A 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

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This supplement contains the following items:

- Original Protocol*
- Protocol Amendment 1 (current)*
- Clarification Memorandum #1
- Clarification Memorandum #2
- Statistical Analysis Plan Version 2.0 (current)*
- Statistical Analysis Plan Amendment 1

*Redacted

CLINICAL TRIAL PROTOCOL

A 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

Protocol Number: EB-P12-01

Investigational Countermeasure: RD-X19

Specific Indication: Treatment of Uncomplicated COVID-19

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

Phase: I/II

Name and Address of Sponsor:

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Name and Address of CRO:

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21 Perry Street
Port Jefferson, NY 11777
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GCP Statement: This trial will be performed in compliance with (c)GCP.

1 INSTITUTIONAL STATEMENT OF COMPLIANCE

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

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

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

2 INVESTIGATOR'S AGREEMENT

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

Principal Investigator Signature:

Signed: _____ Date: _____

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4 PROTOCOL SUMMARY

4.1 Executive Summary

In December 2019 the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknow cause. Coronavirus ribonucleic acid (RNA) was quickly identified in some of these patients. As of October 11, 2020 there were approximately 37 million confirmed cases wordwide (>7.7 million in the US) and over 1,075,000 deaths (~215,000 in the US). The only FDA approved intervention currently is Remdesivir for hospitalized subjects with COVID-19. Other interventions currently being used are through the Emergency Use Authorizations (EUA), against SARS-CoV-2 / COVID-19. Social distancing and personal protective equipment constitute our only viable countermeasures to help reduce incidence of community acquisition and transmission of SARS-CoV-2. Vaccine candidates are being developed at an unprecedented speed, however their efficacy and safety is unknown and will not be fully defined for many months. Remdesivir, Convalescent Immune Plasma and SoluMedrol are all used to treat patients hospitalized with COVID-19, but none has received marketing approval as a therapeutic for uncomplicated COVID-19. Therefore, there remains an urgent public health need for rapid development of novel measures for prevention and treatment of SARS-CoV-2 and COVID-19.

RD-X19 through both direct and intermediate mechanisms, kills cell-free virus by as much as 99.99% and inhibits cell-associated replication of SARS-CoV-2 by 99.9% when measured at 24 hours after a single 5 minute treatment. Putative key virucidal mechanisms include upregulation of nitric oxide in epithelial tissue through increase of nitric oxide synthases (NOSs) and stimulation of the instantaneous release of the body's bound store of nitric oxide. Nitric oxide produced physiologically in epithelial tissues also induces and attracts effector cells of the innate immune system, including natural killer (NK) cells, neutrophils and macrophages to phagocytize virus-infected cells at the site of primary infection. The technology utilized by RD-X19 has been repeatedly demonstrated to provide high-level viral control in multiple, consistent, expert-laboratory in vitro studies. The mechanism of action, utilizing augmented innate immunity, presents an unprecedented opportunity for protection that is not specific antigen-directed or dependent

4.1.1 Study Goals

This is a randomized, sham-controlled dose escalation and bioeffect study. The primary goal of the study is to evaluate the safety of the RD-X19 device in SARS-CoV-2 infected individuals with outpatient COVID-19 at two dosing schedules, and to assess the reduction of SARS-CoV-2 viral load in each dose group compared to sham controls. This is an efficacy hypothesis-generating study; sample size is based on convenience. However, there is adequate power to detect large differences in group SARS-CoV-2 reduction effects. The primary safety measure is absence of device-related serious adverse events or patterns of severity $\geq$2 device-related adverse events.

Safety and tolerability (local reactogenicity) will be assessed actively on each clinic visit by review of potential adverse events (AEs) and targeted physical examination, as required. Volunteers will be encouraged to contact designated clinical trial staff for AEs of a medically-urgent nature as soon as is practically possible and to seek immediate medical care, if needed.

Metabolic, liver, kidney and hematological laboratory evaluations will be performed at baseline and at Day 8 or early termination (and potentially during unscheduled) clinic visits. Methemoglobin assessments will be performed at baseline and Day 8.

4.1.2 **Study Design**

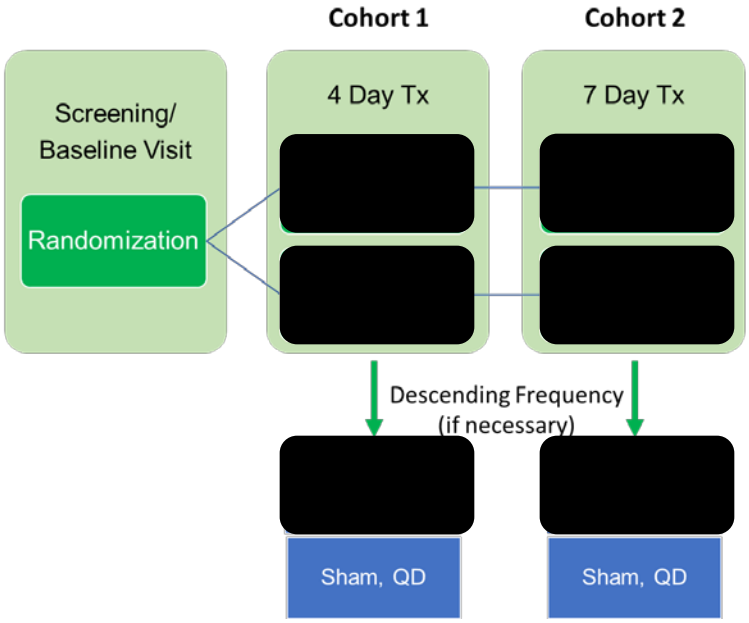
Subjects will provide informed consent prior to initiating any screening procedures. Subjects meeting all screening criteria will be eligible for enrollment and randomization into the study. This study plans to enroll into two treatment arms within two escalating dose cohorts:

Volunteers meeting all inclusion criteria and none of the exclusion criteria will be randomized to the RD-X19 treatment arm or the sham treatment arm within each cohort. Subjects will be randomized in a 2:1 ratio (20 RD-X19 : 10 sham) per dose cohort. The double-blind, sham-controlled treatment period of four (4) days of dosing for Cohort 1 is shown in Figure 1 below; increased weekly doses of light with twice daily dosing will occur in Cohort 2 for a treatment duration of seven (7) days. Light will be administered locally to the mouth and throat only, aiming to eliminate viral load in these targeted portions of the upper respiratory tract. Assessments of treatment response will occur on study days 3 and 5, with the final determination of efficacy made on day 8 (inclusive).

Study Subject safety will be monitored throughout the study by the Investigator and supported by regular review by the Sponsor's Chief Medical Officer.

Upon completion of all subjects in Cohort 1, the results of an unblinded interim analysis will be reviewed by a safety monitoring team and a recommendation will be made to the sponsor on whether the committee recommends proceeding with enrollment for the next cohort at the next planned dose or whether enrollment should continue in the next cohort at a reduced dosing frequency (e.g. once daily). The study is designed to evaluate at least 2 dosing schedules, ascending, or descending based on safety of each previous cohort.

Figure 1: Study Design



The interim analysis at the conclusion of Cohort 1 will consist of the following evaluations:

- A planned efficacy evaluation of the time weighted average change in SARS-CoV-2 viral load from baseline will be conducted as an assessment of benefit to the subjects.
- Safety evaluations, performed by an independent safety monitoring team as outlined in the committee charter, are to ensure that each dose level under evaluation is safe. Specific criteria for safety review will include:
  - Number of subjects experiencing laryngospasm, bronchospasm or anaphylaxis within 2 hours after use of the RD-X19 Device that is considered related to RD-X19.
  - Number of subjects experiencing an allergic reaction such as generalized urticaria (defined as occurring at three or more body parts) within 72 hours after administration of light that is considered related to RD-X19.
  - Number of subjects experiencing an SAE or Grade 3 AE, in the same SOC grouping of Preferred Terms based on Medical Dictionary for Regulatory Activities (MedDRA) coding, considered to be related to RD-X19.

4.1.3 Objectives and Endpoints

Table 1: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Safety Assessments	
• AEs and SAEs*	• The primary safety measure is absence of device-related serious adverse events or any patterns of severity ≥2 device-related adverse events.*
• Methemoglobin	• Mean change in methemoglobin from baseline to Day 8/ET.
Efficacy Assessments	
• viral load	• Time weighted average change in viral load from baseline by RT-qPCR from Day 1 to Day 8
	• Geometric mean viral load as measured in saliva on day 1, 3, 5, and 8 by RT-qPCR*
	• Proportion of subjects demonstrating viral load reduction ≥ 95% by RT-qPCR (at each visit)*
• viral infection	• Time to clearance of viral infection in saliva, defined as a negative test (Ct value ≥32) via RT-qPCR.
	• Proportion of subjects demonstrating clearance of viral infection, defined as a negative test (Ct value ≥32) via RT-qPCR on Day 8/ET.
• symptoms	• Median time to alleviation of symptoms as measured by the time when all eight symptoms (cough, sore throat, nasal congestion, headache, chills/sweats,

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• COVID-19 composite severity score.	muscle or joint pain, fatigue, and nausea) had been assessed by the subject as none (0) or mild (1).
Exploratory Assessment(s)	
• viral load by viral titer (at each visit)	• Geometric mean viral load as measured in saliva on day 1, 3, 5, and 8 by $TCID_{50}$ for replication competent virus.

*- indicates planned analysis for independent monitoring committee review between cohorts.

4.1.4 Inclusion and Exclusion Criteria

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

1. Positive for SARS-CoV-2 antigen via nasal swab detected using BD Veritor™ Plus System.
2. Onset of signs and symptoms consistent with COVID-19* no longer than within the past 3 days and have either a) fever of at least 100 °F or b) at least two moderate or severe symptoms (cough, sore throat, nasal congestion, headache, chills/sweats, muscle or joint pain, fatigue, and nausea) at the time of screening.
3. Provides written informed consent prior to initiation of any study procedures.
4. Be able to understand and agrees to comply with planned study procedures and be available for all study visits.
5. Agrees to the collection of nasopharyngeal swabs, oral saliva specimen collection and venous blood specimens per protocol.
6. Agrees to refrain from using oral antiseptics (e.g. hydrogen peroxide rinse, Listerine) or mouthwashes of any kind during the study.
7. Male or non-pregnant female, 18 to 65 years of age, inclusive, at time of enrollment.
8. No uncontrolled disease process (chronic or acute), other than COVID-19 signs and symptoms*.
9. No physical or mental conditions or attributes at the time of screening, which in the opinion of the PI, will prevent full adherence to, and completion of, the protocol.

*The following COVID-19 onset of signs and symptoms generally appear 2-7 days after exposure to SARS-CoV-2:

- Cough
- Sore throat
- Nasal Congestion
- Headache
- Chills/sweats
- Muscle or joint pain
- Fatigue
- Nausea

Severity of each COVID-19 symptom will be assessed based on definitions used for graded adverse events:

- None (Grade 0): Not present
- 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.

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

1. Positive urine pregnancy test at screening.
2. Any medical disease or condition that, in the opinion of the site Principal Investigator (PI) or appropriate sub-investigator, precludes study participation.
3. Presence of self-reported or medically documented uncontrolled significant medical or psychiatric condition(s) other than COVID-19.
4. Reports a recent positive test result (within the past 6 months) for hepatitis B surface antigen, hepatitis C virus antibody, or HIV-1 antibodies at screening.
5. Has a history of alcohol abuse or other recreational drug (excluding cannabis) use within 1 month of Study Day 1.
6. COVID-19 signs associated with acute respiratory distress or imminent serious medical outcomes.^^
7. BMI ≥36.

8. Has participated in another investigational study involving any intervention for SARS-CoV-2/COVID- 19 within the past 6 months or any clinical trial with interventional investigational product within 30 days of screening.
9. Currently enrolled in or plans to participate in another clinical trial with an interventional investigational agent that will be received during the study period.
10. History of hospitalization within the past 60 days.
11. History of systemic antiviral therapies within the past 30 days.
12. History of oral corticoid steroid use within the past 14 days or steroid injection within the past 6 months. Active use of nasal or inhalable steroids is also exclusionary. Topical steroids are not exclusionary.
13. Has a history of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticaria, angioedema, other significant reaction) to nitrites, nitrates or sun exposure.
14. Has any oral abnormality (e.g. ulcer, oral mucositis, gingivitis) that in the opinion of the investigator would interfere with device use, or 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.

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

- Fever > 104^{o} F
- Cough with sputum production
- Rales and/or rhonchi
- Difficulty breathing or respiratory distress defined by a respiratory rate ≥30 per minute, heart rate ≥125 per minute, SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2 <300.
- Persistent pain or pressure in the chest
- Confusion

4.2 Study Schedule of Activities

Study Procedures	Screening, Enrollment & Randomization	Follow-up Period (Visit Window)			
Study Days	**1**	**2**	**3**	**5 (-1 to +1)**	**8/ET (-1 to +1)**
Informed Consent	X				
COVID19 Screening & SARS-CoV-2 Rapid Antigen Test	X				
Medical History & Physical Examination	X	Changes since last visit only	Changes since last visit only	Changes since last visit only	X
Oropharyngeal Assessment	X*	Changes since last visit only	Changes since last visit only	Changes since last visit only	X
Urine Pregnancy Test	X				X
Concomitant Medication History/New	Baseline	Changes since last visit only	Changes since last visit only	Changes since last visit only	Changes since last visit only
Comprehensive Metabolic Panel & CBC	X				X
Vital Signs	X				X
Methemoglobin	X				X
Adverse Event Assessment / Reactogenicity	Baseline	X	X	X	X
Demographics, Inclusion / Exclusion Review	X				
Diary Dispensation/Collection	X				X
Treatment at Site	X**	X**	X**		
Saliva collection for viral assays (2 specimens)	X		X	X	X
COVID-19 Clinical Score	X		X	X	X
Collect RD-X19 Device	NA			Cohort 1	Cohort 2

*On Day 1 to be evaluated 30 minutes after first illumination at site. **Only one treatment will be done on site, other treatment will be done at home, i.e. if afternoon appointment, subject will complete morning treatment at home and afternoon treatment administered at the site. For scheduling purposes, recommended interval between treatment is approximately 8 – 12 hours but not $\leq$ 4 hours.

5 INTRODUCTION

5.1 Background and Study Rationale

In December 2019 the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknow cause. Coronavirus ribonucleic acid (RNA) was quickly identified in some of these patients. As of October 11, 2020 there were approximately 37 million confirmed cases wordwide (>7.7 million in the US) and over 1,075,000 deaths (~215,000 in the US). The only FDA approved intervention currently is Remdesivir for hospitalized subjects with COVID-19. Other interventions currently being used are through the Emergency Use Authorizations (EUA), against SARS-CoV-2 / COVID-19. Social distancing and personal protective equipment constitute our only viable countermeasures to help reduce incidence of community acquisition and transmission of SARS-CoV-2. Vaccine candidates are being developed at an unprecedented speed, however their efficacy and safety is unknown and will not be fully defined for many months. Remdesivir, Convalescent Immune Plasma and SoluMedrol are all used to treat patients hospitalized with COVID-19, but none has received marketing approval as a therapeutic for uncomplicated COVID-19. Therefore, there remains an urgent public health need for rapid development of novel measures for prevention and treatment of SARS-CoV-2 and COVID-19.

RD-X19 through both direct and intermediate mechanisms, kills cell-free virus by as much as 99.99% and inhibits cell-associated replication of SARS-CoV-2 by 99.9% when measured at 24 hours after a single 5 minute treatment. Putative key virucidal mechanisms include upregulation of nitric oxide in epithelial tissue through increase of nitric oxide synthases (NOSs) and stimulation of the instantaneous release of the body's bound store of nitric oxide. Nitric oxide produced physiologically in epithelial tissues also induces and attracts effector cells of the innate immune system, including natural killer (NK) cells, neutrophils and macrophages to phagocytize virus-infected cells at the site of primary infection. The technology utilized by RD-X19 has been repeatedly demonstrated to provide high-level viral control in multiple, consistent, expert-laboratory in vitro studies. The mechanism of action, utilizing augmented innate immunity, presents an unprecedented opportunity for protection that is not specific antigen-directed or dependent.

5.1.1 EmitBio™ RD-X19 Device Characteristics

Table 2.

Characteristic	Target
Route of Administration	Oral Illumination
Device Configuration	Hand-held, rechargeable
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Target Exposure Area	Oropharynx and surrounding tissues
[redacted]	[redacted]
[redacted]	[redacted]
Depth of Tissue Penetration	< 0.5 mm
Temperature (IEC 60601-1)	< 48 °C (for durations <10 min)

*[redacted]

5.2 Risk/Benefit Assessment

5.2.1 Known Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn and mild, transient, local reactions as measured in RD19-01-3Q20 , a Phase I Open Label, Acute Safety Study of the EmitBio™ RD-X19 Device.

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

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

Eye exposure is to be avoided. Direct illumination of unprotected eyes can result in damage to the retina, and especially the macula. Other eye structures can also experience thermal injury. Study staff must ensure volunteers understand to never point the RD-X19 device toward their or anyone else's eyes.

RD19-01-3Q20 Phase I Trial

This was a first-in-man Phase I study that evaluated the acute safety and tolerability of the RD-X19 device among 25 healthy volunteers between the ages of 18 and 45. A single dose [redacted] and schedule ([redacted]

[redacted]) was evaluated for 14 consecutive days. In total, subjects received a weekly dose of [redacted] per week for a time weighted average of [redacted].

No SAEs were observed during the study. No AEs based on laboratory findings were observed during the study.

Twelve (12) study subjects reported a total of 3 distinct AE terms (local site reaction, headache, nausea) and 23 total AEs. Of the 23 total AEs, 22 were classified as mild (grade 1) with a single headache classified as moderate (grade 2). No AE required treatment or alteration to the study subject's participation in the trial. No study subject withdrew from the trial because of an AE.

All AEs were of short duration, with resolution typically reached the same day or within 24 hours. Since study subjects used the RD-X19 device approximately every 12 hours for 14 contiguous days, there was a continuous temporal association with RD-X19 device use and incident AEs during the course of RD19-01-3Q20. By definition, all local site reactions were attributed to the device; all were mild and transient and there was no pattern of increasing frequency with repeated, cumulative dosing.

Population-based epidemiological data for headaches and nausea were considered when establishing device attribution. Approximately 40% of the general adult population have weekly headache and over 30% suffer from intermittent bouts of nausea of unknown origin. Given the frequencies of headache and nausea reported in RD19-01-3Q20 are less than those reported in population-based epidemiological studies, the relationship with the RD-X19 device cannot be determined.

In summary, the RD19-01-3Q20 Phase I trial demonstrated that EmitBio™ RD-X19 is a safe device, consistent with the sponsor's and IRB's original conclusion that RD-X19 is a NSR device.

Risks to Privacy

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

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

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

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

5.2.2 Known Potential Benefits

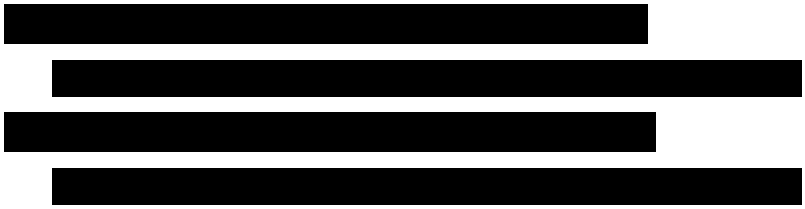
There is no guaranteed benefit to study participants. Use of EmitBio™ RD-X19 is intended to reduce viral load of SARS-CoV-2 and alleviate the symptoms associated with uncomplicated COVID-19. There is also the potential for benefit to society resulting from insights gained from

participation in this study due to the widespread, and accelerating, threat of SARS-CoV-2 and COVID-19.

6 STUDY DESIGN

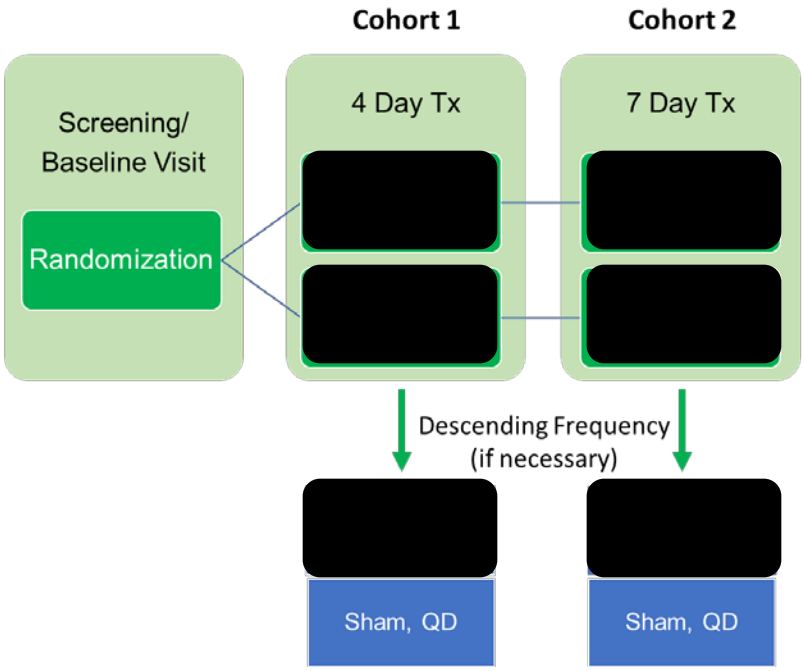
6.1 Overall Design

Volunteers will provide informed consent prior to initiating any screening procedures. Those meeting all screening criteria will be eligible for enrollment and randomization into the study. Study subjects will be enrolled into treatment and control arms within two cohorts:



Volunteers meeting all inclusion criteria and none of the exclusion criteria will be randomized to the RD-X19 treatment arm or the sham treatment arm within each cohort. Study subjects will be randomized in a 2:1 ratio (20 RD-X19 : 10 sham) per dose cohort. The double-blind, sham-controlled period will last 8 days. Assessments of study subjects will occur on study days 1, 2, 3, 5 and the final assessment visit on Day 8. Since CMP and CBC results will not be available until study day 2, all volunteers who have significant abnormalities will be immediately contacted and advised of the abnormality, discontinued from active participation in the protocol and advised regarding appropriate medical follow-up outside the study. All such study subjects will be replaced with a new volunteer. This is a randomized, adaptive, group sequential dose finding study. The primary goal of the study is to evaluate the efficacy and safety of the RD-X19 device in SARS-CoV-2 infected individuals with outpatient COVID-19. The primary efficacy outcome is the time weighted average change in SARS-CoV-2 viral load assessed via RT-qPCR. Safety assessment will include the incidence of device-related serious adverse events or patterns of severity ≥2 device-related adverse events.

