CLINICAL TRIAL PROTOCOL

A Phase I Open Label, First-in-Man Acute Safety,
Tolerability and Acceptability Study of the EmitBio™
RD19 Device

Protocol Number: RD19-01-3Q20

Investigational Device: EmitBio™ RD19

Indication: Respiratory Infectious Diseases, Multiple, Prevention - including SARS-CoV-2

Phase: I

Clinical Trial Site: Carolina Phase I Clinical Trial Unit, Raleigh, NC

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

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

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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.

Principle Investigator Signature:

Signed: _____ Date: _____

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1. PROTOCOL SUMMARY

1.1 Executive Synopsis

Rationale for Proposed Clinical Study

In December 2019 the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus ribonucleic acid (RNA) was quickly identified in some of these patients. As of July, 2020 there were 15.5 million confirmed cases (>4 million in the US) and over 600,000 deaths (~145,000 in the US). There are currently no FDA approved prophylactic interventions against SARS-CoV-2 while social distancing and personal protective equipment constitute our only viable countermeasures to help reduce the incidence of community transmission. While vaccine candidates are being developed at unprecedented speeds, their efficacy is completely unknown and will not be known for many months.

Therefore, there is an urgent public health need for rapid development of novel protective measures, as well as improved therapeutic interventions. The EmitBio™ RD19 device emits visible blue light to stimulate host defenses (as explained below) to eliminate invading pathogens in the oropharynx and surrounding tissues. The RD19 device does this without additional photosensitizers or chemical reagents that are typically employed with traditional photodynamic therapeutics. Specifically, selected wavelengths of light have been evaluated across the visible spectrum, and it was discovered that safe, visible blue light emitted from non-coherent LED sources could perform both of the following functions:

(1) upregulate the sustained production of nitric oxide in epithelial tissue through increase of nitric oxide synthases (NOSs);

(2) stimulate the instantaneous release of the body's bound stores of nitric oxide.

Nitric oxide produced naturally in epithelial tissues also induces and recruits 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.

1.1.1 Claims and Indication:

The EmitBio™ RD19 device uses blue light to boost the body's natural immune response, which when combined with social distancing and proper mask use as part of healthy living, may help to reduce the risk of infection by respiratory viruses like influenza and SARS-CoV-2.

This first-in-man (FIM) phase I study will evaluate the acute safety, tolerability, device acceptability for use among 25 healthy volunteers between the age of 18 and 45. Based on the results of extensive in-house research, a single dose (9 Joules/cm^2) and schedule (twice a day for 3 minutes, separated by at least 4 hours, ideally 8 to 12 hours apart) will be evaluated.

Safety and tolerability (local reactogenicity) will be assessed actively at study day screening (baseline set), 1, 7 and 14, and on non-clinic visit days by collection of these data by history during clinic visits via a memory aid (diary cards). 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 and kidney safety laboratory evaluations, as well as urinalysis, will be performed at screening and at Day 14 or early termination (and potentially during unscheduled) clinic visits. Hematological safety assessments will be performed at all visits.

1.1.2 Objectives and Endpoints

Table 1: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
• Evaluation of the safety and reactogenicity of the RD19 device.	• Frequency, grade and attribution of each incident local and systemic AE during the 14 day study period. • Frequency and attribution of any incident SAEs during the 14 day study period.
Secondary	
• Evaluation of the acceptability of the EmitBio™ RD19 device.	• Ease of use, clarity of user instructions, & compliance with per protocol schedule and, if out of compliance, reason(s) for non-compliance.

1.1.3 Inclusion Criteria (abbreviated)

See full inclusion criteria in Section 4.1

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

1. Provides written informed consent prior to initiation of any study procedures.
2. Be able to understand and agrees to comply with planned study procedures and be available for all study visits.
3. Agrees to the collection of venous blood per protocol.
4. Male or non-pregnant female, 18 to 45 years of age, inclusive, at time of enrollment.
5. Body Mass Index 18-35 kg/m^2, inclusive, at screening.
6. No active disease process (chronic or acute) or physical or mental conditions or attributes at the time of screening, which in the opinion of the PI, will prevent full use and assessment of RD19.
7. Oral temperature is less than 100.0°F (37.8°C).
8. Pulse no greater than 90 beats per minute.
9. Systolic blood pressure (BP) is 85 to 150 mmHg, Diastolic blood pressure (BP) is ≤ 90, inclusive.
10. Clinical screening laboratory evaluations are within acceptable normal reference ranges at the clinical laboratory being used in the study

Exclusion Criteria (abbreviated)

See full exclusion criteria in Section 4.2

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. Has 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 significant medical or psychiatric condition(s).
4. Has an acute illness, as determined by the site PI or appropriate sub-investigator, with or without fever [oral temperature >37.8°C (100.0^0F)] within 72 hours prior to screening.
5. Has participated in another investigational study involving any SARS-CoV-2/COVID-19 interventional investigational product within 30 days of screening.
6. Has a history of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticaria, angioedema, other significant reaction) to nitrites, nitrates or sun exposure.

