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ARTICLE

A randomized, controlled, feasibility study of RD-X19 in subjects with mild-to-moderate COVID-19 in the outpatient setting

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Abstract

The RD-X19 is an investigational, handheld medical device precisely engineered to emit blue light through the oral cavity to target the oropharynx and surrounding tissues. At doses shown to be noncytotoxic in an in vitro three-dimensional human epithelial tissue model, the monochromatic visible light delivered by RD-X19 results in light-initiated expression of immune stimulating cytokines IL-1α and IL-1β, with corresponding inhibition of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) replication. A single exposure of 425 nm blue light at 60 J/cm^2 led to greater than 99% reductions against all SARS-CoV-2 strains tested in vitro, including the more transmissible (Alpha) and immune evasive (Beta) variants. These preclinical findings along with other studies led to a randomized, double-blind, sham-controlled early feasibility study using the investigational device as a treatment for outpatients with mild to moderate coronavirus disease 2019 (COVID-19). The study enrolled 31 subjects with a positive SARS-CoV-2 antigen test and at least two moderate COVID-19 signs and symptoms at baseline. Subjects were randomized 2:1 (RD-X19: sham) and treated twice daily for 4 days. Efficacy outcome measures included assessments of SARS-CoV-2 saliva viral load and clinical assessments of COVID-19. There were no local application site reactions and no device-related adverse events. At the end of the study (day 8), the mean change in $\log_{10}$ viral load was −3.29 for RD-X19 and −1.81 for sham, demonstrating a treatment benefit of −1.48 logs (95% confidence internal, −2.88 to −0.071, nominal $p = 0.040$). Among the clinical outcome measures, differences between RD-X19 and sham were also observed, with a 57-h reduction of median time to sustained resolution of COVID-19 signs and symptoms (log rank test, nominal $p = 0.044$).

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Visible blue light (400–470 nm) has previously been demonstrated to inhibit coronavirus replication in cultured cells and eliminate severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) from infected human epithelial tissue in a laboratory setting.

WHAT QUESTION DID THIS STUDY ADDRESS?

Can precisely engineered doses of visible light inhibit replication of SARS-CoV-2 variants in a laboratory setting and lead to reductions of SARS-CoV-2 viral load in saliva in patients with coronavirus disease 2019 (COVID-19)?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

In this randomized, double-blind, sham-controlled, early feasibility study, light administered in the outpatient setting by the investigational RD-X19 device twice daily over 4 days resulted in clinically meaningful differences in both mean change in SARS-COV-2 viral load by day 8 (-1.48 $\log_{10}$, nominal $p = 0.040$) and median time to sustained symptom resolution (57-h advantage, nominal $p = 0.044$) compared to sham. Unlike the photodamage known to be caused by UV light, photobiomodulation via 425 nm blue light exhibited no cytotoxicity in oral mucosal tissues in vitro and no device-related application site adverse events in the clinic.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Self-administered visible light therapy in the outpatient setting may be capable of interrupting SARS-CoV-2 disease pathology (through inactivation of virus and/or stimulation of host immune response) and useful as a treatment for mild to moderate COVID-19. These nonclinical and clinical findings help to inform dosing schedules for the optimal use of light as a therapeutic in future clinical trials.

INTRODUCTION

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) genetic variants continue to propagate the global coronavirus disease 2019 (COVID-19) pandemic. As diagnostic procedures have evolved throughout the pandemic, reports have demonstrated that SARS-CoV-2 viral load measured in saliva strongly correlates with disease severity and mortality.[1–3] Correspondingly, the importance of the oral cavity in both disease progression and oral-lung transmission via aspiration is now clear, with many tissues and glands in the oral cavity having high levels of ACE2 and TMPRSS2 expression required for SARS-CoV-2 entry into barrier epithelia.[4,5]

Systemically administered antibody cocktails and convalescent plasma have shown clinical evidence of viral load reductions and improved clinical outcomes in non-hospitalized populations[6–8]; however, they are indicated for populations with risk factors for progression to severe disease/hospitalization and require infusion in a clinical setting, limiting these treatments to roughly 25% of the infected population.[9] Further, novel variants of concern, such as the currently circulating Delta and Omicron variants, will continue to emerge with potential enhancements in transmissibility and resistance to existing antibody therapies and vaccines,[10–12] underscoring the need for innovative therapeutics directly targeting the virus in the nasal or oral cavities early in the disease process.

