved telephone call from study staff. Information about the study will be presented to potential subjects and questions about their health and ability to comply with the study visit schedule will be asked of potential subjects to presumptively determine eligibility. Appointments will be made at the clinical trial unit for potential subjects who are interested in the study for further screening procedures and additional protocol-specific information.

7.1.2 Retention

Study retention strategies will include education and explanation of the study schedule and procedures during screening and enrollment visits and restriction of enrollment to persons who can attend all study visits. Participating subjects will be reminded of subsequent visits during each visit, with emphasis on completing the entire visit schedule even after disease resolution. Between visits on Days 2 and 4, to assist with retention and reinforce adherence to at-home study procedures, study personnel will contact each subject via phone. Study staff may also contact subjects prior to appointments to ensure adherence to the trial protocol. Study staff will contact subjects who miss appointments to encourage them to return for completion of safety evaluations.

7.1.3 Compensation Plan for Subjects

Subjects will be compensated for their participation in this trial. Compensation will be ultimately subject to local IRB approval. Reimbursements will be disbursed at specific timepoints during the

study with the total amount contingent on presenting up to date diary card entries and completing study procedures through day 14.

7.1.4 Costs

There is no cost to subjects for the research tests, procedures/evaluations or study device while taking part in this trial. Procedures and treatment for clinical care may be billed to the subject's insurance or third party.

8 STUDY DEVICE

8.1 Regulatory Considerations

8.1.1 Preliminary Regulatory Pathway for EmitBio™ RD-X19

The Food and Drug Administration (FDA) plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the COVID-19 pandemic. To date, the agency has utilized various mechanisms to expand access for drugs, grant emergency use authorization (EUA) for certain diagnostic and treatment approaches and has issued policies for medical devices without premarket notification during the COVID-19 public health emergency.

Risk management activities have been completed according to EmitBio's SOP for Risk Management and a Risk Management Plan was developed, which are compliant with the applicable 21 CFR part 820 regulations, ANSI AAMI ISO 14971, and ISO TR 24971. A Hazard Analysis, including a Failure Effects Mode Analysis, of the device characteristics and use was performed based on ANSI AAMI ISO 14971.

The risks identified, mitigation measures and control strategies, in combination with a review of all available nonclinical and clinical safety information, has led the company to conclude that the RD-X19 operating at the proposed fluence levels is a Nonsignificant Risk Device.

Per the FDA guidance document titled "Significant Risk and Nonsignificant Risk Medical Device Studies," NSR device studies do not have to have an Investigational Device Exemption (IDE) application approved by FDA prior to initiation.

8.1.2 Proposed Label Claim/Indication for Use:

The EmitBio™ RD-X19 device is intended for use as a treatment for mild to moderate COVID-19 in subjects with positive results of direct SARS-CoV-2 viral testing ages 18 years of age and older who are symptomatic for no more than 3 days.

RD-X19 is not intended for individuals who have respiratory distress with clinical signs indicative of severe systemic illness such as a respiratory rate ≥30 breaths per minute, heart rate ≥125 per minute, SpO2 <94% on room air, or a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg.

8.1.3 Medical Device Quality System:

EmitBio™ will operate under an established Quality Management System, with a commitment for continuous improvement and effectiveness, in accordance with the requirements of the customers and applicable international standards. Specifically, the EmitBio™ Quality Management System is compliant with the requirements of the FDA Quality Systems Regulations (QSR).

8.2 Study Device and Use

8.2.1 Device Description

The RD-X19 device is designed to emit safe, visible light to eliminate SARS-CoV-2 and stimulate host defenses in the oropharynx and surrounding tissues. The RD-X19 device does this without additional photosensitizers or chemical reagents that are typically employed with traditional photodynamic therapeutics.

The device consists of three components: (1) Aluminum housing, (2) Light Engine, and (3) Light Guide Assembly; each designed to allow the assembled device to meet specific criteria based on targeted safety and efficacy.

There are two primary accessories required for use of the device. The first accessory, the AC adapter, is used for recharging the device. The AC adapter is plugged into wall voltage and then connected to the device via a micro USB cable between device uses. The user is prompted, via indicator lights, when recharging is necessary, in progress, and complete. The second accessory, the stand, is used for storing the device between uses.

8.3 Use / Storage & Maintenance / Accountability

8.3.1 Acquisition and Accountability

The sponsor will provide clinical sites with RD-X19 devices packaged in appropriately labelled containers containing all components as well as instructions for use by study participants. Each RD-X19 device will be stamped on its power unit with a serial number. Study staff will ensure that each device's serial number (e.g. EB-123) is assigned to a specific study subject and the link between device serial number and study subject study number will be maintained on an accountability log. Subjects will be requested to bring their device to the clinic for each scheduled visit. Upon completion of a subject's treatment regimen in the trial, all RD-X19 devices and components must be returned to the study site and then to the study sponsor.

8.3.2 Device Storage and Maintenance

All RD-X19 devices will be stored in a locked device storage room at the clinical trial site until needed for assignment to an enrolled study volunteer. Upon acquisition by the study subject,

devices should be stored in a dry climate-controlled environment in the original container in which it was provided.

The device should be stored securely out of the reach of children who may mistakenly misuse the device, especially illumination of eyes – which is always to be avoided. The mouthpiece of the device is removable for rinsing with mild soap and warm water. The power housing may be cleaned with a soft cloth that has been dampened in mild dish detergent diluted in water; pieces should then be dried with a soft cloth. The optic of the device can be wiped gently with a dry cloth suitable for cleaning optical glasses.

8.3.3 Preparation for Use and Use

[Refer to Appendix 1: RD-X19 Investigational Device Manual]

8.4 Measures to Maximize Study Subject Compliance

Subjects will be randomized in a 2:1 ratio (RD-X19:Sham) in each dosing Cohort, providing a higher probability that the subjects being enrolled in the trial will receive potential treatment benefit. Subjects will receive appropriate compensation for the disruption to normal daily activities created by this protocol that also considers the frequency with which they are requesting to travel to the site, phone calls on study days 2 and 4, the twice daily journaling and treatment regimen, and the high number of biospecimens scheduled to be collected for microbiology assessments.