Figure 1: Study Design



The interim analysis at the conclusion of Cohort 1 will consist of the following evaluations:

- A planned efficacy evaluation of the time weighted average change in SARS-CoV-2 viral load from baseline will be conducted as an assessment of benefit to the subjects.
- Safety evaluations, performed by an independent safety monitoring team as outlined in the committee charter, are to ensure that each dose level under evaluation is safe through 4 days of treatment. Specific criteria for safety review will include:
  - Number of subjects experiencing laryngospasm, bronchospasm or anaphylaxis within 2 hours after use of the RD-X19 Device that is considered related to RD-X19.
  - Number of subjects experiencing an allergic reaction such as generalized urticaria (defined as occurring at three or more body parts) within 72 hours after administration of light that is considered related to RD-X19.
  - Number of subjects experiencing an SAE or Grade 3 AE, in the same SOC grouping of Preferred Terms based on Medical Dictionary for Regulatory Activities (MedDRA) coding, considered to be related to RD-X19.

Safety and tolerability (local reactogenicity) will be assessed actively on each clinic visit by review of potential adverse events (AEs) and targeted physical examination, as required. Volunteers will be encouraged to contact designated clinical trial staff for AEs of a medically-urgent nature as soon as is practically possible and to seek immediate medical care, if needed.

Metabolic, liver, kidney and hematological laboratory evaluations will be performed at screening and at Day 8 or early termination (and potentially during unscheduled) clinic visits.

Study Subject safety will be monitored throughout the study by the Investigator and supported by regular review by the Medical Monitor and an external Data Monitoring Committee.

6.2 Objectives and Endpoints

Table 1: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Safety Assessments	
• AEs and SAEs*	• The primary safety measure is absence of device-related serious adverse events or any patterns of severity ≥2 device-related adverse events.*
• Methemoglobin	• Mean change in methemoglobin from baseline to Day 8/ET.
Efficacy Assessments	
• Viral load	• Time weighted average change in viral load from baseline by RT-qPCR from Day 1 to Day 8 • Geometric mean viral load as measured in saliva on day 1, 3, 5, and 8 by RT-qPCR* • Proportion of subjects demonstrating viral load reduction ≥ 95% by RT-qPCR (at each visit)*
• Viral infection	• Time to clearance of viral infection in saliva, defined as a negative test (Ct value ≥32) via RT-qPCR. • Proportion of subjects demonstrating clearance of viral infection, defined as a negative test (Ct value ≥32) via RT-qPCR on Day 8/ET.
• Symptoms	• Median time to alleviation of symptoms as measured by the time when all eight symptoms (cough, sore throat, nasal congestion, headache, chills/sweats,

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• COVID-19 composite severity score.	muscle or joint pain, fatigue, and nausea) had been assessed by the subject as none (0) or mild (1).
Exploratory Assessment(s)	
• Viral load by viral titer (at each visit)	• Geometric mean viral load as measured in saliva on day 1, 3, 5, and 8 by $TCID_{50}$ for replication competent virus.

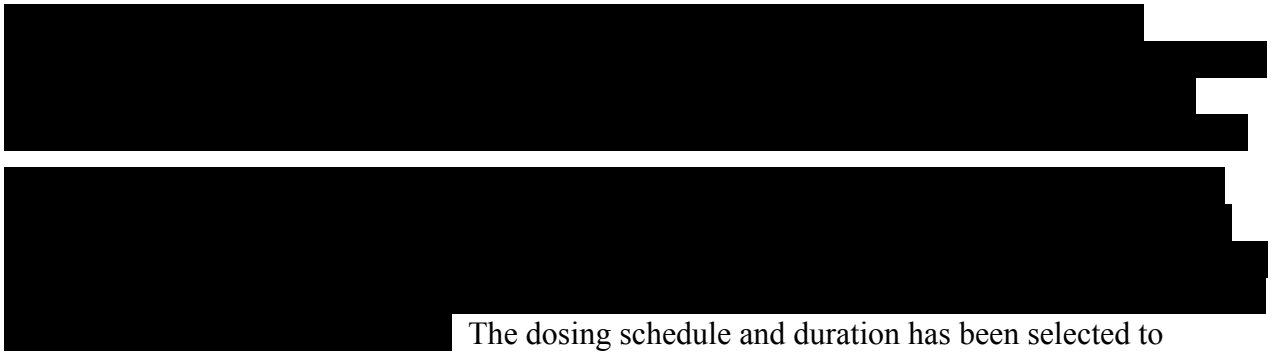
*- indicates planned analysis for independent monitoring committee review between cohorts.

6.3 Scientific Rationale for the Study

RD-X19 through both direct and intermediate mechanisms, kills cell-free virus by as much as 99.99% and inhibits cell-associated replication of SARS-CoV-2 by 99.9% when measured at 24 hours after a single 5 minute treatment. Putative key virucidal mechanisms include upregulation of nitric oxide in epithelial tissue through increase of nitric oxide synthases (NOSs) and stimulation of the instantaneous release of the body's bound store of nitric oxide. Nitric oxide produced physiologically in epithelial tissues also induces and attracts effector cells of the innate immune system, including natural killer (NK) cells, neutrophils and macrophages to phagocytize virus-infected cells at the site of primary infection. The technology utilized by RD-X19 has been repeatedly demonstrated to provide high-level viral control in multiple, consistent, expert-laboratory in vitro studies. The mechanism of action, utilizing augmented innate immunity, presents an unprecedented opportunity for protection that is not specific antigen-directed or dependent.

6.3.1 Justification for Doses

In repeated experiments, including experiments conducted by third party external laboratories, it has been determined that the light emitted by the EmitBio™ RD-X19 device provides for potent antiviral activity against 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. [redacted] These repeated experiments, conducted in multiple labs with multiple cell types, along with years of medical use of licensed devices with comparable [redacted], support the doses proposed in this protocol for dose finding to achieve optimal efficacy and safety.



The dosing schedule and duration has been selected to provide a reduction in viral load and symptomatic relief as rapidly as possible in COVID-19 patients while still maintaining an acceptable safety margin for each individual treatment session.

If patterns of ≥ grade 2 device-related adverse events are observed, dosing will be reduced to one exposure/day for the remainder of treatment time. If serious or severe device-related adverse events are observed, further treatments at that dose will be terminated.

Strict safety oversight will provide rapid detection of significant device/dose-related adverse events warranting pausing or halting the trial.

7 STUDY POPULATION

The study population is individuals infected with SARS-CoV-2 who have symptoms associated with COVID-19 that is either not under active medical treatment or is being treated as an outpatient. Study subjects must be symptomatic for 3 days or less and have a positive COVID-19 antigen test using the BD Veritor^{TM} Plus System. Study subjects will be randomized to treatment arm within dose in a 2:1 ratio according to a fixed schedule using a permuted block design. The targeted number of subjects randomized per dose is 30 (20 volunteers to the RD-X19 arm, 10 subjects to the sham arm). This is a sample size of convenience as this is a hypothesis generating study.

The target population should reflect the subject population with uncomplicated COVID-19 in the community at large.

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

7.1 Inclusion Criteria

A subject must meet all the following criteria to be eligible to participate in this study:

1. Positive for SARS-CoV-2 antigen via nasal swab detected using BD Veritor™ Plus System.
2. Onset of signs and symptoms consistent with COVID-19* no longer than within the past 3 days* and have either a) a fever of at least 100 °F or b) at least two moderate or severe symptoms (cough, sore throat, nasal congestion, headache, chills/sweats, muscle or joint pain, fatigue, and nausea) at the time of screening.
3. Provides written informed consent prior to initiation of any studyprocedures.
4. Be able to understand and agrees to comply with planned study procedures and be available for all study visits.

5. Agrees to the collection of nasopharyngeal swabs, oral saliva specimen collection and venous blood specimens per protocol.
6. Agrees to refrain from using oral antiseptics (e.g. hydrogen peroxide rinse, Listerine) or mouthwashes of any kind during the study.
7. Male or non-pregnant female, 18 to 65 years of age, inclusive, at time of enrollment.
8. No uncontrolled disease process (chronic or acute), other than COVID-19 signs and symptoms*.
9. No physical or mental conditions or attributes at the time of screening, which in the opinion of the PI, will prevent full adherence to, and completion of, the protocol.

*The following COVID-19 onset of signs and symptoms generally appear 2-7 days after exposure to SARS-CoV-2:

- Cough
- Sore Throat
- Nasal Congestion
- Headache
- Chills/sweats
- Muscle or joint pain
- Fatigue
- Nausea

Severity of COVID-19 symptoms will be assessed based on definitions used for graded adverse events:

- None (Grade 0): Not present
- 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.

7.2 Exclusion Criteria

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

1. Positive urine pregnancy test at screening.

2. Any medical disease or condition that, in the opinion of the site Principal Investigator (PI) or appropriate sub-investigator, precludes study participation.
3. Presence of self-reported or medically documented uncontrolled significant medical or psychiatric condition(s) other than COVID-19.
4. Reports a recent positive test result (within the past 6 months) for hepatitis B surface antigen, hepatitis C virus antibody, or HIV-1 antibodies at screening.
5. Has a history of alcohol abuse or other recreational drug (excluding cannabis) use within 1 month of Study Day 1.
6. COVID-19 signs associated with acute respiratory distress or imminent serious medical outcomes. ^^
7. BMI ≥36.
8. Has participated in another investigational study involving any intervention for SARS-CoV-2/COVID- 19 within the past 6 months or any clinical trial with interventional investigational product within 30 days of screening.
9. Currently enrolled in or plans to participate in another clinical trial with an interventional investigational agent that will be received during the study period.
10. History of hospitalization within the past 60 days.
11. History of systemic antiviral therapies within the past 30 days.
12. History of oral corticoid steroid use within the past 14 days or steroid injection within the past 6 months. Active use of nasal or inhalable steroids is also exclusionary. Topical steroids are not exclusionary.
13. Has a history of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticaria, angioedema, other significant reaction) to nitrites, nitrates or sun exposure.
14. Has any oral abnormality (e.g. ulcer, oral mucositis, gingivitis) that in the opinion of the investigator would interfere with device use, or 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.

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

- Fever > 104º F
- Cough with sputum production
- Rales and/or rhonchi
- Difficulty breathing or respiratory distress defined by a respiratory rate ≥30 per minute, heart rate ≥125 per minute, SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2 <300.
- Persistent pain or pressure in the chest
- Confusion

7.3 Study Volunteer Selection, Retention & Compensation

7.3.1 Recruitment

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

7.3.2 Retention

Study retention strategies will include education and explanation of the study schedule and procedures during screening and enrollment visits and restriction of enrollment to persons who can attend all study visits. Participating subjects will be reminded of subsequent visits during each visit, and study staff will contact subjects prior to appointments. Study staff will contact subjects who miss appointments to encourage them to return for completion of safety evaluations.

7.3.3 Compensation Plan for Subjects

Subjects will be compensated for their participation in this trial. Compensation will take into consideration both the urgency and importance of developing new treatments for this COVID-19 pandemic and local IRB guidelines, and will be ultimately subject to local IRB approval. Reimbursements will be disbursed at specific timepoints during the study with the total amount contingent on completing study procedures.

7.3.4 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, subject's insurance or third party.

8 STUDY DEVICE

8.1 Regulatory Considerations

8.1.1 Preliminary Regulatory Pathway for EmitBio™ RD-X19

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

Risk management activities have been completed according to EmitBio's SOP for Risk Management and a Risk Management Plan was developed, which are compliant with the applicable 21 CFR part 820 regulations, ANSI AAMI ISO 14971, and ISO TR 24971. A Hazard

Analysis, including a Failure Effects Mode Analysis, of the device characteristics and use was performed based on ANSI AAMI ISO 14971.

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

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

EmitBio™ conducted RD19-01-3Q20 under 21 CFR 812 as a Non-Significant Risk (NSR), Minimal Risk protocol. The Institutional Review Board agreed with EmitBio™ based on the protocol and supporting documentation submitted with the protocol and granted final approval to conduct the study on September 1, 2020.

8.1.2 Proposed Label Claim/Indication for Use:

The RD-X19 device is intended for use as a treatment to reduce viral load in the upper respiratory tract in subjects ages 12 to 65 who have tested positive for SARS-CoV-2 and who have symptoms consistent with uncomplicated COVID-19 for no more than 3 days.

8.1.3 Medical Device Quality System:

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

8.2 Study Device and Use

8.2.1 Device Description

[redacted]

8.3 Use / Storage & Maintenance / Accountability

8.3.1 Acquisition and Accountability

The sponsor will provide clinical sites with RD-X19 devices packaged in appropriately labelled containers containing all components as well as instructions for use by study participants. Each RD-X19 device will be stamped on its power unit with a serial number. Study staff will ensure that each device's serial number 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 termination of a subject's participation in the trial, all RD-X19 devices and components must be returned to the study site and then to the study sponsor.

8.3.2 Device Storage and Maintenance

All RD-X19 devices will be stored in a locked device storage room at the clinical trial site until needed for assignment to an enrolled study volunteer. Upon acquisition by the study subject, devices should be stored in a dry climate-controlled environment in the original container in which it was provided.

The device should be stored securely out of the reach of children who may mistakenly misuse the device, especially illumination of eyes – which is always to be avoided. The mouthpiece of the device is removable for rinsing with mild soap and warm water. The device tongue depressor and 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 device can be wiped gently with a dry cloth suitable for cleaning optical glasses.

8.3.3 Preparation for Use and Use

[Refer to Appendix 1: RD-X19 User Instructions]

8.4 Measures to Maximize Study Subject Compliance

Randomization between active treatment and sham control devices has been set at 2:1 to provide higher probability of the subjects being randomized to the investigational treatment during the study duration.

Subjects will receive appropriate compensation for the disruption to normal daily activities created by this protocol that also considers the frequency with which they are requesting to travel to the site, the twice daily journaling and treatment regimen, and the number of biospecimens scheduled to be collected for virology assessments.

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

8.5 Device Discontinuation

8.5.1 Study Pausing Criteria

EB-P12-01 enrollment will be paused if any of the following events occur:

- Any subject experiences an SAE after use of the RD-X19 Device that is considered related to RD-X19.
- Any subject experiences laryngospasm, bronchospasm or anaphylaxis within 2 hours after use of the RD-X19 Device that is considered related to RD-X19.
- 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 administration of light that is considered related to RD-X19.
- Three (3) or more subjects experience a Grade 3 AE (systemic and/or clinical laboratory abnormality), in the same SOC grouping of Preferred Terms based on the Medical Dictionary for Regulatory Activities (MedDRA) coding, considered to be related to RD-X19.

Enrollment may resume only after external safety review of the SAE/AEs that caused the pause to the study. Given the frequency of visits and the duration of the protocol, study device use may continue after assessing the safety and AEs for individual subjects at either regulatory scheduled or an unscheduled site visits.

8.5.2 Subject elects to discontinue

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

8.5.3 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, or at least 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 AE, clinical laboratory abnormality or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The occurrence of a SAE.

- If the subject is using the device in any manner inconsistent with instructions and protocol directives and procedures.

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

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

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

8.5.4 Follow-up of Study Subjects Who Discontinue Device Use

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

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Screening Assessments

9.1.1 Screening Procedures

At the screening visit, and prior to any other study-related activities, the participating clinical site PI or appropriate sub-investigator will provide the subject with detailed study information and will obtain written informed consent (see section 11.1.1 for more details).

Subject numbers will be assigned with the three-digit numerical site number beginning with numbers greater than one hundred (e.g. 101) followed by an alphanumeric cohort identifier (e.g. C1) and finally a two digit unique numerical identifier assigned with each new subject (e.g. 01).

Example Subject Number: 101-C1-01

COVID-19 Screening

Eligible subjects presenting with uncomplicated COVID-19 must have an oral temperature of at least 100 ˚F or have at least two moderate or severe symptoms (cough, nasal congestion, or sore throat, headache, chills/sweats, muscle or joint pain, fatigue, or nausea) and consent to be randomized within 3 days of first symptom onset. The subjects will self-assess their COVID-19 symptoms as none (0), mild (1), moderate (2), or severe (3) during screening.

Additionally, subjects who identify with symptomatology associated with COVID-19 will be screened by taking a nasal culture and analyzed for the presence of SARS-CoV-2 by the BD Veritor™ Plus System. The Veritor™ System for rapid detection of SARS-CoV-2 is a chromatographic immunoassay for the direct and qualitative detection of SARS-CoV-2 antigens.

There is a small amount of risk to subjects who report mild-to-moderate symptomatology consistent with COVID-19 may have an unknown health problem or co-morbidity at the time of screening that can lead to worsening of condition or hospitalization during study.

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 medical history focusing on conditions per protocol exclusion criteria.
- Review all pre-study medications, vitamins, supplements, and therapies up to 14 days prior to the start of screening that could impact the use of, or response to, the device and record on the appropriate e-CRF. Subjects are allowed to use over-the-counter medications and remedies to alleviate symptoms (e.g. acetaminophen, ibuprofen, cough drops, etc. and should be recorded.)
- Measure vital signs (HR, BP, and oral temperature) and height and weight for determination of BMI.
- Perform full physical examination which will include assessments of the following organs and organ systems: skin, head, ears, eyes, nose, and throat (HEENT), neck, lungs, heart, liver, spleen, abdomen, extremities, lymph nodes (axillary and cervical), and nervous system.
- Obtain blood and urine for clinical screening laboratory evaluations:
  - Comprehensive Metabolic Panel (fasting or non-fasting)
  - CBC with differential
  - Urine pregnancy test (in women of childbearing potential)
- Review inclusion and exclusion criteria.

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

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

If a physiologic parameter, e.g., vital signs, is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the participating clinical site PI or appropriate sub-investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition (e.g., stress, anxiety or "white coat syndrome") or other source of error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

A subject may be re-screened if there is a transient disease status (e.g., absent signs and symptoms associated with mild COVID-19), or 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 2 days using the same subject number.

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

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

9.1.2 Procedures for Abnormal Clinical Laboratory Values or Findings

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

All abnormal clinical findings that occur post randomization and the first use of the RD-X19 device will be considered AEs.

9.2 Safety and Other Assessments

Study procedures are specified in protocol section 4.2. A study clinician, licensed to make medical diagnoses as the participating clinical site PI or appropriate sub-investigator, will be responsible for all study-related medical decisions.

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

- Targeted physical examinations will primarily focus on assessment of signs and symptoms suggestive of AEs. Interim or unscheduled physical examinations will be performed at the discretion of the participating clinical site PI or appropriate sub-investigator, if necessary, to evaluate AEs.

- Subjects will be observed in the clinic for at least 30 minutes post the first RD-X19 illumination. The oropharynx and surrounding tissues will be examined. Reactogenicity assessments will be performed on Days 1, 2, 3, 5, and 8. An oropharyngeal examination will also be performed on Days 1 and 8 and during unscheduled visits and early termination visits and recorded on the appropriate source document prior to discharge from the clinic. Interim or unscheduled oropharyngeal examinations will be performed, if necessary, to evaluate AEs.

- Vital signs:

  Vital sign measurements will include systolic and diastolic BP, HR, and oral temperature. Vital signs will be measured at timepoints specified in protocol section 4.2. 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.

- Clinical laboratory evaluations:
  - Fasting is not required before collection of clinical laboratory evaluations.
  - Urine pregnancy test will be performed locally by the site laboratory at the screening visit and at the final study visit. Results must be confirmed as negative prior to randomization on Day 1 and allocation and use of the RD-X19 device.
  - Clinical laboratory evaluations CMP and CBC (diff) will be performed locally by the site selected laboratories.
    - Clinical safety laboratory evaluations will be performed locally by the site laboratory.
    - Blood and urine will be collected at timepoints specified in the protocol section 4.2.

9.2.1 Definition of Adverse Event (AE)

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

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

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

All AEs will be assessed for severity and relationship to study intervention. Reporting of all AEs, solicited and unsolicited, will occur during the period from study device administration on Day 1 through Day 8 or until an early termination visit.

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

AEs will be followed to resolution or stabilization.

9.2.2 Solicited Adverse Events - Reactogenicity

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

For this study, solicited AEs include:

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

9.2.3 Unsolicited Adverse Events

All AEs 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.

9.2.4 Adverse Event Reporting

Information on all AEs 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 AE should be grouped together and recorded as a single diagnosis. If the AE is a clinical laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis and be described in terms of duration (start and stop date).

9.2.5 Definition of a Serious Adverse Event (SAE)

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

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

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

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

All SAEs, as with any AE, 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 to the IRB. This report will include severity, association with the study device, action(s) taken, and outcome.

9.2.6 Serious Adverse Event Reporting

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

EmitBio™ Pharmacovigilance

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

Text Immediate Report: 1-843-540-3550

SAE Email: jmcneil@emitbio.com

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

Other supporting documentation of the event may be requested by EmitBio™ Pharmacovigilance and should be provided as soon as possible. The Sponsor Medical Monitor will review and assess

the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

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

9.2.7 Regulatory Reporting of Device-related SAEs

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

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

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

9.2.8 Classification of an Adverse Event

The determination of seriousness, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs and classify AEs based upon medical judgment. This includes, but is not limited to, physicians, physician assistants and nurse practitioners.

9.2.9 Severity of Adverse Events

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

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

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

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate e-CRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

9.2.10 Relationship to Study Intervention

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

- Related – The 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.

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

For this study:

Solicited and Unsolicited AEs will be recorded by clinical trial staff for the entire duration of the study.

9.2.12 Adverse Event Reporting to Study Subjects

All device-attributed AEs and SAEs will be reported to participants in the study to better inform them of the potential risks vs. benefits of participation.

