CLINICAL TRIAL PROTOCOL

A Randomized, Double-Blind, Sham Controlled, Stratified, Pivotal Efficacy and Safety Study of the EmitBio RD-X19 Treatment Device in Individuals 40 Years of Age and Older with Mild COVID-19 in the At-Home Setting

Protocol Number: EB-P30-01 Version 3.1

Investigational Device: EmitBio RD-X19

Specific Indication: Treatment of Mild COVID-19 in Individuals ≥40 years of age

Target Respiratory Disease Pathogen and Disease: SARS-CoV-2, mild COVID-19

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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.

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1.0 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

2.0 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:

Name: _____

Signed: _____ Date: _____

Site Name and Address:

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3.0 TABLE OF CONTENTS

Contents

4.0 PROTOCOL INTRODUCTION

4.1 Background

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], and a higher number of health risk factors is associated with higher viral load. Many of the tissues and glands in the oral cavity have been documented to have high levels of ACE-2 and TMPRSS2 expression, highlighting the importance of the oral cavity in understanding both disease progression and oral-lung transmission via aspiration [2,3].

There are currently no FDA authorized or approved therapies that directly target early (i.e., within 3 days of symptom appearance) mild COVID-19 in the absence of risk factors for progression to severe disease, nor are there treatments directed locally to SARS-CoV-2 that is resident in the upper respiratory tract or oral cavity. Systemically administered antivirals, antibody therapies and convalescent plasma have shown clinical evidence of nasopharyngeal viral load reductions and improved clinical outcomes in non-hospitalized populations [4–6]. However, subsequent Emergency Use Authorizations have restricted these therapies only to individuals at increased risk for severe disease and hospitalization. All immune-based therapies require intravenous administration. The diversity of genetic variants of concern is increasing and new variants have demonstrated enhanced transmissibility and resistance to existing antibody therapies and immunological circumvention of current vaccines [7–9]. Rapidly occurring genetic mutations in SARS-CoV-2, especially in the crucial spike protein ligand to the ACE-2 receptor, are giving rise to a plethora of new viral phenotypes, some of which are highly transmissible and show patterns of increased virulence. Regulatory authorization of potent antivirals such as nirmatrelvir/ritonavir (Paxlovid) and, to a lesser extent, molnupiravir have been a welcome addition to the treatment of individuals with COVID-19 in the outpatient setting. However, these therapies are only indicated for use in individuals with risk factors for progression to more severe forms of disease and there is a growing awareness, and likely prevalence, of COVID-19 symptoms and SARS-CoV-2 rebound associated with the use of these antivirals [10,11]. 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 technology utilized by the RD-X19 device (dosing oral tissues with 425 nm light) has been repeatedly demonstrated to provide high-level viral inactivation of SARS-CoV-2 in multiple, consistent, expert-laboratory *in vitro* studies. There are multiple mechanisms of action by which 425 nm light doses reduce SARS-CoV-2 viral load, including (1) direct cell-free inactivation of virus

and (2) inhibiting replication of cell-associated SARS-CoV-2 by enhancing the innate immune response. Unlike the adaptive immunity induced or provided by vaccines or monoclonal antibodies, 425 nm light dosing is not antigen-specific, antigen-directed, or antigen-dependent. RD-X19 has resulted in the inactivation of all SARS-CoV-2 variants of concern tested to date, including Delta and Omicron. This technology presents an unprecedented opportunity for mitigating the threat posed by current SARS-CoV-2 variants aswell as novel pre-emergent coronavirus strains.

EmitBio's first-in-man (FIM) (NCT04557826) study evaluated the acute safety and tolerability of the RD-X19 device in 25 healthy volunteers. There were no unscheduled clinic visits or adverse events requiring unscheduled medical evaluation or medical care during the study. No Serious Adverse Events (SAEs) were observed during the study. No Treatment Emergent Adverse Events (TEAEs) based on laboratory findings were observed during the study. No significant elevations in methemoglobin over baseline levels were observed during the study period. Solicited reactogenicity and TEAEs for this study included illumination site pain, erythema, edema/induration, headache, difficulty swallowing, nausea, fever, and chills and/or sweats. No TEAEs required medical intervention or alteration to the study subject's participation in the trial. No study subject withdrew from the trial because of a TEAE. All TEAEs were of short duration, with resolution typically reached the same day or within 24 hours. In summary, the trial demonstrated no evidence of risk when the EmitBio RD-X19 (delivering a nominal dose of 9 J/cm^2 twice daily (BID) for 14 days) was used as intended in an at-home environment.

Following the FIM study, EmitBio conducted an early feasibility randomized, sham-controlled, double-blind safety, tolerability and bioeffect study evaluating the RD-X19 device vs. Sham control (EB-P12-01 – *Phase I/II Randomized, Dose Escalation Study to Evaluate the Safety and Antiviral Activity of the RD-X19 Device in SARS-CoV-2 Infected Individuals with Uncomplicated COVID-19 (*NCT04662671) [12]). In summary, a total of 31 study subjects were randomized 2:1 into RD-X19 treatment vs. Sham control groups in this randomized controlled trial (RCT). 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 Adverse Events (AEs)) with initial symptom onset 72 hours or less 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 the mean $\log_{10}$ salivary viral load from baseline through study day 8 via RT-qPCR and time to sustained resolution 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 resolution was achieved.

The EmitBio RD-X19 was safe, reduced 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 the completion of treatment. In our study, the median time to sustained COVID-19 symptom resolution was achieved 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.

Building on the positive results from previous trials, EmitBio conducted a larger randomized, sham-controlled, dose-finding study of the RD-X19 device in subjects with mild to moderate COVID-19 (NCT04966013). Previous preclinical work in human tissue models showed that dosing with 32 J/cm^2 of 425 nm light twice daily for three days reduced Beta and Delta virus titers by up to 99.99% and induced no cytotoxicity in time-matched, uninfected well-differentiated human large airway epithelial cell cultures. Accordingly, the EB-P20-01 trial aimed to demonstrate the feasibility of ascending 24 J/cm^2 and 32 J/cm^2 BID dose cohorts. In total, 241 potential subjects were assessed for inclusion eligibility and 216 were enrolled from 9 clinical study sites in the United States. This trial included subjects who were infected with SARS-CoV-2 for the first time, previously infected, and/or with breakthrough infections who were previously vaccinated. In addition to assessing the treatment benefit in subjects with both mild and moderate COVID-19, genetic sequencing confirms this trial enrolled subjects infected with Delta and Omicron variants. During the course of the study, no predefined safety signals as outlined in the study pausing or stopping criteria were observed. Treatment of Cohort B with 32 J/cm^2 twice daily dosing was considered safe and well tolerated.

Under 21 CFR 812.3(m), the RD-X19 does not meet any of the below criteria that define a Significant Risk (SR) device:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; - *The RD-X19 is neither intended as an implant nor does it present a potential for serious risk to health, safety, or welfare of a subject.*
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; - *The RD-X19 does not present a potential for serious risk to health, safety, or welfare of a subject.*
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; - *The RD-X19 does not present a potential for serious risk to health, safety, or welfare of a subject.*
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. - *The RD-X19 does not present a potential for serious risk to health, safety, or welfare of a subject.*

In addition to the above, the risks identified, mitigation measures and control strategies in combination with a review of all available nonclinical and clinical safety information have confirmed the company's conclusion that the RD-X19 operating at the proposed dose levels is a Nonsignificant Risk (NSR) device.

Through three clinical trials, institutional review boards have agreed with EmitBio's characterization of RD-X19 as an NSR device. The safety data from those trials has thus far further demonstrated the very low-risk nature of the device.

EmitBio therefore intends to continue the experimental investigation and development of RD-X19 as a NSR device and will not apply for an Investigational Device Exemption prior to this proposed study.

The Mechanisms of Action (MOA) of RD-X19 are through both direct and indirect antiviral effects. RD-X19 reduces cell-free SARS-CoV-2 titer by as much as 99.99% and inhibits cell-associated viral titer by 99.9% when measured at 24 hours after a single treatment *in vitro*. One of the putative antiviral mechanism involves upregulation of reactive oxygen species (ROS) and nitric oxide (NO) in epithelial cells. NO production occurs via both a 425 nm light-induced increase in 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 also 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 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.

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. Preliminary results indicate that 425 nm light simultaneously acts on the SARS-CoV-2 spike, nucleocapsid, and RNA. Thus, 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 aswell as novel pre-emergent coronavirus strains. 425 nm light has inactivated all SARS-CoV-2 variants tested to date, including WA1, Alpha, Beta, Gamma, Delta, and Omicron (B.1.1.529 and BA.2), the Lambda variant, and early variant strains from California and New York [13].

Currently, the predominant circulating strains – Omicron subvariants BA.4 and BA.5 – are highly communicable and are responsible for substantial morbidity and mortality, especially among individuals with risk factors for progression to severe COVID-19. What has not been well-characterized is the effect of COVID-19 risk factors on disease pathogenesis and outcomes among individuals who have upper airway COVID-19 at presentation to the health care system, or who never present to the health care system because they manage their COVID-19 at home. Multiple published

sources of evidence are unequivocal in their finding that age is a critical risk factor for disease progression, the development of long COVID and the occurrence of post-COVID sequelae such as chronic pulmonary disease, including interstitial pulmonary fibrosis. EmitBio desires to initially target the use of RD-X19 to those who will most benefit from its use.

As shown in Table 1. below and as reported previously by others [14–17], among individuals meeting the FDA/NIH definition of mild COVID-19, age is a strong prognostic factor for time to COVID-19 symptom resolution, with subjects 40 years or older having substantially increased times to sustained symptom resolution.

Table 1. Age is a prognostic factor for time to COVID-19 symptom resolution in sham treated subjects with mild COVID-19.

Age category	Sham median time to sustained symptom resolution (hours)
18-29	89.9
30-39	85.4
40-49	170.3
50-65	241.2

In view of the above findings, in this pivotal trial we plan to enroll subjects with mild COVID-19 who are age 40 or older, as described in detail below.