Additionally, the subjects will be educated on the role of their individual contribution in clinical research as it relates to developing a solution for mild to moderate COVID-19.

8.5 Device Discontinuation

8.5.1 Study Pausing Criteria

If observations of an SAE or patterns of discrete or non-resolving device-related TEAEs grade 2 or higher in the same SOC PT are observed in a single subject, dosing will be discontinued for that subject and observed at regulary scheduled follow up visits.

EB-P20-01 enrollment in any Cohort will be paused if any of the following events occur:

- Any subject experiences a device related SAE.
- Any subject experiences laryngospasm, bronchospasm or anaphylaxis within 2 hours after treatment.
- Two (2) or more subjects experience an allergic reaction such as generalized urticaria (defined as occurring at three or more body parts) within 72 hours after treatment.
    - Potential photoallergy or phototoxicity to one or more photosensitizing drugs in the subject's medical history should be investigated in all cases.

See "Medications that Increase Sensitivity to Light: A 1990 Listing (Levine 1990)."

- Three (3) or more subjects experience a Grade 2 or higher TEAE (including local, systemic and/or clinical laboratory abnormalities), in the same SOC grouping of Preferred Terms based on the Medical Dictionary for Regulatory Activities (MedDRA) coding, considered to be related to RD-X19.

While the study is paused, attribution will be determined and assigned and the SMC will be notified that a consultation is required. Given the frequency of visits and the duration of the protocol, study device use may continue in unaffected subjects within a cohort until a recommendation is provided to unpause or terminate cohort enrollment by the SMC.

The SMC, when convened by the sponsor, will not only make a recommendation to unpause enrollment or discontinue dosing in a given cohort, but will also make a reccomendation to the sponsor for ascending, or descending from Cohort A in the event safety/tolerability signals are observed with the first 24 J/cm^2 RD-X19 device.

A study volunteer may elect to discontinue participation in the trial at any time. Investigative staff will ask the volunteer to return for an early termination evaluation, but they are under no obligation to do so. All study subjects must return the RD-X19 device at study termination and study staff must verify that the device serial number matches the study subject to whom it was assigned.

8.5.2 Study Stopping Criteria

When a device-related SAE or two or more device-related severe TEAEs (grade 3) in the same SOC PT are observed within a given cohort, further enrollment and treatment in that Cohort will be discontinued.

8.5.3 Investigator Decision to Discontinue Subject Use of Device

A subject may be removed from the study for the following reasons post initial device use; however, whenever possible the subject should be followed for safety evaluations per protocol:

- Study non-compliance to protocol requirements that in the opinion of the participating clinical site PI or appropriate sub-investigator poses an increased risk (e.g., missing safety labs) or compromises the validity of the data.

- Lost to follow-up. A subject will be considered lost to follow-up if he or she fails to appear for a follow-up assessment. Extensive effort (i.e., generally three documented contact attempts via telephone calls, e-mail, etc., made on separate occasions) will be made to locate or recall the subject, followed by a couriered delivery of study documents to the subjects home address to determine the subject's health status. These efforts will be documented in the subject's study file.

- Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the participating clinical site PI or appropriate sub-investigator, might compromise the safety of the subject, interfere with the subject's successful completion of this study, or interfere with the evaluation of safety.
- If any TEAE, clinical laboratory abnormality or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The occurrence of a SAE.
- If the subject is using the device in any manner inconsistent with instructions and protocol directives and procedures.

If the subject agrees, every attempt will be made to follow all AEs through resolution or stabilization.

Subjects who withdraw or are lost to follow-up after signing the informed consent form (ICF) and use of the RD-X19 device will not be replaced. Subjects who withdraw or are withdrawn from this study after signing the ICF during screening but before use of the device may be replaced.

The reason for subject discontinuation or withdrawal from the study will be recorded on the appropriate e-CRF.

8.5.4 Follow-up of Study Subjects Who Discontinue Device Use

Discontinuation of study device use does not constitute discontinuation from the study, and the study procedures should be completed as indicated by the Study Schedule of Activities. If a clinically significant finding is identified, including, but not limited to, changes from baseline, after enrollment, the participating clinical trial site PI or qualified designee will determine if any change in subject management is needed. Any new clinically relevant finding will be reported as an AE.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Screening Assessments

9.1.1 Screening Procedures

At the screening visit, and prior to any other study-related activities, designated study personnel will provide the subject with detailed study information and will obtain written informed consent (see section 11.1.1 for more details).

Subject numbers will be assigned with the three-digit numerical site number beginning with numbers greater than two hundred (e.g. 201) followed by an alphanumeric protocol identifier (P20) and finally a three digit unique numerical identifier assigned with each new subject (e.g. 001).

Example Subject Number: 201-P20-001

COVID-19 Screening

Subjects who identify with symptomatology associated with COVID-19 will be first screened by taking a nasal culture and analyzed for the presence of SARS-CoV-2 by an FDA authorized SARS-CoV-2 antigen test (e.g. BD Veritor™ Plus System, AccessBio Carestart). These systems allow for rapid detection of SARS-CoV-2 via immunoassay for the direct and qualitative detection of SARS-CoV-2 antigens. Subjects presenting at the time of screening that have tested positive via a SARS-CoV-2 rapid antigen test within the past 24 hours and can provide documentation confirming proper identification, the date of the test and testing location, positivity of the result, and name/identity of the assay used to generate the result, are also eligible for enrollment.

Eligible subjects for enrollment must present with uncomplicated COVID-19 and have at least two moderate or severe symptoms (cough, sore throat, nasal congestion, headache, unexplained chills and/or sweats, myalgia, fatigue, nausea (with or without vomiting) and consent to be randomized within 3 days of first symptom onset. The subjects will self-assess their COVID-19 symptoms as none (0), mild (1), moderate (2), or severe (3) during screening as part of a disease assessment questionnaire.