9.2.13 Pregnancy Reporting

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

9.3 Efficacy Assessments

Efficacy comparisons will be made in the ITT Population with the intent of estimating the effect of the RD-X19 device relative to sham in several outcome measures. Subjects will be instructed to fill out diary cards twice daily to assess their symptoms associated with disease progression and record the number of treatments completed. Additionally, at Baseline and days 3, 5, and 8, subjects will provide two saliva specimens for virology endpoint assessments. One saliva specimen will be collected, preserved, and shipped fresh to a central lab for assessment of SARS-CoV-2 mRNA via RT-qPCR. The second specimen will be collected in a separate collection tube, frozen, and stored at the site and shipped to a central lab at the end of each cohort.

9.3.1 Efficacy assessments

Various endpoints will explore the impact of RD-X19 treatment on the reduction in log10 SARS-CoV-2 viral load and alleviation of symptoms associated with COVID-19. Both the magnitude of

reduction as a function of dose as well as time to clearance will be assessed in support of the primary efficacy analysis. Subjects will be instructed to fill out a diary card or electronic equivalent to assess their signs and symptoms of disease twice daily. Each of the eight symptoms will be rated on a scale from none (0) to severe (3).

- Time weighted average change in viral load from baseline by RT-qPCR from Day 1 to Day 8
- Geometric mean viral load as measured in saliva on day 1, 3, 5, and 8 by RT-qPCR
- Proportion of subjects demonstrating viral load reduction ≥95% by RT-qPCR (at each visit)
- Time to undetectable viral load in saliva by RT-qPCR.
- Proportion of subjects demonstrating clearance of viral infection, defined as a negative test via RT-qPCR on Day 8/ET.
- Median time to alleviation of symptoms,
    - The time to alleviation of symptoms endpoint, is defined as the time when all eight symptoms (cough, sore throat, nasal congestion, headache, chills/sweats, muscle or joint pain, fatigue, and nausea) had been assessed by the subject as none or mild.
- Change in COVID-19 Severity Score from baseline
    - The COVID-19 Severity Score is defined as the sum of all the individual symptom severity scores divided by the total number of symptoms assessed (8).
- Viral load by viral titer (at each visit)

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

This is a randomized, ascending dose finding study. The primary goal of the study is to evaluate the safety and efficacy of the RD-X19 device in SARS-CoV-2 infected individuals with uncomplicated COVID-19.

10.2 Power and Sample Size:

This is a double-blind study and hypothesis generating in nature. The sample size was selected for convenience.

Subjects will be randomized to treatment arm within dose in a 2:1 ratio according to a fixed schedule using a permuted block design and stratified by clinical site. The target number of subjects randomized per dose is 30 (20 subjects to the RD-X19 arm, 10 subjects to the sham arm.

One interim analysis is planned at the end of Cohort 1.

10.3 Populations for Analyses

Three analysis populations are defined for this study.

- The Safety Population includes all randomized subjects who receive at least 1 study treatment. This population will be used for all safety analyses. Subjects will be analyzed based on actual treatment received.
- The Intent-to-treat Population (ITT) includes all randomized subjects who received treatment and were not discontinued due to a significant abnormality from the baseline CMP and CBC tests. This population will be used for all efficacy analyses as the primary population. Subjects will be analyzed based on randomized treatment, regardless of the actual treatment received.
- The Per Protocol (PP) Population includes all randomized subjects who complete the study and did not have a major protocol deviation (MPD). The PP population will be used for supportive analysis of the efficacy endpoints. MPDs are those that could have interfered with the administration of treatment or the precise evaluation of treatment efficacy (e.g. violation of inclusion/exclusion criteria, no Day 3 visit, etc.). All MPDs will be identified before the database lock and study unblinding for analysis.

10.4 Statistical Analyses

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

In general, missing data will not be imputed with the exception that for the ITT analysis, missing viral load results will be imputed using the last-observation-carried-forward (LOCF) methodology.

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

10.4.1 Efficacy Analyses

The primary efficacy endpoint is defined as time-weighted average (TWA) change in log10-transformed viral load by RT-qPCR from baseline to Day 8, where TWA will be derived using the trapezoidal rule. At the final analysis, each dose of the RD-X19 device will be compared to sham using an Analysis of Covariance (ANCOVA) model with baseline viral load as a covariate and treatment group as an independent variable. Geometric means and their 95% CIs will be computed by exponentiating (base 10) the least squares means and 95% CIs of the log10-transformed viral load.

Secondary efficacy endpoints include:

- log10-transformed Viral load as measured in saliva by RT-qPCR at each visit
- proportion of subjects with ≥95% reduction in SARS-CoV-2 viral load at each visit
- time to undetectable viral load in saliva by RT-qPCR
- proportion of subjects demonstrating clearance of viral infection, defined as a negative test via RT-qPCR at Day 8/ET visit
- COVID-19 composite severity score at each visit
- time to alleviation of COVID-19 symptoms, defined as the time when all eight symptoms had been assessed by the subject as none or mild.

Exploratory efficacy endpoint includes log10-transformed viral load at each visit as measured by $TCID_{50}$ for replication competent virus.

All secondary and exploratory efficacy endpoints will be summarized using descriptive statistics by visit (as appropriate) for each treatment group. For log10-transformed viral load data, geometric means will be computed by exponentiating (base 10) the group means of the log10-transformed viral load. Time-to-event variables will be evaluated using the Kaplan-Meier method.

10.4.2 Safety Analyses

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

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

11 OPERATIONAL CONSIDERATIONS AND SUPPORTING DOCUMENTS

11.1 Ethical Considerations

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

An OHRP-registered IRB will review and approve this protocol, associated informed consent documents, recruitment material, and handouts or surveys intended for the subjects, prior to the recruitment, screening, and enrollment of subjects. The IRB review shall be in accordance with 45 CFR 46 and 21 CFR 50, 21 CFR 56 (IRBs), 21 CFR 812 and other federal, state, and local regulations and policies, as applicable.

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

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

11.1.1 Informed Consent Process

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

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

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

Subjects will be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential. Subjects will be informed, even if identifiers are removed, that information collected from this research and/or specimens may be used for secondary research, including the sharing of deidentified data.

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

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

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

11.1.2 Confidentiality and Privacy

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

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

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

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

11.1.3 Clinical Monitoring

Monitoring will be conducted during the conduct of the trial, and will include, but is not limited to, source document verification, review of regulatory files, device accountability records, e-CRFs, ICFs, medical and laboratory reports, training records, and protocol and GCP compliance. The monitors will have access to all study related documents and will meet with appropriate clinical site staff to discuss any problems and outstanding issues. Visit findings and discussions will be documented. Some monitoring visits may be conducted remotely.

11.1.4 Quality System

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

11.1.5 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the participating clinical trial site under the supervision of the participating clinical site PI and the overall study PI. The participating clinical trial site PI must maintain complete and accurate source documentation. Clinical research data from source documentation, including, but not limited to, 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.

11.1.6 Source Documents

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

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

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

11.1.7 Study Record Retention

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

11.1.8 Protocol Deviations

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

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

It is the responsibility of the participating clinical site PI and study staff to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to EmitBio Inc's Senior Clinical Program Manager. Protocol deviations must be sent to the IRB of record. The participating clinical site PI and study staff are responsible for knowing and adhering to the IRB requirements. A completed copy of an approved Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart if the deviation is subject specific.

11.1.9 Publication and Data Sharing Policy

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

11.1.10 Conflict of Interest Policy

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

11.1.11 Research Related Injuries

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

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

12 APPENDIX 1: RD-X19 USER INSTRUCTIONS

Confidential

13 APPENDIX 2: TOXICITY GRADING SCALES

Available upon request.

CLINICAL TRIAL PROTOCOL

A 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

Protocol Number: EB-P12-01 Version 2.0 (Amendment 1)

Amendment 1 Date of Issuance: November 6, 2020

Original Date of Issuance: October 28, 2020

Investigational Countermeasure: RD-X19

Specific Indication: Treatment of Uncomplicated COVID-19

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

Phase: I/II

Name and Address of Sponsor:

EmitBio Inc.
Suite 470, 4222 Emperor Blvd
Durham, NC 27703
Tel: + 1 (843) 540-3569

Name and Address of CRO:

Symbio, LLC
21 Perry Street
Port Jefferson, NY 11777
Tel: +1 (631) 403-5125

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

1 INSTITUTIONAL STATEMENT OF COMPLIANCE

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

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

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

2 INVESTIGATOR'S AGREEMENT

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

Principal Investigator Signature:

Signed: _____ Date: _____

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4 PROTOCOL SUMMARY

4.1 Executive Summary

In December 2019 the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknow cause. Coronavirus ribonucleic acid (RNA) was quickly identified in some of these patients. As of October 11, 2020 there were approximately 37 million confirmed cases wordwide (>7.7 million in the US) and over 1,075,000 deaths (~215,000 in the US). The only FDA approved intervention currently is Remdesivir for hospitalized subjects with COVID-19. Other interventions currently being used are through the Emergency Use Authorizations (EUA), against SARS-CoV-2 / COVID-19. Social distancing and personal protective equipment constitute our only viable countermeasures to help reduce incidence of community acquisition and transmission of SARS-CoV-2. Vaccine candidates are being developed at an unprecedented speed, however their efficacy and safety is unknown and will not be fully defined for many months. Remdesivir, Convalescent Immune Plasma and SoluMedrol are all used to treat patients hospitalized with COVID-19, but none has received marketing approval as a therapeutic for uncomplicated COVID-19. Therefore, there remains an urgent public health need for rapid development of novel measures for prevention and treatment of SARS-CoV-2 and COVID-19.

RD-X19 through both direct and intermediate mechanisms, kills cell-free virus by as much as 99.99% and inhibits cell-associated replication of SARS-CoV-2 by 99.9% when measured at 24 hours after a single 5 minute treatment. Putative key virucidal mechanisms include upregulation of nitric oxide in epithelial tissue through increase of nitric oxide synthases (NOSs) and stimulation of the instantaneous release of the body's bound store of nitric oxide. Nitric oxide produced physiologically in epithelial tissues also induces and attracts effector cells of the innate immune system, including natural killer (NK) cells, neutrophils and macrophages to phagocytize virus-infected cells at the site of primary infection. The technology utilized by RD-X19 has been repeatedly demonstrated to provide high-level viral control in multiple, consistent, expert-laboratory in vitro studies. The mechanism of action, utilizing augmented innate immunity, presents an unprecedented opportunity for protection that is not specific antigen-directed or dependent

4.1.1 Study Goals

This is a randomized, sham-controlled dose escalation and bioeffect study. The primary goal of the study is to evaluate the safety of the RD-X19 device in SARS-CoV-2 infected individuals with outpatient COVID-19 at two dosing schedules, and to assess the reduction of SARS-CoV-2 viral load in each dose group compared to sham controls. This is an efficacy hypothesis-generating study; sample size is based on convenience. However, there is adequate power to detect large differences in group SARS-CoV-2 reduction effects. The primary safety measure is absence of device-related serious adverse events or patterns of severity $\geq$2 device-related adverse events.

Safety and tolerability (local reactogenicity) will be assessed actively on each clinic visit by review of potential adverse events (AEs) and targeted physical examination, as required. Volunteers will be encouraged to contact designated clinical trial staff for AEs of a medically-urgent nature as soon as is practically possible and to seek immediate medical care, if needed.

Metabolic, liver, kidney and hematological laboratory evaluations will be performed at baseline and at Day 8 or early termination (and potentially during unscheduled) clinic visits. Methemoglobin assessments will be performed at baseline and Day 8.

4.1.2 **Study Design**

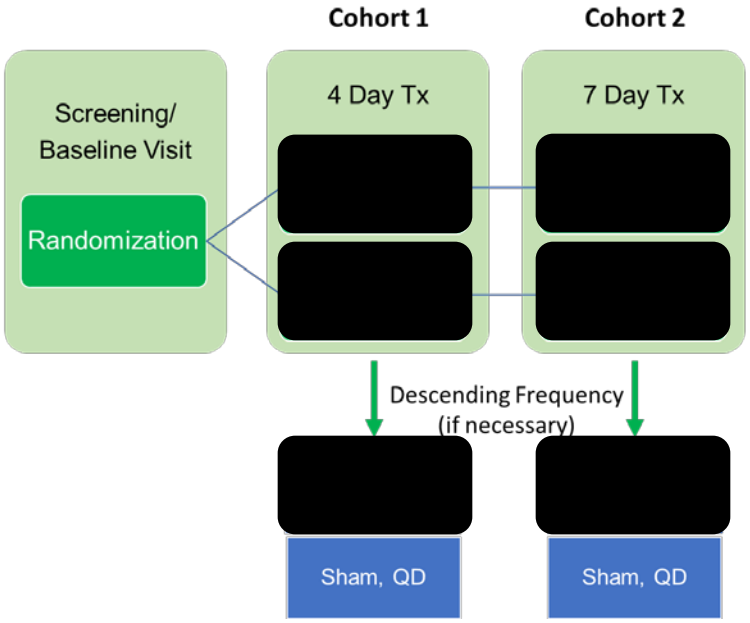
Subjects will provide informed consent prior to initiating any screening procedures. Subjects meeting all screening criteria will be eligible for enrollment and randomization into the study. This study plans to enroll into two treatment arms within two escalating dose cohorts:

Volunteers meeting all inclusion criteria and none of the exclusion criteria will be randomized to the RD-X19 treatment arm or the sham treatment arm within each cohort. Subjects will be randomized in a 2:1 ratio (20 RD-X19 : 10 sham) per dose cohort. The double-blind, sham-controlled treatment period of four (4) days of dosing for Cohort 1 is shown in Figure 1 below; increased weekly doses of light with twice daily dosing will occur in Cohort 2 for a treatment duration of seven (7) days. Light will be administered locally to the mouth and throat only, aiming to eliminate viral load in these targeted portions of the upper respiratory tract. Assessments of treatment response will occur on study days 3 and 5, with the final determination of efficacy made on day 8 (inclusive).

Study Subject safety will be monitored throughout the study by the Investigator and supported by regular review by the Sponsor's Chief Medical Officer.

Upon completion of all subjects in Cohort 1, the results of an unblinded interim analysis will be reviewed by a safety monitoring team and a recommendation will be made to the sponsor on whether the committee recommends proceeding with enrollment for the next cohort at the next planned dose or whether enrollment should continue in the next cohort at a reduced dosing frequency (e.g. once daily). The study is designed to evaluate at least 2 dosing schedules, ascending, or descending based on safety of each previous cohort.

Figure 1: Study Design



The interim analysis at the conclusion of Cohort 1 will consist of the following evaluations:

- A planned efficacy evaluation of the time weighted average change in SARS-CoV-2 viral load from baseline will be conducted as an assessment of benefit to the subjects.
- Safety evaluations, performed by a ~~independent~~ safety monitoring team as outlined in the committee charter, are to ensure that each dose level under evaluation is safe. Specific criteria for safety review will include:
  - Number of subjects experiencing laryngospasm, bronchospasm or anaphylaxis within 2 hours after use of the RD-X19 Device that is considered related to RD-X19.
  - Number of subjects experiencing an allergic reaction such as generalized urticaria (defined as occurring at three or more body parts) within 72 hours after administration of light that is considered related to RD-X19.
  - Number of subjects experiencing an SAE or Grade 3 AE, in the same SOC grouping of Preferred Terms based on Medical Dictionary for Regulatory Activities (MedDRA) coding, considered to be related to RD-X19.

4.1.3 Objectives and Endpoints

Table 1: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Safety Assessments	
• AEs and SAEs*	• The primary safety measure is absence of device-related serious adverse events or any patterns of severity ≥2 device-related adverse events.*
• Methemoglobin	• Mean change in methemoglobin from baseline to Day 8/ET.
Efficacy Assessments	
• viral load	• Time weighted average change in viral load from baseline by RT-qPCR from Day 1 to Day 8
	• Geometric mean viral load as measured in saliva on day 1, 3, 5, and 8 by RT-qPCR*
	• Proportion of subjects demonstrating viral load reduction ≥ 95% by RT-qPCR (at each visit)*
• viral infection	• Time to clearance of viral infection in saliva, defined as a negative test (Ct value ≥32) via RT-qPCR.
	• Proportion of subjects demonstrating clearance of viral infection, defined as a negative test (Ct value ≥32) via RT-qPCR on Day 8/ET.
• symptoms	• Median time to alleviation of symptoms as measured by the time when all eight symptoms (cough, sore throat, nasal congestion, headache, chills/sweats,

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• COVID-19 composite severity score.	muscle or joint pain, fatigue, and nausea) had been assessed by the subject as none (0) or mild (1).
Exploratory Assessment(s)	
• viral load by viral titer (at each visit)	• Geometric mean viral load as measured in saliva on day 1, 3, 5, and 8 by $TCID_{50}$ for replication competent virus. • **Geometric mean viral load as measured by oropharyngeal swab on day 1, 3, 5, and 8 by $TCID_{50}$ for replication competent virus.**

*- indicates planned analysis for safety monitoring committee review between cohorts.

4.1.4 Inclusion and Exclusion Criteria

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

1. Positive for SARS-CoV-2 antigen via nasal swab **at or within the past 24 hours of the screening visit as detected using an FDA authorized SARS-CoV-2 antigen test.**
2. Onset of signs and symptoms consistent with COVID-19* no longer than within the past 3 days and have either a) fever of at least 100 °F or b) at least two moderate or severe symptoms (cough, sore throat, nasal congestion, headache, chills/sweats, muscle or joint pain, fatigue, and nausea) at the time of screening.
3. Provides written informed consent prior to initiation of any study procedures.
4. Be able to understand and agrees to comply with planned study procedures and be available for all study visits.
5. Agrees to the collection of nasopharyngeal swabs, **oropharyngeal swabs,** oral saliva specimen collection and venous blood specimens per protocol.
6. Agrees to refrain from using oral antiseptics (e.g. hydrogen peroxide rinse, Listerine) or mouthwashes of any kind during the study.
7. Male or non-pregnant female, 18 to 65 years of age, inclusive, at time of enrollment.
8. No uncontrolled disease process (chronic or acute), other than COVID-19 signs and symptoms*.

9. No physical or mental conditions or attributes at the time of screening, which in the opinion of the PI, will prevent full adherence to, and completion of, the protocol.

*The following COVID-19 onset of signs and symptoms generally appear 2-7 days after exposure to SARS-CoV-2:

- Cough
- Sore throat
- Nasal Congestion
- Headache
- Chills/sweats
- Muscle or joint pain
- Fatigue
- Nausea

Severity of each COVID-19 symptom will be assessed based on definitions used for graded adverse events:

- None (Grade 0): Not present
- 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.

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

1. Positive urine pregnancy test at screening.
2. Any medical disease or condition that, in the opinion of the site Principal Investigator (PI) or appropriate sub-investigator, precludes study participation.
3. Presence of self-reported or medically documented uncontrolled significant medical or psychiatric condition(s) other than COVID-19.
4. Reports a recent positive test result (within the past 6 months) for hepatitis B surface antigen, hepatitis C virus antibody, or HIV-1 antibodies at screening.

5. Has a history of alcohol abuse or other recreational drug (excluding cannabis) use within 1 month of Study Day 1.
6. COVID-19 signs associated with acute respiratory distress or imminent serious medical outcomes.^^
7. BMI ≥36.
8. **Subjects living (e.g., siblings, spouses, relatives, roommates) in the same household cannot be enrolled.**
9. Has participated in another investigational study involving any intervention for SARS-CoV-2/COVID- 19 within the past 6 months or any clinical trial with interventional investigational product within 30 days of screening.
10. Currently enrolled in or plans to participate in another clinical trial with an interventional investigational agent that will be received during the study period.
11. History of hospitalization within the past 60 days.
12. History of systemic antiviral therapies within the past 30 days.
13. History of oral corticoid steroid use within the past 14 days or steroid injection within the past 6 months. Active use of nasal or inhalable steroids is also exclusionary. Topical steroids are not exclusionary.
14. Has a history of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticaria, angioedema, other significant reaction) to nitrites, nitrates or sun exposure.
15. Has any oral abnormality (e.g. ulcer, oral mucositis, gingivitis) that in the opinion of the investigator would interfere with device use, or 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.

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

- Fever > 104° F
- Cough with sputum production
- Rales and/or rhonchi
- Difficulty breathing or respiratory distress defined by a respiratory rate ≥30 per minute, heart rate ≥125 per minute, SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2 <300.
- Persistent pain or pressure in the chest
- Confusion

4.2 Study Schedule of Activities

Study Procedures	Screening, Enrollment & Randomization	Follow-up Period (Visit Window)			
Study Days	**1**	**2**	**3**	**5 (-1 to +1)**	**8/ET (-1 to +1)**
Informed Consent	X				
COVID19 Screening & SARS-CoV-2 Rapid Antigen Test***	X				
Medical History & Physical Examination	X	Changes since last visit only	Changes since last visit only	Changes since last visit only	X
Oropharyngeal Assessment	X*	Changes since last visit only	Changes since last visit only	Changes since last visit only	X
Urine Pregnancy Test	X				X
Concomitant Medication History/New	Baseline	Changes since last visit only	Changes since last visit only	Changes since last visit only	Changes since last visit only
Comprehensive Metabolic Panel & CBC	X				X
Vital Signs	X				X
Methemoglobin	X				X
Adverse Event Assessment / Reactogenicity	Baseline	X	X	X	X
Demographics, Inclusion / Exclusion Review	X				
Diary Dispensation/Collection	X				X
Treatment at Site	X**	X**	X**		
Biospecimen collection for viral assays (**3** specimens)****	X		X	X	X
COVID-19 **Severity** Score	X				X
Collect RD-X19 Device	NA			Cohort 1	Cohort 2

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

**Only one treatment will be done on site, other treatment will be done at home, i.e. if afternoon appointment, subject will complete morning treatment at home and afternoon treatment administered at the site. For scheduling purposes, recommended interval between treatment is approximately 8 – 12 hours but not ≤ 4 hours.