4.2 Study Goals

This is a randomized, double-blind, sham controlled, stratified, pivotal efficacy and safety study of the EmitBio RD-X19 device in individuals age 40 and older with mild COVID-19 (as defined by NIH and FDA) in the at-home setting. Study subjects will self-administer treatment twice daily, 5 minutes per treatment for 7 consecutive days. Subjects will remain on study for a total of 14 study days (± 2 days) for treatment and follow-up. Neither study subject nor clinical trial personnel will be aware of the subject's treatment assignment. Clinical safety and efficacy outcomes will be assessed by, (a) self-assessed signs and symptoms (e-diary entries twice a day during the entire study period), (b) televisits for all at home study treatments, (c) remote study staff checks on days 8-14 and, (d) clinic visits on study days 1, 5, 8, and 14 for objective clinical assessments (vital signs, targeted physical exams, oropharyngeal exams).

The primary goal of the study is to evaluate the safety and efficacy of the RD-X19 treatment device to provide sufficient evidence to FDA to justify the authorization and/or approval of the device for treatment of subjects with mild COVID-19, age 40 and older in the home setting. Every attempt will be made to continute to follow safety in any study subject choosing to terminate the study early and all study subjects who progress to moderate or more severe forms of COVID-19 will be immediately referred for appropriate medical care. Medically necessary care of study participants will always take precedence over research.

4.3 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 more than 72 hours from onset will be given instructions to see their primary care provider, urgent care or emergency treatment in accordance with current standards of medical practice.

This pivotal efficacy and safety registration trial will initially randomize 326 volunteers total at a 1:1 ratio into RD-X19 treatment and sham treatment groups. Sample size calculations are described more fully in Section 9.2, Power and Sample Size. The study population and inclusion/exclusion criteria are defined fully in Section 4.4, Study Population, and Inclusion/Exclusion Criteria, 4.6 respectively. Briefly, enrollment requires subjects to be age 40 or older on the date of enrollment, have a positive COVID-19 test with time since symptom onset of 72 hours or less, and to meet the definition of mild COVID-19 described in Section 4.4, Study Population. Subjects will be stratified by age **(**age categories 40-49 and ≥50) and baseline disease severity score (< 1.25, ≥ 1.25). The baseline disease severity score is defined as the sum of the eight individual scores divided by eight.

The primary endpoint will be time to sustained resolution of COVID-19 signs and symptoms without subsequent symptom recurrence or disease progression until the end of the study. Resolution of COVID-19 signs and symptoms is defined as the earliest time 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 absent (0) or mild (1) and temperature is less than 100.5 °F. Sustained resolution of COVID-19 signs and symptoms is achieved when all signs and symptoms remain at this level for five consecutive assessments (corresponding to an approximate 48-hour period). After sustained resolution is achieved, symptom recurrence is defined as having three or more consecutive assessments (corresponding to an approximately 24-hour period) where two or more of the nine signs and symptoms do not meet the resolution condition. “Disease progression” is defined as having evidence of involvement of the lower respiratory tract: shortness of breath (defined as respiratory rate of 20 or more breaths per minute) and SpO_2 <96% (both ascertained from the average of three replicate assessments) and/or respiratory distress requiring pulmonary imaging that demonstrates COVID-19 pneumonia.

The key secondary virological endpoint will be the time to the first of two consecutive negative SARS-CoV-2 antigen tests (with a minimum time between tests of 6 hours) without subsequent virological rebound, during the subjects' remaining time on study. Virological rebound (after having achieved two such consecutive negative tests) is defined as having two or more positive tests out of three consecutive assessments (corresponding to an approximately 24-hour period).

Safety and tolerability (local reactogenicity) will be assessed as numbers and proportions of documented Treatment Emergent Adverse Events (TEAEs). Adverse Events (AEs) are any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, whether or not related to the investigational medical device and whether anticipated or unanticipated. TEAEs are adverse events (AEs) that either start after initial

treatment, or which are present prior to treatment initiation but which increase in severity after treatment. No AEs that are not TEAEs are expected in this study since the time between enrollmen t and first treatment is very brief. TEAEs will be determined by self-assessment and reported to decentralized team members during televisits. These unsolicited TEAEs will be reported by the decentralized team members to the clinical site staff. TEAEs will also be captured objectively by clinic staff during physical and oropharyngeal examinations on study days 5, 8 and 14, or during early termination. Volunteers will be instructed to contact designated clinical trial staff for TEAEs of a medically-urgent nature as soon as is practically possible and to seek immediate medical care, if needed. Study subjects who experience progression of disease to moderate severity will be instructed to seek care from their primary care provider or an urgent care center and will be advised to request a pulmonary imaging study (preferrably CT) as part of their healthcare evaluation to document the presence and extent, or absence, of COVID-19 pneumonia. Study subjects who progress to severe disease will be instructed to seek urgent medical care at their nearest Emergency Department. All study subjects who require a medically-attended visit will be asked to provide the results of their evaluations to study staff to assess whether COVID-19 progression has occurred. Study subjects who are hospitalized will be tracked to assess the date and time of hospital admission to discharge or death and these events will be captured as part of the trial data.

Previous clinical trials of RD-X19 have demonstrated very infrequent, transient and mild device-related TEAEs. In the unexpected event that device-related SAEs or patterns of device-related TEAEs are observed, the Sponsor's Medical Monitor/Chief Medical Officer will immediately consult with and refer these data to the Independent Medical Monitor for review and recommendations.

Assessments of safety and clinical outcomes will occur as outlined in Section 4.7, Study Schedule of Activities, below. A clinic-based visit will occur at baseline (Day 1) with subsequent clinic visits on study days 5 (±1), 8 (±1) and 14 (±2). Televisits will occur on days 1-7. Direct observation of each treatment will occur either during the clinic or televisit, depending on the study day. Subjects should plan to bring devices and supplies with them to the clinic.

Subject safety will be monitored throughout the study by the Site Investigators, supported by regular review by the Sponsor's Medical Monitor/Chief Medical Officer (CMO) with pre-specified pausing and stopping criteria (see Section 7.5, Device Discontinuation).

As described in Section 9.4.3, Interim Analysis, a blinded sample size review will be carried out by an independent statistician based on the first 164 randomized subjects. Briefly, if the pooled proportion of subjects with an event for the primary endpoint is less than assumed, then to maintain the power of the study the total number of randomized subjects will be increased; subject to a cap of 380 subjects.

4.4 Study Population

The study population is subjects age 40 and older with a positive COVID-19 test who meet the definition of mild COVID-19 below and have time since symptom onset of 72 hours or less.

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, nasal congestion (including rinorrhea), headache, muscle or joint pain, fatigue, unexplained chills and/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 dyspnea, abnormal chest imaging, or any other clinical signs indicative of Moderate or Severe COVID-19, *AND*
- Have a mean respiratory rate of <20 breaths/minute and mean heart rate of <90 beats/minute

Moderate COVID-19

- Positive testing by an FDA-authorized SARS-CoV-2 diagnostic test, *AND*
    - The symptoms of mild *WITH:*
    - Clinical signs suggestive of lower airway involvement such as resting respiratory rate ≥20 but <30 breaths per minute, imaging indicating lower respiratory disease involving <50% of the lung tissue, or clinical signs suggestive of moderate illness with COVID-19 such as heart rate ≥ 90 but < 125 beats per minute, and 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*
    - The symptoms of moderate illness *WITH:*
    - Clinical signs indicative of severe systemic illness, such as resting respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, lung infiltrates involving > 50% of the lung tissue, or SpO2 <94% on room air at sea level.

4.4.1. Symptom Severity Grading

Guidance to study subjects for severity grading of COVID-19 signs and symptoms will be based on definitions used for severity grading TEAEs and a severity scoring card will be provided to study subjects at their screening and enrollment visit:

- 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.
- Fever will be severity scored as dichotomous: $\geq 100.5^0$F (fever) vs $<100.5^0$F (afebrile)

4.5 Objectives and Endpoints

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Safety Assessments	
• Device-related 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 local site reactions.	• Collection of all TEAEs reported from study subjects' daily diary entries 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. TEAEs will be presented in tables, and listings.
Primary Outcome Assessment	
• Sustained resolution of COVID-19 signs and symptoms.	• Time to sustained resolution of COVID-19 signs and symptoms without subsequent symptom recurrence or disease progression until the end of the study (as described in Section 4.3, Study Design).
Secondary Outcome Assessment	
• Time to first of two consecutive negative antigen tests	• **[Key]** Time to the first of two consecutive negative SARS-CoV-2 antigen tests without subsequent virological rebound.

4.6 Inclusion and Exclusion Criteria

4.6.1 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 the screening/baseline visit.
2. Negative for Influenza A and B antigen using an FDA-authorized rapid diagnostic test.
3. At least two moderate or greater COVID-19 signs and symptoms from the following list: cough, sore throat, nasal congestion, headache, chills and/or sweats, myalgia, fatigue, nausea (with or without vomiting) or one moderate or greater symptom and fever (temperature ≥ 100.5° F).
4. Time from appearance of first COVID-19 sign or symptom to screening must be 72 hours or less.
5. Males or females, including pregnant and fecund females, 40 years of age and older on the date of enrollment.
6. BMI <40.
7. Provides written informed consent prior to initiation of any study procedures.
8. Be able to understand and agrees to fully comply with defined and described study procedures and be available for all study visits for the entire study duration.
9. Agrees to collection of a nasopharyngeal swab for qPCR at baseline for the purposes of assessing viral burden as a potential covariate in data analyses and for genetic sequencing to characterize the predominant SARS-CoV-2 variants present in the study population.
10. Agrees to perform self-diagnostic home testing twice a day, separated by ≥ 6 hours for the entire length of the study.
11. Agrees to restrict medications used for symptomatic relief of signs and symptoms of COVID-19 during the study period, and, if used, to report ALL such medications (including home remedies) to the study staff.
12. Agrees to avoid the use of oral rinses and toothpastes containing alcohol-based compounds (e.g. Eucalyptol, Menthol, Thymol, Phenol) and/or Salicylates during the study period. Oral rinses, breath fresheners and toothpaste not containing these compounds are allowed.
13. Agrees to avoid nasal and sinus saline lavage during the study period.
14. No uncontrolled disease process (chronic or acute), other than COVID-19 signs and symptoms (See section 8.1.1 – General Screening)*.
15. 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.