- Subjects with the presence of at least one moderate symptom and either a) a fever with an oral temperature of at least 100.5 °F or b) shortness of breath/difficulty breathing on exertion (e.g., walking, going up and down stairs) are also eligible for enrollment.
    - If subjects present with dyspnea on exertion or at rest, SpO_2 should be measured and recorded. See I/E criteria for eligibility of enrollment.
    - For demographic purposes, all subjects reporting shortness of breath at baseline will be categorized as having ‘Moderate COVID-19’ consistent with NIH guidelines (Section 7.0).

Subjects with COVID-19 disease with signs and symptoms reported > 72 hours from onset will be given instructions to see their primary care physician or be advised to seek potential treatment (if eligible) at a local antibody infusion center. Additionally, subjects will also be asked to report if they have been previously diagnosed with COVID-19 via a laboratory confirmed diagnostic test and whether or not they report that they have been previously vaccinated with at least one dose of COVID-19 vaccine.The month and year for one or both events will be recorded. The complete COVID-19 disease assessment will include vital signs recorded as part of general screening, ask subjects to assess their loss of taste and loss of smell (binary assessments at each assessment*), report if they experience any shortness of breath on exertion, and pose the following patient-reported global impression assessments on Days 8 and 14:

a) In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)? Yes or No

b) In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)? Yes or No

* COVID-related loss of sense of taste and loss of sense of smell are well understood to normalize over a prolonged period of time given the neurological etiology, long after SARS-CoV-2 has been eliminated from the body. As these signs of COVID-19 have been reported to vary with each variant, this information is being collected for demographic purposes and will be assessed only as part of the qualitative patient reported global assessment.

General Screening

Some or all of the following assessments are performed during the screening visit to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Obtain subject-reported medical history focusing on conditions per protocol exclusion criteria.
- Review all pre-study medications, vitamins, supplements, and therapies up to 14 days prior to the start of screening that could impact the use of, or response to, the device and record on the appropriate source document. The use of any medications to treat some of the COVID-19-related symptoms (e.g., analgesics, antipyretics) should be recorded and the name of medication, dose, dosage form, and date and time(s) of administration should be reported. Antibiotics are not indicated as a treatment for COVID-19 and prior use of antibiotics (e.g. tetracycline, azithromycin) should be documented accordingly. Subjects receiving antibiotics for treatment of COVID-19 must discontinue use prior to study enrollment and this information should be documented. Subjects should be informed not to take antibiotics or other medications purported to treat COVID-19 (such as hydroxychloroquine or ivermectin) during their participation in the study. Antibiotic treatment of a bacterial infection during screening is a protocol exclusion because of the existence of an active concurrent disease. During the study, the decision to prescribe antibiotics is a clinical decision that should be made by the subject's primary care provider outside of the protocol. Such use, and the reason for such use, will be documented. While actively participating in the study, if antibiotics or other putative COVID-19 treatment drugs are

prescribed for treatment of COVID-19, volunteers must not use these drugs if they desire to remain in the active protocol. Subjects presenting at baseline with a fever of 100.5 or higher as measured via oral temperature will be advised to take acetaminophen for use in accordance with its labeling instructions. There is no prohibition on the use of analgesics for symptomatic treatment of pain. Any such use should be recorded on the concomitant medication form along with reason for use.

- Measure oxygen saturation via pulse oximeter
- Measure vital signs (HR, BP, RR, and oral temperature) and height and weight for determination of BMI.
- Perform full physical examination which will include assessments of the following organs and organ systems: skin, head, ears, eyes, nose, and throat (HEENT), neck, lungs, heart, liver, spleen, abdomen, extremities, lymph nodes (axillary and cervical), and nervous system.
- Obtain blood and urine for clinical screening laboratory evaluations:
  - Comprehensive Metabolic Panel (fasting or non-fasting)
  - CBC with differential
    - Absolute Neutrophil Count to Absolute Lymphocyte Count Ratio (N/L ratio) ≥4.5 may be a clinically significant risk factor for progression to severe COVID-19
    - Red cell distribution width (RDW) ≥15 may be a clinically significant risk factor for progression to severe COVID-19.
  - Urine pregnancy test (in women of childbearing potential)
  - Anti-SARS-CoV-2 Spike, IgG
- Review inclusion and exclusion criteria.

The overall eligibility of the subject to participate in the study will be assessed once all screening values are available. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team.

Subjects with COVID-19 disease diagnosed via a rapid antigen test with signs and symptoms reported ≥72 hours from onset are not eligible for enrollment.

Study subjects who qualify for inclusion will be immediately randomized for their day 1 visit.

If a physiologic parameter, e.g., vital signs, is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the participating clinical site PI or appropriate sub-investigator, the abnormality is the result of an acute, short-term, rapidly

reversible condition (e.g., stress, anxiety or "white coat syndrome") or other source of error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

A subject may be re-screened if a protocol eligibility criterion that is not met at the initial time of screening, will be met by rescreening of all assessments within the next 24 hours using the same subject number, provided their number of days since symptom onset remains ≤3 days.

No subjects may be screened more than twice due to a screening failure result as defined above.

Subjects will be provided the results of abnormal clinical laboratory test values or abnormal clinical findings necessitating follow-up with their primary care provider.

9.1.2 Procedures for Clinically Significant Laboratory Values or Findings

If in the judgement of the PI the finding poses a previously unknown risk to the subject or leads to a diagnosis of a disease or condition that would have disqualified the subject for enrollment, the subject will be withdrawn from the study immediately.

All clinically significant findings that occur post randomization and after the first use of the RD-X19 device will be considered TEAEs. Clinically significant lab findings based on Visit 1 lab draws are considered Medical History and not Adverse Events.