1.1.4 Study Key Characteristics

Study Phase

- I

Study Population

- Twenty-five (25) males and non-pregnant females, 18 to 45 years of age, inclusive, who are in good health and meet all eligibility criteria will be enrolled.

Sites

- Carolina Phase I, Raleigh, NC

RD19 Device

- The EmitBio™ RD19 device emits visible blue light to stimulate host defenses (as explained below) and eliminate invading pathogens in the oropharynx and surrounding tissues. The RD19 device does this without additional photosensitizers or chemical reagents that are typically employed with traditional photodynamic therapies. Specifically, selected wavelengths of light have been evaluated across the visible spectrum, and it was discovered that a narrow wavelength band blue light emitted from non-coherent LED sources could perform both of the following functions: upregulate the sustained production of nitric oxide in epithelial tissue through the increase of NO synthases (NOSs); and stimulate the instantaneous release of the body's bound stores of nitric oxide. Nitric oxide also induces and recruits 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.

Table 2: Treatment Group

Group	RD19	Duration
OL	25	3' x 2/day

Study Duration

- The duration of the entire study is anticipated to be ≤ 18 days (from start of screening to last subject last visit).

Subject Duration

- The duration on trial for each individual subject is ≤ 18 days (from start of screening to last visit).

Safety

- The study will use study pausing rules
- This study will involve the Sponsor's Chief Medical Officer as medical monitor, who along with the study PI(s) will assess severe AEs and SAEs, and together will constitute the attribution team.

1.2 Schedule of Activities (SOA) - Table 3

Study Procedures	Screening Visit	Preliminary Observation	Full Assessment Period	
Study Day	**≤ -7 to 0**	**1**	**7**	**Day 14/ Early Term**
Study Procedures				
Informed Consent	X			
Inclusion/Exclusion Criteria	X	X		
Demographics Questionnaire	X			
Medical History	X	* Changes since last visit only	*Changes since last visit only	*Changes since last visit only
Physical Examination	X	*Targeted only	*Targeted only	*Targeted only
BMI	X			
Vital Signs	X	X	X	X
Methemoglobin	X	*Before and 60 minutes after device use	*Before and 60 minutes after device use	*Before and 60 minutes after device use
Lab Sample Collection & Processing	X			X
CBC and differential	X			X
CMP	X			X
Urinalysis	X			X
Urine Pregnancy Test	X			X
Concomitant Medication History/New	X	X	X	X
Device Illumination		X	X	X
Acceptability Assessment of Device		X	X	X
Distribution and train diary card		X		

2. INTRODUCTION

2.1 Background and Study Rationale

In December 2019 the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel Coronavirus (nCoV) has been abbreviated as 2019-nCoV and is now named SARS-CoV-2 (due to its similarity to the Severe Acute Respiratory Syndrome [SARS] Coronavirus [CoV; SARS-CoV]). It has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV (Chan JF et al., 2020). The disease caused by SARS-CoV-2 is called Coronavirus disease 2019 (COVID-19). As of July, 2020 there were 15.5 million confirmed cases (> 4 million in the US) and over 600,000 deaths (~145,000 in the US). There are currently no FDA approved prophylactic interventions against SARS-CoV-2 while social distancing and personal protective equipment constitute our only viable countermeasures to help reduce the incidence of community transmission. While vaccine candidates are being developed at unprecedented speeds, their efficacy is completely unknown and will not be known for many months. Outbreak forecasting and modeling suggest that these numbers will continue to rise. Global efforts to evaluate novel antivirals and therapeutic strategies to treat 2019-nCoV severe infections have intensified.

Therefore, there is an urgent public health need for rapid development of novel protective measures, as well as improved therapeutic interventions. The EmitBio™ RD19 device emits visible blue light to stimulate host defenses and eliminate invading pathogens in the oropharynx and surrounding tissues. The RD19 device does this without the additional photosensitizers or chemical reagents that are typically employed with traditional photodynamic therapy approaches. Specifically, selected wavelengths of light have been evaluated across the visible spectrum, and it was discovered that a narrow wavelength band blue light emitted from non-coherent LED sources could perform both of the following functions: upregulate the sustained production of nitric oxide in epithelial tissue through the increase of NO synthases (NOSs); and stimulate the instantaneous release of the body's bound stores of nitric oxide. Nitric oxide also induces and recruits 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.