4.6.2 Exclusion Criteria

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

1. Positive for Influenza A and B antigen using an FDA-authorized rapid diagnostic test.
2. Individuals < age 40 on study day 1.
3. Individuals who are symptomatic for COVID-19 for more than 72 hours on study day 1.
4. COVID-19 signs associated with moderate or greater disease with evidence of lower respiratory involvement including shortness of breath (SOB) at rest or as determined by an exertional SOB protocol, SpO2 ≤94, respiratory rate ≥20 breaths per minute, heart rate ≥90 beats per minute, or abnormal pulmonary imaging.
5. Any medical disease or condition that, in the opinion of the site Principal Investigator (PI) or appropriate sub-investigator, precludes study participation.
6. History of use of a rescue inhaler for uncontrolled asthma within one month of study day 1.
7. History of recurrent alcohol intoxication or other recreational drug use (excluding medically prescribed cannabis) within one month of study day 1.
8. History of use, within one month of study day 1, of any FDA-authorized treatment for COVID-19. Use of non-approved putative therapies for COVID-19 (hyroxycholorquine, ivermectin, azithromycin) must be discontinued prior to enrollment in the study.
9. History of any systemic antiviral therapies within one month of study day 1.
10. History of oral or parenteral corticosteroid use within one month of study day 1. Active use of nasal or inhalable steroids is also exclusionary. Topical steroids are not exclusionary.
11. History of any chronic medical condition that has required adjustments to the type, dose or schedule of medical treatments within one month of study day 1.
12. Requirement to use narcotic medication for analgesia.
13. History of vasomotor rhinitis with or without post-nasal drip within one month of study day 1.
14. History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticaria, angioedema, other significant reaction) to sun exposure.
15. Presence of any oral abnormality (e.g., including, but not limited to, ulcer, oral candidiasis, oral mucositis, symptomatic gingivitis, history of frequent recurrent aphthous ulcers, burning mouth syndrome, dry mouth syndrome, a disease that can result in xerostomia (e.g., Sjogren's syndrome), Temporomandibular Joint Syndrome, or other oral disorder that in the opinion of the investigator would interfere with device use and evaluation.

16. Any intra-oral metal body piercings that cannot be removed for the duration of the study. Metal orthodontia is permitted as braces will be covered by the device mouthpiece.
17. Any individual without teeth or with a dental malformation that precludes directed use of the device as intended.
18. Currently enrolled in or plans to participate in another clinical trial with a therapeutic investigational agent for any medical indication that will be received during the study period.

4.7 Study Schedule of Activities

Study Procedures	Screening, Enrollment & Randomization	Treatment (Visit Window)	Treatment (Visit Window)	Follow Up[2,5] Days 8-14 (Visit Window)	
At Each Study Day	Baseline[1, 2] (Day 1 Clinic)	Day 5[2] (± 1)	Days 2, 3, 4, 6, 7	Day 8 (±1)	Day 14/ET[7] (±2)
Informed Consent	X				
SARS-CoV-2 Rapid Antigen & Flu A and B Rapid Antigen Tests	X				
SARS-CoV-2 Rapid Antigen Test (Days 1-14)	X [8] (1 at home, 1 in clinic)	X (1 at home, 1 in clinic)	Twice daily		
Nasopharyngeal Swab for qPCR and viral sequencing	X				
Medical History & Physical Examination[3,4]	X	X Changes Since Last Visit (CSLV)		X CSLV	X CSLV
Oropharyngeal Assessment[4]	X	X		X	X
Urine Pregnancy Test	X				X
Concomitant Medication History/New Medications	X	X Changes Since Last Visit (CSLV)		X CSLV	X CSLV
Vital Signs	X	X		X	X
Temp and SpO_2 (Twice Daily, Days 1-14)	X[8] (1 at home, 1 in clinic)	X (1 at home, 1 in clinic)	X	X (1 at home, 1 in clinic)	X
TEAE Assessments[4]	X	X		X	X
Demographics, Inclusion / Exclusion Review	X				

e-Diary Training	X				
RD-X19 Device Dispensing/Collection	X			X[5]	X[5]
Treatments	X [8] (1 at home, 1 in clinic)	X (1 at home, 1 in clinic)	Twice Daily (Record in e-Diary twice daily)		
Televisit By DCT Study Staff	X (1 Televisit on clinic days)	X (1 Televisit on clinic days)	X (2 Televisits on non-clinic days)		
Investigational Device, RD-X19, Retrieval				X	X
COVID-19 Symptom Assessment (e-Diary Completion, Days 1-14)	X	X (1 at home, 1 in clinic)	Record in e-Diary twice daily, including Temp & SpO_2 Daily QA of e-Diary		

1. Must be Clinic-based visit.

2. Days 1 and 5 have one treatment in the clinic and one at home. Study Days 5(+/-1), 8(+/-1) and 14(+/-2) visits are clinic based. Clinic visits on Study Days 5 and 8 must be separated by ≥ 48 hours.

3. Physical Examinations at Baseline (Day 1) and on Day 14 or early termination are full physical examinations. Examinations on study days 5 and 8 are targeted examinations based on the assessment of reported or observed TEAEs.

4. PEs and oropharyngeal assessments, as well as TEAE scoring and attribution, must be performed by appropriately trained and experienced medical personnel. **TEAE attribution requires medical personnel credentialled to make clinical decisions.**

5. Retrieved by study staff during clinic visit on Day 8 or 14.

6. SARS-CoV-2 rapid antigen test & Influenza A and B rapid antigen test (separate tests) at baseline (Day 1); SARS-CoV-2 alone thereafter; Baseline counts as SARS-CoV-2 test #1 for study day1

7. Early termination.

8. Exception if using Split Treatment on Day 1. See the Split Treatment section

5.0 PROTOCOL

5.1 Background and Study Rationale

In laboratory studies, the light-dosing 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 the 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* models. The mechanism of action via direct cell-free inactivation of virus by 425 nm visible blue light and an augmented innate immune response presents a breakthrough opportunity for therapy that is not specific pathogen-directed or dependent on antigen-specific adaptive immunity.

5.2 Risks and Benefits

5.2.1 Potential Risks (Anticipated Device Related Adverse Events)

The potential risks of participating in this trial are mild, transient, local reactions as measured in previous EmitBio clinical studies. See the Clinical Investigators Brochure for more detail.

EmitBio has classified RD-X19 as a “Not Significant Risk” (NSR) device per FDA guidelines and three IRBs have concurred with this designation; refer to Section 7.1.1, Preliminary Regulatory Pathway.

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.
- Exposure of tissues to blue light may cause mild, transient localized oropharyngeal pain, erythema, edema, and induration at the illumination site.
- Exposure of tissues to blue light may cause mild transient pain, redness, swelling, lesion, or dryness of the oral mucosa.
- May result in jaw discomfort when used by individuals with a small oral cavity.
- 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 from approximately 1 cm away has the potential to induce mild erythema.

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 Potential Benefits

There are no guaranteed benefits to study participants; however, based on our previous clinical studies, we expect to observe benefits including faster resolution of COVID-19 signs and symptoms. The use of the EmitBio RD-X19 is intended to alleviate the clinical signs and symptoms associated with COVID-19 and to reduce the time to a negative antigen test. There is also the potential for benefit to society resulting from insights gained from participation in this, and other similar studies.

6.0 STUDY DESIGN DETAIL

The primary goal of the study is to establish the efficacy and safety of the RD-X19 treatment device to treat eligible subjects who have mild COVID-19 with sufficient data to support a regulatory filing for authorization and approval by FDA.

The study population is subjects age 40 or older who have a positive COVID-19 test with time since symptom onset of 72 hours or less, and who meet the definition of mild COVID-19 described in Protocol Section 4.4, Study Population. The target study population will reflect the underlying communities age 40 and over experiencing mild COVID-19, possessing both seropositive and seronegative subjects from a mixture of those who have previously had COVID-19, as well as vaccinated and unvaccinated subjects. Viral genetic sequencing will be performed in order to characterize SARS-CoV-2 variants present in the study population (at the time of protocol writing, Omicron sublineages BA.4 and BA.5 are the predominant circulating variants worldwide).

The targeted number of subjects (N = 326) will be randomized 1:1 per treatment group. This sample size has >90% power to detect a clinically meaningful and statistically significant reduction in time to sustained resolution of COVID-19 signs and symptoms (without subsequent symptom recurrence or disease progression) in active RD-X19 vs Sham treatment groups. Full details on the sample size and power calculations are given in Section 9.2, Power and Sample Size. As described in Section 9.4.3, Interim Analysis, a blinded sample size review will be carried out by an independent statistician based on the first 164 randomized subjects. If the pooled proportion of subjects with an event for the primary endpoint is less than assumed, the total number of randomized subjects will be increased to maintain the power of the study; subject to a preliminary cap of 380. The number of randomized subjects will not be decreased.

The primary efficacy endpoint will be time to sustained resolution of COVID-19 signs and symptoms without subsequent symptom recurrence or disease progression as defined in Study Design, Section 4.3.

The key secondary endpoint will be the time to the first of two consecutive negative SARS-CoV-2 antigen tests without subsequent virological rebound, as defined in Section 4.3, Study Design.

Subjects will be stratified by age **(**age categories 40-49 and ≥50) and baseline composite disease severity score (< 1.25, ≥1.25). The baseline disease severity score is calculated using the symptom severity score data provided by the subject during the baseline/day 1 study visit. Self-assessments by study subjects will occur on each study day, with post-baseline assessments conducted by study investigators on Day 5 (± 1 day), Day 8 (± 1 day) and Day 14 (± 2 days). 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.