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

****** At Baseline and days 3, 5, and 8, subjects will provide two saliva specimens and an oropharyngeal swab for virology endpoint assessments. One saliva specimen will be collected, preserved, and shipped fresh to a central lab for assessment of SARS-CoV-2 mRNA via RT-qPCR. The second specimen and the oropharyngeal swab will be collected in separate collection tubes, frozen, and stored at the site and shipped to a central lab at the end of each cohort.**

5 INTRODUCTION

5.1 Background and Study Rationale

In December 2019 the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknow cause. Coronavirus ribonucleic acid (RNA) was quickly identified in some of these patients. As of October 11, 2020 there were approximately 37 million confirmed cases wordwide (>7.7 million in the US) and over 1,075,000 deaths (~215,000 in the US). The only FDA approved intervention currently is Remdesivir for hospitalized subjects with COVID-19. Other interventions currently being used are through the Emergency Use Authorizations (EUA), against SARS-CoV-2 / COVID-19. Social distancing and personal protective equipment constitute our only viable countermeasures to help reduce incidence of community acquisition and transmission of SARS-CoV-2. Vaccine candidates are being developed at an unprecedented speed, however their efficacy and safety is unknown and will not be fully defined for many months. Remdesivir, Convalescent Immune Plasma and SoluMedrol are all used to treat patients hospitalized with COVID-19, but none has received marketing approval as a therapeutic for uncomplicated COVID-19. Therefore, there remains an urgent public health need for rapid development of novel measures for prevention and treatment of SARS-CoV-2 and COVID-19.

RD-X19 through both direct and intermediate mechanisms, kills cell-free virus by as much as 99.99% and inhibits cell-associated replication of SARS-CoV-2 by 99.9% when measured at 24 hours after a single 5 minute treatment. Putative key virucidal mechanisms include upregulation of nitric oxide in epithelial tissue through increase of nitric oxide synthases (NOSs) and stimulation of the instantaneous release of the body's bound store of nitric oxide. Nitric oxide produced physiologically in epithelial tissues also induces and attracts effector cells of the innate immune system, including natural killer (NK) cells, neutrophils and macrophages to phagocytize virus-infected cells at the site of primary infection. The technology utilized by RD-X19 has been repeatedly demonstrated to provide high-level viral control in multiple, consistent, expert-laboratory in vitro studies. The mechanism of action, utilizing augmented innate immunity, presents an unprecedented opportunity for protection that is not specific antigen-directed or dependent.

5.1.1 EmitBio™ RD-X19 Device Characteristics

Table 2.

Characteristic	Target
Route of Administration	Oral Illumination
Device Configuration	Hand-held, rechargeable
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Target Exposure Area	Oropharynx and surrounding tissues
[redacted]	[redacted]
[redacted]	[redacted]
Depth of Tissue Penetration	< 0.5 mm
Temperature (IEC 60601-1)	< 48 °C (for durations <10 min)

*[redacted]

5.2 Risk/Benefit Assessment

5.2.1 Known Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn and mild, transient, local reactions as measured in RD19-01-3Q20 , a Phase I Open Label, Acute Safety Study of the EmitBio™ RD-X19 Device.

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

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

Eye exposure is to be avoided. Direct illumination of unprotected eyes can result in damage to the retina, and especially the macula. Other eye structures can also experience thermal injury. Study staff must ensure volunteers understand to never point the RD-X19 device toward their or anyone else's eyes.

RD19-01-3Q20 Phase I Trial

This was a first-in-man Phase I study that evaluated the acute safety and tolerability of the RD-X19 device among 25 healthy volunteers between the ages of 18 and 45. A single dose [redacted] and schedule ([redacted]

[redacted]) was evaluated for 14 consecutive days. In total, subjects received a weekly dose of [redacted] per week for a time weighted average of [redacted].

No SAEs were observed during the study. No AEs based on laboratory findings were observed during the study.

Twelve (12) study subjects reported a total of 3 distinct AE terms (local site reaction, headache, nausea) and 23 total AEs. Of the 23 total AEs, 22 were classified as mild (grade 1) with a single headache classified as moderate (grade 2). No AE required treatment or alteration to the study subject's participation in the trial. No study subject withdrew from the trial because of an AE.

All AEs were of short duration, with resolution typically reached the same day or within 24 hours. Since study subjects used the RD-X19 device approximately every 12 hours for 14 contiguous days, there was a continuous temporal association with RD-X19 device use and incident AEs during the course of RD19-01-3Q20. By definition, all local site reactions were attributed to the device; all were mild and transient and there was no pattern of increasing frequency with repeated, cumulative dosing.

Population-based epidemiological data for headaches and nausea were considered when establishing device attribution. Approximately 40% of the general adult population have weekly headache and over 30% suffer from intermittent bouts of nausea of unknown origin. Given the frequencies of headache and nausea reported in RD19-01-3Q20 are less than those reported in population-based epidemiological studies, the relationship with the RD-X19 device cannot be determined.

In summary, the RD19-01-3Q20 Phase I trial demonstrated that EmitBio™ RD-X19 is a safe device, consistent with the sponsor's and IRB's original conclusion that RD-X19 is a NSR device.

Risks to Privacy

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

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

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

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

5.2.2 Known Potential Benefits

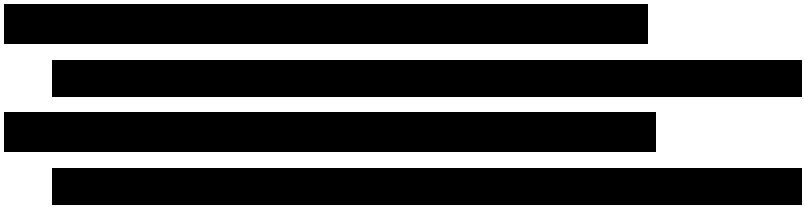
There is no guaranteed benefit to study participants. Use of EmitBio™ RD-X19 is intended to reduce viral load of SARS-CoV-2 and alleviate the symptoms associated with uncomplicated COVID-19. There is also the potential for benefit to society resulting from insights gained from

participation in this study due to the widespread, and accelerating, threat of SARS-CoV-2 and COVID-19.

6 STUDY DESIGN

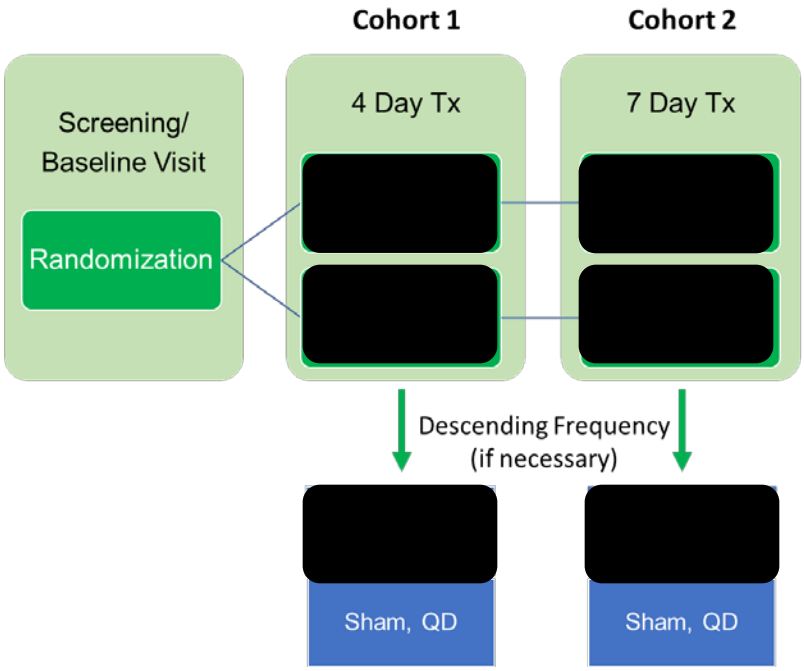
6.1 Overall Design

Volunteers will provide informed consent prior to initiating any screening procedures. Those meeting all screening criteria will be eligible for enrollment and randomization into the study. Study subjects will be enrolled into treatment and control arms within two cohorts:



Volunteers meeting all inclusion criteria and none of the exclusion criteria will be randomized to the RD-X19 treatment arm or the sham treatment arm within each cohort. Study subjects will be randomized in a 2:1 ratio (20 RD-X19 : 10 sham) per dose cohort. The double-blind, sham-controlled period will last 8 days. Assessments of study subjects will occur on study days 1, 2, 3, 5 and the final assessment visit on Day 8. Since CMP and CBC results will not be available until study day 2, all volunteers who have significant abnormalities will be immediately contacted and advised of the abnormality, discontinued from active participation in the protocol and advised regarding appropriate medical follow-up outside the study. All such study subjects will be replaced with a new volunteer. This is a randomized, adaptive, group sequential dose finding study. The primary goal of the study is to evaluate the efficacy and safety of the RD-X19 device in SARS-CoV-2 infected individuals with outpatient COVID-19. The primary efficacy outcome is the time weighted average change in SARS-CoV-2 viral load assessed via RT-qPCR. Safety assessment will include the incidence of device-related serious adverse events or patterns of severity ≥2 device-related adverse events.

Figure 1: Study Design



The interim analysis at the conclusion of Cohort 1 will consist of the following evaluations:

- A planned efficacy evaluation of the time weighted average change in SARS-CoV-2 viral load from baseline will be conducted as an assessment of benefit to the subjects.
- Safety evaluations, performed by a ~~independent~~ safety monitoring team as outlined in the committee charter, are to ensure that each dose level under evaluation is safe through 4 days of treatment. Specific criteria for safety review will include:
  - Number of subjects experiencing laryngospasm, bronchospasm or anaphylaxis within 2 hours after use of the RD-X19 Device that is considered related to RD-X19.
  - Number of subjects experiencing an allergic reaction such as generalized urticaria (defined as occurring at three or more body parts) within 72 hours after administration of light that is considered related to RD-X19.
  - Number of subjects experiencing an SAE or Grade 3 AE, in the same SOC grouping of Preferred Terms based on Medical Dictionary for Regulatory Activities (MedDRA) coding, considered to be related to RD-X19.

Safety and tolerability (local reactogenicity) will be assessed actively on each clinic visit by review of potential adverse events (AEs) and targeted physical examination, as required. Volunteers will be encouraged to contact designated clinical trial staff for AEs of a medically-urgent nature as soon as is practically possible and to seek immediate medical care, if needed.

Metabolic, liver, kidney and hematological laboratory evaluations will be performed at screening and at Day 8 or early termination (and potentially during unscheduled) clinic visits.

Study Subject safety will be monitored throughout the study by the Investigator and supported by regular review by the Medical Monitor and an external Data Monitoring Committee.

6.2 Objectives and Endpoints

Table 1: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Safety Assessments	
• AEs and SAEs*	• The primary safety measure is absence of device-related serious adverse events or any patterns of severity ≥2 device-related adverse events.*
• Methemoglobin	• Mean change in methemoglobin from baseline to Day 8/ET.
Efficacy Assessments	
• Viral load	• Time weighted average change in viral load from baseline by RT-qPCR from Day 1 to Day 8
	• Geometric mean viral load as measured in saliva on day 1, 3, 5, and 8 by RT-qPCR*
	• Proportion of subjects demonstrating viral load reduction ≥ 95% by RT-qPCR (at each visit)*
• Viral infection	• Time to clearance of viral infection in saliva, defined as a negative test (Ct value ≥32) via RT-qPCR.
	• Proportion of subjects demonstrating clearance of viral infection, defined as a negative test (Ct value ≥32) via RT-qPCR on Day 8/ET.
• Symptoms	• Median time to alleviation of symptoms as measured by the time when all eight symptoms (cough, sore throat, nasal congestion, headache, chills/sweats,

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• COVID-19 composite severity score.	muscle or joint pain, fatigue, and nausea) had been assessed by the subject as none (0) or mild (1).
Exploratory Assessment(s)	
• Viral load by viral titer (at each visit)	• Geometric mean viral load as measured in saliva on day 1, 3, 5, and 8 by $TCID_{50}$ for replication competent virus. • **Geometric mean viral load as measured via oropharyngeal swab on day 1, 3, 5 and 8 by $TCID_{50}$ for replication competent virus.**

*- indicates planned analysis for safety monitoring committee review between cohorts.

6.3 Scientific Rationale for the Study

RD-X19 through both direct and intermediate mechanisms, kills cell-free virus by as much as 99.99% and inhibits cell-associated replication of SARS-CoV-2 by 99.9% when measured at 24 hours after a single 5 minute treatment. Putative key virucidal mechanisms include upregulation of nitric oxide in epithelial tissue through increase of nitric oxide synthases (NOSs) and stimulation of the instantaneous release of the body's bound store of nitric oxide. Nitric oxide produced physiologically in epithelial tissues also induces and attracts effector cells of the innate immune system, including natural killer (NK) cells, neutrophils and macrophages to phagocytize virus-infected cells at the site of primary infection. The technology utilized by RD-X19 has been repeatedly demonstrated to provide high-level viral control in multiple, consistent, expert-laboratory in vitro studies. The mechanism of action, utilizing augmented innate immunity, presents an unprecedented opportunity for protection that is not specific antigen-directed or dependent.

6.3.1 Justification for Doses

In repeated experiments, including experiments conducted by third party external laboratories, it has been determined that the light emitted by the EmitBio™ RD-X19 device provides for potent antiviral activity against 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. [redacted]

[redacted] These repeated experiments, conducted in multiple labs with multiple cell types, along with years of medical use of licensed devices with comparable [redacted], support the doses proposed in this protocol for dose finding to achieve optimal efficacy and safety.

[redacted] The dosing schedule and duration has been selected to provide a reduction in viral load and symptomatic relief as rapidly as possible in COVID-19 patients while still maintaining an acceptable safety margin for each individual treatment session.

If patterns of ≥ grade 2 device-related adverse events are observed, dosing will be reduced to one exposure/day for the remainder of treatment time. If serious or severe device-related adverse events are observed, further treatments at that dose will be terminated.

Strict safety oversight will provide rapid detection of significant device/dose-related adverse events warranting pausing or halting the trial.

7 STUDY POPULATION

The study population is individuals infected with SARS-CoV-2 who have symptoms associated with COVID-19 that is either not under active medical treatment or is being treated as an outpatient. Study subjects must be symptomatic for 3 days or less and have a positive COVID-19 antigen test using **an FDA authorized SARS-CoV-2 antigen diagnostic test at or within the past 24 hours of screening.** Study subjects will be randomized to treatment arm within dose in a 2:1 ratio according to a fixed schedule using a permuted block design. The targeted number of subjects randomized per dose is 30 (20 volunteers to the RD-X19 arm, 10 subjects to the sham arm). This is a sample size of convenience as this is a hypothesis generating study.

The target population should reflect the subject population with uncomplicated COVID-19 in the community at large.

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

7.1 Inclusion Criteria

A subject must meet all the following criteria to be eligible to participate in this study:

1. Positive for SARS-CoV-2 antigen via nasal swab **at or within the past 24 hours of the screening visit detected using an FDA authorized SARS-CoV-2 antigen test**.
2. Onset of signs and symptoms consistent with COVID-19* no longer than within the past 3 days* and have either a) a fever of at least 100 °F or b) at least two moderate or severe

symptoms (cough, sore throat, nasal congestion, headache, chills/sweats, muscle or joint pain, fatigue, and nausea) at the time of screening.

3. Provides written informed consent prior to initiation of any study procedures.
4. Be able to understand and agrees to comply with planned study procedures and be available for all study visits.
5. Agrees to the collection of nasopharyngeal swabs, oropharyngeal swabs, oral saliva specimen collection and venous blood specimens per protocol.
6. Agrees to refrain from using oral antiseptics (e.g. hydrogen peroxide rinse, Listerine) or mouthwashes of any kind during the study.
7. Male or non-pregnant female, 18 to 65 years of age, inclusive, at time of enrollment.
8. No uncontrolled disease process (chronic or acute), other than COVID-19 signs and symptoms*.
9. No physical or mental conditions or attributes at the time of screening, which in the opinion of the PI, will prevent full adherence to, and completion of, the protocol.

*The following COVID-19 onset of signs and symptoms generally appear 2-7 days after exposure to SARS-CoV-2:

- Cough
- Sore Throat
- Nasal Congestion
- Headache
- Chills/sweats
- Muscle or joint pain
- Fatigue
- Nausea

Severity of COVID-19 symptoms will be assessed based on definitions used for graded adverse events:

- None (Grade 0): Not present
- 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.

7.2 Exclusion Criteria

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

1. Positive urine pregnancy test at screening.
2. Any medical disease or condition that, in the opinion of the site Principal Investigator (PI) or appropriate sub-investigator, precludes study participation.
3. Presence of self-reported or medically documented uncontrolled significant medical or psychiatric condition(s) other than COVID-19.
4. Reports a recent positive test result (within the past 6 months) for hepatitis B surface antigen, hepatitis C virus antibody, or HIV-1 antibodies at screening.
5. Has a history of alcohol abuse or other recreational drug (excluding cannabis) use within 1 month of Study Day 1.
6. COVID-19 signs associated with acute respiratory distress or imminent serious medical outcomes. ^^
7. BMI ≥36
8. **Subjects living (e.g., siblings, spouses, relatives, roommates) in the same household cannot be enrolled.**
9. Has participated in another investigational study involving any intervention for SARS-CoV-2/COVID- 19 within the past 6 months or any clinical trial with interventional investigational product within 30 days of screening.
10. Currently enrolled in or plans to participate in another clinical trial with an interventional investigational agent that will be received during the study period.
11. History of hospitalization within the past 60 days.
12. History of systemic antiviral therapies within the past 30 days.
13. History of oral corticoid steroid use within the past 14 days or steroid injection within the past 6 months. Active use of nasal or inhalable steroids is also exclusionary. Topical steroids are not exclusionary.
14. Has a history of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticaria, angioedema, other significant reaction) to nitrites, nitrates or sun exposure.
15. Has any oral abnormality (e.g. ulcer, oral mucositis, gingivitis) that in the opinion of the investigator would interfere with device use, or 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.

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

- Fever > 104º F
- Cough with sputum production
- Rales and/or rhonchi
- Difficulty breathing or respiratory distress defined by a respiratory rate ≥30 per minute, heart rate ≥125 per minute, SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2 <300.
- Persistent pain or pressure in the chest
- Confusion

7.3 Study Volunteer Selection, Retention & Compensation

7.3.1 Recruitment

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

7.3.2 Retention

Study retention strategies will include education and explanation of the study schedule and procedures during screening and enrollment visits and restriction of enrollment to persons who can attend all study visits. Participating subjects will be reminded of subsequent visits during each visit, and study staff will contact subjects prior to appointments. Study staff will contact subjects who miss appointments to encourage them to return for completion of safety evaluations.

7.3.3 Compensation Plan for Subjects

Subjects will be compensated for their participation in this trial. Compensation will take into consideration both the urgency and importance of developing new treatments for this COVID-19 pandemic and local IRB guidelines, and will be ultimately subject to local IRB approval. Reimbursements will be disbursed at specific timepoints during the study with the total amount contingent on completing study procedures.

7.3.4 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, subject's insurance or third party.

8 STUDY DEVICE

8.1 Regulatory Considerations

8.1.1 Preliminary Regulatory Pathway for EmitBio™ RD-X19

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

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

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

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

EmitBio™ conducted RD19-01-3Q20 under 21 CFR 812 as a Non-Significant Risk (NSR), Minimal Risk protocol. The Institutional Review Board agreed with EmitBio™ based on the protocol and supporting documentation submitted with the protocol and granted final approval to conduct the study on September 1, 2020.

8.1.2 Proposed Label Claim/Indication for Use:

The RD-X19 device is intended for use as a treatment to reduce viral load in the upper respiratory tract in subjects ages 12 to 65 who have tested positive for SARS-CoV-2 and who have symptoms consistent with uncomplicated COVID-19 for no more than 3 days.

8.1.3 Medical Device Quality System:

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

8.2 Study Device and Use

8.2.1 Device Description

[redacted]

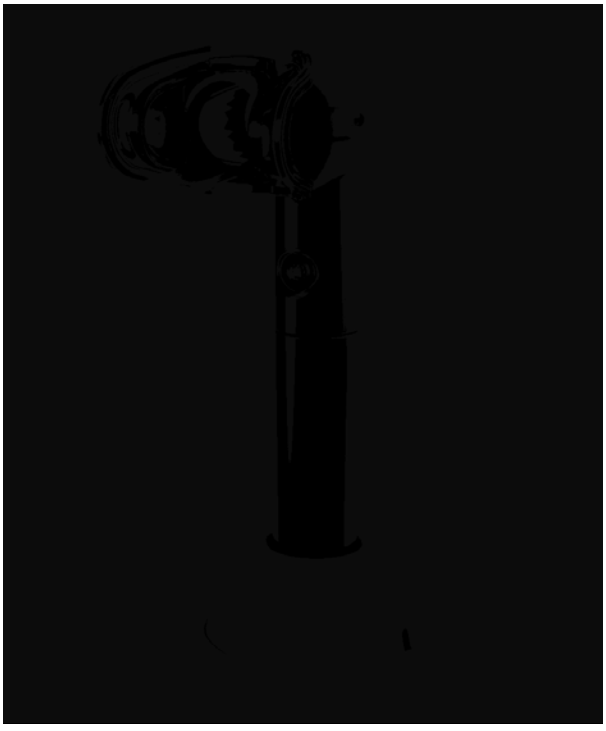
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

8.3 Use / Storage & Maintenance / Accountability

8.3.1 Acquisition and Accountability

The sponsor will provide clinical sites with RD-X19 devices packaged in appropriately labelled containers containing all components as well as instructions for use by study participants. Each RD-X19 device will be stamped on its power unit with a serial number. Study staff will ensure that each device's serial number 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 termination of a subject's participation in the trial, all RD-X19 devices and components must be returned to the study site and then to the study sponsor.

8.3.2 Device Storage and Maintenance

All RD-X19 devices will be stored in a locked device storage room at the clinical trial site until needed for assignment to an enrolled study volunteer. Upon acquisition by the study subject, devices should be stored in a dry climate-controlled environment in the original container in which it was provided.

The device should be stored securely out of the reach of children who may mistakenly misuse the device, especially illumination of eyes – which is always to be avoided. The mouthpiece of the device is removable for rinsing with mild soap and warm water. The device tongue depressor and 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 device can be wiped gently with a dry cloth suitable for cleaning optical glasses.