2.1.1 EmitBio™ RD19 Device Characteristics:

Characteristic	Target
Route of Administration	Oral Illumination
Device Configuration	Hand-held, rechargeable
Blue Light Source	Non-coherent, light emitting diode (LED) array
UVA Content (315 nm – 400 nm)	<1%
UVB Content (280 nm - 315 nm)	not detectable*
UVC Content (100 nm - 280 nm)	not detectable*
Target Exposure Area	Oropharynx and surrounding tissues
Exposure Time	3 min per treatment, 2X/day at least 4 hrs apart
Single Light Dose (@ 90 mm)	~ 9 J/cm^2 Joules = Watts x seconds
Total Daily Dose (@ 90 mm)	~ 18 J/cm^2
Depth of Tissue Penetration	< 0.5 mm
Temperature (IEC 60601-1)	< 48 °C (for durations <10 min)

*UVA/UVB not detectable in Labsphere 1M Integrating Sphere equipped with CDS-610 Mini CCD Array Spectrometer

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn and unlikely, but possible, mild local reactions to the EmitBio™ RD19, entirely unknown adverse events, and inadvertent breach of confidentiality.

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 RD19 and similar energy-based devices routinely used for oral and skin care purposes have resulted in the Sponsor, after careful consideration, making the determination that RD19 as a "Not Significant Risk" (NSR) device per FDA guidelines. EmitBio™ RD19 is expected to be without significant risk for acute adverse events when used as directed. If the RD19 device is not used as directed, for example is inserted into the oral cavity improperly it is possible the user could induce a gag reflex. If the RD19 device is used for a period of time in excess of the time directed, it is possible the user could experience mild to moderate erythema, and under extreme overuse conditions the user could experience oral mucosal thermal injury, especially to the uvula.

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 RD19 device toward their or anyone else's eyes.

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 will not include information that can identify subjects.

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

2.2.2 Known Potential Benefits

There is no guaranteed benefit to study participants. There is 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. Use of EmitBio™ RD19 may or may not provide protection against SARS-CoV-2 infection and subsequent COVID-19 disease.

3. STUDY DESIGN

3.1 Overall Design

This first-in-man (FIM) phase I study will evaluate the acute safety, tolerability, and device acceptability for use among 25 healthy volunteers between the age of 18 and 45. Based on the results of numerous preclinical studies, a single dose (9 joules/cm^2) and schedule (twice a day, separated by at least 4 hours, preferably 8 to 12 hours apart) will be evaluated.

Safety and tolerability (local reactogenicity) will be assessed actively at the following study days: screening (baseline set), 1, 7 and 14, and on non-clinic visit days by collection of these data by history during clinic visits via a memory aid (diary cards). Volunteers will be encouraged to promptly contact designated clinical trial staff or the one of the Sponsor's Emergency Response Team for AEs of a medically urgent nature.

A Comprehensive Metabolic Panel, as well as CBC with differential, urinalysis, and pregnancy testing will be performed at screening and at Day 14 or early termination (and potentially during unscheduled) clinic visits. Hematological safety assessments (evaluation of methemoglobinemia) will be performed at all visits.

Study volunteers will be asked to immediately contact the clinical coordinator and/or the PI in all instances where they experience an AE of greater than moderate intensity. Volunteers will be instructed to report to the clinical trial unit for an unscheduled visit or to seek the appropriate level of medical care based on the nature of their AE/SAE. In all such instances, all relevant information pertaining to these significant medical events will be captured on the appropriate e-CRFs.

Hematology safety laboratory evaluations will be performed at screening, as well during all scheduled clinic visits. Laboratory assessments may be part of the evaluation of medically attended AE evaluation and for all SAEs.

Upon ratification of the CTA, the site will begin pre-recruitment outreach efforts of potential volunteers within M3-WRA's database to ascertain "interest in general" in this study. Official recruitment which may include fliers, letters, telephone calls, etc. and specific recruitment of potential subjects who have previously participated in other clinical studies conducted at the site will occur only after formal IRB approval. Other forms and/or mechanisms of recruitment may also be used. The IRB will approve the recruitment process and all materials prior to use.

Schedule of assessments can be found in Section 1.2, Schedule of Activities (Table 3).

3.2 Objectives and Outcomes

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
• Evaluation of the acute safety of the EmitBio™ RD19 device.	• Frequency, grade and attribution of each incident local and systemic AE during the 14 day study period. • Frequency and attribution of any incident SAEs during the 14 day study period.
Secondary	
• Evaluation of the acceptability of the EmitBio™ RD19 device.	• Ease of use, clarity of user instructions, & compliance with per protocol schedule and, if out of compliance, reason(s) for noncompliance.