9.1.3 Bio-specimen Collection

At Baseline and on days 3, 5, 8, and 14, subjects will provide one saliva specimen and one nasopharyngeal swab for virology endpoint assessments. Biospecimens will be collected, preserved, and shipped to a central lab for assessment of SARS-CoV-2 mRNA via RT-qPCR as outlined in the EB-P20-01 Laboratory Manual. To minimize the potential impact of diurnal variation on saliva excretion rates, a subject with a morning baseline visit (before 12 pm), should target morning follow-up visits and subjects with an afternoon baseline visit (after 12 pm) should target afternoon follow-up visits. If a visit must switch from morning to afternoon or vice versa, the visit must occur within ± 1 hour of the noon timepoint, e.g, if the previous visit is at 8:00 am and the next visit is at 12:45 pm this would be acceptable; if the previous visit is at 11 am and the next visit is at 2:00 pm, then this would be considered a deviation.

Optionally, the sponsor may perform additional genetic sequencing on one or both baseline specimens (saliva or nasopharyngeal) to obtain prevalence of variants of interest (VOI) or variants of concern (VOC) in the study population. Specific variants to be identified include B.1.1.7 (UK), B.1.351 (South Africa), B.1.427 (CA), B.1.429 (CA), P.1 (Brazil), and B.1.617.2 (India), and any others that are classified as VOI or VOC during the study.

A second saliva sample (third biospecimen), will be collected at baseline and on days 8 and 14, and at Sponor's option shipped to a third party laboratory to evaluate the effects of RD-X19 on

the microbial flora of the oral microbiome. Change in α and β diversity in microbial flora from baseline will be analyzed by 16S rRNA subunit analysis from saliva samples.

9.2 Safety and Other Assessments

Study procedures are specified in protocol section 4.3 Schedule of Activities. A study clinician, licensed to make medical diagnoses as the participating clinical site PI or appropriate sub-investigator, will be responsible for all study-related medical decisions.

- Medical history:
  - A complete medical history will be obtained by interview of subjects at the screening visit. Subjects will be queried regarding a history of significant medical disorders of the head, ears, eyes, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited.
  - At all subsequent visits, an interim medical history will be obtained by interview of subjects and any changes since the previous clinic visit will be noted. The interim medical history should include an assessment for new medical conditions and symptoms suggestive of an AE.
- Physical examination:
  - A full physical examination will be performed at the screening visit and on days 8 and 14, and a symptom-directed (targeted) physical examination will be performed if indicated during other clinic visits
    - A full physical examination will include assessments of the following organs and organ systems: skin, HEENT, neck, lungs, heart, liver, spleen, abdomen, extremities, lymph nodes (axillary and cervical), and nervous system.
    - Height and weight will be measured, and BMI calculated, at the screening visit only.
  - A symptom-directed (targeted) physical examination will be performed if indicated during other scheduled clinical site visits.

- Targeted physical examinations will primarily focus on assessment of signs and symptoms suggestive of AEs and an examination of the oral cavity that demonstrates findings of thrush or other pathology that may indicate clinically-relevant changes to the oral microbiome. Interim or unscheduled physical examinations will be performed at the discretion of the participating clinical site PI or appropriate sub-investigator, if necessary, to evaluate AEs.

- Subjects will be observed in the clinic for at least 30 minutes post the first RD-X19 illumination. The oropharynx and surrounding tissues will be examined. Reactogenicity assessments will be performed on Day 1 in the clinic on days 3, 5, 8, and 14 by subjects' diary card entries. Interim or unscheduled targeted physical examinations will be performed, if necessary, to evaluate TEAEs.

- Vital signs:

  Vital sign measurements will include systolic and diastolic BP, HR, breaths per minute, oral temperature and oxygen saturation via a pulse co-oximeter. Vital signs will be measured at timepoints specified in protocol section 4.3. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking their oral temperature or using the RD-X19 device. All subjects will be issued thermometers and small pulse oximeters to measure oral temperature and O_2 saturation on a twice daily basis and record the results on their diary card.

- Clinical laboratory evaluations:

  - Fasting is not required before collection of clinical laboratory evaluations.
  - Urine pregnancy test will be performed locally by the site laboratory at the screening visit. Results must be confirmed as negative prior to randomization on Day 1 and allocation and use of the RD-X19 device.
  - Clinical laboratory evaluations CMP and CBC (diff) will be performed locally by the site selected laboratories.
    - Clinical safety laboratory evaluations will be performed locally by the site laboratory.

- Blood will be collected at timepoints specified in the protocol section 4.3.
- Methemoglobin will be measured as stipulated in the study procedures table using the Massimo® non-invasive pulse oximetry device.
- Anti-Spike IgG will be measured at screening/baseline and on Day 14.
- Absolute Neutrophil Count to Absolute Lymphocyte Count Ratio (N/L ratio) and Red cell distribution width (RDW) will both be recorded from the CBC panel.

- Diary Cards:
  - Subjects will be instructed to fill out diary cards twice daily to assess their symptoms associated with disease progression and record the number of treatments completed. Each of the eight symptoms will be rated on a 4-point scale from none (0) to severe (3). Temperature and oxygen saturation will also be measured and recorded via devices provided by site personnel and taken home by the subject. Subjects will also be asked if they experience any shortness of breath. Reminders will be sent to each subject twice daily via an appropriate communication platform (e.g. text messaging) and up to date diary cards should be presented at each clinical visit to be eligible for subject payments. Between visits on Days 2 and 4, to enhance safety monitoring and reinforce adherence to at-home study procedures, each subject will be contacted via phone and verbally go through diary procedures and document any AEs.

- Severe COVID-19 Clinical Outcomes
  - There is a small amount of risk that subjects with mild-to-moderate COVID-19 may have an unknown health problem or co-morbidity at the time of screening that can lead to rapid worsening of condition or hospitalization during study. Worsening of condition will be characterized by study subjects who experience COVID-19 progression defined by an increase of the composite COVID-19 severity score greater than baseline at any point in the study on or after day 3.

- Medically attended visits as a result of severe COVID-19 clinical outcomes will be aggregated into the following categories:

  1) those who require medical attention attributed to COVID-19;

  2) those who progress to severe disease with respiratory rate >30/minute and/or O2 saturation ≤93% on room air or FiO2 ≥300% with any respiratory distress;

  3) those who require hospitalization for severe COVID-19;

  4) those who require endotracheal ventilation or ECMO with or without the use of solumedrol; and

  5) those who die.