8.3.3 Preparation for Use and Use

[Refer to Appendix 1: RD-X19 User Instructions]

8.4 Measures to Maximize Study Subject Compliance

Randomization between active treatment and sham control devices has been set at 2:1 to provide higher probability of the subjects being randomized to the investigational treatment during the study duration.

Subjects will receive appropriate compensation for the disruption to normal daily activities created by this protocol that also considers the frequency with which they are requesting to travel to the site, the twice daily journaling and treatment regimen, and the number of biospecimens scheduled to be collected for virology assessments.

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

8.5 Device Discontinuation

8.5.1 Study Pausing Criteria

EB-P12-01 enrollment will be paused if any of the following events occur:

- Any subject experiences an SAE after use of the RD-X19 Device that is considered related to RD-X19.
- Any subject experiences laryngospasm, bronchospasm or anaphylaxis within 2 hours after use of the RD-X19 Device that is considered related to RD-X19.
- 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 administration of light that is considered related to RD-X19.
- Three (3) or more subjects experience a Grade 3 AE (systemic and/or clinical laboratory abnormality), in the same SOC grouping of Preferred Terms based on the Medical Dictionary for Regulatory Activities (MedDRA) coding, considered to be related to RD-X19.

Enrollment may resume only after external safety review of the SAE/AEs that caused the pause to the study. Given the frequency of visits and the duration of the protocol, study device use may continue after assessing the safety and AEs for individual subjects at either regulatory scheduled or an unscheduled site visits.

8.5.2 Subject elects to discontinue

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

8.5.3 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, or at least 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 AE, clinical laboratory abnormality or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The occurrence of a SAE.
- If the subject is using the device in any manner inconsistent with instructions and protocol directives and procedures.

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

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

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

8.5.4 Follow-up of Study Subjects Who Discontinue Device Use

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

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Screening Assessments

9.1.1 Screening Procedures

At the screening visit, and prior to any other study-related activities, the participating clinical site PI or appropriate sub-investigator will provide the subject with detailed study information and will obtain written informed consent (see section 11.1.1 for more details).

Subject numbers will be assigned with the three-digit numerical site number beginning with numbers greater than one hundred (e.g. 101) followed by an alphanumeric cohort identifier (e.g. C1) and finally a two digit unique numerical identifier assigned with each new subject (e.g. 01).

Example Subject Number: 101-C1-01

COVID-19 Screening

Eligible subjects presenting with uncomplicated COVID-19 must have an oral temperature of at least 100 ˚F or have at least two moderate or severe symptoms (cough, nasal congestion, or sore throat, headache, chills/sweats, muscle or joint pain, fatigue, or nausea) and consent to be randomized within 3 days of first symptom onset. The subjects will self-assess their COVID-19 symptoms as none (0), mild (1), moderate (2), or severe (3) during screening.

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

There is a small amount of risk to subjects who report mild-to-moderate symptomatology consistent with COVID-19 may have an unknown health problem or co-morbidity at the time of screening that can lead to worsening of condition or hospitalization during study.

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 medical history focusing on conditions per protocol exclusion criteria.
- Review all pre-study medications, vitamins, supplements, and therapies up to 14 days prior to the start of screening that could impact the use of, or response to, the device and record on the appropriate e-CRF. Subjects are allowed to use over-the-counter medications and remedies to alleviate symptoms (e.g. acetaminophen, ibuprofen, cough drops, etc. and should be recorded.)
- Measure vital signs (HR, BP, **RR**, and oral temperature) and height and weight for determination of BMI.
- Perform full physical examination which will include assessments of the following organs and organ systems: skin, head, ears, eyes, nose, and throat (HEENT), neck, lungs, heart, liver, spleen, abdomen, extremities, lymph nodes (axillary and cervical), and nervous system.
- Obtain blood and urine for clinical screening laboratory evaluations:
  - Comprehensive Metabolic Panel (fasting or non-fasting)
  - CBC with differential
  - Urine pregnancy test (in women of childbearing potential)
- Review inclusion and exclusion criteria.

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

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

If a physiologic parameter, e.g., vital signs, is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the participating clinical site PI or appropriate sub-investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition (e.g., stress, anxiety or "white coat syndrome") or other source of error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

A subject may be re-screened if there is a transient disease status (e.g., absent signs and symptoms associated with mild COVID-19), or 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 2 days using the same subject number.

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

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

9.1.2 Procedures for ~~Abnormal~~ Clinically Significant Laboratory Values or Findings

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

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

9.2 Safety and Other Assessments

Study procedures are specified in protocol section 4.2. A study clinician, licensed to make medical diagnoses as the participating clinical site PI or appropriate sub-investigator, will be responsible for all study-related medical decisions.

- Medical history:
  - A complete medical history will be obtained by interview of subjects at the screening visit. Subjects will be queried regarding a history of significant medical disorders of the head, ears, eyes, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited.

- At all subsequent visits an interim medical history will be obtained by interview of subjects and any changes since the previous clinic visit will be noted. The interim medical history should include an assessment for new medical conditions and symptoms suggestive of an AE.

- Physical examination:
  - A full physical examination will be performed at the screening visit and Day 8, and a symptom-directed (targeted) physical examination will be performed if indicated during other clinic visits
    - A full physical examination will include assessments of the following organs and organ systems: skin, HEENT, neck, lungs, heart, liver, spleen, abdomen, extremities, lymph nodes (axillary and cervical), and nervous system.
    - Height and weight will be measured, and BMI calculated, at the screening visit only.
  - A symptom-directed (targeted) physical examination will be performed if indicated during other scheduled clinical site visits.
    - Targeted physical examinations will primarily focus on assessment of signs and symptoms suggestive of AEs. Interim or unscheduled physical examinations will be performed at the discretion of the participating clinical site PI or appropriate sub-investigator, if necessary, to evaluate AEs.
  - Subjects will be observed in the clinic for at least 30 minutes post the first RD-X19 illumination. The oropharynx and surrounding tissues will be examined. Reactogenicity assessments will be performed on Days 1, 2, 3, 5, and 8. An oropharyngeal examination will also be performed on Days 1 and 8 and during unscheduled visits and early termination visits and recorded on the appropriate source document prior to discharge from the clinic. Interim or unscheduled oropharyngeal examinations will be performed, if necessary, to evaluate AEs.

- Vital signs:

  Vital sign measurements will include systolic and diastolic BP, HR, **RR**, and oral temperature. Vital signs will be measured at timepoints specified in protocol section 4.2. 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.

- Clinical laboratory evaluations:
  - Fasting is not required before collection of clinical laboratory evaluations.

- Urine pregnancy test will be performed locally by the site laboratory at the screening visit and at the final study visit. Results must be confirmed as negative prior to randomization on Day 1 and allocation and use of the RD-X19 device.
- Clinical laboratory evaluations CMP and CBC (diff) will be performed locally by the site selected laboratories.
    - Clinical safety laboratory evaluations will be performed locally by the site laboratory.
    - Blood and urine will be collected at timepoints specified in the protocol section 4.2.

9.2.1 Definition of Adverse Event (AE)

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

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

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

All AEs will be assessed for severity and relationship to study intervention. Reporting of all AEs, solicited and unsolicited, will occur during the period from study device administration on Day 1 through Day 8 or until an early termination visit.

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

AEs will be followed to resolution or stabilization.

9.2.2 Solicited Adverse Events - Reactogenicity

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

For this study, solicited AEs include:

- Illumination site Pain

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

9.2.3 Unsolicited Adverse Events

All AEs 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.

9.2.4 Adverse Event Reporting

Information on all AEs 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 AE should be grouped together and recorded as a single diagnosis. If the AE is a clinical laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis and be described in terms of duration (start and stop date).

9.2.5 Definition of a Serious Adverse Event (SAE)

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

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

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

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

All SAEs, as with any AE, 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 to the IRB. This report will include severity, association with the study device, action(s) taken, and outcome.

9.2.6 Serious Adverse Event Reporting

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

EmitBio™ Pharmacovigilance

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

Text Immediate Report: 1-843-540-3550

SAE Email: jmcneil@emitbio.com

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

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

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

9.2.7 Regulatory Reporting of Device-related SAEs

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

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

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

9.2.8 Classification of an Adverse Event

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

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

9.2.9 Severity of Adverse Events

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

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

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

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate e-CRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

9.2.10 Relationship to Study Intervention

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

- Related – The 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.

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

For this study:

Solicited and Unsolicited AEs will be recorded by clinical trial staff for the entire duration of the study.

9.2.12 Adverse Event Reporting to Study Subjects

All device-attributed AEs and SAEs will be reported to participants in the study to better inform them of the potential risks vs. benefits of participation.

9.2.13 Pregnancy Reporting

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

9.3 Efficacy Assessments

Efficacy comparisons will be made in the ITT Population with the intent of estimating the effect of the RD-X19 device relative to sham in several outcome measures. Subjects will be instructed to fill out diary cards twice daily to assess their symptoms associated with disease progression and record the number of treatments completed. Additionally, at Baseline and days 3, 5, and 8, subjects will provide two saliva specimens **and an oropharyngeal swab** for virology endpoint assessments. One saliva specimen will be collected, preserved, and shipped fresh to a central lab for assessment of SARS-CoV-2 mRNA via RT-qPCR. The second specimen **and the oropharyngeal swab** will be collected in separate collection tubes, frozen, and stored at the site and shipped to a central lab at the end of each cohort.

9.3.1 Efficacy assessments

Various endpoints will explore the impact of RD-X19 treatment on the reduction in log10 SARS-CoV-2 viral load and alleviation of symptoms associated with COVID-19. Both the magnitude of reduction as a function of dose as well as time to clearance will be assessed in support of the primary efficacy analysis. Subjects will be instructed to fill out a diary card or electronic equivalent to assess their signs and symptoms of disease twice daily. Each of the eight symptoms will be rated on a scale from none (0) to severe (3).

- Time weighted average change in viral load from baseline by RT-qPCR from Day 1 to Day 8
- Geometric mean viral load as measured in saliva on day 1, 3, 5, and 8 by RT-qPCR
- Proportion of subjects demonstrating viral load reduction ≥95% by RT-qPCR (at each visit)
- Time to undetectable viral load in saliva by RT-qPCR.
- Proportion of subjects demonstrating clearance of viral infection, defined as a negative test via RT-qPCR on Day 8/ET.
- Median time to alleviation of symptoms,
    - The time to alleviation of symptoms endpoint, is defined as the time when all eight symptoms (cough, sore throat, nasal congestion, headache, chills/sweats, muscle or joint pain, fatigue, and nausea) had been assessed by the subject as none or mild.
- Change in COVID-19 Severity Score from baseline
    - The COVID-19 Severity Score is defined as the sum of all the individual symptom severity scores divided by the total number of symptoms assessed (8).
- Viral load by viral titer (at each visit)

- **The paired oropharyngeal swab and saliva sample from each subject at each visit allows for independent analysis via two different live virus sampling methodologies and also a direct paired sample comparison of the viral load present in the back of the throat versus saliva.**

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

This is a randomized, ascending dose finding study. The primary goal of the study is to evaluate the safety and efficacy of the RD-X19 device in SARS-CoV-2 infected individuals with uncomplicated COVID-19.

10.2 Power and Sample Size:

This is a double-blind study and hypothesis generating in nature. The sample size was selected for convenience.

Subjects will be randomized to treatment arm within dose in a 2:1 ratio according to a fixed schedule using a permuted block design and stratified by clinical site. The target number of subjects randomized per dose is 30 (20 subjects to the RD-X19 arm, 10 subjects to the sham arm.

One interim analysis is planned at the end of Cohort 1.

10.3 Populations for Analyses

Three analysis populations are defined for this study.

- The Safety Population includes all randomized subjects who receive at least 1 study treatment. This population will be used for all safety analyses. Subjects will be analyzed based on actual treatment received.
- The Intent-to-treat Population (ITT) includes all randomized subjects who received treatment and were not discontinued due to a significant abnormality from the baseline CMP and CBC tests. This population will be used for all efficacy analyses as the primary population. Subjects will be analyzed based on randomized treatment, regardless of the actual treatment received.
- The Per Protocol (PP) Population includes all randomized subjects who complete the study and did not have a major protocol deviation (MPD). The PP population will be used for supportive analysis of the efficacy endpoints. MPDs are those that could have interfered with the administration of treatment or the precise evaluation of treatment efficacy (e.g. violation of inclusion/exclusion criteria, no Day 3 visit, etc.). All MPDs will be identified before the database lock and study unblinding for analysis.

10.4 Statistical Analyses

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

In general, missing data will not be imputed with the exception that for the ITT analysis, missing viral load results will be imputed using the last-observation-carried-forward (LOCF) methodology.

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

10.4.1 Efficacy Analyses

The primary efficacy endpoint is defined as time-weighted average (TWA) change in log10-transformed viral load by RT-qPCR from baseline to Day 8, where TWA will be derived using the trapezoidal rule. At the final analysis, each dose of the RD-X19 device will be compared to sham using an Analysis of Covariance (ANCOVA) model with baseline viral load as a covariate and treatment group as an independent variable. Geometric means and their 95% CIs will be computed by exponentiating (base 10) the least squares means and 95% CIs of the log10-transformed viral load.

Secondary efficacy endpoints include:

- log10-transformed Viral load as measured in saliva by RT-qPCR at each visit
- proportion of subjects with ≥95% reduction in SARS-CoV-2 viral load at each visit
- time to undetectable viral load in saliva by RT-qPCR
- proportion of subjects demonstrating clearance of viral infection, defined as a negative test via RT-qPCR at Day 8/ET visit
- COVID-19 composite severity score at each visit
- time to alleviation of COVID-19 symptoms, defined as the time when all eight symptoms had been assessed by the subject as none or mild.

Exploratory efficacy endpoints includes log10-transformed viral load at each visit as measured by $TCID_{50}$ for replication competent virus **via both expelled saliva specimen and oropharyngeal swab collection methodologies**.

All secondary and exploratory efficacy endpoints will be summarized using descriptive statistics by visit (as appropriate) for each treatment group. For log10-transformed viral load data, geometric means will be computed by exponentiating (base 10) the group means of the log10-transformed viral load. Time-to-event variables will be evaluated using the Kaplan-Meier method.

10.4.2 Safety Analyses

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

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

preferred term will be counted only once under the strongest severity and relationship, accordingly.

11 OPERATIONAL CONSIDERATIONS AND SUPPORTING DOCUMENTS

11.1 Ethical Considerations

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

An OHRP-registered IRB will review and approve this protocol, associated informed consent documents, recruitment material, and handouts or surveys intended for the subjects, prior to the recruitment, screening, and enrollment of subjects. The IRB review shall be in accordance with 45 CFR 46 and 21 CFR 50, 21 CFR 56 (IRBs), 21 CFR 812 and other federal, state, and local regulations and policies, as applicable.

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

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

11.1.1 Informed Consent Process

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

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

Subjects will receive an explanation that they will be compensated for their participation on a per visit basis, and medical treatments are available if device-related injury occurs, and, if so, what that treatment is, or where further information may be obtained. Subjects will be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any

anticipated prorated payments, if any, to the subject for participating in the trial. They will be informed of whom to contact (e.g., the participating clinical site PI and the Sponsor) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. The subjects will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Subjects will be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential. Subjects will be informed, even if identifiers are removed, that information collected from this research and/or specimens may be used for secondary research, including the sharing of deidentified data.

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

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

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

11.1.2 Confidentiality and Privacy

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

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

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

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

11.1.3 Clinical Monitoring

Monitoring will be conducted during the conduct of the trial, and will include, but is not limited to, source document verification, review of regulatory files, device accountability records, e-CRFs, ICFs, medical and laboratory reports, training records, and protocol and GCP compliance. The monitors will have access to all study related documents and will meet with appropriate clinical site staff to discuss any problems and outstanding issues. Visit findings and discussions will be documented. Some monitoring visits may be conducted remotely.

11.1.4 Quality System

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

11.1.5 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the participating clinical trial site under the supervision of the participating clinical site PI and the overall study PI. The participating clinical trial site PI must maintain complete and accurate source documentation. Clinical research data from source documentation, including, but not limited to, 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.

11.1.6 Source Documents

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

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

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

11.1.7 Study Record Retention

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

11.1.8 Protocol Deviations

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

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

It is the responsibility of the participating clinical site PI and study staff to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to EmitBio Inc's Senior Clinical Program Manager. Protocol deviations must be sent to the IRB of record. The participating clinical site PI and study staff are responsible for knowing and adhering to the IRB requirements. A completed copy of an approved Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart if the deviation is subject specific.

11.1.9 Publication and Data Sharing Policy

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

11.1.10 Conflict of Interest Policy

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

11.1.11 Research Related Injuries

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

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

12 APPENDIX 1: RD-X19 USER INSTRUCTIONS

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13 APPENDIX 2: TOXICITY GRADING SCALES

Available upon request.

Clarification Memorandum #1 for:
EB-P12-01

A 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

DATE: November 23, 2020

TO: Beth Landis
Senior Clinical Project Manager
SymBio Inc.

FROM: Sponsor's Chief Medical Officer (Dr. John G. McNeil, MD MPH PHD)

SUBJECT: Clarification Memo# 1 to Protocol EB-P12-01, Version 2.0, 11/6/20 entitled, "A 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"

This clarification outlines the procedure for documenting emergent signs and symptoms of COVID-19 on Diary Cards vs Adverse Event source documents.

1. Study subjects meeting enrollment criteria related to COVID-19 signs and symptoms are still in a phase of disease pathogenesis where additional COVID-19 signs and symptoms not present at screening may emerge. A timeframe of up to and including study day three will document new COVID-related signs and symptoms as associated with COVID-19 and documented as COVID-19 signs and symptoms with participant-assessed severity scores on diary cards.

2. New signs and symptoms consistent with COVID-19 that first occur on or after study day 4 will be assessed and severity graded and documented as adverse events by site investigators on adverse event source documents. The assessing investigator will be responsible for using their best clinical judgment in assigning attribution of the adverse event.

3. Kindly forward this Clarification Memorandum to Investigators, CRAs and other appropriate staff at the clinical sites. Sites should also forward a copy to their IRBs and maintain a copy with protocol documentation.

Clarification Memorandum #2 for:
EB-P12-01

A 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

DATE: December 1, 2020

TO: EB-P12-01 Sites

FROM: Sponsor's Chief Scientific Officer (Nathan Stasko, PHD)

SUBJECT: Clarification Memo# 2 to Protocol EB-P12-01, Version 2.0, 11/6/20 entitled, "A 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"

This clarification outlines the sponsors decision to allow enrollment for up to a 20% overage of the proposed number of subjects.

1. Up to 36 total subjects meeting enrollment criteria related to COVID-19 signs and symptoms may be enrolled per each dose Cohort. This clarification is intended to allow for enrollment of Hispanic subjects for at least 7 days post translation of all study documents into Spanish that was approved and available on November 25th, 2020 for Cohort 1.

STATISTICAL ANALYSIS PLAN

Protocol EB-P12-01

Version 2.0
January 25, 2021

A 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

EmitBio Inc.

Suite 470, 4222 Emperor Blvd
Durham, NC 27703

Approved By:

/s/ Ye Wang	01/25/2021
Ye Wang, PhD Director of Statistics Symbio LLC	Date
/s/ John McNeil	01/25/2021
John McNeil, MD, MPH, PhD Chief Medical Officer EmitBio Inc.	Date
/s/ Nathan Stasko	01/25/2021
Nathan Stasko, PhD Chief Scientific Officer EmitBio Inc.	Date

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Table of Contents

Statistical Analysis Plan

1 Purpose of Statistical Analysis Plan

The purpose of the statistical analysis plan is to describe in detail all the data, statistical methods, and summary tables required to implement the statistical analysis of Clinical Study Protocol EB-P12-01 (Section 10 in the study protocol version 2.0 (Amendment 1), dated November 06, 2020).

2 Study Objectives

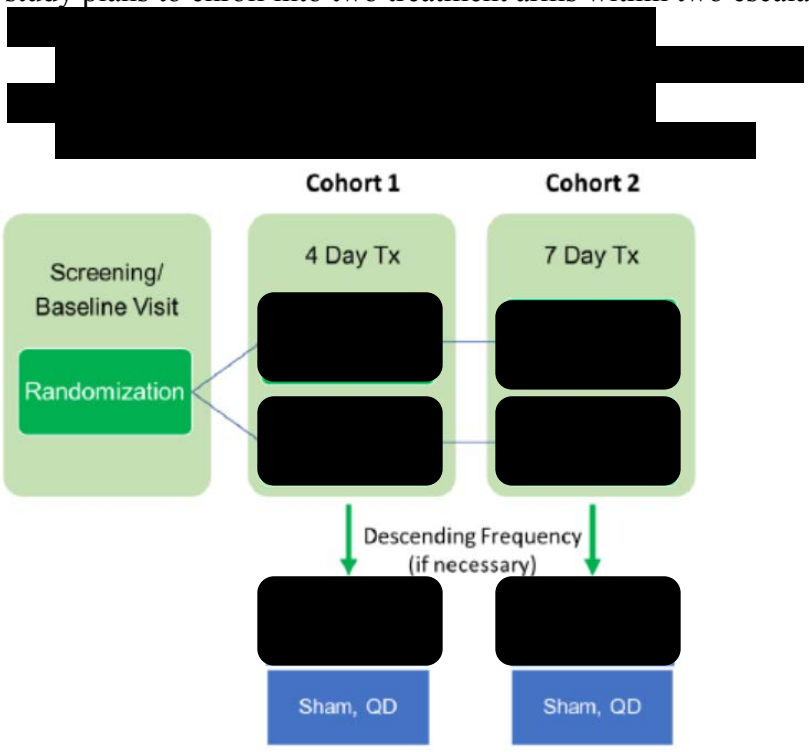
To assess the efficacy and safety of the RD-X19 device in SARS-CoV-2 infected individuals with outpatient COVID-19.

3 Study Design and Sample Size Determination

3.1 Study Design

For the purpose of exploring the above objectives, the study will be conducted as a randomized, double-blind, sham-controlled dose escalation study in SARS-CoV-2 infected individuals with outpatient COVID-19 at two dosing schedules.