3.3 Scientific Rationale for Study Design

The EmitBio™ RD19 device is designed to place a protective countermeasure in the hands of at population-risk individuals in order to reduce the incidence of SARS-CoV-2 and COVID-19. At population-risk individuals are those living where community-transmission of SARS-CoV-2 is likely to occur and where community transmission is actively occurring. Through the identified mechanisms of virus killing and inhibition of virus replication, the RD19 device is expected to reduce SARS-CoV-2 viral load which in combination with other lifestyle measures, may help reduce the incidence of SARS-CoV-2 infection. This type of active protection is urgently needed for high-risk individuals (e.g. individuals exposed to a known infected person and healthcare workers and eldercare facility staff exposed to SARS-CoV-2 infected / COVID-19 patients and residents, respectively). The RD19 device has been engineered with the intent to help curb community transmission of SARS-CoV-2, thereby reducing the incidence of COVID-19. The CDC estimates that 40% of secondary coronavirus transmission occurs before people feel ill, highlighting the need for a broadly distributed protective countermeasure.

The RD19 optical illumination device is inserted into the mouth to shine light on the proximal repository for respiratory tract pathogens in the pharynx. The RD19 device uses a precise color of visible blue light (absent of UV light) to stimulate host defense and eliminate invading pathogens. This color of blue light has been found to both stimulate the instantaneous release of the body's reserves of nitric oxide and to increase endogenous production of nitric oxide in barrier epithelial cells. This naturally produced nitric oxide is substantially elevated over background levels and promotes innate immune responses capable of disrupting SARS-CoV-2 infection and inhibit viral replication of human coronaviruses. In addition to its direct antiviral activity, nitric oxide is an important pro-inflammatory cell signal to elicit induction and recruitment of other innate immune effectors, including NK cells, neutrophils, and macrophages.

3.4 Justification for Dose

In repeated experiments, including experiments conducted by third party external laboratories, it has been determined that the light emitted by the EmitBio™ RD19 device provides for potent antiviral activity against SARS-CoV-2. Reductions in viral infectivity of ≥99% have been observed after a single illumination at an energy level of 9 Joules/cm^2. Separately, the yield of replicating SARS-CoV-2 virus in infected cells is inhibited by ≥ 99.9% in the range of 9 – 15 J/cm^2. Dosing twice a day (total of 18 J/cm^2) also allows endogenous nitric oxide levels to be elevated to an extent and for a time period expected to result in high level antiviral effects.

4. STUDY POPULATION

Twenty-five (25) males and non-pregnant females, 18 to 45 years of age inclusive, who are in good health and meet all eligibility criteria will be enrolled. The target population should reflect the community at large. The estimated time from initiation of enrollment to completion of the day 1 visit for the last subject enrolled is one week.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician, licensed to make medical diagnoses and signatory to The Statement of Compliance as the site PI. Exemptions will be only be granted on Subject Inclusion or Exclusion in rare instances and based on the approval of the Sponsor's Chief Medical Officer.

4.1 Full Inclusion Criteria

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

1. Provides written informed consent prior to initiation of any study procedures.
2. Agrees to comply with planned study procedures and be available for all study visits.
3. Agrees to the collection of venous blood per protocol.
4. Male or non-pregnant female, 18 to 45 years of age, inclusive, at time of enrollment.
5. Body Mass Index 18-35 kg/m^2, inclusive, at screening.
6. Woman of childbearing potential must have a negative urine pregnancy test within 7 days prior to study initiation.
7. Oral temperature is less than 100.0°F (37.8°C).
8. Pulse no greater than 90 beats per minute.
9. Systolic BP is 85 to 150 mmHg and Diastolic BP ≤ 90 mmHg, inclusive.
10. Clinical screening laboratory evaluations are within acceptable normal reference ranges at the clinical laboratory being used.

4.2 Full 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. Has any medical disease or condition that, in the opinion of the site PI or appropriate sub-investigator, precludes study participation.[1]
3. Plans to travel away from the study site area during the term of study to a location or in a manner that may interfere with full completion of the study per protocol.
4. Presence of self-reported or medically documented significant medical or psychiatric condition(s).[2]
5. Has an acute illness[3], as determined by the site PI or appropriate sub-investigator, with or without fever [oral temperature >37.8°C (100.0°F)] within 72 hours of study day 1.
6. Reports a recent positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or HIV-1 antibodies at screening.
7. Currently enrolled in or plans to participate in another clinical trial with an interventional investigational agent that will be received during the study period.[5]
8. Has a history of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticaria, angioedema, other significant reaction) to nitrates, nitrites or sun exposure.
9. Active use of any medications that may be associated oral pharyngeal or mucosal irritation.
10. Has any blood dyscrasias or significant disorder of coagulation.
11. Has a history of alcohol abuse or other recreational drug (excluding cannabis) use within 1 month of Study Day 1.
12. Has any oral abnormality that 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.
13. Receipt of any other SARS-CoV-2 or COVID19 experimental coronavirus investigational product within 30 days of screening.