- Subjects with a primary care, urgent care, or emergency room visit that are not hospitalized as a result of their medical consultation, may continue treatment with the investigational device and should attend regularly scheduled follow up visits per protocol. Subjects that are admitted to the hospital should discontinue all treatment in lieu of standard of care for severe/critical COVID-19 illness.

9.2.1 Definition of Treatment Emergent Adverse Event (TEAE)

TEAE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An TEAE can therefore be any unfavorable and unintended sign (including an abnormal clinical laboratory finding), symptom or disease temporally associated with the use of medicinal (investigational) product.

COVID-19 is a progressive disease and any worsening or new signs and symptoms consistent with mild to moderate COVID-19 disease during the first 3 days will not be recorded as TEAEs. Worsening of disease will be recorded as a clinical outcome measure as outlined in Section 6.4. Any worsening of the eight individual COVID-19 signs and symptoms from baseline (moderate or greater) or new signs and symptoms that first occur on or after study day 4 (moderate or greater), as reported on participant self-assessment daily diary cards or during clinic visits, will be recorded as a TEAE with attribution to COVID-19 disease pathogenesis or the investigational device at the discretion of site investigators. Any COVID-19 related TEAEs will be assessed daily and considered resolved when the symptom is none (0) or mild (1) on the Diary Card.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an TEAE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an TEAE.

TEAEs can be further divided into solicited TEAEs and unsolicited TEAEs. Solicited TEAEs are those for which the study team will specifically query the subject whether they occurred. Unsolicited TEAEs are those events that the subject report occurring without being queried about the specific event.

All TEAEs will be assessed for severity and relationship to study intervention. Reporting of all TEAEs, solicited and unsolicited, will occur during the period from study device administration on Day 1 through Day 14 or until an early termination visit.

All TEAEs, solicited and unsolicited, will be captured on the appropriate source documents and e-CRFs. Information to be collected for TEAEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis as the participating clinical site PI or appropriate sub-investigator), date of resolution, seriousness, and outcome. All TEAEs will be documented regardless of relationship.

TEAEs will be followed to resolution or stabilization.

9.2.2 Solicited Treatment Emergent Adverse Events - Reactogenicity

Solicited TEAEs are anticipated TEAEs for which consistent collection of information is desired. Study clinicians will follow and collect resolution information for any reactogenicity symptoms that are not resolved during the active study period.

Solicited TEAEs (i.e., reactogenicity) will be collected by direct questioning of study subjects and recorded on the appropriate source document and e-CRF during the entire course of the study.

For this study, solicited AEs include:

- Illumination site Pain
- Illumination site Erythema
- Illumination site Edema/Induration
- Any other pain, redness, swelling or lesion of the oral mucosa

9.2.3 Unsolicited Treatment Emergent Adverse Events

All TEAEs spontaneously reported by the subject and/or in response to an open question from study staff or revealed by observation, physical examination or other diagnostic procedures must be recorded on the appropriate source document and e-CRF.

Unsolicited TEAEs of all severities will be reported during the entire course of the study.

9.2.4 Treatment Emergent Adverse Event Reporting

Information on all TEAEs should be recorded on the appropriate source document and e-CRF. All clearly related signs, symptoms and results of diagnostic procedures performed because of an TEAE should be grouped together and recorded as a single diagnosis. If the TEAE is a clinical laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis and be described in terms of duration (start and stop date).

9.2.5 Definition of a Serious Adverse Event (SAE)

An SAE is defined in 21 CFR 312.32 as follows: "An AE is considered serious if, in the view of either the participating clinical site PI or appropriate sub-investigator or the sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening AE,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Or a congenital anomaly/birth defect.

Important medical events that may not result in death, are not immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. An example of such a medical event would be an allergic bronchospasm requiring intensive treatment in an emergency room or at home to prevent the development of one of the definitions above.

"Life-threatening" refers to an TEAE that at occurrence represents an immediate risk of death to a subject. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered an SAE.

All SAEs, as with any TEAE, will be assessed for severity and relationship to study intervention. All SAEs will be recorded on the appropriate AE e-CRF.

All SAEs will be followed through resolution or stabilization by a study clinician, licensed to make medical diagnoses and listed as the participating clinical site PI or appropriate sub-investigator.

All SAEs will be reviewed and evaluated by the Sponsor and will be reported to the IRB. This report will include severity, association with the study device, action(s) taken, and outcome.

9.2.6 Serious Adverse Event Reporting

Any TEAE that meets a protocol-defined criterion as an SAE must be submitted immediately (within 24 hours of site awareness) on an SAE form to CRO/EmitBio Inc. Pharmacovigilance:

EmitBio Pharmacovigilance

SAE Hot Line: 1-843-540-3550 or 1-610-570-7425

Text Immediate Report: 1-843-540-3550

SAE Email: jmcneil@emitbio.com

In addition to the SAE form, all SAE data must be entered into the AE e-CRF.

Other supporting documentation of the event may be requested by EmitBio Pharmacovigilance and should be provided as soon as possible. The Sponsor Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the participating clinical site PI or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the participating clinical site PI or appropriate sub-investigator will report the event to the EmitBio Pharmacovigilance Group.

9.2.7 Regulatory Reporting of Device-related SAEs

Following notification from the participating clinical site PI or appropriate sub-investigator, EmitBio Inc., as the sponsor, will report to the FDA and will copy the clinical site investigators on all reports of potential serious risks from clinical studies of RD-X19, as soon as possible. EmitBio Inc. will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the event is not fatal or life-threatening, an SAE safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32.

Relevant follow-up information to the safety report will be submitted as soon as the information is available. Upon request from FDA, EmitBiowill submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

SAEs that are not considered related to RD-X19 will not be reported to the FDA.

9.2.8 Classification of a Treatment Emergent Adverse Event

The determination of seriousness, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose TEAE information, provide a medical evaluation of TEAEs and

classify TEAEs based upon medical judgment. This includes, but is not limited to, physicians, physician assistants and nurse practitioners.