This study plans to enroll into two treatment arms within two escalating dose cohorts:



Volunteers meeting all inclusion criteria and none of the exclusion criteria will be randomized to the RD-X19 treatment arm or the sham treatment arm within each cohort in a 2:1 ratio (20 RD-X19 : 10 sham), according to a fixed schedule via a permuted block design and stratified by clinical site. Light will be administered twice daily locally to the mouth and throat only for four days for Cohort 1 and for seven days for Cohort 2.

The clinic visits will occur at:

- Visit 1 / Screening, Enrollment & Randomization

- Visit 2 / Day 2
- Visit 3 / Day 3
- Visit 4 / Day 5 (± 1 day)
- Visit 5 / Day 8 (± 1 day) / Early Termination (ET)

Assessments of treatment response will occur on study days 3 and 5, with a final determination of efficacy made on day 8 (inclusive).

Efficacy will be evaluated through evaluation of viral load through quantitation of SARS-CoV-2 mRNA by RT-qPCR and via quantitation of replication competent virus by viral titer. Severity of the symptoms of disease will also be aggregated to produce a composite COVID-19 severity score. Safety and tolerability assessments will include solicited and unsolicited adverse events (AEs), physical examinations, vital signs, and clinical laboratory tests.

One unblinded interim analysis is planned upon completion of all subjects in Cohort 1. The results of the interim analysis will be reviewed by a safety monitoring team and a recommendation will be made to the sponsor on whether enrollment should proceed for the next cohort at the next planned dose or at a reduced dosing frequency (e.g. once daily). The study is designed to evaluate at least 2 dosing schedules, ascending, or descending based on safety of each previous cohort.

3.2 Sample Size Determination

The study is hypothesis generating in nature. Hence, the sample size was selected for convenience.

The target number of subjects randomized is 60 in total, and 30 per cohort (20 subjects to RD-X19 and 10 subjects to sham).

4 Populations To Be Analyzed

Three subject populations are defined as follows:

(1) Safety: This population will include all subjects who receive at least 1 study treatment. The Safety Population will be used for analysis of safety and tolerability data. Subjects will be analyzed based on actual treatment received.

(2) Intent-to-Treat (ITT): This population will include all randomized subjects who receive treatment and were not discontinued due to a significant abnormality from the baseline CMP and CBC tests. This population will be used for all efficacy analyses as the primary population. Subjects will be analyzed based on randomized treatment, regardless of the actual treatment received.

(3) Per-Protocol Population (PP): This population will include subjects who complete the study and did not have a major protocol deviation (MPD). The PP population will be used for supportive analysis of the efficacy endpoints. MPDs are those that could have interfered with the administration of treatment or the precise evaluation of treatment efficacy.

MPDs may include but will not be limited to the following:

- Violation of inclusion/exclusion criteria;
- Use of prohibited concomitant medications during the treatment period;
- No Day 3 Visit;

- Returned for Day 8 Visit outside the designated visit window;
- Was not compliant with the dosing regimen.

All MPDs will be identified before the database lock and study unblinding for analysis.

5 Planned Analyses

5.1 Methodological Considerations

General Conventions

SAS software (version 9.4 or higher) will be used for all data analyses and tabulations.

The study is not powered for hypothesis testing. P-values will be considered descriptive and will not be adjusted for multiplicity.

Data for all investigational centers will be pooled for analysis.

Unless specified elsewhere, baseline is defined as the last available measurement prior to administration of study drug. Change from baseline will be calculated as the post-baseline value minus the baseline value.

Summary tables will include the data based upon the protocol scheduled time points. For subjects who are early discontinued from the study, all efficacy assessments captured at the ET visit will be assigned to the nearest protocol scheduled time point.

Visit of Treatment Period	**Range***	**Target Day**
Visit 1 / Baseline (Day 1)	Study Day = 1	Day 1
Visit 2 / Day 2	Study Day = 2	Day 2
Visit 3 / Day 3	Study Day = 3	Day 3
Visit 4 / Day 5 (± 1 day)	Study Day 4 to 6	Day 5
Visit 5 / Day 8 (± 1 day)	Study Day 7 to 9	Day 8

*Study day = date of visit - date of first treatment + 1

Descriptive statistics of continuous variables will include n, mean, standard deviation (SD), median, minimum and maximum. Generally, the minimum and maximum values will be presented to the same decimal precision as the raw values, the mean and median values to one more, and the SD, to two more decimal places than the raw values. Summaries for categorical data will include frequencies and percentages. Percentages will be presented to one decimal place.

5.2 Handling of Missing Data

5.2.1 Missing Efficacy Endpoints

Missing data will be replaced for the efficacy endpoint in the ITT analyses using the Last observation carried forward (LOCF) method.

5.2.2 Missing or Incomplete Dates for Adverse Events and Concomitant Medications

Adverse Events

Handling of partial dates is only considered for the start date. An adverse event with a partial start date is considered treatment emergent if:

- only the day is missing and the start month/year is the same or after the month/year of the first treatment
- the day and month are missing and the start year is the same or greater than the year of the first treatment date
- the start date is completely missing

Concomitant Medications

Handling of partial dates is only considered for the stop date. A medication with a partial stop date is considered concomitant if:

- only the day is missing and the stop month/year is the same or after the month/year of the first treatment
- the day and month are missing and the stop year is the same or greater than the year of the first treatment date
- the stop date is completely missing or the medication is ongoing.

5.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively for the Safety population.

5.4 Subject Accountability

A summary of subject disposition will be provided for all subjects descriptively, including reason for discontinuation and analysis populations.

5.5 Efficacy Variables and Analyses

All efficacy analyses will be performed for both the ITT and PP populations with results in ITT as primary and PP as supportive.

Viral load (log base 10 copies/mL) and cycle threshold (Ct) data that are continuous in nature but may be reported as "undetermined" or "inconclusive" or "<LOQ". All virology data will be included in the efficacy analysis except the samples with "Inconclusive" viral load quantitation and the samples with an "Undetermined" RNase P (RP) internal control Ct value.

For analysis-qualified samples, results of "undetermined" and "<LOQ" will be handled as follows for data summary purpose:

- For viral load reported as "Undetermined", value 1 will be used to calculate descriptive statistics. This will support the need for logarithm transformation.
- For viral load reported as "<LOQ", value $5x10^1$ will be used to calculate descriptive statistics.

In conjuncture with above handling of the viral data scenarios, for purposes of this protocol, clearance of viral infection is defined as achievement of: [1] RP Ct ≥0, AND [2] Average N1 Ct ≥32 or Average N1 Ct = "Undetermined".

5.5.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is defined as time-weighted average (TWA) change in log10-transformed viral load by RT-qPCR from baseline to Day 8, where TWA will be derived using the trapezoidal rule:

$$\frac{\sum_{i=a}^{b-1} \{0.5 \times (Y_i + Y_{i+1}) \times (t_{i+1} - t_i)\}}{(t_b - t_a)}$$

Yi is the change from baseline in in log10-transformed viral load by RT-qPCR at Visit i, t is the actual study day at the specified timepoint, a is the baseline visit at Day 1, and b is the Day 8 visit.

At the final analysis, each dose of the RD-X19 device will be compared to sham using an Analysis of Covariance (ANCOVA) model with baseline viral load on log10 scale as a covariate and treatment group as an independent variable.

An example of SAS code for the analysis is as follows:

```
proc glm data=datain;
  class trt;
  model aval = trt base /ss3;
  estimate '4x RD-X19 vs Sham' trt 1 0 -1;
  estimate '7x RD-X19 vs Sham' trt 0 1 -1;
  lsmeans trt /pdiff stderr cl;
run;
```

where AVAL denotes the variable to be analyzed, BASE denotes the covariate baseline value, and TRT denotes treatment group with values 1 for 4 Days RD-X19, 2 for 7 Days RD-X19, and 3 for Sham.

5.5.2 Analysis of Secondary Efficacy Endpoints

The following 6 secondary efficacy endpoints will be summarized using descriptive statistics by visit, as appropriate:

- log10-transformed Viral load as measured in saliva by RT-qPCR at each visit by RT-qPCR
- proportion of subjects with ≥95% reduction in SARS-CoV-2 viral load by RT-qPCR at each visit
- time to clearance of viral infection in saliva via RT-qPCR
- proportion of subjects demonstrating clearance of viral infection via RT-qPCR at Day 8/ET visit
- COVID-19 composite severity score at each visit
- time to alleviation of COVID-19 symptoms, defined as the number of hours from the first dose to the first time when all eight symptoms had been assessed by the subject as none (0) or mild (1)
- time to sustained alleviation of COVID-19 symptoms, defined the number of hours from the first dose to the time when all eight symptoms had been assessed by the subject as none (0) or mild (1) and no single symptom reoccurs later at a level above mild (1).

Both time to alleviation of COVID-19 symptoms and time to sustained alleviation of COVID-19 symptoms will be derived from self-assessment by study subjects and recorded on the subjects' diary cards.

For log10-transformed viral load data, geometric means will be computed by exponentiating (base 10) the group means of the log10-transformed viral load. Time-to-event variables will be evaluated using the Kaplan-Meier method and p-values for treatment comparison will be provided via log rank test.

5.5.3 Analysis of Exploratory Efficacy Endpoint

Exploratory efficacy endpoint includes log10-transformed viral load at each visit as measured by $TCID_{50}$ for replication competent virus via both expelled saliva specimen and oropharyngeal swab collection methodologies. The sponsor will analyze the data collected for each biospecimen after the study is unblinded and provide details on the R&D test method and geometric means for inclusion in the complete study report.

5.6 Safety and Tolerability Variables and Analyses

Safety and tolerability analyses will be performed for the Safety Population. All safety listings and tables will be stratified by treatment assignment.

5.6.1 Adverse Events

All adverse events (AEs) occurring during the study will be recorded and coded in the Medical Dictionary for Regulatory Activities (MedDRA), version 22.1 or higher. TEAEs are defined as AEs recorded after first application of the study treatment.

Frequency and percent of subjects reporting TEAEs will be tabulated for each treatment by system organ class (SOC) and preferred terms (PT) for the following:

- all TEAEs
- all TEAEs by severity
- all TEAEs by relationship to study treatment

In the summaries of incidence (frequencies and percentages) of all TEAEs, subjects who report more than one event that are mapped to the same PT will be counted only once. In the summaries of incidence of TEAEs by severity and by relationship to study treatment, subjects who report more than one event that are mapped to the same PT will be counted only once under the strongest severity and relationship, accordingly. The composite of study subjects captured in this analysis will then be tabulated by what study day the 'most severe' observation was made.

Tabulations will be generated for solicited AEs (reactogenicity) separate from unsolicited AEs. Numbers and percentages of illumination site reactions, as well as unsolicited AEs, will be tabulated for each study day 1 through 8 so daily AE point prevalence may be determined. Likewise, tabulate oropharyngeal assessment overall and for each study visit.

Treatment-Emergent Serious Adverse Events (TESAEs) will be discussed within the clinical study report. TEAEs, TESAEs and TEAEs that led to treatment interruption or discontinuation will be presented in data listing.

5.6.2 Vital Signs

For each vital sign (systolic and diastolic blood pressure, heart rate, and oral temperature), actual values and change from baseline values will be summarized using descriptive statistics for each treatment group by visit.

5.6.3 Methemoglobin

Actual values of methemoglobin at baseline and Day 8/ET as well as change from baseline values will be summarized using descriptive statistics for each treatment group.

5.6.4 Other Assessments

Following assessment results will be presented in subject data listing: medical history, physical examination, clinical laboratory evaluations, concomitant medications.

Interim Analysis

Upon completion of all subjects in Cohort 1, an unblinded interim analysis will be conducted focusing on the following evaluations:

- Efficacy:
  - Geometric mean viral load as measured in saliva on day 1, 3, 5 and 8 by RT-qPCR
  - Proportion of subjects demonstrating viral load reduction ≥95% on day 3, 5 and 8 by RT-qPCR.
  - Time to alleviation of COVID-19 signs and symptoms
  - Time to sustained alleviation of COVID-19 signs and symptoms

- Safety:
  - All safety tabulations as listed in section 5.6.1 will be assessed as part of the interim analysis.
  - Summary or Treatment Emergent Adverse Events including a review of listings to monitor:
    - Number of study subjects experiencing any Serious Adverse Reaction (SAE).
    - Number of study subject experiencing treatment site reactions, including pain, induration or erythema of the oropharyx or oral mucosa, including the uvula and tongue.
    - Number of study subjects with any laboratory result that is out-of-range using the testing laboratory's institutional standards, including blood, urine and methemoglobin measured by pulse oxymetry.
    - Number of subjects experiencing laryngospasm, bronchospasm or anaphylaxis within 2 hours after use of the RD-X19 Device that is considered related to RD-X19.
    - Number of subjects experiencing an allergic reaction such as generalized urticaria (defined as occurring at three or more body parts) within 72 hours after use of study treatment that is considered related to RD-X19.
    - Number of subjects experiencing Grade 3 TEAE, in the same SOC grouping of PT, considered to be related to RD-X19.

As study subjects in cohort 1 are essentially a separate study, there is no prohibition to sponsor being unblinded for the interim analysis. Cohort 1 subjects are not tied to cohort 2 in any way and unblinding data from cohort 1 has no operational or statistical implications for cohort 2 assessment by sponsor. Study site personnel may not be unblinded to cohort 1 as there is a reasonable possibility that this information could be the basis for bias in the assessment of cohort 2.

To meet above review interest, the following summary tables (treatment groups: 4 Days RD-X19 vs. Sham) and by-subject data listings will be prepared for the interim analysis:

Tables / Listing	Description	Population
Efficacy		
Table 14.1.3	Demographic and Baseline Characteristics	Safety Population Cohort 1
Table 14.2.1.1	Time-Weighted Average Change in Log10-Transformed Viral Load by RT-qPCR from Baseline to Day 8	ITT Population of Cohort 1
Table 14.2.2.1	Log10-Transformed Viral Load via RT-qPCR by Visit	ITT Population of Cohort 1
Table 14.2.2.3	Proportion of Subjects with At Least 95% Reduction by Visit in SARS-Cov-2 Viral Load via RT-qPCR	ITT Population of Cohort 1
Table 14.2.5.1	Time to Alleviation of COVID-19 Symptoms	ITT Population of Cohort 1
Table 14.2.5.2	Time to Sustained Alleviation of COVID-19 Symptoms	ITT Population of Cohort 1
Safety		
Table 14.3.1.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population of Cohort 1
Table 14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity	Safety Population of Cohort 1
Table 14.3.1.3	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Causality to Study Device	Safety Population of Cohort 1
Table 14.3.2	Reactogenicity by Visit	Safety Population of Cohort 1
Table 14.3.3	Oropharyngeal assessment by Visit	Safety Population of Cohort 1
Listing 16.2.7	Adverse Events	Cohort 1 subjects
Listing 16.2.8.1	Out-of-Range Results of Clinical Laboratory Tests	Cohort 1 subjects
Listing 16.2.9.1	Reactogenecity Assessment	Cohort 1 subjects
Listing 16.2.9.2	Oropharyngeal Assessment	Cohort 1 subjects
Listing 16.2.9.6	Methemoglobin Measurement	Cohort 1 subjects

6 Tables and Listings

The following is an example of tables, listings and figures that will be included in the clinical study report. They may be modified as needed during the data analyses.

7 Appendices

7.1 Study Schedule of Activities

The schedule of visits and procedures to be conducted at each visit are summarized in the Study Schedule of Activities.

Study Procedures	Screening, Enrollment & Randomization	Follow-up Period (Visit Window)			
Study Days	**1**	**2**	**3**	**5 (-1 to +1)**	**8/ET (-1 to +1)**
Informed Consent	**X**				
COVID19 Screening & SARS-CoV-2 Rapid Antigen Test***	**X**				
Medical History & Physical Examination	**X**	**Changes since last visit only**	**Changes since last visit only**	**Changes since last visit only**	**X**
Oropharyngeal Assessment	**X***	**Changes since last visit only**	**Changes since last visit only**	**Changes since last visit only**	**X**
Urine Pregnancy Test	**X**				**X**
Concomitant Medication History/New	**Baseline**	**Changes since last visit only**	**Changes since last visit only**	**Changes since last visit only**	**Changes since last visit only**
Comprehensive Metabolic Panel & CBC	**X**				**X**
Vital Signs	**X**				**X**
Methemoglobin	**X**				**X**
Adverse Event Assessment / Reactogenicity	Baseline	**X**	**X**	**X**	**X**
Demographics, Inclusion / Exclusion Review	**X**				
Diary Dispensation/Collection	**X**				**X**
Treatment at Site	**X****	**X****	**X****		
Biospecimen collection for viral assays (**3** specimens)****	**X**		**X**	**X**	**X**
COVID-19 **Severity** Score	**X**				**X**
Collect RD-X19 Device	**NA**			Cohort 1	Cohort 2

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

**Only one treatment will be done on site, other treatment will be done at home, i.e. if afternoon appointment, subject will complete morning treatment at home and afternoon treatment administered at the site. For scheduling purposes, recommended interval between treatment is approximately 8 – 12 hours but not ≤ 4 hours.

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

****** At Baseline and days 3, 5, and 8, subjects will provide two saliva specimens and an oropharyngeal swab for virology endpoint assessments. One saliva specimen will be collected, preserved, and shipped fresh to a central lab for assessment of SARS-CoV-2 mRNA via RT-qPCR. The second specimen and the oropharyngeal swab will be collected in separate collection tubes, frozen, and stored at the site and shipped to a central lab at the end of each cohort.**

7.2 List of Summary Tables, Data Listings and Figures

List of Summary Tables

Number	Description	Analysis Set	Source Listing(s)
14.1	**Demographic and Baseline Data Summaries**		
14.1.1	Subject Final Study Disposition	All Randomized Subjects	16.2.1
14.1.2	Subject Analysis Population	All Randomized Subjects	16.2.1, 16.2.2.1
14.1.3	Demographic and Baseline Characteristics	Safety Population	16.2.4.1, 16.2.9.3
14.2	**Efficacy Data Summary Tables**		
14.2.1.1	Time-Weighted Average Change in Log10-Transformed Viral Load by RT-qPCR from Baseline to Day 8	ITT Population	16.2.6.4
14.2.1.2	Time-Weighted Average Change in Log10-Transformed Viral Load by RT-qPCR from Baseline to Day 8	PP Population	16.2.6.4
14.2.2.1	Log10-Transformed Viral Load via RT-qPCR by Visit	ITT Population	16.2.6.4
14.2.2.2	Log10-Transformed Viral Load via RT-qPCR by Visit	PP Population	16.2.6.4
14.2.2.3	Proportion of Subjects with At Least 95% Reduction by Visit in SARS-Cov-2 Viral Load via RT-qPCR	ITT & PP Populations	16.2.6.3
14.2.3	Clearance of Viral Infection in Saliva via RT-qPCR	ITT & PP Populations	16.2.6.4
14.2.4	COVID-19 Composite Severity Score by Visit	ITT & PP Populations	16.2.6.1
14.2.5.1	Time to Alleviation of COVID-19 Symptoms	ITT & PP Populations	16.2.6.1.2, 16.2.5.3
14.2.5.2	Time to Sustained Alleviation of COVID-19 Symptoms	ITT & PP Populations	16.2.6.1.2, 16.2.5.3
14.3	**Safety Data Summaries**		
14.3.1.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	16.2.7
14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity	Safety Population	16.2.7
14.3.1.3	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Causality to Study Device	Safety Population	16.2.7
14.3.1.4	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Study Day of Most Severe Observation	Safety Population	16.2.7
14.3.2	Reactogenicity by Visit	Safety Population	16.2.9.1
14.3.3	Oropharyngeal Assessment by Visit	Safety Population	16.2.9.2
14.3.4	Vital Signs by Visit	Safety Population	16.2.9.3
14.3.5	Methemoglobin by Visit	Safety Population	16.2.9.6

List of Data Listings

List of Figures

Summary Tables

Table 14.1.1 – Subject Final Study Disposition

	Treatment Group			
	4 Days RD-X19 n (%)	7 Days RD-X19 n (%)	Sham n (%)	Total n (%)
Subjects Randomized	XX	XX	XX	XX
Subjects Completed Study	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Subjects Discontinued	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Reason for Discontinuations:				
Withdrawal by Subject	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Adverse Event	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Medication Code Unblinded	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Lost to Follow-Up	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Pregnancy	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Physician Decision	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Failure to Meet Entry Criteria	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)

Source: Listing 16.2.1
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.1.2 – Subject Population

	Treatment Group			
	4 Days RD-X19 n (%)	7 Days RD-X19 n (%)	Sham n (%)	Total n (%)
Randomized	XX	XX	XX	XX
Safety population	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Exclusion from Safety population	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Reason for exclusion from Safety:				
No record of first dose	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Intent-to-Treat (ITT) population	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Exclusion from ITT population	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Reason for exclusion from ITT:				
No record of first dose	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Discontinued due to a significant abnormality from the baseline CMP and CBC tests	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Per-Protocol (PP) population	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Exclusion from PP population	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Reason for exclusion from PP				
No record of first dose	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Discontinued due to a significant abnormality from the baseline CMP and CBC tests	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Inclusion/exclusion criteria violation	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
…				

Subjects with multiple exclusion reasons are presented under each category of Reason for Exclusion as appropriate.
Source: Listing 16.2.1, 16.2.2.1
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.1.3 – Demographic and Baseline Characteristics for Safety Population

		Treatment Group			
	Category	4 Days RD-X19	7 Days RD-X19	Sham	Total
Age (Years)	N	XX	XX	XX	XX
	Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
	Median	XX.X	XX.X	XX.X	XX.X
	Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Gender n (%)	Male	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Female	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Ethnicity n (%)	Hispanic or Latino	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Not Hispanic or Latino	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Not Willing to Provide	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Race n (%)	American-Indian or Alaska Native	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Asian	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Black or African-American	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Native Hawaiian or Other Pacific Islander	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	White or Caucasian	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Other	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Body Mass Index (kg/m^2)	N	XX	XX	XX	XX
	Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
	Median	XX.X	XX.X	XX.X	XX.X
	Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