The presence of TEAEs will be self-assessed by study subjects throughout the study and may be reported to the DCT team member during a televisit or to the site Study Coordinator at any time. All TEAEs will be evaluated by clinical investigators during clinic visits by targeted physical examination, as required, and oropharyngeal examination.

Pregnancy testing will be performed at screening and at Day 14 or early termination visits.

Subjects will be instructed to enter data into their e-Diaries twice daily to assess COVID-19 signs and symptoms and record the time of treatments. Each assessed COVID-19 symptom will be rated on a 4-point scale from none (0) to severe (3) and a summary severity average will be calculated. Fever will be assessed dichotomously as present ($\geq 100.5^0$ F) or absent ($<100.5^0$ F). Twice daily oral temperatures and oxygen saturation levels (SpO2) will be measured by study-provided thermometers and pulse co-oximeters for home use. Study staff will make personal contact with study participants through televisits on each of the first seven (7) days of the study to ensure compliance with the treatment regimen and ascertainment and recording of clinical data.

Study Subject safety will be monitored throughout the study by the Investigator and supported by regular review by the Sponsor's Medical Monitor/Chief Medical Officer and, as needed, by the independent Medical Monitor.

The statistical analysis methods for efficacy and safety data as well as details on the sample size calculation are described in Section 9, Statistical Considerations.

6.1 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. EB-P20-01 established that there continued to be a high level of safety and tolerability when RD-X19 delivered a dose of 32 J/cm^2, BID for 7 consecutive days. Subsequent analyses demontrated the utility in individuals 40 years of age and older with mild COVID-19 and informed the design of this pivotal trial.

6.1.1 Justification for Dose

In repeated laboratory experiments, including experiments conducted by external third parties with bench top LED arrays capable of delivering precise wavelengths, irradiances, and doses 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 J/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, irradiances, and doses, all support the dose and schedule herein.

6.2 Study Volunteer Selection, Retention & Compensation

6.2.1 Recruitment

Individuals 40 years of age and older are the target for this study. The perspective and experience of these individuals is critical to develop a distinctive study brand that optimizes study awareness and educational materials that will attract individuals eligible for the study. A Decentralized Clinical Trial (DCT) paradigm will reduce burden on study subjects by offering most of the required study procedures through televisits.

Sites and PIs chosen for the studies will be in areas of high population density with well-defined community outreach mechanisms. Sites will include a combination of EmitBio's prior well-qualified sites as well as new, well-experienced sites who have been conducting COVID-19 treatment studies and are established in their communities. The sites will have access to the desired study population as they are the first place to call or visit to receive COVID-19 advice and treatments. Having the EmitBio device study available to sites should help maximize the current site's potential database and visits already scheduled to find a study opportunity for their clients. The over-arching goal is to make the process of study recruitment as easy as possible for sites by providing them the support they need through audio, video and printed materials and educational content for their staff and the individuals in their supported communites. Online content (social media post, clinical trial web listing, and banner) will be created to post on study site websites. Study fliers will be available at multiple community locations, and posters created to hang in key locations to raise awareness of the study. Physician referral letters will be sent to notify existing provider networks of the study opportunity available for their patients as well. Symptom awareness will be the primary focus of key materials so that those with mild COVID-19 will be reminded of the necessity to test and the opportunity to participate in a novel treatment study that stresses not needing to take systemic medication. Quick reference materials such as a lay language protocol synopsis, eligibility criteria booklet with self-assessment instructions, study information slides and a principal investigator welcome letter to explain the intended use of the materials will be made available.

Community-based awareness campaigns will proactively reach potential study subjects. Creative ads and messaging with graphics will be developed to appeal to individuals 40 years and older who may qualify for the study. All recruitment materials will be translated into Spanish for Hispanic communities as needed for the study. Campaign ads will direct interested participants to a central website to learn more about the study and complete a brief online pre-screening questionnaire focusing

on inclusion and exclusion criteria for the study. Recruitment methods will be assessed to determine what works and what doesn't work, with adjustments made accordingly.

No site will be allowed to randomize more than 15% of the total number of subjects randomized.

6.2.2 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. Contact with study subjects will occur on a twice daily basis on days 1-7 to ensure study compliance. The importance of conducting treatments as instructed as well as capturing timely, accurate COVID-19 signs and symptoms and TEAE data will be stressed.

6.2.3 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.

6.2.4 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.

7.0 STUDY DEVICE

7.1 Regulatory Considerations

7.1.1 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.

Under 21 CFR 812.3(m), the RD-X19 does not meet any of the below criteria that define a Significant Risk (SR) device:

- *Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject.* The RD-X19 is neither intended as an implant nor does it present a potential for serious risk to health, safety, or welfare of a subject.
- *Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject.* The RD-X19 does not present a potential for serious risk to health, safety, or welfare of a subject.
- *Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject.* The RD-X19 does not present a potential for serious risk to health, safety, or welfare of a subject.
- *Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.* The RD-X19 does not present a potential for serious risk to health, safety, or welfare of a subject.

In addition to the above, the risks identified, mitigation measures and control strategies in combination with a review of all available nonclinical and clinical safety information have confirmed the company's conclusion that the RD-X19 operating at the proposed fluence levels is a Nonsignificant Risk (NSR) device.

Through three clinical trials, institutional review boards have agreed with EmitBio's characterization of RD-X19 as an NSR device. The safety data from those trials has thus far further demonstrated the low-risk nature of the device.

EmitBio has implemented a Risk Management process that is compliant with ANSI AAMI ISO 14971:2019 and, with the guidance of ISO/RT 24971:2020, developed a Risk Management Plan specifically for the RD-X19 system. Risk Management activities have been conducted in accordance with to the Risk Management Plan and internal Standard Operating procedures, including a Hazards Analyis to identify characteristics of the RD-X19 device that could affect safety and separate risk analyses that focus on the design and use/misuse related hazards.

The Sponsor intends to continue development of RD-X19 as a NSR device and conduct this clinical study without an Investigational Device Exemption (IDE) application approved by FDA prior to initiation.

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

7.1.2 Proposed Label Claim/Indication for Use:

The EmitBio RD-X19 device is intended for use as a treatment for mild COVID-19 in subjects with positive results of direct SARS-CoV-2 viral testing ages 40 years of age and older who are symptomatic for 72 hours or less.

7.1.3 Medical Device Quality System:

EmitBio will operate under an established Quality Management System (QMS), 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). Any device that malfuntions during the trial will be fully evaluated and documented in compliance with EmitBio's QMS.

7.2 Study Device and Use

7.2.1 Device Description

The RD-X19 device is designed to emit visible light to inactivate 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 two components: (1) Light Engine, and (2) Light Guide; 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 USB Cable between device uses. The user is prompted via indicator

lights when recharging is necessary, in progress, and complete. The second accessory, the Device Storage Base, is used for storing the device between uses.

7.3 Use / Storage & Maintenance / Accountability

7.3.1 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 thermo-labelled on its power unit with a serial number. Study staff will ensure that each device's serial number (e.g. P30-123) 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 staff and then to the study sponsor. If a RD-X19 device should malfunction, study subjects must immediately notify the site staff to obtain a replacement device. Site staff will contact the designated randomization and device type key holder and and an appropriate device will identified to replace the malfunctioning device. Malfunctioning devices should be stored at the applicable study site and returned to the sponsor at the end of the study with the other devices.

7.3.2 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.

7.3.3 Preparation for Use

Refer to Appendix: RD-X19 Instructions For Use.

7.4 Measures to Maximize Study Subject Compliance

Study staff will make direct contact with study subjects via televisits for all at home treatments. Throughout the term of the study, study staff will remind subjects of the importance of capturing all clinical data within the e-Diary and to report any suspected AEs. All study subject data with be quality assured on a daily basis.

Subjects will receive appropriate compensation for the disruption to normal daily activities created by this protocol.

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 COVID-19.

7.5 Device Discontinuation

7.5.1 Study Pausing Criteria

If observations of any potential device-related SAE or patterns of non-resolving device-related TEAEs with severity grade 2 or higher in the same System Organ Classification Preferred Term (SOC PT) are observed in a single subject, treatment will be discontinued for that subject and they will continue with the full study schedule including collection of all data as if they had continued to be treated.

EB-P30-01 enrollment may 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 photo-allergy 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 within the same SOC PT based on the Medical Dictionary for Regulatory Activities (MedDRA) coding, considered to be related to RD-X19.

While the study is paused, a complete review of safety findings will be performed by an Independent Medical Monitor at the earliest opportunity and will make a recommendation to the Sponsor regarding continuation or termination of all or some of the study subjects and/or the overall study protocol. The Independent Medical Monitor has no affiliation with the design or conduct of the trial. The recommendation will be taken under advisement by the study Sponsor who has responsibility for any final decision.

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.

7.5.2 Study Stopping Criteria

If ≥2 device-related SAEs or ≥3 device-related severe TEAEs (grade 3) in the same SOC PT are observed, further enrollment and treatment will be discontinued. Subjects on trial at the time on discontinuation will continue to be followed per protocol.

7.5.3 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 subject's 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 TEAEs through resolution or stabilization.

Subjects who withdraw or are lost to follow-up after signing the informed consent form (ICF) and use 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 randomization will be replaced.

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

7.5.4 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 (Day 1), 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 a TEAE.

8.0 STUDY ASSESSMENTS AND PROCEDURES

8.1 Screening Assessments

8.1.1 Screening Procedures

Subjects will provide written informed consent prior to initiating any 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.

Subject numbers will be assigned with the three-digit numerical site number beginning with numbers greater than three hundred (e.g. 301) followed by an alphanumeric protocol identifier (P30) and finally a three digit unique numerical identifier assigned with each new subject (e.g. 001).