Light therapy has successfully been used for many years as a treatment for skin disorders[13] but has yet to be successfully adapted to respiratory medicine. Several potential mechanisms of action have been postulated following host-directed photobiomodulation, including the release of endogenous nitric oxide[14] and alteration of cellular redox states that activate transcription factors and other immune signaling pathways.[15] In the exploration of light as an antiviral, Zupin et al. administered 10–20 J/cm^2 doses of various blue light wavelengths (450, 454, and 470 nm) that were non-toxic to cells in vitro and reduced SARS-CoV-2 viral replication for up to 48 h post-infection.[16] Effects for all three wavelengths were observed once the virus entered the cells, suggesting that blue light also interferes with intracellular viral replication. Recently, Cockrell and coworkers reported that 425 nm blue light dramatically inhibited SARS-CoV-2 infection and replication in primary human 3D tracheal/bronchial tissue at doses ($\leq$32 J/cm^2) that are non-cytotoxic to epithelial tissues.[17]

Experiments in our laboratory indicate that light therapy is neither antigen-directed nor antigen-dependent, affording a novel therapeutic approach that can be widely deployed to mitigate the threat posed by current SARS-CoV-2 variants, pre-emergent coronaviruses, and potentially other non-coronavirus pathogens. Herein, we report confirmatory evidence of the antiviral effects of 425 nm blue light in a second three-dimensional model of SARS-CoV-2 infected oral epithelial tissues, including the dose-dependent reduction of SARS-CoV-2 variants. Given the continued emergence of variants of concern, this translationally relevant human tissue model enables the rapid evaluation of fixed wavelength and irradiance combinations of visible light against each new variant. The studies in these epithelial tissue models have led to the translation of this technology into an investigational device, RD-X19, where a twice-daily dosing schedule of visible light was evaluated in a randomized, double-blind, sham-controlled, early feasibility study in outpatients with mild to moderate COVID-19.

METHODS

Oral epithelial tissue model

Primary oral mucosal tissues derived from human buccal epithelial cells (EpiOral ORL-200; MatTek Corporation – 40-year-old White male tissue donor) were cultured for 28 days in transwell inserts, as described previously.[18] Following transport, upon arrival, the transwell inserts were removed and placed in hanging well plates with ORL-200-MM maintenance media in the basal compartment; no media was added to the apical surface. Tissues were incubated at 37°C and 5% CO_2 overnight prior to experimental use.

SARS-CoV-2 infected tissues

SARS-CoV-2 isolates WA1 (NR-52281), Alpha (NR-54000), and Beta (NR-54009) were obtained through BEI Resources and passaged, as previously described.[17] For SARS-CoV-2 infections of ORL-200 tissue cultures, 200 µl of SARS-CoV-2 diluted in virus diluent at an MOI of 0.1 (MEM supplemented with 2% FBS; Gibco, 1% nonessential amino acids; Gibco, and 1% antibiotic-antimycotic; Gibco) was inoculated on the apical surface and incubated for 2 h at 37°C and 5% CO_2. The virus was then removed from the apical surface and the transwell cultures were further incubated for 1 additional hour at 37°C and 5% CO_2 until administration of the first dose of light. Infected transwell cultures were illuminated at room temperature with 425 nm light at doses of 0 J/cm^2, 16 J/cm^2, 32 J/cm^2, or 60 J/cm^2 using LED array biological light units and viral titers were measured from apical washes taken 12- and 24-h post-infection, as described previously.[17] All work with live virus was conducted in a Centers for Disease Control and Prevention (CDC) certified, BSL-3 laboratory at EmitBio with adherence to established safety guidelines.