[1] *Including medical diseases or conditions that would place the subject at an unacceptable risk of injury, render the subject unable to meet the requirements of the protocol or may interfere with the evaluation of responses or the subject's successful completion of this trial.*

[2] *Significant medical or psychiatric conditions include but are not limited to: respiratory disease (e.g., chronic obstructive pulmonary disease [COPD], asthma) requiring current daily medication.*
Significant cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease).
Neurological or neurodevelopmental conditions (e.g., epilepsy, stroke, seizures in the last 3 months, encephalopathy, focal neurologic deficits, Guillain-Barré syndrome, encephalomyelitis or transverse myelitis).

Ongoing malignancy or malignancy in remission within the last six months excluding basal cell and squamous cell carcinoma of the skin, which are allowed.

An autoimmune disease without a defined non-autoimmune cause.

Any active immunodeficiency of any cause.

[3]An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the site PI or appropriate sub-investigator, the residual symptoms will not interfere with the ability to assess safety parameters as required by the protocol.

[4]study drug, biologic or device.

[5]Including licensed or unlicensed vaccine, drug, biologic, device, blood product, or medication.

4.3 Study Volunteer Selection, Retention & Compensation

4.3.1 Recruitment

Potential subjects will learn about the study via IRB-approved recruitment strategies, including direct mailing, recruitment from an IRB-approved trial registry and local advertisements/flyers. Screening will 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.

4.3.2 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.

4.3.3 Compensation Plan for Subjects

Subjects will be compensated for their participation in this trial. Compensation will be in accordance with local IRB requirements, and subject to local IRB approval. Reimbursements will be disbursed at specific timepoints during the study with the total amount contingent on completing study procedures.

4.3.4 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.

5. STUDY DEVICE

5.1 Regulatory Considerations

5.1.1 Preliminary Regulatory Pathway for EmitBio™ RD19

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.

The most applicable policy document for the EmitBio™ RD19 device and its proposed indication for use is the *"General Wellness: Policy for Low Risk Devices"* issued by the Food and Drug Administration Center for Devices and Radiological Health (FDA-CDRH) on September 27, 2019.

At this time RD19 is one of multiple products under development at EmitBio™ across the respiratory infection landscape. The safety data collected will be useful in determining the final regulatory pathway for RD19 and subsequent devices.

With the above guidance and policy documents from the FDA, and the company's assessment that RD19 is a Not Significant Risk (NSR) device (August 3, 2020), EmitBio™ will follow the guidance of 21 CFR 812 as an NSR device and seek IRB approval for this protocol as a minimal risk protocol requiring only IRB, but not FDA-CDRH, review and approval.

EmitBio™ will undertake a Phase I clinical trial, RD19-01-3Q20, under 21 CFR 812 as a Not Significant Risk (NSR), Minimal Risk protocol to assess the acute safety and local reactogenicity of RD19 commencing this month (August 2020). Results will be available in September 2020.

5.1.2 Proposed Label Claim/Indication for Use:

The EmitBio™ RD19 device uses blue light to boost the body's natural immune response, which when combined with social distancing and proper mask use as part of healthy living, may help to reduce the risk of infection by respiratory viruses like influenza and SARS-CoV-2.

5.1.3 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).

5.2 Study Device and Use

5.2.1 Device Description

The EmitBio™ RD19 Device has been designed for ease of assembly in mass production and is comprised of the following three primary building blocks:

Aluminum Housing – The aluminum housing has been engineered for function and designed for ergonomics. The housing contains the LED metal core printed circuit board, the electronic LED power management circuit, an on/off switch interlocked with a timer, a rechargeable battery, and a removable cap for battery access. Dynamic modeling has been utilized to improve the dissipation of excess heat from the LED array by the housing to keep the RD19 within safe operating temperature limits. Incorporating a right angle, the housing also provides an ergonomic transition from the light source to the light delivery assembly as well as for single-handed use.

Light source - Located inside of the aluminum housing, the light source consists of an array of LEDs on a metal core circuit board, an electronic LED power management circuit, and a rechargeable battery. The quantity and characteristics (e.g. optical power and wavelength) of the individual LEDs in the LED array have been chosen to promote light-stimulated release and upregulation of nitric oxide. The focused zoom assembly has been engineered to improve homogenization of the light emitted from the LED array, transmit the pre-shaped beam into the oral cavity to a position approximately 9 cm from the target area, and to disperse the transmitted light over the target area for stimulation of the host tissue.

Mouthpiece – A comfort shield made of biomedical grade plastic is applied to the exterior of the optical element to enhance oral comfort during use and to improve light delivery. The positioning guard provides for repeatable placement of the RD-19 device while also preventing over insertion and preventing the lips from coming into contact with the aluminum housing. While the RD-19 device is in use, the mouthpiece is fixed to the aluminum housing and the tongue rests beneath the extended tongue depressor. When not in use, the assembly is removable for cleaning and, if necessary, replacement.