Example Subject Number: 301-P30-001

8.1.2 COVID-19 and Influenza A and B Screening

Individuals who identify with symptoms associated with mild COVID-19 present for 72 hours or less will be tested for the presence of SARS-CoV-2 and Influenza A or B using FDA-authorized rapid antigen diagnostic tests. These systems allow for rapid detection of SARS-CoV-2 and Influenza A and B via laminar flow immunoassays for the direct and qualitative detection of target antigens. All potential study subjects must be tested, regardless if they have a documented recent positive PCR or antigen test results for SARS-CoV-2.

Study volunteers 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 per guidance provided in protocol section 4.4.1, Symptom Severity Grading. Eligible subjects for enrollment must present with mild COVID-19 and test negative for Influenza A and B, and have at least two moderate or severe symptoms (cough, sore throat, nasal congestion, headache, chills and/or sweats, myalgia, fatigue, nausea (with or without vomiting) or at least one moderate symptom and an oral temperature of $\geq$ 100.5 °F are also eligible for enrollment. All eligible subjects must have had the onset of sign/symptoms $\leq$72 hours prior to consenting.

- Potential subjects with any evidence of lower airway involvement, including shortness of breath either at rest on upon exertion, are ineligible for the study and should be referred to their primary care provider or urgent care center.
- Potential subjects with COVID-19 signs and symptoms reported more than 72 hours from onset are ineligible for the study and should be referred to their primary care provider or urgent care center.
- Potential subjects will also be asked to report if they have been previously diagnosed with COVID-19 via an FDA-approved diagnostic test and whether or not they report that they have been previously vaccinated against COVID-19. The date(s) of prior COVID-19 diagnoses and the number and approximate dates of COVID-19 vaccinations and the vaccine manufacturer will be documented. Asking potential subjects to bring the CDC (or national equivalent, if such exists for non-US subjects) COVID-19 vaccination card will ease the time and burden of this task.
- All vital sign measurements (HR, BP, RR, SpO_2%), should be assessed as three measures over a 10-minute period and the average value should be captured for the purposes of this clinical trial.
- A complete COVID-19 disease assessment will include vital signs recorded as part of general screening.
- Subjects will be asked to assess their loss of taste and loss of smell (binary assessments at each assessment*). and pose the following patient-reported global impression assessments on Days 5, 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 informational purposes and will be assessed only as part of the qualitative patient reported global assessment and will not be included as a component of the primary efficacy endpoint.

8.1.3 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 and those associated with an increased risk of progression of COVID-19 (Asthma, Cancer, Cerebrovascular Disease, Chronic Kidney or Liver Disease, Chronic Lung Disease, Tuberculosis, Diabetes Mellitus, Hypertension, Heart Disease, Recent Pregnancy, Immune Deficiency, Smoking, Physical Activity level, Mood Disorders). It is particularly important to capture and document medical conditions that include signs and symptoms of COVID-19 but that are not due to the current episode of COVID-19.
- History of exposure to someone with COVID-19 or participation in an event that poses a significant risk of exposure to SARS-CoV-2 (commercial flight, major sporting or entertaining events, etc) over the past two weeks, including start and end dates.
- 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 any of the COVID-19-related symptoms (e.g., analgesics, antipyretics, decongestants) 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 use of antibiotics (e.g. tetracycline, azithromycin) for this purpose should be documented accordingly. Individuals receiving antibiotics for treatment of COVID-19 must discontinue use prior to study enrollment and this information should be documented. Individuals should be informed not to take antibiotics or other medications purported to treat COVID-19 (such as hydroxychloroquine or ivermectin) or known to treat COVID-19 (such as nirmatrelvir/ritonavir or molnupiravir) 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 for bacterial infections is a clinical decision that should be made by a licensed medical care provider outside of the protocol. Likewise, FDA authorized COVID-19 therapies for progressed COVID-19 are, of course, both appropriate and necessary when medically indicated but will result in study subjects being right censored for the efficacy analysis. These subjects will continue to be followed, per protocol, for safety assessments. Such use, and the reason for such use, will be documented. Study subjects will be requested to refrain from use of medications to treat COVID-19 symptoms. Any such use should be recorded on the concomitant medication form along with reason for use. The requirement to use narcotics for analgesia is prohibited and exclusionary. The use of acetaminophen (two

500mg tablets every 4-6 hours) as an antipyretic is allowed, but must be captured as a concomitant medication, if used.

- Medications to treat chronic medical disorders must not be in a period of adjustment or alteration within 30 days prior to enrollment. If medications have been adjusted within the past 30 days, or are currently being adjusted, this constitutes a chronic medical condition not under adequate control and is exclusionary.
- Measure oxygen saturation at rest via pulse oximeter. Oxygen saturation at rest should be measured after the study subject has been in a sitting position for 5 minutes. Hands should be warm and resting in the lap. Any fingernail polish must be removed prior to obtaining readings. Readings are taken three times over a 10 minute period and the average value recorded. This procedure should be used by study subjects during self-assessments at home.
- Measure vital signs (HR, BP, RR, and oral temperature) and height and weight for determination of BMI. Vital signs at rest should be measured after the study subject has been in a sitting position for 5 minutes. Readings are taken three times over a 10 minute period and the average value recorded. RR and HR should be measured over a full 60 second period. This procedure should be used by study subjects during self-assessments at home.
- Assess dyspnea on exertion: have potential study subject walk in place for 30 seconds; have the subject sit down and wait 30 seconds and measure RR and oxygen saturation. If RR $\geq$ 20/min and $SpO_2 < 96\%$, then individual is excluded from the study.
- 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 urine for pregnancy testing in fecund females
- Review inclusion and exclusion criteria. For clarification, subjects who are participating in other diagnostic or observational clinical studies are not prohibited from participation based on the exclusion criteria, "Currently enrolled in or plans to participate in another clinical trial with a therapeutic investigational agent for any medical indication that will be received during the study period."

The overall eligibility of the individual 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.

Individuals with a diagnosis of COVID-19 severity greater than mild or, signs and symptoms present for more than 72 hours are not eligible for enrollment.

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

BP, pulse, and respiration should be measured 3 times over an approximate 10 minute period. The average of the 3 measurements constitutes the value to be captured on the e-CRF an EDC. It is important that BP cuffs and sphygnomonometers are adequately sized and calibrated.

An individual 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 72 hours or less.

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

Individuals will be provided the results of any screening abnormality necessitating follow-up with their primary care provider.

8.2 Enrollment Process

The enrollment process occurs in the following order: Pre-screen, Consent, Enroll, Screen, Randomize or Exclude, Train, Treat, Follow-up.

Pre-screening is optional. Pre-screening may be an informal process to verify age, SARS-CoV-2 test results performed independently by the subject, COVID-19 symptoms, and the onset of symptoms within the past 72 hours. If a subject appears eligible and interested, the subject is consented and considered as officially enrolled. The subject is assigned a subject identification number.

Pre-screening may also be a formal process whereby COVID-19 testing is performed at the clinic to aid in confirming eligibility. In this instance, a pre-screen or testing informed consent is required. (Clinical sites are responsible for developing pre-screen informed consent forms and submission to the IRB for approval.) If a subject appears eligible based on pre-screen results, the subject is consented again and considered as officially enrolled. The subject is assigned a subject identification number.

Following consent, formal screening occurs. The data collected during screening sets baseline values. Screening occurs on Day 1, therefore Screening/Baseline = Day 1. During screening, subjects complete a self assessment of COVID-19 symptoms guided by the site utilizing a grading reference that mimicks what the subjects see in their e-diaires. The data from this self assessment is recorded by the clinical site on source documents. The result of this assessment is auto-calculated in EDC as the composite baseline symptom severity score which is used along with age (40-49 or ≥50) as stratifying factors for randomization. Following completion of all screening evaluations, the site will use this data to determine eligibility using the inclusion/exclusion criteria. If the subject meets the inclusion/exclusion criteria, they are eligible for randomization. If the subject fails the screening process, they are considered a screen failure. A study exit form is completed for all subjects who received a subject ID number.

Subject data is entered into the RMP (Research Management Platform) EDC system in order to receive randomization to either the active or sham investigational device. Once randomized, the

subject receives a nasopharyngeal swab for a qPCR test and viral sequencing. Additional information about the subject's COVID-19 exposure and history are recorded. As applicable, a pregnancy test is performed.

Following randomization, the subject is dispensed the assigned device and trained on the use of the device.

8.3 Day 1 Device Assignment, Training, and Treatment

On Day 1, subjects will be assigned either the active or sham device. Training will be provided to the subject on the use of the device.

Other materials will be dispensed to subjects as well including the following:

-SpO2 Monitor

-Thermometer

-SARS-CoV-2 Rapid Antigen Tests

-500mg Acetaminophen to be used as needed for fever based on PI discretion(must be documented as a concomitant medication if used)

- Mobile phone, if necessary the subject is assigned a mobile device to record their self assessments.

The subject is assisted with downloading the eCOA application called Study Hub (electronic mobile app designed as an e-Diary) and trained on how to enter data. A training entry is completed.

Subjects are trained on how to perform daily at home assessments.

Of note, on Day 1, subjects must receive the first in clinic treatment by 1700 hours so that the second at home treatment occurs after 2300 hours but in time to complete the e-diary and televisit before 2400 hours. The e-diary will not allow entries for Day 1 past 2400 hours. The time for the Day 1 PM televisit, as well as for the Day 5 clinic visit, will be scheduled by clinic staff during the Day 1 clinic visit.

Subjects will be advised of the importance of a minimum of 6 hours between the twice daily treatments and should understand that their treatments will be observed either during their clinic or televisits depending on the study day.

At least 30 minutes after the first in clinic treatment, a physical examination of the oropharynx and surrounding tissue will be performed and subjects will be asked to report any local site reactions post the RD-X19 treatment. All solicited local site reactions are considered to be device-related TEAEs and an adverse event form should be completed. Any other unanticipated adverse events are also recorded as applicable.

8.3.1 Split Treatment

In the event that a subject is enrolled late in the day on Day 1 and does not complete the first treatment by 1700 hours such that the second treatment on Day 1 cannot be completed by 2300 hours, the subject's first treatment will be on Day 1 PM and the second treatment and televisit will

occur on Day 2 AM. Thereafter, am/morning and pm/evening treatments will continue until the 14th treatment with the final treatment on Day 8.