Tissue viability

Using separate, uninfected transwell cultures, the cytotoxicity of each dose of light was assayed at 24 h post-exposure using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) following the manufacturer's instructions (MTT-100; MatTek Corporation). Briefly, tissues were rinsed with TEER buffer and placed into 300 µl of pre-warmed MTT reagent and incubated at 37°C and 5% CO_2 for 3 h. The MTT stained tissue inserts were then extracted for 2 h and the absorbance of 200 µl of extract solution was measured at 560 nm on a GloMax Discover (Promega). The viability of light-exposed tissues was calculated relative to dark controls using the following equation: Relative viability = [OD_{sample}/Mean OD_{neg} ctrl] × 100.

Gene expression analysis

To assess the immunomodulatory effects of 425 nm light on oral epithelial tissues, uninfected ORL-200 transwell cultures were illuminated with a single dose of 425 nm light (0 J/cm^2, 3 J/cm^2, 7.5 J/cm^2, 15 J/cm^2, 30 J/cm^2, or 60 J/cm^2) and incubated at 37°C, 5% CO_2. After 24 h, ORL-200 tissues were lysed with the QuantiGene Sample Processing Kit for Cultured Cells (Thermo Scientific) following the manufacturer's instructions for "Cells grown in 3D cell matrix." Lysates were stored individually at −80°C until hybridization and RNA expression analysis on the Magpix Instrument System (Luminex Corporation) according to the manufacturer's instructions. Gene expression was normalized to the geometric mean of three housekeeping genes (PPIB, TBP, and HPRT1) and presented as fold change over mock-illuminated tissues (0 J/cm^2) +/- SD.

Early feasibility clinical study design

This randomized, double-blind, sham-controlled, early feasibility study was conducted in the outpatient setting at two centers in the United States. Subjects were required to

have symptomatic COVID-19 and active SARS-CoV-2 infection confirmed by a US Food and Drug Administration (FDA)-approved rapid antigen test. The trial was conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonization of Good Clinical Practice guidelines, and all applicable regulatory requirements, including oversight by a local institutional review board for each trial center (Advarra, Inc. October 30, 2020). All subjects provided written informed consent before participating in the trial. ClinicalTrials.gov Identifier: NCT04662671.

Subjects

Eligible subjects were 18 to 65 years old with positive results on testing for SARS-CoV-2 via an FDA-authorized rapid antigen test (e.g., BD Veritor Plus System) within 24 h of enrollment. Entry criteria also required participants to have either a fever of at least 100°F or at least two of the eight protocol-designated signs and symptoms of COVID-19 graded as moderate or higher. Signs and symptoms were cough, sore throat, nasal congestion, headache, unexplained chills or sweats, muscle or joint pain, fatigue, and nausea where each was assessed on a four-point scale (symptom score of 0 = absent, 1 = mild, 2 = moderate, and 3 = severe). The Composite Severity Score (ranging from 0 to 3 and ≥0.5 at baseline) was defined as the sum of the eight individual COVID-19 signs and symptoms severity scores divided by eight. Individuals displaying these signs and symptoms longer than 3 days, with a body mass index greater than or equal to 36 kg/m^2, or with COVID-19 signs or symptoms indicative of imminent acute respiratory distress syndrome or severe COVID-19 were excluded. A full listing of inclusion and exclusion criteria can be found in the Supplementary Information.