9.2.9 Severity of Treatment Emergent Adverse Events

All TEAEs will be assessed for severity, according to the toxicity grading scales provided at **Appendix 2**.

For TEAEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.
- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living,causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

TEAEs characterized as intermittent require documentation of onset and duration of each episode. The TEAE is not counted as a separate or new TEAE if at the next clinic visit, the TEAE is persistent. It shall only be recorded as a new TEAE if the adverse event worsens in severity. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity. The start and stop date of each reported TEAE will be recorded on the appropriate e-CRF. All device-related grade 3 TEAEs will be reported to the medical monitor / Sponsor CMO within 48 hours of ascertainment. See SAE source document for information to be submitted.

9.2.10 Relationship to Study Intervention

For each reported adverse event, the participating clinical site PI or qualified designee must assess the relationship of the event to the study device using the following guidelines:

- Related – The TEAE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a close temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

9.2.11 Time Period and Frequency for Event Assessment and Follow-Up

For this study:

Solicited and Unsolicited TEAEs will be recorded by clinical trial staff for the entire duration of the study, beginning after device administration and through day 14 (±2 days) or an early termination visit.

9.2.12 Treatment Emergent Adverse Event Reporting to Study Subjects

All device-attributed

TEAEs and SAEs will be reported to participants in the study to better inform them of the potential risks vs. benefits of participation.

9.2.13 Pregnancy Reporting

All positive urine pregnancy tests will be reported during screening and at the end of the study. Women who screen positive for pregnancy will be encouraged to see their primary health care provider for a serological confirmatory test.

At any study visit, if there is reason to believe that a female subject of child-bearing potential may have become pregnant, a urine pregnancy test must be performed. If the result is positive, they will be followed per protocol for pregnancy and birth outcomes and referred to an appropriate obstetrician.

9.3 Efficacy Assessments

Various outcome assessments will explore the impact of each dose of RD-X19 treatment compared to sham on the sustained resolution of clinical signs and symptoms (in all subjects, and separately in all mild subjects), COVID-19 clinical outcomes, and the $\log_{10}$ reduction of SARS-CoV-2 viral load.

The primary efficacy outcomes are:

- Sustained resolution of COVID-19 signs and symptoms in all subjects (with Mild or Moderate disease at baseline)
- Sustained resolution of COVID-19 signs and symptoms in subjects with Mild disease at baseline

Subjects will be instructed to fill out a diary card or electronic equivalent to assess their signs and symptoms of disease twice daily. Each of the eight symptoms will be rated on a scale from none (0) to severe (3).

Success on sustained resolution will be recorded as at the time (in hours) when cough, sore throat, nasal congestion, headache, chills and or sweats, myalgia, fatigue, and nausea (with or without

vomiting) have been assessed by the subject as none (0) or mild (1) and all symptoms remain at or below 1 until study Day 14.

*Subjects reporting a persistent fever via oral temperature of 100.5 (36 hours or more) or SpO_2 levels <96% with shortness of breath fail to meet the success criterion on that day even if all other symptoms are reported as none (0) or mild (1).

Additional secondary efficacy outcomes include:

- Proportion of study subjects who achieve Day 8 Composite Resolution defined as both a negative SARS-CoV-2 antigen test within the window for Visit 4 (Days 7 – 9) and all symptoms assessed by the subject as none (0) or mild (1), absence of fever and SpO2 ≥96% without shortness of breath at study day 8 (as reported on the Diary Card Day 8-Assessment 1).
- Proportion of study subjects who experience worsening of COVID-19 disease as defined by an increase of the composite COVID-19 severity score greater than baseline at any point in the study on or after day 3.
- Proportion of study subjects who affirm they have returned to Pre-COVID Health at day 8 and day 14.
- Proportion of study subjects progressing to "severe" clinical outcomes associated with COVID-19.
- Mean change in nasopharyngeal SARS-CoV-2 viral load from baseline on days 3, 5, 8, and 14 by RT-qPCR
- Proportion of subjects demonstrating clearance of viral infection, defined as a negative nasopharyngeal swab via RT-qPCR on each of Days 3, 5, 8 and 14.

Exploratory outcome assessments will evaluate effects of RD-X19 on the microbial flora of the oral microbiome and on salivary viral load. Current in vitro and clinical evidence suggests that the proposed doses will have negligible impact on the viability of these commensal bacteria. Change in α and β diversity in microbial flora from baseline on day 8 and day 14 as analyzed by 16S rRNA subunit analysis from frozen saliva samples. The mean change in SARS-CoV-2 viral load as measured in saliva will be assessed on days 3, 5, 8, and 14 by RT-qPCR.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

The study has two primary endpoints: (i) Sustained resolution of COVID-19 signs and symptoms in all subjects (with Mild or Moderate disease at baseline); and (ii) Sustained resolution of COVID-19 signs and symptoms in subjects with Mild disease at baseline. The only hypothesis testing in

this study will be carried out for these two endpoints for which the single dose of the RD-X19 device will be compared with Sham based on the Final Cohort.

10.2 Power and Sample Size:

The target number of subjects to be randomized initially is 60 individuals seronegative for SARS-CoV-2 Spike IgG antibodies (20 subjects to each of two RD-X19 treatment arms and 20 subjects for Sham control). At the sponsors option, the total number of subjects can be increased to enroll up to 150 additional subjects to include all serostatuses based on adequate safety/tolerability observed in the final dose cohort. As described in Section 4.1.2 the RD-X19 dose to be used for the final cohort is determined based only on blinded data from Cohorts A and B.

Based on findings in the EB-P12-01 and the hazard ratio observed for the median time to sustained symptom resolution in the proof of concept trial, the option to increase the sample size with an anticipated roughly equal number of antibody positive to negative individuals in the final cohort has at least 90% power in the modified full analysis set (mFAS) population with the ability to detect meaningful changes in SARS-CoV-2 symptom resolution from baseline (Hazard ratio of 0.4 between active RD-X19 and Sham observed in EB-P12-01).

10.3 Populations for Analyses

Three subject populations are defined for this study.