Each of the building blocks described are designed to allow the assembled device to meet specific criteria based on targeted safety and efficacy. The key target product device characteristics are summarized in:

Table 4: RD19 Device Characteristics

Characteristic	Target
Route of Administration	Oral Illumination
Device Configuration	Hand-held, rechargeable
Blue Light Source	Non-coherent, light emitting diode (LED) array
UVA Content (315 nm – 400 nm)	<1%
UVB Content (280 nm - 315 nm)	not detectable*
UVC Content (100 nm - 280 nm)	not detectable*
Target Exposure Area	Oropharynx and surrounding tissues
Exposure Time	3 min per treatment, 2X/day at least 4 hrs apart
Single Light Dose (@ 90 mm)	~ 9 J/cm^2 Joules = Watts x seconds
Total Daily Dose (@ 90 mm)	~ 18 J/cm^2
Depth of Tissue Penetration	< 0.5 mm
Temperature (IEC 60601-1)	< 48 °C (for durations <10 min)

*UVA/UVB not detectable in Labsphere 1M Integrating Sphere equipped with CDS-610 Mini CCD Array Spectrometer

5.2.2 Selection of Study Dose

In repeated experiments, including experiments conducted by external academic collaborators, it has been determined that the EmitBio™ RD19 device provides for a powerful reduction in viral infectivity of host cells after a single five (3) minute illumination at a modest energy level of 9 Joules/cm^2. SARS-CoV-2 virus infectivity is inhibited by 99% (approximately 2 logs) at this dose. Viral replication is inhibited by 99.9% (3 logs). Dosing twice a day allows NO levels to be elevated to an extent and for a time period expected to result in a high level anti-viral effect.

5.3 Use / Storage & Maintenance / Accountability

5.3.1 Acquisition and Accountability

The sponsor will provide 27 RD19 (25 volunteers with two reserves) devices packaged in appropriately labelled separate clear containers containing all components as well as instructions for use by study participants. Each RD19 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 and study staff will confirm serial number and subject number are in concordance. Upon termination of a subject's participation in the trial, all RD19 devices and components must be returned to the study site and then to the study sponsor.

5.3.2 Device Appearance

RD19 Handle: ~6in.; Optic: ~3in.

5.3.3 Device Storage and Maintenance

All RD19 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 plastic 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.

5.3.4 Preparation for Use and Use

[Refer to **Appendix 1: User Instructions**]

5.5 Device Discontinuation

5.5.1 Study Pausing Criteria

RD19-01-3Q20 will be paused if any of the following events occur:

- Any subject experiences an SAE after use of the RD19 Device that is considered related to RD19.
- Any subject experiences laryngospasm, bronchospasm or anaphylaxis within 2 hours after use of the RD19 Device that is considered related to RD19.
- 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 RD19.
- 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 RD19.

Study device use and enrollments may resume only after review of the AEs that caused the pause results.

5.5.2 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, but they are under no obligation to do so. All study subjects must return the RD19 device at study termination.

5.5.3 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 withdrawn from this study, or are lost to follow-up after signing the informed consent form (ICF) and use of the RD19 device will not be replaced. Subjects who withdraw, or are withdrawn from this study, or are lost to follow-up 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.

5.5.4 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 SOA (Table 3). 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.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Screening Assessments

6.1.1 Screening Procedures

There is a small amount of risk to subjects who report that they are in good health but have an unknown health problem at the time of screening. 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.

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 pre-study medications and therapies up to 10 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.
- 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:
  - Hematology
    - CBC with differential
    - Methemoglobin level (Pulse Ox method)
  - CMP (fasting or non-fasting)
  - Urine pregnancy test (in women of childbearing potential)
- Review inclusion and exclusion criteria.

Clinical screening laboratory evaluations will be performed locally by the site laboratory.

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 scheduled for enrollment and their day 1 visit.

If a physiologic parameter, e.g., vital signs or clinical laboratory value, 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., subject complained of a "cold or fever" and met a temporary delaying enrollment criterion of acute illness or fever), or if a protocol eligibility criterion that is not met at the initial time of screening, will be met by rescreening within the next 2 days.

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

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

6.1.2 Procedures to be Followed in the Event of Abnormal Clinical Laboratory Test Values or Abnormal Clinical Findings

If a physiologic parameter, e.g., vital signs, or clinical laboratory value, is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the participating clinical trial 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).

All abnormal clinical findings or abnormal clinical laboratory tests values that occur post RD19 device use will be considered AEs.

6.1.3 Informed Consent – See Section 8.1.1

6.2 Safety and Other Assessments

Study procedures are specified in the SOA (Table 3). 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 a symptom-directed (targeted) physical examination will be performed if indicated at all other timepoints specified in the SOA.
    - 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.