The 14th treatment on Day 8 may or may not occur in the clinic depending on the scheduling of the Day 8 follow up visit. The site clinical staff must determine whether the Day 8 treatment will be in clinic or via televisit and convey to the DCT staff. The DCT staff cannot make decisions on treatment or clinic visits; they are only responsible for televisits and televisit scheduling.

A split schedule will occur as follows:

Treatment 1	Day 1 PM	Treatment Diary Only In RMP: -COVID-19 Symptom Assessment -Temperature and Oxygen -Antigen Test -Treatment Administration
Treatment 2 Diary	Day 2 AM	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Test Treatment Administration
Treatment 3 Diary	Day 2 PM	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Test Treatment Administration
Treatment 4 Diary	Day 3 AM	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Test Treatment Administration
Treatment 5 Diary	Day 3 PM	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Test Treatment Administration
Treatment 6 Diary	Day 4 AM	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Test Treatment Administration
Treatment 7 Diary	Day 4 PM	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Test Treatment Administration
Treatment 8 Diary	Day 5 AM	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Test Treatment Administration
Treatment 9 Diary	Day 5 PM	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Tes Treatment Administration
Treatment 10 Diary	Day 6 AM	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Test Treatment Administration
Treatment 11 Diary	Day 6 PM	COVID-19 Symptom Assessment

		Temperature and Oxygen Antigen Test Treatment Administration
Treatment 12 Diary	Day 7 AM	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Tes Treatment Administration
Treatment 13 Diary	Day 7 PM	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Test Treatment Administration
Treatment 14 Diary	Day 8 AM or PM	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Test Treatment Administration Treatment 14 on Day 8 may occur either in the clinic or by televisit, thereafter all e-Diary entries are completed by the study subject without a televisit
Clinic Check	Day 8	
Morning and Afternoon Diaries	Days 8 -14	COVID-19 Symptom Assessment Temperature and Oxygen Antigen Test Return mobile device

8.4 Procedures for Clinically Significant Findings

If in the judgement of the PI any finding poses a previously unknown risk to an individual or leads to a diagnosis of a disease or condition that would have disqualified the individual for enrollment, the study 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.

8.5 Bio-specimen Collection

A single nasopharyngeal swab and sample will be collected at the baseline (Day 1) visit to assess quantitative viral load and for genetic sequencing in a subset of samples.

Twice daily swabs of the nares will be taken by study subjects to assess the presence or absence of SARS-CoV-2 antigen. This is a FDA-authorized home diagnostic test that involves little to no discomfort and takes approximately 15-20 minutes to complete.

8.6 Safety and Other Assessments

Study procedures are specified in protocol Section 4.6, 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 starting since initiating treatment that are suggestive of a TEAE.

- Physical examination:
  - A full physical examination will be performed at the screening visit and on study day 14, and a symptom-directed (targeted) physical examination will be performed if indicated on study days 5 and 8 or at any time an unscheduled visit is required.
    - 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 starting since initiating treatment that are suggestive of TEAEs and an examination of the oropharynx. 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 TEAEs.
  - 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 and on days 5, 8, and 14 during clinic evaluations. Interim or unscheduled targeted physical examinations will be performed, if necessary, to evaluate potential 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. BP, pulse and respirations and oxygen saturation will be assessed as previously described. 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.

  - Urine pregnancy test will be performed locally by the site laboratory at the screening visit. Results will be recorded as study data and referrals made for serological confirmation and follow-up as required.
  - e-Diaries: Subjects will be instructed to fill out e-Diaries twice daily to assess their COVID-19 signs and symptoms 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. Televisit contact will be made by with subjects by the decentralized study staff during the home treatments on days 1-7. Observation of use of the device and recording of study data should be timed to coincide with the study subject encounter. Daily contact with study subjects will enhance safety monitoring and reinforce adherence to at-home study procedures.

- COVID-19 Severity Progression

  - There is a risk that subjects with mild COVID-19 may progress to moderate or more severe disease while on study. In such cases, appropriate medical referrals for evaluation and treatment outside of the protocol will be made.
  - Medically attended visits as a result of COVID-19 will be classified into the following categories:

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

2) those who require medical attention attributed to any SAE;

3) Those who progress to moderate disease indicated by new onset shortness of breath (respiratory rate ≥20/minute) and SpO2 of < 96% confirmed by pulmonary imaging or lower airway disease diagnosed by pulmonary imaging involving < 50% of lung parenchyma;

4) Those who progress to severe disease with respiratory rate >30/minute and/or O2 saturation ≤93% on room air or lower airway disease confirmed by pulmonary imaging involving ≥ 50% of lung parenchyma;

5) Those who require hospitalization for severe COVID-19;

6) Those who require endotracheal ventilation or ECMO with or without the use of solumedrol; and

7) 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 or other SAEs. Such subjects' endpoint data will be right censored as specified in the Statistical Analysis Plan (SAP).
  - Subjects who are treated with any FDA-authorized COVID-19 therapy will discontinue treatment but will continue to be followed per protocol. Such subjects' endpoint data will be right censored as specified in SAP.
  - Subjects who first reach clinical resolution on or after study day 11 should be scheduled for their day 14 visit, which has a +/- 2 day window, so that a total of five consecutive visits (including the first resolution visit) are captured where resolution *may* be observed thus allowing the primary clinical sustained resolution endpoint to be met. Under no circumstances, however, may a study subject be scheduled for their day 14 visit beyond study day 16.

8.6.1 Definition of Treatment Emergent Adverse Event (TEAE)

Adverse Events (AEs) are any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, whether or not related to the investigational medical device and whether anticipated or unanticipated. TEAEs are adverse events (AEs) that either start after initial treatment, or which are present prior to treatment initiation but which increase in severity after treatment. No AEs that are not TEAEs are expected in this study since the time between enrollment and first treatment is very brief.

Any medical condition that is present at the time that the subject is screened will be captured as part of the study subject's baseline medical history and will serve as the basis for capturing AEs that are treatment-emergent based on worsening severity.

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/investigational device. 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 such 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.

8.6.2 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 TEAEs include:

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

8.6.3 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 AEs of all severities will be reported during the entire course of the study.

8.6.4 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.

8.6.5 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 adverse event,
- 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 or 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 AE that at occurrence represents an immediate risk of death to a subject. It does not include an adverse event or suspected adverse reaction that, had it occurred in more severe form, might cause death. Similarly, a hospital admission for an elective procedure is not considered an SAE.

All SAEs will be assessed for severity and relationship to study intervention. All SAEs will be recorded on the appropriate SAE 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 according to the Reporting Requirements. This report will include severity, association with the study device, action(s) taken, and outcome.

8.6.6 Serious Adverse Event Reporting

Any TEAE that meets a protocol-defined criterian as an SAE must be reported immediately (within 24 hours of site awareness) using the electronic data collection tool, eCRF. Investigators must report all Safety Events (AEs, SAEs and Device Deficiencies) via the Electronic Data Capture (EDC) system. If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours and send to the IQVIA MedTech Safety management team by email: Emitbio@iqvia.com.

Other supporting documentation of the event may be requested by EmitBio's Medical Monitor 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 U.S Food and Drug Administration using MedWatch, FDA's Safety Information and Adverse Event Reporting Program.

8.6.7 Regulatory Reporting of Device-related AEs

EmitBio Inc. will report to the FDA any unanticipated device-related TEAEs and SAEs as soon as possible, but in no case later than 10 working days after the sponsor's initial receipt of the information.

Relevant follow-up information to the safety report will be submitted as soon as the information is available. Upon request from FDA, EmitBio will submit to the FDA any additional data or information that the agency deems necessary.

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

8.6.8 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.

8.6.9 Severity of Treatment Emergent Adverse Events

All TEAEs will be assessed for severity according to the toxicity grading scale of mild, moderate, and severe..

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. A TEAE is not counted as a separate or new TEAE if at the next clinic visit, the TEAE is persistent at the same of lesser severity level. It shall be recorded as a new TEAE if it worsens in severity. The same TEAE verbatim term with a worsened severity score will be documented as an independent event, including start and stop dates. The start and stop date of each reported TEAE will be recorded on the appropriate e-CRF. All device-related grade ≥2 TEAEs (any grade greater than mild is considered unanticipated) will be reported.

See SAE source document for information to be submitted.

8.6.10 Relationship to Study Intervention/Investigational Device

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 AE 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.

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

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.

8.6.12 Treatment Emergent Adverse Event Reporting to Study Subjects

The Sponsor will ensure all device-attributed TEAEs and SAEs are reported to participants in the study to better inform them of the potential risks vs. benefits of participation.

8.7 Reporting Summary

Report	Time to Report	Responsibility	Report To
Unanticipated (in terms of nature, severity (≥ 2), or degree of incidence) Adverse Device-Related Event including Serious Unanticipated Adverse Device Events [21 CFR 812.150]	Within 10 working days after becoming aware	Investigator	CRO/Sponsor IRB
Unanticipated Adverse Device-Related Event including Serious Unanticipated Adverse Device-Related Events – *Results of Evaluation* [21 CFR 812.150]	Within 10 working days after becoming aware File as an IDE report to FDA	Sponsor	FDA IRBs, all Investigators, all
TEAE - unsolicited	Within 24 hours of becoming aware	DCT	Investigator
SAEs or TEAEs that are unanticipated, including a change in severity (≥ 2), and are treatment/device related	Within 10 working days after becoming aware	Investigator	CRO/Sponsor IRB
SAEs or TEAEs that are unanticipated, including a change in severity (≥ 2), and are treatment/device related	Within 10 working days after becoming aware File as an IDE report to FDA	Sponsor	FDA IRBs, all Investigators, all
Use of Investigational Device Without Informed Consent [21 CFR 812.150]	Within 5 working days of the device use	Investigator	CRO/Sponsor IRB

Use of Investigational Device Without Informed Consent [21 CFR 812.150]	Within 5 working days of becoming aware	Sponsor	FDA
Unapproved protocol deviations/violations (an accidental or unintentional change to the IRB-approved protocol) – Major Deviation	Within 10 business days from the time of identification of the unplanned or unintentional protocol deviation/violation	Investigator	IRB
Deviations from the investigational plan to protect the life or physical well-being of a subject in an emergency. [21 CFR 812.150]	Within 5 working days of the emergency	Investigator	IRB CRO/Sponsor

8.8 Pregnancy Reporting

All positive urine pregnancy tests will be recorded during screening and at the end of the study or early termination in the study. Women who screen positive for pregnancy will be encouraged, if not already scheduled or completed, to see their primary health care provider or obstetrician for a serological confirmatory test and to be followed thereafter by their obstetrician per best practice guidelines.