- The Safety/Full Analysis Set (FAS) includes all randomized study subjects who received at least one study treatment. This population will be used for all safety analyses, and is also the primary analysis population for efficacy. Subjects will be analyzed based on actual treatment received.
- The Modified Full Analysis Set (mFAS) includes all randomized subjects who received treatment and who tested negative for SARS-CoV-2 antibodies at baseline. Subjects will be analyzed based on actual treatment received.
- The Per Protocol (PP) Population includes all randomized subjects in the FAS population who complete the study and did not have a major protocol deviation (MPD). The PP population will be used as supportive analysis. MPDs are those that could have interfered with the administration of treatment or the precise evaluation of treatment efficacy (e.g., violation of inclusion/exclusion criteria). Subjects who do not complete certain key scheduled doses, 100% (6 out of 6) of doses in the first 3 days or at least 75% (11 out of 14), regardless of the time of enrollment on Day 1, are major protocol deviations. All MPDs will be listed in the statistical analysis plan and identified before the database lock and study unblinding for analysis.

10.4 Statistical Analyses

For continuous variables, descriptive summaries will display number of subjects, arithmetic mean, geometric mean (as appropriate), standard deviation, median, minimum, and maximum by treatment group. For categorical variables, counts and percentages will be displayed.

Time to event analyses will use the log-rank test, a Cox Proportional Hazards Regression model, and Kaplan-Meier methods.

In general, missing data will not be imputed with the exception that for the missing viral load results post baseline will be imputed using multiple imputation.

Additional details regarding statistical methods will be provided in the Statistical Analysis Plan.

10.4.1 Efficacy Analyses

The primary analysis for each of the two primary endpoints will be via an unstratified log-rank test based on the Final Cohort in the FAS population. This analysiswill be supplemented with a graphical display and medians derived by the Kaplan Meier method. Cox proportional hazards regression models (with a single term for treatment) will be employed to analyze the primary efficacy endpoints to provide a hazard ratio in each case for the RD-X19 treatment arm relative to the sham arm.

In addition, to assess potential impact of subject baseline characteristics to the treatment effect estimation the Cox proportional hazards regression will be performed adjusting for the following set of covariates:

- the COVID-19 Composite Severity Score at baseline defined as the sum of the eight individual COVID-19 signs and symptoms severity scores divided by eight (grouping of <1.25, ≥ 1.25)
- baseline disease status of mild vs. moderate disease (subjects meeting entry criteria are considered to be mild unless the physical/vital signs examination documents clinical signs suggestive of moderate illness)
- gender
- age (grouping of <50, ≥ 50)
- baseline antibody status (positive, negative)

For the second primary endpoint the term for baseline disease status of mild vs. moderate disease will not be included.

Supportive analyses in each case for the two primary endpoints will be produced for the mFAS and the Per Protocol population. For the mFAS population the Cox proportional hazards regression model will not include the covariate related to baseline antibody status.

Analysis of the primary endpoints will also be produced for pooled RD-X19 doses vs. pooled Sham and for RD-X19 low dose (i.e., the dose not expanded to produce the Final Cohort), but where in all cases these p-values will be viewed as descriptive only.All secondary and exploratory efficacy endpoints will be summarized using descriptive statistics by visit (as appropriate) for each treatment group. For $\log_{10}$-transformed viral load data, geometric means will be computed by exponentiating (base 10) the group means of the $\log_{10}$-transformed viral load.

Additional details are provided for analysis of each outcome assessment in the Statistical Analysis Plan. Additional details including on multiplicity adjustment for the two primary endpoints will be provided in the Statistical Analysis Plan.

10.4.2 Safety Analyses

Summaries will be presented by treatment arm on the Safety Population. Adverse device effects will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent Adverse Events (TEAE), vital signs, and methemoglobin will be summarized using descriptive statistics. Other safety data including prior and concomitant medications will be listed.

TEAEs are any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity following exposure to the treatments. Number and percent of subjects reporting TEAEs will be tabulated by treatment group. Summaries will be presented by system organ class and preferred term, and further by severity and relationship to study treatment. In the summaries of incidence rates (frequencies and percentages), severity and relationship to treatment, subjects who report more than one event that are mapped to the same preferred term will be counted only once under the strongest severity and relationship, accordingly.

11 OPERATIONAL CONSIDERATIONS AND SUPPORTING DOCUMENTS

11.1 Ethical Considerations

This study will be conducted in conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; April 18, 1979), and the federal policy for the Protection of Human Subjects codified in 45 CFR Part 46, 21 CFR Part 50 (Protection of Human Subjects), and the ICH E6(R2).

An OHRP-registered IRB will review and approve this protocol, associated informed consent documents, recruitment material, and handouts or surveys intended for the subjects, prior to the recruitment, screening, and enrollment of subjects. The IRB review shall be in accordance with

45 CFR 46 and 21 CFR 50, 21 CFR 56 (IRBs), 21 CFR 812 and other federal, state, and local regulations and policies, as applicable.

Any amendments to the protocol or informed consent documents will be approved by the IRB before they are implemented. The participating clinical site PI will notify the Sponsor of deviations from the protocol and reportable SAEs, and, as applicable, to the IRB.

EmitBio Inc must receive the documentation that verifies IRB approval for this protocol, informed consent documents, and associated documents prior to the recruitment, screening, and enrollment of subjects and the provision of adequate numbers of RD-X19 devices to conduct the protocol.

11.1.1 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Investigators or designated research staff will obtain a subject's informed consent in accordance with the requirements of 45 CFR 46, 21 CFR 50 and 21 CFR 56, state and local regulations and policy, and ICH E6 GCP before any study procedures or data collection are performed. The participating clinical site PI or other study staff may obtain oral or written information for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject if the process is approved by the IRB.