- Note presence of signs or symptoms consistent with solicited AEs to establish a baseline for subsequent assessment purposes (**see Sec 6.2.2**).

- A symptom-directed (targeted) physical examination will be performed if indicated at all other timepoints specified in the SOA.
  - Targeted physical examinations should also include an assessment for 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 or abnormal clinical laboratory test results.
  - Reactogenicity assessments will include an assessment of illumination site reactions – erythema, edema/induration, pain and difficulty swallowing, as well as systemic reactions–fever, chills, headache, and nausea. Pre-illumination reactogenicity assessments will be performed immediately prior to first RD19 use to establish a baseline, then the use of the RD19 device will occur.
- Subjects will be observed in the clinic for at least 60 minutes post each RD19 illumination. The illumination site will be examined, post-use reactogenicity assessments will be performed, and any AEs/SAEs will be recorded on the appropriate e-CRF prior to discharge from the clinic. The oropharynx and surrounding tissues will also be examined on Days 1, 7, 14 and during unscheduled visits and early termination visits.

- Vital signs:

- Vital sign measurements will include systolic and diastolic BP, HR, and oral temperature. Vital signs will be measured at timepoints specified in the SOA. On Days 1, 7 and 14, vital sign measurements will be collected prior to device administration. Vital signs assessed on Day 1 prior to the first use of RD19 will be considered as baseline. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking their oral temperature or using the RD19 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 RD19 device.
  - Clinical screening laboratory evaluations (CMP and CBC (diff) will be performed locally by the site laboratory).
    - Clinical safety laboratory evaluations will be performed locally by the site laboratory.
    - Methemoglobin will be measured prior to use of the device in the clinic and just prior to discharge from the clinic after 1 hour.
    - Blood and urine will be collected at timepoints specified in the SOA.

- Diary Cards:
    - All subjects will complete a Diary Card daily for the entire term of the study. Diary Cards will be reviewed with the subjects for any AEs (solicited injection site and systemic reactions, as well as unsolicited AEs), SAEs and concomitant medications. Diary Cards will be collected at the end of a volunteer's participation in the study.
- Acceptability Assessment:
    - All subjects will complete a brief survey of device tolerability and acceptability. This will be completed during the 60 minute follow-up period after device use in the clinic.

6.2.1 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 14 or until an early termination visit.

All AEs, solicited and unsolicited, will be captured on the appropriate 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. AEs occurring during the study-collection and reporting period will be documented appropriately regardless of relationship.

AEs will be followed to resolution or stabilization.

6.2.2 Solicited Adverse Events

Solicited AEs are anticipated local and systemic 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 using a diary card and recorded on the appropriate e-CRF from the during the entire course of the study.

For this study, solicited AEs include:

- Illumination site Pain
- Illumination site Erythema
- Illumination site Edema/Induration
- Headache
- Difficulty swallowing
- Nausea
- Fever
- Chills

6.2.3 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 e-CRF.

Unsolicited AEs of all severities will be reported from the time of study device administration through study termination.

6.2.4 Adverse Event Reporting

Information on all AEs should be recorded on the appropriate 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).

6.2.5 Definition of a Serious Adverse Event (SAE)

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

- Death,
- A life-threatening AE,

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

Important medical events that may not result in death, are not immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or 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.

6.2.6 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 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.

Regulatory Reporting of Device-related SAEs

Following notification from the participating clinical site PI or appropriate sub-investigator, EmitBio Inc., as the sponsor, will report to the FDA and will copy the clinical site investigators on all reports of potential serious risks from clinical studies of RD19, 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 RD19 will not be reported to the FDA.

6.2.7 Classification of an Adverse Event

The determination of seriousness, severity 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.

6.2.8 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.

6.2.9 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.
- Null Determination – The direction and magnitude towards related and not related is null. The investigator is stating simply, "I cannot determine a relationship".
- 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.

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

For this study:

- Solicited and Unsolicited AEs will be recorded by volunteers daily on the Diary Card and collected on Clinic visit days 7, 14 and any unscheduled clinical trial unit visits.

6.2.11 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.

6.2.12 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.

7. STATISTICAL CONSIDERATIONS

7.1 Statistical Hypotheses

This is a phase I, open-label, safety study and is not designed to test any statistical hypotheses. Rather, this is a descriptive study intended to obtain preliminary estimates in healthy adults of the safety, including reactogenicity, of the EmitBio™ RD19 Device.

7.2 Sample Size Determination

SAMPLE SIZE CONSIDERATION - OPEN LABEL

This study is designed as an open-label study, without a placebo arm. Given the small sample size, the use of a placebo group is unlikely to improve understanding of AEs. Additionally, having the study unblinded will facilitate the need for rapid review and dissemination of study data for public health reasons.