Source: Listing 16.2.4.1, 16.2.9.3
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.2.1.1 – Time-Weighted Average Change in Log10-Transformed Viral Load by RT-qPCR from Baseline to Day 8 for Intent-to-Treat Population

	Statistics	4 Days RD-X19	7 Days RD-X19	Sham
TWA Change in Log10-Transformed Viral Load	N	XX	XX	XX
	Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
	Median	XX.X	XX.X	XX.X
	Min, Max	XX, XX	XX, XX	XX, XX
	LSM (SE)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	95% CI for LSM	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
	RD-X19 vs. Sham			
	LSMD (SE)	XX (XX.X)	XX (XX.X)	
	95% CI for LSMD	(XX.X, XX.X)	(XX.X, XX.X)	
	P-value	0.XXX	0.XXX	

Abbreviation: CI = Confidence Interval; GTM = Geometric Mean; LSM = Least Square Mean; LSMD = Least Square Mean Difference; SE = Standard Error
Note 1: Missing data will be replaced for the efficacy endpoint in the ITT analyses using the Last observation carried forward (LOCF) method.
Note 2: LSM, LSMD, 95% CI for LSMD, and p-values are based on an Analysis of Covariance (ANCOVA) model with baseline viral load on log10 scale as a covariate and treatment group as an independent variable.
Source: Listing 16.2.6.4
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Repeat Table 14.2.1.1 for the following:

Table 14.2.1.2 – Time-Weighted Average Change in Log10-Transformed Viral Load by RT-qPCR from Baseline to Day 8 for Per-Protocol Population (with Note 1 removed)

Table 14.2.2.1 – Log10-Transformed Viral Load via RT-qPCR by Visit for Intent-to-Treat Population

Study Visit	Statistics	4 Days RD-X19 (N=XX)	7 Days RD-X19 (N=XX)	Sham (N=XX)
Visit 1 /Day 1	N	XX	XX	XX
	Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
	Median	XX.X	XX.X	XX.X
	Min, Max	XX, XX	XX, XX	XX, XX
	Geometric Mean on Original Scale	XX.X	XX.X	XX.X
Visit 3 /Day 3	N	XX	XX	XX
	Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
	Median	XX.X	XX.X	XX.X
	Min, Max	XX, XX	XX, XX	XX, XX
	Geometric Mean on Original Scale	XX.X	XX.X	XX.X
Visit 4 /Day 5				
Visit 5 /Day 8				

Missing data will be replaced for the efficacy endpoint in the ITT analyses using the Last observation carried forward (LOCF) method.
Note: Geometric Means are computed by exponentiating (base 10) the Means of the log10-transformed viral load.
Source: Listing 16.2.6.4
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Repeat Table 14.2.2.1 for the following:

Table 14.2.2.2 – Log10-Transformed Viral Load via RT-qPCR by Visit for Per-Protocol Population
(with footnote 1 removed)

Table 14.2.2.3 – Proportion of Subjects with At Least 95% Reduction by Visit in SARS-Cov-2 Viral Load via RT-qPCR

Population	Study Visit	Statistics	4 Days RD-X19	7 Days RD-X19	Sham
Intent-to-Treat	Visit 3 /Day 3	N	XX	XX	XX
		n (%) Subjects with >=95% Reduction	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Visit 4 /Day 5	N	XX	XX	XX
		n (%) Subjects with >=95% Reduction	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Visit 5 /Day 8	N	XX	XX	XX
		n (%) Subjects with >=95% Reduction	XX (XX.X)	XX (XX.X)	XX (XX.X)
Per-Protocol	Visit 3 /Day 3	N	XX	XX	XX
		n (%) Subjects with >=95% Reduction	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Visit 4 /Day 5	N	XX	XX	XX
		n (%) Subjects with >=95% Reduction	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Visit 5 /Day 8	N	XX	XX	XX
		n (%) Subjects with >=95% Reduction	XX (XX.X)	XX (XX.X)	XX (XX.X)

Note: Missing data will be replaced for the efficacy endpoint in the ITT analyses using the Last observation carried forward (LOCF) method.
Source: Listing 16.2.6.3
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.2.3 – Clearance of Viral Infection in Saliva via RT-qPCR

Population	Endpoint	Statistics	4 Days RD-X19	7 Days RD-X19	Sham
Intent-to-Treat	Time to Clearance of Viral Infection	N	XX	XX	XX
		n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Median of Time	XX.X	XX.X	XX.X
		25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
		95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
		P-value RX-X19 vs. Sham	0.XXX	0.XXX	
	Subjects Demonstrating Clearance of Viral Infection at Day 8/ET Visit	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Per-Protocol	Time to Clearance of Viral Infection	N	XX	XX	XX
		n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Median of Time	XX.X	XX.X	XX.X
		25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
		95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
		P-value RX-X19 vs. Shamn	0.XXX	0.XXX	
	Subjects Demonstrating Clearance of Viral Infection at Day 8/ET Visit	(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)

Abbreviation: CI = Confidence Interval
Subjects with clearance of viral infection at baseline are excluded from the analysis of time-to-clearance of viral infection.
Note 1: Clearance of viral infection in saliva is defined as a negative test (Ct value ≥32) via RT-qPCR, i.e. achievement of [1] RP Ct =0, AND [2] Average N1 Ct =32 or Average N1 Ct ='Undetermined'. Subjects who did not achieve clearance at the last assessment of the study are considered censored at the time of the last assessment.
Note 2: Subjects who did not achieve clearance at the exit of study are considered censored.
Note 3: Percentiles and 95% CI of median are derived using the Kaplan-Meier method. P-values for treatment comparison are from Log Rank Test.
Source: Listing 16.2.6.4, 16.2.5.3
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Figure 15.1.1 - Kaplan-Meier Plot of Time to Clearance of Viral Infection for Intent-to-Treat Population
Figure 15.1.2 - Kaplan-Meier Plot of Time to Clearance of Viral Infection for Per-Protocol Population

Table 14.2.4 – COVID-19 Composite Severity Score by Visit

Population	Study Visit	Category	Statistics	4 Days RD-X19	7 Days RD-X19	Sham
Intent-to-Treat	Visit 1 /Day 1 (Baseline)	Actual Value	N	XX	XX	XX
			Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
			Median	XX.X	XX.X	XX.X
			Min, Max	XX, XX	XX, XX	XX, XX
	Visit 5 /Day 8	Actual Value	N	XX	XX	XX
			Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
			Median	XX.X	XX.X	XX.X
			Min, Max	XX, XX	XX, XX	XX, XX
		Change from Baseline	Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
			Median	XX.X	XX.X	XX.X
			Min, Max	XX, XX	XX, XX	XX, XX
Per-Protocol	Visit 1 /Day 1 (Baseline)	Actual Value	N	XX	XX	XX
			Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
			Median	XX.X	XX.X	XX.X
			Min, Max	XX, XX	XX, XX	XX, XX
	Visit 5 /Day 8	Actual Value	N	XX	XX	XX
			Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
			Median	XX.X	XX.X	XX.X
			Min, Max	XX, XX	XX, XX	XX, XX
		Change from Baseline	Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
			Median	XX.X	XX.X	XX.X
			Min, Max	XX, XX	XX, XX	XX, XX

Note: Missing data will be replaced for the efficacy endpoint in the ITT analyses using the Last observation carried forward (LOCF) method.
Source: Listing 16.2.6.1
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.2.5.1 – Time to Alleviation of COVID-19 Symptoms

Population	Statistics	4 Days RD-X19	7 Days RD-X19	Sham
Intent-to-Treat	N	XX	XX	XX
	n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Median of Time	XX.X	XX.X	XX.X
	25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
	95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
	P-value RX-X19 vs. Sham	0.XXX	0.XXX	
Per-Protocol	N	XX	XX	XX
	n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Median of Time	XX.X	XX.X	XX.X
	25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
	95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
	P-value RX-X19 vs. Sham	0.XXX	0.XXX	

Abbreviation: CI = Confidence Interval
Note 1: Alleviation of COVID-19 symptoms is defined as all eight symptoms assessed by the subject as none (0) or mild (1).
Note 2: Time to alleviation is calculated as the number of hours from the first dose to the time of the first occurrence of symptoms alleviation. Subjects who did not achieve alleviation at the last assessment of study are considered censored at the time of the last assessment.
Note 3: Percentiles and 95% CI of median are derived using the Kaplan-Meier method. P-values for treatment comparison are from Log Rank Test.
Source: Listing 16.2.6.1.2, 16.2.5.3
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Figure 15.2.1 - Kaplan-Meier Plot of Time to Alleviation of COVID-19 Symptoms for Intent-to-Treat Population
Figure 15.2.2 - Kaplan-Meier Plot of Time to Alleviation of COVID-19 Symptoms for Per-Protocol Population

Table 14.2.5.2 – Time to Sustained Alleviation of COVID-19 Symptoms

Population	Statistics	4 Days RD-X19	7 Days RD-X19	Sham
Intent-to-Treat	N	XX	XX	XX
	n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Median of Time	XX.X	XX.X	XX.X
	25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
	95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
	P-value RX-X19 vs. Sham	0.XXX	0.XXX	
Per-Protocol	N	XX	XX	XX
	n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Median of Time	XX.X	XX.X	XX.X
	25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
	95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
	P-value RX-X19 vs. Sham	0.XXX	0.XXX	

Abbreviation: CI = Confidence Interval
Note 1: Sustained alleviation of COVID-19 symptoms is defined as all eight symptoms assessed by the subject as none (0) or mild (1) AND no single symptom reoccurs later at a level above mild (1).
Note 2: Time to sustained alleviation is calculated as the number of hours from the first dose to the time of the occurrence of sustained symptoms alleviation. Subjects who did not
achieve sustained alleviation at the last assessment of the study are considered censored at the time of the last assessment.
Note 3: Percentiles and 95% CI of median are derived using the Kaplan-Meier method. P-values for treatment comparison are from Log Rank Test.
Source: Listing 16.2.6.1.2, 16.2.5.3
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Figure 15.3.1 - Kaplan-Meier Plot of Time to Sustained Alleviation of COVID-19 Symptoms for Intent-to-Treat Population
Figure 15.3.2 - Kaplan-Meier Plot of Time to Sustained Alleviation of COVID-19 Symptoms for Per-Protocol Population

Table 14.3.1.1 - Treatment-Emergent Adverse Events by System Organ Class and Preferred Term for Safety Population

System Organ Class Preferred Term	4 Days RD-X19 (N=XX) n (%)	7 Days RD-X19 (N=XX) n (%)	Sham (N=XX) n (%)
Subjects Reporting at Least One Adverse Event	XX (XX.X)	XX (XX.X)	XX (XX.X)
System Organ Class #1	XX (XX.X)	XX (XX.X)	XX (XX.X)
Preferred Term #1	XX (XX.X)	XX (XX.X)	XX (XX.X)
Preferred Term #2	XX (XX.X)	XX (XX.X)	XX (XX.X)
…			
System Organ Class #2	XX (XX.X)	XX (XX.X)	XX (XX.X)
Preferred Term #1	XX (XX.X)	XX (XX.X)	XX (XX.X)
Preferred Term #2	XX (XX.X)	XX (XX.X)	XX (XX.X)
…			

Counts reflect numbers of subjects reporting one or more TEAE that map to the MedDRA system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one TEAE are counted only once.
Source: Listing 16.2.7
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.3.1.2 - Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity for Safety Population

System Organ Class Preferred Term	Severity	4 Days RD-X19 (N=XX) n (%)	7 Days RD-X19 (N=XX) n (%)	Sham (N=XX) n (%)
Subjects Reporting at Least One Adverse Event	Mild	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Moderate	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Severe	XX (XX.X)	XX (XX.X)	XX (XX.X)
System Organ Class #1	Mild	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Moderate	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Severe	XX (XX.X)	XX (XX.X)	XX (XX.X)
Preferred Term #1	Mild	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Moderate	XX (XX.X)	XX (XX.X)	XX (XX.X)
…	Severe	XX (XX.X)	XX (XX.X)	XX (XX.X)
…				
…				

Counts reflect numbers of subjects reporting one or more TEAE that map to the MedDRA system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one TEAE are counted only once (under the greatest reported severity).
Source: Listing 16.2.7
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.3.1.3 - Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Causality to Study Device for Safety Population

System Organ Class Preferred Term	Causality	4 Days RD-X19 (N=XX) n (%)	7 Days RD-X19 (N=XX) n (%)	Sham (N=XX) n (%)
Subjects Reporting at Least One Adverse Event	Not Related	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Related	XX (XX.X)	XX (XX.X)	XX (XX.X)
System Organ Class #1	Not Related	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Related	XX (XX.X)	XX (XX.X)	XX (XX.X)
Preferred Term #1	Not Related	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Related	XX (XX.X)	XX (XX.X)	XX (XX.X)
…				
…				
…				

Counts reflect numbers of subjects reporting one or more TEAE that map to the MedDRA system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one TEAE are counted only once (under the greatest reported causality).
Source: Listing 16.2.7
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.3.1.4 –Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Study Day of Most Severe Observation for Safety Population

System Organ Class Preferred Term	Study Day*	4 Days RD-X19 (N=XX) n (%)	7 Days RD-X19 (N=XX) n (%)	Sham (N=XX) n (%)
Subjects Reporting at Least One Adverse Event	Day 1	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Day 2	XX (XX.X)	XX (XX.X)	XX (XX.X)
	…			
System Organ Class #1	Day 1	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Day 2	XX (XX.X)	XX (XX.X)	XX (XX.X)
	…			
Preferred Term #1	Day 1	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Day 2	XX (XX.X)	XX (XX.X)	XX (XX.X)
…	…			
…				
…				

*Study Day is calculated relative to date of first treatment. Day 1 is the day of first treatment. For the summary, Study Day is the day number when the most severe observation was made of an event.
Counts reflect numbers of subjects reporting one or more TEAE that map to the MedDRA system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one TEAE are counted only once under the earliest Study Day when the event of greatest severity was reported.
Source: Listing 16.2.7
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.3.2 – Reactogenicity by Visit for Safety Population

Study Visit	Category	4 Days RD-X19 n (%)	7 Days RD-X19 n (%)	Sham n (%)
Visit 1 /Day 1	N	XX	XX	XX
	n (%) subject with illumination site pain	XX (XX.X)	XX (XX.X)	XX (XX.X)
	n (%) subject with illumination site erythema	XX (XX.X)	XX (XX.X)	XX (XX.X)
	n (%) subject with illumination site Edema/Induration	XX (XX.X)	XX (XX.X)	XX (XX.X)
	n (%) subject with other pain, redness, swelling, or lesion of the oral mucosa	XX (XX.X)	XX (XX.X)	XX (XX.X)
Visit 2 /Day 2	N	XX	XX	XX
	n (%) subject with illumination site pain	XX (XX.X)	XX (XX.X)	XX (XX.X)
	n (%) subject with illumination site erythema	XX (XX.X)	XX (XX.X)	XX (XX.X)
	n (%) subject with illumination site Edema/Induration	XX (XX.X)	XX (XX.X)	XX (XX.X)
	n (%) subject with other pain, redness, swelling, or lesion of the oral mucosa	XX (XX.X)	XX (XX.X)	XX (XX.X)
Visit 3 /Day 3	…			
Visit 4 /Day 5	…			
Visit 5 /Day 8/ET	…			

Source: Listing 16.2.9.1
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.3.3 – Oropharyngeal Assessment by Visit for Safety Population

Study Visit	Category	4 Days RD-X19 n (%)	7 Days RD-X19 n (%)	Sham n (%)
Overall*	N	XX	XX	XX
	Normal	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Abnormal	XX (XX.X)	XX (XX.X)	XX (XX.X)
Visit 1 /Day 1	N	XX	XX	XX
	Normal	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Abnormal	XX (XX.X)	XX (XX.X)	XX (XX.X)
Visit 2 /Day 2	N	XX	XX	XX
	Normal	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Abnormal	XX (XX.X)	XX (XX.X)	XX (XX.X)
Visit 3 /Day 3	…			
Visit 4 /Day 5	…			
Visit 5 /Day 8/ET	…			

*For Overall, Normal category includes subjects with a normal result for all visits; Abnormal category includes subjects with an abnormal result at any visit.
Source: Listing 16.2.9.2
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.3.4 – Vital Signs by Visit for Safety Population

Vital Sign	Study Visit	Category	Statistics	4 Days RD-X19 (N=XX)	7 Days RD-X19 (N=XX)	Sham (N=XX)
Systolic Blood Pressure (mmHg)	Visit 1 /Day 1 (Baseline)	Actual Value	N	XX	XX	XX
			Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
			Median	XX.X	XX.X	XX.X
			Min, Max	XX, XX	XX, XX	XX, XX
	Visit 5 /Day 8/ET	Actual Value	N	XX	XX	XX
			Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
			Median	XX.X	XX.X	XX.X
			Min, Max	XX, XX	XX, XX	XX, XX
		Change from Baseline	Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
			Median	XX.X	XX.X	XX.X
			Min, Max	XX, XX	XX, XX	XX, XX
Diastolic Blood Pressure (mmHg)	…					
Heart Rate (beats/min)	…					
Temperature (F)	…					
Respiratory (breaths/min)	…					

Source: Listing 16.2.9.3
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Table 14.3.5 – Methemolgobin by Visit for Safety Population

Study Visit	Category	Statistics	4 Days RD-X19 (N=XX)	7 Days RD-X19 (N=XX)	Sham (N=XX)
Visit 1 /Day 1 (Baseline)	Actual Value	N	XX	XX	XX
		Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
		Median	XX.X	XX.X	XX.X
		Min, Max	XX, XX	XX, XX	XX, XX
Visit 5 /Day 8/ET	Actual Value	N	XX	XX	XX
		Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
		Median	XX.X	XX.X	XX.X
		Min, Max	XX, XX	XX, XX	XX, XX
	Change from Baseline	Mean ± SD	XX.X ± XX.X	XX.X ± XX.X	XX.X ± XX.X
		Median	XX.X	XX.X	XX.X
		Min, Max	XX, XX	XX, XX	XX, XX

Source: Listing 16.2.9.6
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Data Listings

Listing 16.2.1 - Subject Disposition

Subject	Cohort	Safety Population	ITT Population	PP Population	Date of First Treatment	Study Exit Date (Study Day)	Completed Study?	Primary Reason for Study Discontinuation
Treatment:								

Abbreviations: ITT, Intent-to-Treat; PP, Per-Protocol
Study Day is calculated relative to date of first treatment. Day 1 is the day of first treatment.
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Listings\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Listing 16.2.2.1 - Protocol Deviations

Subject	Cohort	Major (Significant) Protocol Deviation?	Description of Deviation
Treatment:			

Major (Significant) protocol deviations are those that exclude subjects from the per-protocol analysis.
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Listings\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Listing 16.2.2.2 - Informed Consent and Eligibility Criteria

			SARS-CoV-2 Rapid Antigen Test		Baseline/Randomization	
Subject	Cohort	Date of Informed Consent	Nasal swab collected and analyzed?	Result of Antigen Test	Subject met all Entry Criteria?	If No, Criterion Not Met
Treatment:						

Listing 16.2.2.3 - General Comments

Subject	Cohort	Date of Comment	eCRF Form/Module	Comment
Treatment:				

Listing 16.2.4.1 - Demographics

Subject	Cohort	Date of Birth	Age	Sex	Ethnicity	Race
Treatment:						

Age is calculated relative to date of informed consent.
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Listing 16.2.4.2 - Medical/Surgical History

Subject	Cohort	Subject had medical or surgical history?	Condition or Procedure	Onset Date	Stop Date	Concomitant medications?
Treatment:						

Listing 16.2.5.1 - Subject Randomization, Dosing Diary and Study Device Dispensing at Visit 1/Day 1, and Illumination Treatment at Site

Subject	Cohort	Randomization Number	Date of Randomization	Dosing instructions reviewed and dosing diary dispensed?	Investigational device dispensed to the subject?	Initials of Dispenser	Illumination treatment performed on site under supervision?		
							Visit 1 /Day 1	Visit 2 /Day 2	Visit 3 /Day 3
Treatment:									

Listing 16.2.5.2 – Treatment Record and Subject Diary Collection at End of Study

Subject	Cohort	Subject applied at least one treatment?	Total Illumination Treatments	Total Treatments Missed	Subject diary collected?	Investigational device collected?	Initials of Collector
Treatment:							

Listing 16.2.5.3 – Treatment Application Log

Subject	Cohort	Dose Number	Date of Dose	Time of Dose	Missed Dose	Dose Not Applicable	Unknown
Treatment:							

Listing 16.2.6.1.1 – COVID-19 Symptom Assessment and Severity Score

			Assessment											
Subject	Cohort	Visit	Study Day	Date:Time	Cough	Sore Throat	Nasal Congestion	Headache	Chills/ Sweats	Muscle or Joint pain	Fatigue	Nausea	Fever (F)	COVID-19 Severity Score
Treatment:														

COVID-19 Symptom: 0=None, 1=Mild, 2=Moderate, 3=Severe. Study Day is calculated relative to date of first treatment. Day 1 is the day of first treatment.
Note: Assessment at a visit was based on symptoms the subject reports as occurring within the past 3 days of that visit.
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Listings\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Listing 16.2.6.1.2- COVID-19 Symptom Assessment and Severity Score from Subject Diary

				Assessment											
Site-Subject	Cohort	Not Done	Day	Study Day	Date:Time	Cough	Sore Throat	Nasal Congestion	Headache	Chills/ Sweats	Muscle or Joint pain	Fatigue	Nausea	Fever (F)	COVID-19 Severity Score
Treatment:															
xxxx	x		Day 1- Assessment 1	1											
			Day 1- Assessment 2	1											
			Day 2- Assessment 1	2											

COVID-19 Symptom: 0=None, 1=Mild, 2=Moderate, 3=Severe. Study Day is calculated relative to date of first treatment. Day 1 is the day of first treatment.
Note: Assessment at a visit was based on symptoms the subject reports as occurring within the past 3 days of that visit.
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Listings\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Listing 16.2.6.2 – Clearance of COVID-19 Symptoms