Randomization and intervention

All participants were centrally randomized using randomly permuted blocks of six. The subjects, investigators, site personnel, and EmitBio employees who were involved in collecting and analyzing data were unaware of the treatment group assignments. A total of 31 study subjects were randomized 2:1 (RD-X19:sham). Each study subject was trained how to insert the device into the mouth and instructed to treat twice daily for a duration of 4 days. The RD-X19 treatment times were controlled via a preprogrammed timer integrated into the RD-X19 device to deliver a nominally designed light dose of 16 J/cm^2 per treatment to the oropharynx. The sham devices were designed to provide the same user experience as the active devices while delivering blue light at more than 20-times lower fluence (<0.8 J/cm^2 per treatment). The total daily sham dose, when compared to the total daily dose of light delivered by the active devices, has an estimated 500-fold lower inactivation potential against SARS-CoV-2 based on in vitro experiments. Illumination throughout the oral cavity and the nominal light doses provided by RD-X19, as determined by optical modeling, are illustrated in Figure 1 (Methods S1).

The nominal RD-X19 dose of 16 J/cm^2 and a b.i.d. treatment schedule (32 J/cm^2 daily) were selected based on preclinical evidence generated using SARS-CoV-2 infected large airway tissues[17] and the oral epithelial tissues described herein that demonstrates a minimum 1 log (90%) reduction for 32 J/cm^2 against all coronaviruses

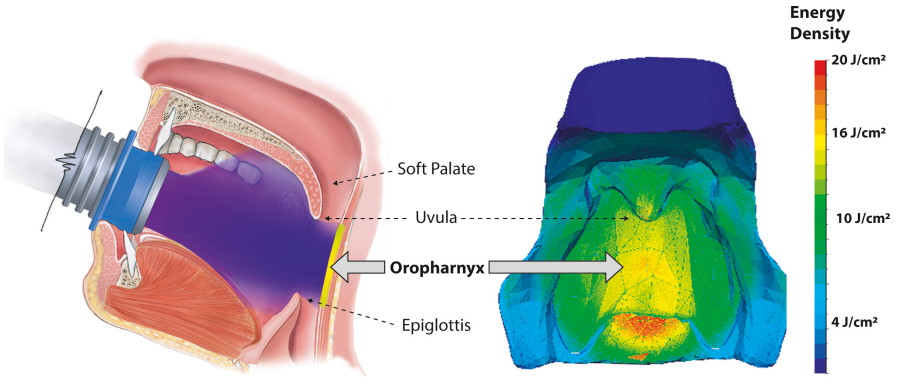

FIGURE 1 RD-X19 intervention and optical modeling of energy density in the oral cavity. (a) Sagittal view showing a schematic RD-X19 device positioned in the oral cavity to deliver a dose of light to the oropharynx and surrounding tissues. The blue shading is included as a guide to the eye to illustrate the approximate shape of the light beam and coverage of anatomical features. (b) Results of optical modeling of nominally designed light dose of 16 J/cm^2 emitted from a typical RD-X19 device and projected onto the surfaces of the oral cavity. Elements of the anatomic model (e.g., cheeks) have been removed for better visualization of the light projection. LightTools, a Monte-Carlo-based ray-tracing program for 3D simulations of complex systems with the ability to incorporate volumetric optical effects, scattering, and absorption throughout the oral cavity, was used to generate the dose contour plot (Methods S1)

tested. The in vitro data in this model as well as supporting data generated in a prior phase I safety trial of RD-X19 (NCT04557826) supported the exploration of these doses as a non-significant risk device in this early feasibility study (Advarra, Inc. October 30, 2020).

Safety assessments

Safety assessments included evaluation of vital signs, local application site reactions via oropharyngeal examination, treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs). For safety and tolerability, local site reactions (pain, induration, and erythema) and the presence, type, severity, and attribution of any device-related TEAEs were assessed. Hematological, metabolic, liver, and kidney function evaluations were also performed at baseline and at day 8. Safety was continuously monitored by the medical monitor and a Safety Monitoring Committee (SMC) comprised by physicians with clinical research experience operating under an approved charter to convene when protocol specified safety signals were identified and make recommendations concerning continuation and/or stopping of a study subject's participation in the study.