Rare AEs are not demonstrable in a clinical study of this size; however, the probabilities of observing one or more AEs given various true event rates are presented in the table below. With the assumption that all enrolled subjects will likely complete the trial and safety visits in this relatively short duration study, the following statistical considerations apply. With 25 subjects, the chance of observing at least one AE of probability 20% or more is approximately 97%. Therefore, if no AEs of a given type occur in the study, we can be 97% confident that they will occur in fewer than 20% of people once RD19 is implemented. Also with 25 subjects, the chance of observing at least one AE of probability 5% or more is 90%. Therefore, if no AEs of a given type occur in the study, we can be 90% confident that such adverse event will occur in fewer than 5% of people once RD19 is implemented.

N	"True" Event Rate	Probability of Observation (%)
25	0.1%	2.5
	0.5%	12.0
	1.0%	23.4
	2.0%	43.4
	3.0%	61.3
	4.0%	74.8
	5.0%	90.3
	10.0%	92.4
	15.0%	94.3
	20.0%	97.5

7.3 Populations for Analyses

The full safety analyses population is by intention-to-treat (ITT) including all subjects who received at least a single use of RD19.

A modified per protocol population for analyses will include all study volunteers who complied with study procedures and remained on study, per protocol, until at least the day 7 clinic visit.

The per protocol population for analyses will include all study volunteers who complied will all protocol procedures and remained on the study until their day 14 visit.

7.4 Statistical Analyses

7.4.1 Primary Safety Analyses

Summaries and analyses of safety data will be presented for the Safety Analysis Population.

Solicited AEs will be summarized overall and by maximum severity post through study day 7, post study period days 7 -14 and overall. Additionally, solicited AEs will be analyzed by taking the most severe response (grouped as either modified per protocol or per protocol), dichotomizing into a binary variable (none versus mild, moderate, or severe) and using standard techniques, such as exact confidence intervals (CI), to summarize the proportion of subjects reporting each solicited sign or symptom.

Unsolicited non-serious AEs will be collected from the time of first device use through study day 14. Unsolicited AEs will be coded by MedDRA™ for preferred term and system organ class (SOC). All SAEs will be collected from the time of first device use through the study day 14. The number of SAEs will be reported by detailed listings showing the event description, MedDRA™ preferred term and SOC, study day of occurrence, severity, relatedness, and outcome for each event. Non-serious unsolicited AEs will be summarized as number and percentage of subjects reporting at least one event in each MedDRA□preferred term and SOC, cross tabulated by severity and relationship to the study device. Additionally, the proportion of subjects and exact 95% CIs of AEs in aggregate and by MedDRA□categories will be computed.

Clinical laboratory data, including methemoglobin measurements, will be summarized by severity and as the maximum numeric value over the entire study. Graphical presentations may include box plots and shift plots.

7.4.2 Analysis of the Secondary Endpoint(s)

Summaries and analysis of acceptability variables will be presented for both the modified and per-protocol study populations.

Device use and protocol procedures compliance rates will be calculated and presented.

A device acceptability source document has been created and provided to DCAC for database build and e-CRF production. Descriptive statistics for each variable will be calculated and presented.

7.4.3 Baseline Descriptive Statistics

Summaries of demographic variables such as age, sex, ethnicity, and race will be presented. Summaries of baseline clinical laboratory values will be presented.

Absolute numbers and ratios of Screened:Enrolled, Enrolled:Modified Per-Protocol and Enrolled:Per-Protocol will be presented.

8. OPERATIONAL CONSIDERATIONS AND SUPPORTING DOCUMENTS

8.1 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 RD19 devices to conduct the protocol.

8.1.1 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.

8.1.2 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 specmens 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.

8.1.3 Clinical Monitoring

Monitoring for this study will be performed by EmitBio Inc.'s Clinical Program Manager. Monitoring will be conducted at frequent time points 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 monitor 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 make be conducted remotely.

8.1.4 Quality Control (QC) and Quality Assurance (QA)

To ensure the reliability of study data, the clinical sites must maintain a Clinical Quality Management Plan (CQMP). The CQMP describes routine internal quality control (QC) and quality assurance (QA) activities 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.Data Handling and Record Keeping

8.1.5 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 clincial 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 (TAB Clinical, Inc; Cary, NC). 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.

TAB Clinical Inc 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.

8.1.6 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.

8.1.7 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™.

8.1.8 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.

8.1.9 Publication and Data Sharing Policy

All study data and reports of study data are the property of the study sponsor. The sponsor my 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.

8.1.10 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.

8.1.11 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.

9. REFERENCES

9.1. https://pubmed.ncbi.nlm.nih.gov/7690156/

9.2. https://pubmed.ncbi.nlm.nih.gov/8390481/

9.3. https://pubmed.ncbi.nlm.nih.gov/23562771/

9.4. https://pubmed.ncbi.nlm.nih.gov/31319090/

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