Pregnant women and women who may become pregnant during the study will be permitted to participate in the study since RD-X19 presents no possible exposure or hazard to germline cells or developing embryo or fetus.

9.0 STATISTICAL CONSIDERATIONS

9.1 Primary Endpoint and Key Secondary Endpoint

Primary Endpoint

The primary endpoint will be time to sustained resolution of COVID-19 signs and symptoms without subsequent symptom recurrence or disease progression until the end of the study.

Resolution of COVID-19 signs and symptoms is defined as cough, sore throat, nasal congestion, headache, chills and/or sweats, myalgia, fatigue, and nausea (with or without vomiting) having been assessed by the subject as absent (0) or mild (1) and temperature is less than 100.5 °F.

Sustained resolution of COVID-19 signs and symptoms is achieved when all signs and symptoms are resolved for five consecutive assessments (corresponding to an approximately 48-hour period).

After sustained resolution is achieved, symptom recurrence is defined as having three or more consecutive assessments (corresponding to an approximately 24-hour period) where two or more of the nine signs and symptoms do not meet the resolution condition.

"Disease progression" is defined as having evidence of involvement of the lower respiratory tract: shortness of breath (defined as respiratory rate of 20 or more breaths per minute) and SpO2 < 96% (both ascertained from the average of three replicate assessments) and/or pulmonary imaging demonstrating COVID-19 pneumonia.

Key Secondary Endpoint:

The key secondary endpoint will be time to the first of two consecutive negative SARS-CoV-2 antigen tests (with a minimum time between tests of 6 hours) without subsequent virological rebound during the subject's remaining time on study. Virological rebound (after having achieved two such consecutive negative tests) is defined as having two or more positive tests out of three consecutive assessments.

9.2 Power and Sample Size:

For Mild subjects (including the additional requirement that baseline heart rate < 90, as in the FDA definition of mild COVID-19 [18]) age 40 or older in the EB-P20-01 trial, the hazard ratio in the full analysis set (FAS) was 0.62. Assuming an overall type 1 error of 0.025 one-sided a total of 228 events for the primary endpoint gives 95% power for this hazard ratio of 0.62 and also gives 90% power for a hazard ratio of 0.65, as well as 80% power for a hazard ratio of 0.69.

A total of 326 subjects will be initially randomized 1:1 (to RD-X19 and Sham) and this will give approximately 228 events assuming that 90% of RD-X19 subjects and 50% of Sham subjects will have the event. Section 9.4.3, Interim Analysis, describes a blinded sample size review that will be carried out based on the pooled event rate, after which the number of randomized subjects could potentially be increased.

9.3 Analysis Populations:

Three analysis populations are defined as follows:

- Full Analysis Set (FAS) which will consist of all randomized subjects. This population will be the primary analysis population for all efficacy endpoints. Subjects will be analyzed on the basis of the treatment to which they were randomized.
- Safety Population which will consist of all randomized subjects who received any study treatment. This population will be the primary analysis population for all safety analyses. Subjects will be analyzed on the basis of the treatment that they received.
- Per Protocol (PP) Population will exclude from the FAS: (i) study subjects who experienced one or more of a pre-specified subset of major protocol deviations/protocol violations while on study, and (ii) subjects who did not meet certain pre-specified criteria concerning number of treatments received. The full list of reasons for exclusion from the FAS population will

be defined in the Statistical Analysis Plan prior to unblinding. Protocol deviations are not exclusionary for the PP population. Major deviations/violations will be defined within the Statistical Analysis Plan prior to unblinding.

- Protocol deviations/violations are defined in the Definitions Section.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

Details on Derivation of the Primary Endpoint

The primary endpoint is defined in Section 9.1, Primary Endpoint, and this current section provides further details on the exact derivation of this endpoint.

The eight symptoms included in the definition of the primary endpoint are cough, sore throat, nasal congestion, headache, chills and/or sweats, myalgia, fatigue, and nausea (with or without vomiting). The single sign included in the definition of the primary endpoint is temperature. Together these nine signs and symptoms are used to define resolution.

The first step in derivation of the primary endpoint is at each of the twice-daily assessments at which the subject records signs and symptoms in the e-diary to classify subjects on the basis of which of the following applies:

(i) Success (S), which corresponds to resolution, if all of the above eight symptoms are graded with a severity score of 0 (absent) or 1 (mild), and temperature < 100.5° F;

(ii) Failure (F_n) if n (≥1) of the nine signs and symptoms do not meet the condition described in (i) above;

(iii) Disease progression (D) if the subject has RR ≥ 20/min and SpO2 < 96% (both based on the average of three replicate assessments over 10 minutes) and

(iv) Missing (M) if the subject did not record all signs and symptoms entries in their e-diary at this timepoint.

Note: For subjects that at a particular timepoint are missing data for a subset of their nine signs and symptoms the data handling rules will be described in the SAP.

To achieve "sustained resolution" a subject must first record five consecutive timepoints (corresponding to an approximately 48-hour period) at which the signs and symptoms have resolved (i.e., assessment results SSSSS).

Time to sustained resolution of COVID-19 signs and symptoms is the time (in hours) of the first "S" in a sequence "SSSSS" for which there is no subsequent symptom recurrence and no subsequent disease progression during the subjects' remaining time on study.

After recording "SSSSS" a subject is defined to have had symptom recurrence if there are three (corresponding to an approximately 24-hour period) or more consecutive values of F_n with n ≥ 2 in

each case, i.e., three or more consecutive assessments where two or more of the nine signs and symptoms do not meet the condition described in (i) above.

A subject is defined to have had subsequent disease progression if, after recording "SSSSS", they have "D" (disease progression) at even a single timepoint, or if pulmonary imaging demonstrates COVID-19 pneumonia

Note: A subject that has symptom recurrence and/or disease progression is still eligible to later have the event for the primary endpoint, if they subsequently have five consecutive assessments at which the signs and symptoms have resolved ("SSSSS"), but with no further subsequent rebound or subsequent disease progression during the subjects' remaining time on study.

Analyses of the Primary Endpoint

The method of primary analysis for the primary endpoint is nonparametric randomization-based covariate adjustment for time-to-event outcomes using Efron's method for handling ties, with stratification by the design's stratifications factors (age category [40-49, ≥50] and baseline disease severity score [<1.25, ≥1.25]), and with between one to four pre-specified (in the SAP) prognostic baseline covariates to improve precision of the estimate of the hazard ratio. This analysis will be based on the methods of Saville and Koch [20] as extended to stratified analyses by Hussey et al [21]. Testing for treatment will be carried out at the 5% two-sided significance level, and 95% two-sided confidence interval (CI) for the hazard ratio will also be derived. This primary analysis will be based on the FAS.

The non-parametric Kaplan-Meier method will also be used for the FAS to estimate the survival curves, within the plot of which the number of subjects at risk will also be displayed. The median survival time will be estimated for each treatment group, together with its 95% CI using the Brookmeyer & Crowley method [19]. Estimates of the 25^{th} and 75^{th} percentiles will also be derived together with their corresponding 95% CIs.

A secondary analysis will be carried out on the FAS for the primary endpoint based on a Cox Proportional Hazards model, using Efron's method for handling ties, including the same stratification factors and covariates as included in the primary analysis. In the analyses described above the following rules for event times and censoring will be implemented:

(i) Subjects that are hospitalized will be censored at 360 hours (which corresponds to the end of the time window for the Day 14 visit) and this rule takes precedence over all other rules;

(ii) A subject that records "SSSSS" i.e., five consecutive timepoints (corresponding to an approximately 48-hour period) at which the signs and symptoms have resolved who does not have any subsequent symptom recurrence or subsequent disease progression during the subject's remaining time on study, will have the event at the time of the first "S" in this sequence;

(iii) A subject not satisfying case (i) or (ii), who takes nirmatrelvir/ritonavir or molnupiravir after initiating study treatment will be censored at the time that they first took this antiviral medication; and

(iv) Subjects not satisfying case (i), (ii), or (iii) will be censored at the last time that they have e-diary data recorded.

Note: Subjects taking nirmatrelvir/ritonavir or molnupiravir after initiating study treatment must have recorded "SSSSS" (or equivalent) prior to starting this antiviral medication to be counted under case (ii), and if not then they will be counted under case (iii).

Further details on data handling rules will be provided in the SAP.

Supportive analyses for each of the methods described in this section will also be carried out for the PP population. Further sensitivity analyses for the primary endpoint will be described in the SAP.

Analyses of the Key Secondary Endpoint

At each of the twice-daily assessment times at which the subject is scheduled to take the SARS-CoV-2 antigen test the results will be either Negative (N), Positive (P), Inconclusive (I) or Missing (M).

The first step in defining the key secondary endpoint is to identify cases that will be counted as having “two consecutive negative SARS-CoV-2 antigen tests”. The following sequences will be counted as satisfying this condition: (a) “NN” and the two tests are at least six hours apart; (b) multiple consecutive “N” values where the first and last must be at least six hours apart; or (c) “N” followed by up to three “M” or “I” values followed by "N" where the two "N" values must be at least six hours apart. In the remainder of Section 9.4.1.3 the use of "NN" will be refer to any of cases (a)-(c).