Outcome assessments

Virologic outcomes

The primary outcome was the time-weighted average change (TWAC) in SARS-CoV-2 viral load from baseline through day 8 as measured by saliva specimens obtained from each participant via OMNIgene Oral collections kits (OM-505, DNA Genotek) and analyzed by quantitative reverse-transcriptase-polymerase-chain-reaction (qRT-PCR) testing at a central laboratory (log10 copies per milliliter; Methods S2). Other prespecified key virologic outcome measures included the change in viral load from baseline (D1) at days 3, 5, and 8 (D3, D5, and D8) and proportion of subjects achieving clearance of viral infection defined as undetectable levels of SARS-CoV-2 in saliva via qRT-PCR on day 8/ET.

Clinical outcomes

Clinical outcomes included time to event analyses of symptoms resolution and change in Composite Severity Score from baseline. Participants self-assessed severity of the eight protocol-designated COVID-19 signs and symptoms twice daily via diary cards (Figure S1). The time (measured in hours) to alleviation of COVID-19 signs and symptoms was defined as the point at which the eight COVID-19 signs and symptoms scores were first reported by the participant to all be 0 (none) or 1 (mild). The time to sustained resolution of COVID-19 signs and symptoms was established as a post hoc analysis, incorporating FDA Guidance,[19] where sustained symptom resolution uses the same "success" definition above but without rebound of any score greater than 1 for the remainder of the trial.

Sample size and statistical analyses

This was a hypothesis generating, proof-of-concept trial where the number of participants was chosen to provide a preliminary assessment of safety and efficacy. As such, no a priori power calculations were performed. All clinical and safety analyses were conducted on the intent-to-treat population. All virologic efficacy assessments were conducted on a modified analysis set, including all study subjects with laboratory confirmed SARS-CoV-2 positivity via qRT-PCR at baseline. The prespecified primary efficacy end point of TWAC in log10-transformed viral load was derived using the trapezoidal rule with RD-X19 compared to sham using an Analysis of Covariance (ANCOVA) model with baseline viral load on $\log_{10}$ scale as a covariate and treatment group as an independent variable using a two-sided test with an alpha level of 0.05. Using the 1-log SD reported in the phase I/II study of casirivimab/imdevimab for the TWAC from baseline to day 8 end point,[7] this feasibility study had 75% power to detect a 1-log treatment difference between groups with at least 30 total subjects (20 RD-X19: 10 sham). Kaplan-Meier product limit estimates to compare the time to reach symptom resolution end points were performed using log-rank tests. Cox proportional hazards models were also calculated along with 95% confidence intervals as supportive analyses. No adjustments for multiplicity were conducted for this study and all statistical tests on secondary and post hoc end points were performed at a nominal alpha level of 0.05 (2-sided). For the retrospective analysis in mean change in ΔCt values, given the non-normality in the sham arm, the most valid statistical method was determined to be the Mann-Whitney (Wilcoxon) *U* test. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc.).

RESULTS

Photobiomodulation of oral mucosal tissue with 425 nm light

Based on the evidence generated previously on SARS-CoV-2 infected tracheal/bronchial airway epithelial tissues,[17] experiments were conducted to evaluate whether

SARS-CoV-2 replicates in oral mucosal epithelia and to evaluate whether doses of 425 nm light could inhibit virus replication with minimal cellular toxicity. Similar to data reported using primary human large airway tissues, single exposures of 16, 32, or 60 J/cm^2 of 425 nm light all inhibited infection and replication of the parental SARS-CoV-2 (WA1) in oral epithelial tissues at 12- and 24-h post-infection (Figure 2a). Only the lowest dose tested, 16 J/cm^2 had any detectable virus at both timepoints evaluated. The SARS-CoV-2 Alpha and Beta variants replicated faster in the ORL-200 tissue as evidenced by the increasing viral titers observed in the unexposed (0 J/cm^2) controls 24 h post-infection (Figure 2b, 2c). The dose-dependent effects of 425 nm light were observed against both the Alpha (B.1.1.7) and Beta (B.1.351) variants, where a single dose of 60 J/cm^2 inhibited replication of Alpha by greater than 99% in this model. Commensurate with the previously observed tolerability data, single exposures up to 60 J/cm^2 demonstrated no loss in tissue viability after 24 h (Figure 2d). The slight increase in cell viability observed through assessment of metabolic activity with MTT is consistent with results previously reported for visible blue light where low fluences have been shown to induce a hyperproliferative phenomenon in epithelial cells.[17,20]