At the screening or first study visit, informed consent will be obtained and documented before any study procedures are performed. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The key information about the purpose of the study, the procedures and experimental aspects of the study, study device, potential risks, benefits and discomforts, the expected duration of the subject's participation in the trial, and alternative treatments and procedures that may be available to the subject. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

Subjects will receive an explanation that they will be compensated for their participation on a per visit basis, and medical treatments are available if device-related injury occurs, and, if so, what that treatment is, or where further information may be obtained. Subjects will be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They will be informed of whom to contact (e.g., the participating clinical site PI and the Sponsor) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. The subjects will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Subjects will be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If

the results of the trial are published, the subject's identity will remain confidential. Subjects will be informed, even if identifiers are removed, that information collected from this research and/or specimens may be used for secondary research, including the sharing of deidentified data.

Subjects will be informed that the monitor(s), auditors(s), IRB, and Sponsor will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written ICF, the subject is authorizing such access.

ICFs will be IRB-approved, and subjects will be asked to read and review the consent form. Subjects must sign the ICF prior to starting any study procedures being done specifically for this trial. Once signed, a copy of the ICF will be given to the subject for their records.

New information will be communicated by the participating clinical site PI to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and subjects will be re-consented per IRB requirements, if necessary.

11.1.2 Confidentiality and Privacy

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to subjects, test results of biological specimens and all other information generated during participation in the study. No identifiable information concerning subjects in the study will be released to any unauthorized third party. Subject confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the sponsor and representatives of the IRB may inspect all documents and records required to be maintained by the participating clinical site PI, including, but not limited to, screening, medical and laboratory results for the subjects in this study. The participating clinical site will permit access to such records.

All source records, including electronic data, will be stored in secured systems in accordance with institutional policies and federal regulations.

All study data and research specimens that leave the site (including any electronic transmission of data) will be identified only by a coded number that is linked to a subject through a code key maintained at the clinical site. Names or readily identifying information will not be released unless strictly required by law.

11.1.3 Clinical Monitoring

Monitoring will be conducted during the conduct of the trial, and will include, but is not limited to, source document verification, review of regulatory files, device accountability records, e-CRFs, ICFs, medical and laboratory reports, training records, and protocol and GCP compliance. The monitors will have access to all study related documents and will meet with appropriate

clinical site staff to discuss any problems and outstanding issues. Visit findings and discussions will be documented. Some monitoring visits may be conducted remotely.

11.1.4 Quality System

To ensure the reliability of study data, the clinical sites must maintain an appropriate quality system for the purposes of measuring, documenting and reporting study conduct, protocol adherence, human subjects' protections, and reliability of the protocol-driven data collected independent of sponsor site monitoring.

11.1.5 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the participating clinical trial site under the supervision of the participating clinical site PI and the overall study PI. The participating clinical trial site PI must maintain complete and accurate source documentation. Clinical research data from source documentation, including, but not limited to, diary cards, TEAEs/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory data, will be entered by the participating clinical site into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by the Sponsor's delegated data coordinating and analysis clinical support organization. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. TEAEs and concomitant medications will be coded according to the most current versions of MedDRA and WhoDrug, respectively. The data coordinating and analysis CRO will be responsible for data management, quality review, analysis, and reporting of the study data for this study. The study sponsor is responsible for review of data collection tools and processes, and review of data and reports.

TEAEs will be coded according to the MedDRA dictionary version 23.0 or higher.

11.1.6 Source Documents

Source documents contain all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Each participating clinical site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. Data recorded in the e-CRF derived from source documents should be consistent with the data recorded on the source documents.

Interview of subjects is sufficient for obtaining medical history. Solicitation of medical records from the subject's primary care provider is not required.

At the end of the study, a copy of all datasets, including annotated CRFs and data dictionary, will be provided to EmitBio Inc.

11.1.7 Study Record Retention

Study-related records, including the regulatory file, study device accountability records, consent forms, subject source documents and electronic records, should be maintained for a period of 2 years following the date a marketing application is approved for the investigational device for the indication for which it is being investigated; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the Sponsor is notified. These documents should be retained for a longer period, however, if required by local policies or regulations. No records will be destroyed without the written consent of EmitBio.

11.1.8 Protocol Deviations

A protocol deviation is any non-compliance with the clinical trial protocol, any process that is noted in the protocol and refers to details in the protocol or GCP requirements, or any critical study procedures with specific instructions in ancillary documents referenced in the protocol.

The non-compliance may be either on the part of the subject, the participating clinical site PI, or the study site staff. Following a deviation(s), corrective actions should be developed by the site and implemented promptly. All individual protocol deviations will be addressed in study volunteer study records.

It is the responsibility of the participating clinical site PI and study staff to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations will be kept in a log and must be promptly reported to EmitBio Inc. Protocol deviations must be sent to the IRB in accordance with the IRB reporting guidelines. The participating clinical site PI and study staff are responsible for knowing and adhering to the IRB requirements. Document protocol deviations and violations will be recorded on the case report form, as well as in the subject's chart if the deviation is subject specific.

11.1.9 Publication and Data Sharing Policy

All study data and reports of study data are the property of the study sponsor. The sponsor may grant the PI the right to publish the results of this research in a scientific journal, conditional upon the review and concurrence of the sponsor.

11.1.10 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. EmitBio Inc requires that all study team members disclose any conflict of interest.

Clinical Study sites are required to maintain a mechanism for the management of all reported dualities of interest.

11.1.11 Research Related Injuries

For any potential research related injury, the participating clinical site PI or designee will assess the subject. Study staff will try to reduce, control and treat any complications from this trial. Immediate medical treatment may be provided by the participating clinical site, such as giving emergency medications to stop immediate allergic reactions. As needed, referrals to appropriate health care facilities will be provided to the subject. The participating clinical site PI should then determine if an injury occurred as a direct result of procedures or the device used in this trial.

If it is determined by the participating clinical site PI that an injury occurred to a subject as a direct result of the procedures or device used in this trial, then referrals to appropriate health care facilities will be provided to the subject. No financial compensation will be provided to the subject by EmitBio Inc. or the participating clinical site for any injury suffered due to participation in clinical research.

12 APPENDICES

12.1.1 **RD-X19 Investigational Device Manual**

12.1.2 **Toxicity Grading Scale**