The second step is to identify cases that are counted as subsequent virological rebound which is defined as "having two or more positive tests out of three consecutive assessments". This would include "PPP", "PPN", "PNP", "NPP", or "PP". In addition, if a "P" is followed by an "M" or “I” then the "P" will be carried forward so that this will also be counted as a rebound.

The key secondary endpoint is then calculated as time to first of two consecutive negative SARS-CoV-2 antigen tests (with a minimum time between tests of 6 hours) without subsequent virological rebound, during the subjects' remaining time on study. Subsequent virological rebound is defined as having two or more positive tests out of three consecutive assessments.

The following rules for event times and censoring of the key secondary endpoint will be implemented:

(i) Subjects that are hospitalized, who progress to more severe forms of COVID-19, or who require therapy with an FDA-authorized COVID-19 treatment will be censored at 360 hours (which corresponds to the end of the time window for the Day 14 visit) and this rule takes precedence over all other rules;

(ii) A subject that records "NN" based on two tests at least six hours apart without subsequent rebound during the subject's remaining time on study will have the event at the time of the first "N" in

this sequence, and

(iii) Subjects not satisfying case (i) or (ii) will be censored at the time of their last self-assessment /diagnostic test.

The primary analysis of this key secondary endpoint will be nonparametric randomization-based covariate adjustment for time-to-event outcomes using Efron's method for handling ties, with stratification by the design's stratifications factors, and with the same 1-4 pre-specified prognostic baseline covariates as included in the primary analysis of the primary endpoint. The 95 % two-sided CI for the hazard ratio will also be derived. The primary analysis will be based on the FAS. In addition, the same Kaplan-Meier-based analyses as described for the primary endpoint will also be provided for this key secondary endpoint.

A secondary analysis of this key secondary endpoint will be carried out on the FAS based on a Cox Proportional Hazards model, using Efron's method for handling ties, including the same stratification factors and covariates as included in the primary analysis of this endpoint.

Multiplicity Adjustment

The key secondary endpoint will only be formally tested if statistical significance has been obtained for the primary endpoint. This step-down procedure ensures that there will be strong control of the experiment-wise type 1 error across the primary endpoint and the key secondary endpoint.

9.4.2 Safety Analyses

Summaries for all safety data will be presented by treatment group based on the Safety population. The number of hospitalizations will be tabulated and full details will be provided in listing form for any such hospitalizations. **See section on Reporting Requirements for regulatory reporting of presumed device-related SAEs and patterns of device-related AEs.**

A TEAE is defined to be an adverse event (AE) which starts after initiation of treatment, or an AE which was present prior to initiating treatment but which increases in severity after starting treatment, excluding signs and symptoms of COVID-19. Incidence tables by system organ class and preferred term will be produced for AEs, SAEs, TEAEs, device related TEAEs (including separately those that are anticipated and unanticipated, as designated by severity level, and resulting clinical outcomes such as treatment discontinuation/withdrawal), TEAEs that led to discontinuation of treatment, and TEAEs by severity. The details of SAEs and any deaths will also be summarized.

Protocol deviations will be summarized in tabular and listing form.

9.4.3 Interim Analysis

A blinded sample size review will be carried out by an independent statistician based on the first 164 randomized subjects after the last of these subjects has reached the Day 14/ET visit. The pooled proportion (p_{OBS}) of subjects with an event will be determined and if this is less than 0.70 then in order to obtain approximately 228 events at the end of the study the total number of randomized subjects will be increased to 326 * 0.70/p_{OBS} (rounded up to the nearest multiple of 2, due to the 1:1 active:sham randomization) subject to a cap of 380. The number of randomized subjects will not be decreased, and no unblinded assessment of efficacy will be carried out at this time.

10.0 OPERATIONAL CONSIDERATIONS AND SUPPORTING DOCUMENTS

10.1 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 per the Reporting Requirements.

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.

10.1.1 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.

10.1.2 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.

10.2 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.

10.3 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.

10.4 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, AEs/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. AEs 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.

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

10.5 DCT (Decentralized Team) Responsibilities

- Perform remote televisits via StudyHub. Televisits may be performed via telephone if StudyHub not available.
- Schedule remote televisits with subjects. At each televisit, schedule the next upcoming visit. If a subject does not show up for a televisit, complete the Visit Completion Report and document/mark as a missed visit.
- Verify completion of the twice daily, SARS-CoV-2 rapid antigen tests. Preferably visual observation during televisit.
- Observe SpO2 and temperature completion during televisit.
- Direct observation and documentation of RD-X19 device administration during the televisit.
- Verify completion of the eDiary for each televisit.
- Subject re-training where necessary.
- Completion of Visit Completion Report (source document). Upload report to StudyHub within 24 hours following televisit. Maintain originals of Visit Completion Reports until end of study and provide to Data Management.
- Document any reported adverse events on the Visit Completion Report. Immediately following televisit, send an email to the applicable clinical site coordinator. (The clinical site is responsible to follow up with the subject to evaluate and document any possible adverse events.)
- Document any known study deviations on the Visit Completion Report. Immediately following televisit, send an email to the applicable clinical site coordinator.

10.6 Sponsor Responsibilities

The sponsor is responsible for the following activities within the protocol. While many responsibilities and obligations may be formally transferred to third parties, the Sponsor is ultimately responsible:

- Provision of investigational devices (RD-X19 and sham devices).

- System for stratified randomization.
- Supplement investigator and site staff training.
- Provision of all study supplies and materials required to conduct the protocol as written and approved.
- Communication with regulatory bodies as defined in 21 CFR, ICH, and The Central IRB handbook.
- Providing acetaminophen packets directly to the clinical sites for dispersement to study subjects. The sponsor files dispersement information to the CRO who maintains a study materials log to be included in the trial file.
- The sponsor is responsible for review of deviations to verify whether a deviation is minor or major (violation).
- The sponsor is responsible for reporting as specified in the Reporting Requirements.
- Medical Monitoring – The Medical Monitor ensures the safety and integrity of study subjects throughout the trial, from the initial design of the study to the final close-out. A medical monitor acts as the point of reference for study team members and investigative sites.
- Research and Data Compliance Monitoring

10.7 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.

10.8 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.

10.9 Protocol Deviations and Violations

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. A protocol violation is a deviation that has the potential to impact the primary and key outcome measures of the trial, including safety and efficacy. See Definitions for more information.

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 protocol deviations will be addressed in either general study, site, or subject study records.

It is the responsibility of the participating clinical site PI and study staff to use continuous vigilance to identify and report deviations per the Reporting Requirements. The participating clinical site PI and study staff are responsible for knowing and adhering to the IRB requirements. Protocol deviations/violations will be recorded on the case report form, as well as in the subject's chart, if the deviation is subject specific.

10.10 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.

10.11 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.

10.12 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.

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12.0 DEFINITIONS

- Medical Device - Adverse Event

Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in *subjects*, users or other persons, whether or not related to the *investigational medical device* and whether anticipated or unanticipated.
[ISO 14155]

- Medical Device - Serious Adverse Event

Adverse event that led to any of the following:
A) death.
B) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
a) a life-threatening illness or injury, or
b) a permanent impairment of a body structure or a body function including chronic diseases, or
c) in-patient or prolonged hospitalization, or
d) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function;
e) fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment.
[ISO 14155]

- Unanticipated Adverse Device Effect

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
[21 CFR 812.3]

- Treatment Emergent Adverse Event

A TEAE is any untoward medical condition that either starts after initiating treatment, or which was present prior to initiating treatment but increases in severity after starting treatment (21 CFR 312.32 (a)). A TEAE can therefore be any unfavorable and unintended sign (including an abnormal clinical laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product.
[21 CFR 312.32]

- Serious Adverse Event

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:

A) Death,
B) A life-threatening adverse event,

C) Inpatient hospitalization or prolongation of existing hospitalization,
D) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
E) A congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
[21 CFR 312.32]

- Treatment Emergent Serious Adverse Event

An SAE is defined in 21 CFR 312.32 as follows: "An TEAE 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:

A) Death,
B) A life-threatening TEAE,
C) Inpatient hospitalization or prolongation of existing hospitalization,
D) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or,
E) A congenital anomaly or birth defect.

[21 CFR 312.32]

- Device Deficiency/Malfunction

Failure of an *investigational medical device* to perform in accordance with its intended purpose when used in accordance with the instructions for use, clinical protocol, or investigator's brochure.
[ISO 14155]

- Deviation

Instance of failure to follow, intentionally or unintentionally, the requirements of the clinical protocol or investigation plan.
[ISO 14155]

- Deviation - Minor

There are many unplanned or unintentional violations/deviations or changes in study status that do not cause harm, place subjects at increased risk of harm, or adversely affect data integrity. The IRB does not require that these minor violations/deviations be reported. Examples of minor violations/deviations that do not need to be reported may include the following:
• Out of window visits
• Study procedures conducted out of timeframe
• Subject failure to initial each page of the ICF (as applicable)
• Subject failure to return subject materials (e.g., diaries, journals, etc.).
• Administrative hold on a study not related to safety issues
[Advarra IRB Handbook, Version 5]

- Deviations – Major/Violation

Examples of accidental or unintentional protocol violations/deviations that must be submitted to the IRB include:

• Changes necessary to eliminate apparent immediate hazards to the subject
• Failure to document informed consent
• Informed consent obtained after initiation of study procedures
• Enrollment of a subject who did not meet all inclusion/exclusion criteria
• Performing study procedure not approved by the IRB
• Failure to report serious adverse event to the IRB and/or sponsor
• Failure to perform a required lab test that, in the opinion of the investigator, may affect subject safety or data integrity
• Device/Drug/study medication dispensing or dosing error
• Study visit conducted outside of required timeframe that, in the opinion of the investigator, may affect subject safety
• Failure to follow safety monitoring plan
• Missing or unreturned investigational product

[Advarra IRB Handbook, Version 5]

13.0 APPENDICES

Appendix 1 - RD-X19 Investigational Device Manual (Instructions for Use)