Subject	Cohort	Has there been a timepoint/day that ALL of the subject's Covid-19 symptom assessment scores reached 0 and/or 1?	Date (Study Day)	Time
Treatment:				

Study Day is calculated relative to date of first treatment. Day 1 is the day of first treatment.
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Listing 16.2.6.3 – Viral Load via Saliva Specimen and Oropharyngeal Swab Collection

				Sample Received						
Subject	Cohort	Type of Biospecimen	Visit	Date (Study Day)	Time	Test Date (Study Day)	Test Result	Average N1 Ct	RP Ct	Viral Load Quantitation (copies/mL)
Treatment:										

Study Day is calculated relative to date of first treatment. Day 1 is the day of first treatment.
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Listings\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Listing 16.2.6.4 – Derived Clearance of Viral Infection and Time-Weighted Average Change from Baseline in Log10-Transformed Viral Load via RT-qPCR

		Clearance of Viral Infection (Study Day)				Change from Baseline in Log10-Transformed Vital Load (Study Day)			TWA Change from
Subject Cohort	Analysis	Visit 2 /Day 2	Visit 3 /Day 3	Visit 4 /Day 5	Visit 5 /Day 8	Visit 3 /Day 3	Visit 4 /Day 5	Visit 5 /Day 8	Day 1 to Day 8
Treatment:									
	ITT	No (2)	No (3)	No (5)	No (9)	xx.x (3)	xx.x (5)	xx.x (9)	xx.x
	PP	No (2)	No (3)		No (9)	xx.x (3)		xx.x (9)	xx.x

Abbreviation: ITT = Intent-to-Treat, PP = Per-Protocol, TWA = Time-Weighted Average, LOCF = Last observation carried forward
Study Day is calculated relative to date of first treatment. Day 1 is the day of first treatment.
For the ITT analysis, missing viral load will be imputed using the LOCF method.
Note 1: Clearance of viral infection is defined, based on viral load via RT-qPCR, as achievement of: [1] RP Ct ≥0, AND [2] Average N1 Ct ≥32 or Average N1 Ct = "Undetermined".
Note 2: TWA Change from Day 1 to Day 8 is calculated using the trapezoidal rule.
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Listings\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Listing 16.2.7 - Adverse Events

Subject	Cohort	AE No.	System Organ Class / Preferred Term / Event Name	Occurred prior to first dose?	Start Date (Study Day)	Stop Date (Study Day)	Serious AE?	Intensity	Causality to Study Device	Action Taken	Outcome
Treatment:											

Note: Adverse events coded in MedDRA, version xx.x
Study Day is calculated relative to date of first treatment. Day 1 is the day of first treatment while Day -1 is the day prior to first treatment.
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Listing 16.2.8.1 – Out-of-Range Results of Clinical Laboratory Tests

Subject	Cohort	Visit	Lab Panel	Test Name	Result	Flag	Out of Range: NCS or CS
Treatment:							

Abbreviation: CS = clinically significant, NCS = not clinically significant
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Listings\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Listing 16.2.8.2 - Pregnancy Test (Female Subjects Only)

Subject	Cohort	Visit	Pregnancy Test Done?	If not done, subject is not of childbearing potential due to	Date of Test (Study Day)	Result
Treatment:						

Study Day is calculated relative to date of first treatment. Day 1 is the day of first treatment.
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Listings\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Listing 16.2.9.1 - Reactogenicity Assessment

Subject	Cohort	Visit	Illumination Site Pain?	Illumination Site Erythema?	Illumination Site Edema/ Induration?	Other pain, redness, swelling, or lesion of the oral mucosa?
Treatment:						

Listing 16.2.9.2 - Oropharyngeal Assessment

Subject	Cohort	Visit	Oropharyngeal Assessment performed?	Any changes since previous visit?	Assessment Result	Description of Abnormality
Treatment:						

Listing 16.2.9.3 - Vital Signs

Subject	Cohort	Visit	Height (in)	Weight (lb)	Body Mass Index (kg/m^2)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Temperature (F)
Treatment:										
									XX /NCS	XXX /NCS

For out-of-range results, CS = clinically significant, NCS = not clinically significant.
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Listings\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Listing 16.2.9.4 - Physical Examination

Subject	Cohort	Visit	PE Performed?	Subject requires a targeted PE?	Test Name	Description of Abnormality
Treatment:						

Listing 16.2.9.5 - Prior and Concomitant Medications

Subject	Cohort	WHO Class / WHO Drug Name / Medication Name	Start Date (Study Day)	End Date (Study Day)	Dose	Unit	Route	Frequency	Indication
Treatment:									

Abbreviations: ATC = anatomic therapeutic chemical; WHODDE, World Health Organization Drug Dictionary Enhanced
Medications are coded to ATC class and drug names using the WHODDE, version xxxxx.
Study Day is calculated relative to date of first treatment. Day 1 is the day of first treatment while Day -1 is the day prior to first treatment.
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Listings\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Programming Note:

- *If specifications for indications are reported as an AE or MH #, merge with AE/MH data to present the actual reported event as the specification.*
- *When creating WHO Class, utilize ATC level 4 drug class; utilize level 3 term if level 4 is missing and level 2 if both level 3 and level 4 are missing in the dataset*

Listing 16.2.9.6 - Methemoglobin Measurement

Subject	Cohort	Visit	Methemoglobin measured?	Methemoglobin Result (Percent)
Treatment:				

Statistical Analysis Plan Amendment #1

Protocol No.:	EB-P12-01
Title:	A 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
Previous SAP (v1.0) Date:	December 17, 2020
Amendment 01 Date:	January 25, 2021
Sponsor:	EmitBio Inc. Suite 470, 4222 Emperor Blvd Durham, NC 27703

Amendments:

Per sponsor request, diary of COVID-19 symptom assessments have been added to the database. Time to alleviation of COVID-19 symptoms should be derived based on the diary entries. Time to sustained alleviation is added to the list of secondary efficacy endpoints. For all time-to-event variables, Kaplan-Meier plots and log rank p-values for treatment comparisons will be provided. Content of interim analysis is adjusted.

1. Original Text and Location

5.5.2 Analysis of Secondary Efficacy Endpoints

The following 6 secondary efficacy endpoints will be summarized using descriptive statistics by visit, as appropriate:

- log10-transformed Viral load as measured in saliva by RT-qPCR at each visit by RT-qPCR
- proportion of subjects with ≥95% reduction in SARS-CoV-2 viral load by RT-qPCR at each visit
- time to clearance of viral infection in saliva via RT-qPCR
- proportion of subjects demonstrating clearance of viral infection via RT-qPCR at Day 8/ET visit
- COVID-19 composite severity score at each visit
- time to alleviation of COVID-19 symptoms, defined as the time when all eight symptoms had been assessed by the subject as none (0) or mild (1).

For log10-transformed viral load data, geometric means will be computed by exponentiating (base 10) the group means of the log10-transformed viral load. Time-to-event variables will be evaluated using the Kaplan-Meier method.

Revised Text and Location

5.5.2 Analysis of Secondary Efficacy Endpoints

The following 7 secondary efficacy endpoints will be summarized using descriptive statistics by visit, as appropriate:

- log10-transformed Viral load as measured in saliva by RT-qPCR at each visit by RT-qPCR
- proportion of subjects with ≥95% reduction in SARS-CoV-2 viral load by RT-qPCR at each visit
- time to clearance of viral infection in saliva via RT-qPCR
- proportion of subjects demonstrating clearance of viral infection via RT-qPCR at Day 8/ET visit
- COVID-19 composite severity score at each visit
- time to alleviation of COVID-19 symptoms, defined as the number of hours from the first dose to the first time when all eight symptoms had been assessed by the subject as none (0) or mild (1)
- time to sustained alleviation of COVID-19 symptoms, defined the number of hours from the first dose to the time when all eight symptoms had been assessed by the subject as none (0) or mild (1) and no single symptom reoccurs later at a level above mild (1).

Both time to alleviation of COVID-19 symptoms and time to sustained alleviation of COVID-19 symptoms will be derived from self-assessment by study subjects and recorded on the subjects' diary cards.

For log10-transformed viral load data, geometric means will be computed by exponentiating (base 10) the group means of the log10-transformed viral load. Time-to-event variables will be evaluated using the Kaplan-Meier method and p-values for treatment comparison will be provided via log rank test.

2. **Original Text and Location**

Interim Analysis

Upon completion of all subjects in Cohort 1, an unblinded interim analysis will be conducted focusing on the following evaluations:

- Efficacy:
  - Geometric mean viral load as measured in saliva on day 1, 3, 5 and 8 by RT-qPCR
  - Proportion of subjects demonstrating viral load reduction ≥95% on day 3, 5 and 8 by RT-qPCR.

- Safety:
  - All safety tabulations as listed in section 5.6.1 will be assessed as part of the interim analysis.

- Summary or Treatment Emergent Adverse Events including a review of listings to monitor:
  - Number of subjects experiencing laryngospasm, bronchospasm or anaphylaxis within 2 hours after use of the RD-X19 Device that is considered related to RD-X19.
  - Number of subjects experiencing an allergic reaction such as generalized urticaria (defined as occurring at three or more body parts) within 72 hours after use of study treatment that is considered related to RD-X19.
  - Number of subjects experiencing SAE or Grade 3 AE, in the same SOC grouping of PT, considered to be related to RD-X19.

As study subjects in cohort 1 are essentially a separate study, there is no prohibition to sponsor being unblinded for the interim analysis. Cohort 1 subjects are not tied to cohort 2 in any way and unblinding data from cohort 1 has no operational or statistical implications for cohort 2 assessment by sponsor. Study site personnel may not be unblinded to cohort 1 as there is a reasonable possibility that this information could be the basis for bias in the assessment of cohort 2.

To meet above review interest, the following summary tables (treatment groups: 4 Days RD-X19 vs. Sham) and by-subject data listings will be prepared for the interim analysis:

Tables / Listing	**Description**	**Population**
Efficacy		
Table 14.2.2.1	Log10-Transformed Viral Load via RT-qPCR by Visit	ITT Population of Cohort 1
Table 14.2.2.3	Proportion of Subjects with At Least 95% Reduction by Visit in SARS-Cov-2 Viral Load via RT-qPCR	ITT Population of Cohort 1
Safety		
Table 14.3.1.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population of Cohort 1
Table 14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity	Safety Population of Cohort 1
Table 14.3.1.3	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Causality to Study Device	Safety Population of Cohort 1
Table 14.3.2	Reactogenicity by Visit	Safety Population of Cohort 1
Table 14.3.3	Oropharyngeal assessment by Visit	Safety Population of Cohort 1
Listing 16.2.7	Adverse Events	Cohort 1 subjects
Listing 16.2.9.1	Reactogenecity Assessment	Cohort 1 subjects
Listing 16.2.9.2	Oropharyngeal Assessment	Cohort 1 subjects

Revised Text and Location

Interim Analysis

Upon completion of all subjects in Cohort 1, an unblinded interim analysis will be conducted focusing on the following evaluations:

- Efficacy:
  - Geometric mean viral load as measured in saliva on day 1, 3, 5 and 8 by RT-qPCR
  - Proportion of subjects demonstrating viral load reduction ≥95% on day 3, 5 and 8 by RT-qPCR.
  - Time to alleviation of COVID-19 signs and symptoms
  - Time to sustained alleviation of COVID-19 signs and symptoms

- Safety:
  - All safety tabulations as listed in section 5.6.1 will be assessed as part of the interim analysis.
  - Summary or Treatment Emergent Adverse Events including a review of listings to monitor:
    - Number of study subjects experiencing any Serious Adverse Reaction (SAE).
    - Number of study subject experiencing treatment site reactions, including pain, induration or erythema of the oropharyx or oral mucosa, including the uvula and tongue.
    - Number of study subjects with any laboratory result that is out-of-range using the testing laboratory's institutional standards, including blood, urine and methemoglobin measured by pulse oxymetry.
    - Number of subjects experiencing laryngospasm, bronchospasm or anaphylaxis within 2 hours after use of the RD-X19 Device that is considered related to RD-X19.
    - Number of subjects experiencing an allergic reaction such as generalized urticaria (defined as occurring at three or more body parts) within 72 hours after use of study treatment that is considered related to RD-X19.
    - Number of subjects experiencing Grade 3 TEAE, in the same SOC grouping of PT, considered to be related to RD-X19.

As study subjects in cohort 1 are essentially a separate study, there is no prohibition to sponsor being unblinded for the interim analysis. Cohort 1 subjects are not tied to cohort 2 in any way and unblinding data from cohort 1 has no operational or statistical implications for cohort 2 assessment by sponsor. Study site personnel may not be unblinded to cohort 1 as there is a reasonable possibility that this information could be the basis for bias in the assessment of cohort 2.

To meet above review interest, the following summary tables (treatment groups: 4 Days RD-X19 vs. Sham) and by-subject data listings will be prepared for the interim analysis:

Tables / Listing	Description	Population
Efficacy		
Table 14.1.3	Demographic and Baseline Characteristics	Safety Population Cohort 1
Table 14.2.1.1	Time-Weighted Average Change in Log10-Transformed Viral Load by RT-qPCR from Baseline to Day 8	ITT Population of Cohort 1
Table 14.2.2.1	Log10-Transformed Viral Load via RT-qPCR by Visit	ITT Population of Cohort 1
Table 14.2.2.3	Proportion of Subjects with At Least 95% Reduction by Visit in SARS-Cov-2 Viral Load via RT-qPCR	ITT Population of Cohort 1
Table 14.2.5.1	Time to Alleviation of COVID-19 Symptoms	ITT Population of Cohort 1
Table 14.2.5.2	Time to Sustained Alleviation of COVID-19 Symptoms	ITT Population of Cohort 1
Safety		
Table 14.3.1.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population of Cohort 1
Table 14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity	Safety Population of Cohort 1
Table 14.3.1.3	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Causality to Study Device	Safety Population of Cohort 1
Table 14.3.2	Reactogenicity by Visit	Safety Population of Cohort 1
Table 14.3.3	Oropharyngeal assessment by Visit	Safety Population of Cohort 1
Listing 16.2.7	Adverse Events	Cohort 1 subjects
Listing 16.2.8.1	Out-of-Range Results of Clinical Laboratory Tests	Cohort 1 subjects
Listing 16.2.9.1	Reactogenecity Assessment	Cohort 1 subjects
Listing 16.2.9.2	Oropharyngeal Assessment	Cohort 1 subjects
Listing 16.2.9.6	Methemoglobin Measurement	Cohort 1 subjects

3. Original Summary Table 14.2.3

Table 14.2.3 – Clearance of Viral Infection in Saliva via RT-qPCR

Population	Endpoint	Statistics	4 Days RD-X19	7 Days RD-X19	Sham
Intent-to-Treat	Time to Clearance of Viral Infection	N	XX	XX	XX
		n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Median of Time	XX.X	XX.X	XX.X
		25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
		95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
	Subjects Demonstrating Clearance of Viral Infection at Day 8/ET Visit	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Per-Protocol	Time to Clearance of Viral Infection	N	XX	XX	XX
		n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Median of Time	XX.X	XX.X	XX.X
		25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
		95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
	Subjects Demonstrating Clearance of Viral Infection at Day 8/ET Visit	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)

Abbreviation: CI = Confidence Interval
Note 1: Clearance of viral infection in saliva is defined as a negative test (Ct value ≥32) via RT-qPCR.
Note 2: Subjects who did not achieve clearance at the exit of study are considered censored.
Note 3: Percentiles and 95% CI of median are derived using the Kaplan-Meier method.
Source: Listing 16.2.6.4
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Revised Summary Table and Added Figures

Table 14.2.3 – Clearance of Viral Infection in Saliva via RT-qPCR

Population	Endpoint	Statistics	4 Days RD-X19	7 Days RD-X19	Sham
Intent-to-Treat	Time to Clearance of Viral Infection	N	XX	XX	XX
		n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Median of Time	XX.X	XX.X	XX.X
		25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
		95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
		P-value RX-X19 vs. Sham	0.XXX	0.XXX	
	Subjects Demonstrating Clearance of Viral Infection at Day 8/ET Visit	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Per-Protocol	Time to Clearance of Viral Infection	N	XX	XX	XX
		n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Median of Time	XX.X	XX.X	XX.X
		25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
		95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
		P-value RX-X19 vs. Sham	0.XXX	0.XXX	
	Subjects Demonstrating Clearance of Viral Infection at Day 8/ET Visit	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)

Abbreviation: CI = Confidence Interval
Subjects with clearance of viral infection at baseline are excluded from the analysis of time-to-clearance of viral infection.
Note 1: Clearance of viral infection in saliva is defined as a negative test via RT-qPCR, i.e. achievement of [1] RP Ct =0, AND [2] Average N1 Ct =32 or Average N1 Ct ='Undetermined'. Subjects who did not achieve clearance at the last assessment of the study are considered censored at the time of the last assessment.
Note 2: Percentiles and 95% CI of median are derived using the Kaplan-Meier method. P-values for treatment comparison are from Log Rank Test.
Source: Listing 16.2.6.4, 16.2.5.3
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Figure 15.1.1 - Kaplan-Meier Plot of Time to Clearance of Viral Infection for Intent-to-Treat Population
Figure 15.1.2 - Kaplan-Meier Plot of Time to Clearance of Viral Infection for Per-Protocol Population

4. Original Summary Table 14.2.5

Table 14.2.5 – Time to Alleviation of COVID-19 Symptoms

Population	Statistics	4 Days RD-X19	7 Days RD-X19	Sham
Intent-to-Treat	N	XX	XX	XX
	n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Median of Time	XX.X	XX.X	XX.X
	25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
	95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
Per-Protocol	N	XX	XX	XX
	n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Median of Time	XX.X	XX.X	XX.X
	25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
	95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)

Abbreviation: CI = Confidence Interval
Note 1: Alleviation of COVID-19 symptoms is defined as all eight symptoms assessed by the subject as none (0) or mild (1).
Note 2: Subjects who did not achieve alleviation at the exit of study are considered censored.
Note 3: Percentiles and 95% CI of median are derived using the Kaplan-Meier method.
Source: Listing 16.2.6.1, 16.2.6.2
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Revised Summary Table and Added Figures

Table 14.2.5.1 – Time to Alleviation of COVID-19 Symptoms

Population	Statistics	4 Days RD-X19	7 Days RD-X19	Sham
Intent-to-Treat	N	XX	XX	XX
	n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Median of Time	XX.X	XX.X	XX.X
	25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
	95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
	P-value RX-X19 vs. Sham	0.XXX	0.XXX	
Per-Protocol	N	XX	XX	XX
	n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Median of Time	XX.X	XX.X	XX.X
	25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
	95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
	P-value RX-X19 vs. Sham	0.XXX	0.XXX	

Abbreviation: CI = Confidence Interval
Note 1: Alleviation of COVID-19 symptoms is defined as all eight symptoms assessed by the subject as none (0) or mild (1).
Note 2: Time to alleviation is calculated as the number of hours from the first dose to the time of the first occurrence of symptoms alleviation. Subjects who did not achieve alleviation at the last assessment of study are considered censored at the time of the last assessment.
Note 3: Percentiles and 95% CI of median are derived using the Kaplan-Meier method. P-values for treatment comparison are from Log Rank Test.
Source: Listing 16.2.6.1.2, 16.2.5.3
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Figure 15.2.1 - Kaplan-Meier Plot of Time to Alleviation of COVID-19 Symptoms for Intent-to-Treat Population
Figure 15.2.2 - Kaplan-Meier Plot of Time to Alleviation of COVID-19 Symptoms for Per-Protocol Population

5. New Summary Table and Figures

Table 14.2.5.2 – Time to Sustained Alleviation of COVID-19 Symptoms

Population	Statistics	4 Days RD-X19	7 Days RD-X19	Sham
Intent-to-Treat	N	XX	XX	XX
	n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Median of Time	XX.X	XX.X	XX.X
	25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
	95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
	P-value RX-X19 vs. Sham	0.XXX	0.XXX	
Per-Protocol	N	XX	XX	XX
	n (%) Censored	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Median of Time	XX.X	XX.X	XX.X
	25th, 75th Percentiles	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
	95% CI of Median	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)
	P-value RX-X19 vs. Sham	0.XXX	0.XXX	

Abbreviation: CI = Confidence Interval
Note 1: Sustained alleviation of COVID-19 symptoms is defined as all eight symptoms assessed by the subject as none (0) or mild (1) AND no single symptom reoccurs later at a level above mild (1).
Note 2: Time to sustained alleviation is calculated as the number of hours from the first dose to the time of the occurrence of sustained symptoms alleviation. Subjects who did not
achieve sustained alleviation at the last assessment of the study are considered censored at the time of the last assessment.
Note 3: Percentiles and 95% CI of median are derived using the Kaplan-Meier method. P-values for treatment comparison are from Log Rank Test.
Source: Listing 16.2.6.1.2, 16.2.5.3
O:\Studies\EmitBio\EB-P12-01\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Figure 15.3.1 - Kaplan-Meier Plot of Time to Sustained Alleviation of COVID-19 Symptoms for Intent-to-Treat Population
Figure 15.3.2 - Kaplan-Meier Plot of Time to Sustained Alleviation of COVID-19 Symptoms for Per-Protocol Population

6. New Subject Data Listing

Listing 16.2.6.1.2- COVID-19 Symptom Assessment and Severity Score from Subject Diary

				Assessment											
Site-Subject	Cohort	Not Done	Day	Study Day	Date:Time	Cough	Sore Throat	Nasal Congestion	Headache	Chills/ Sweats	Muscle or Joint pain	Fatigue	Nausea	Fever (F)	COVID-19 Severity Score
Treatment:															
xxxx	x		Day 1- Assessment 1	1											
			Day 1- Assessment 2	1											
			Day 2- Assessment 1	2											

COVID-19 Symptom: 0=None, 1=Mild, 2=Moderate, 3=Severe. Study Day is calculated relative to date of first treatment. Day 1 is the day of first treatment.
Note: Assessment at a visit was based on symptoms the subject reports as occurring within the past 3 days of that visit.
O:\Studies\ EmitBio\EB-P12-01\Biometrics\Programs\Listings\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year

Note: The original Listing 16.2.6.1 is changed to Listing 16.2.6.1.1.