Gene expression analysis was also conducted on uninfected ORL-200 epithelial tissues illuminated with doses ranging from 3–60 J/cm^2 to assess biomarkers of cellular stress and key host immune response cytokines. As show in Figure 2e, dose-dependent increases in interleukin-1 cytokines (IL-1α and IL-1β) were observed with greater than three-fold increase after a single illumination of 60 J/cm^2. Blue light appears to have a selective impact on certain promoters of innate immune response with no corresponding increases of IL-6 or IL-8 in uninfected epithelial tissue; the impact on these biological processes in SARS-CoV-2-infected tissue has not been determined. Importantly, no dose-dependent increases were observed in several markers of cellular (CASP3 and LDH-B), metabolic (HSPD1), and oxidative stress (NRF2 and KEAP1) with the same dosing schedule of light (Figure S2A).

Feasibility study demographics and baseline disease burden

Subjects were randomized within 3 days or less from the onset of COVID-19 signs and symptoms. Demographics, baseline disease characteristics, and baseline saliva viral load are listed in Table 1. Of the 31 study participants who underwent randomization, 20 received RD-X19 and 11 received the sham device (Figure 3). The subjects who tested positive for SARS-CoV-2 in saliva by RT- qPCR at randomization (28 of 31, 90%) comprised the modified analysis set for virologic end point analyses. The mean baseline Composite Severity Score, similar to the total symptom scores used by other sponsors during the clinical development of COVID-19 therapeutics,[6] was 1.29 (SD, 0.35) for the total study population and was similarly balanced between treatment groups.

Safety and tolerability

Safety and tolerability were assessed actively at each clinic visit through assessment of vital signs, targeted physical examination, oropharyngeal examination as needed, review of potential TEAEs, and review of daily diary cards. There were no changes in vital signs nor observed adverse oropharyngeal or oral mucosal reactions in any study subject throughout the course of the trial. The device was well-tolerated, there were no clinical observations indicative of device-related TEAEs, and the SMC was not convened to review any patterns of adverse events (AEs) or SAEs during the conduct of the study. The most frequently reported AEs were attributed to perturbations of COVID-19 disease severity, with no discernable difference between treatment groups (Table S1). There were no SAEs and no laboratory values that were out of range with laboratory standards resulting from treatment and no hospitalizations or requirement for acute medical intervention.

Virologic outcomes

The prespecified primary outcome measure was TWAC in saliva viral load from baseline through day 8 where the RD-X19 least-squares mean difference was −0.47 $\log_{10}$ copies/ml lower than sham (95% confidence interval [CI], −1.41 to 0.45, $p = 0.307$). The mean change from baseline ($\log_{10}$ transformed data) at each visit for both treatment arms is shown in Figure 4a. On day 8, the change in $\log_{10}$ viral load for the RD-X19 treated group was −3.29 and for the sham treated group was −1.81, resulting in an RD-X19 group advantage of −1.48 (95% CI, −2.88 to −0.07, nominal $p = 0.040$). The quantitative determination of SARS-CoV-2 copies/ml determined via qRT-PCR using an RNA standard curve for each individual subject have been provided to illustrate the distribution of SARS-CoV-2 viral load over time (Figure S3). Raw C_t values were also normalized to the human RNAse P control gene to calculate mean ΔCt values at baseline and day 8 for each subject as depicted in Figure 4b. The mean change observed in ΔCt for RD-X19 of −7.6 (95% CI, −10.3 to −4.9) compared to −4.1

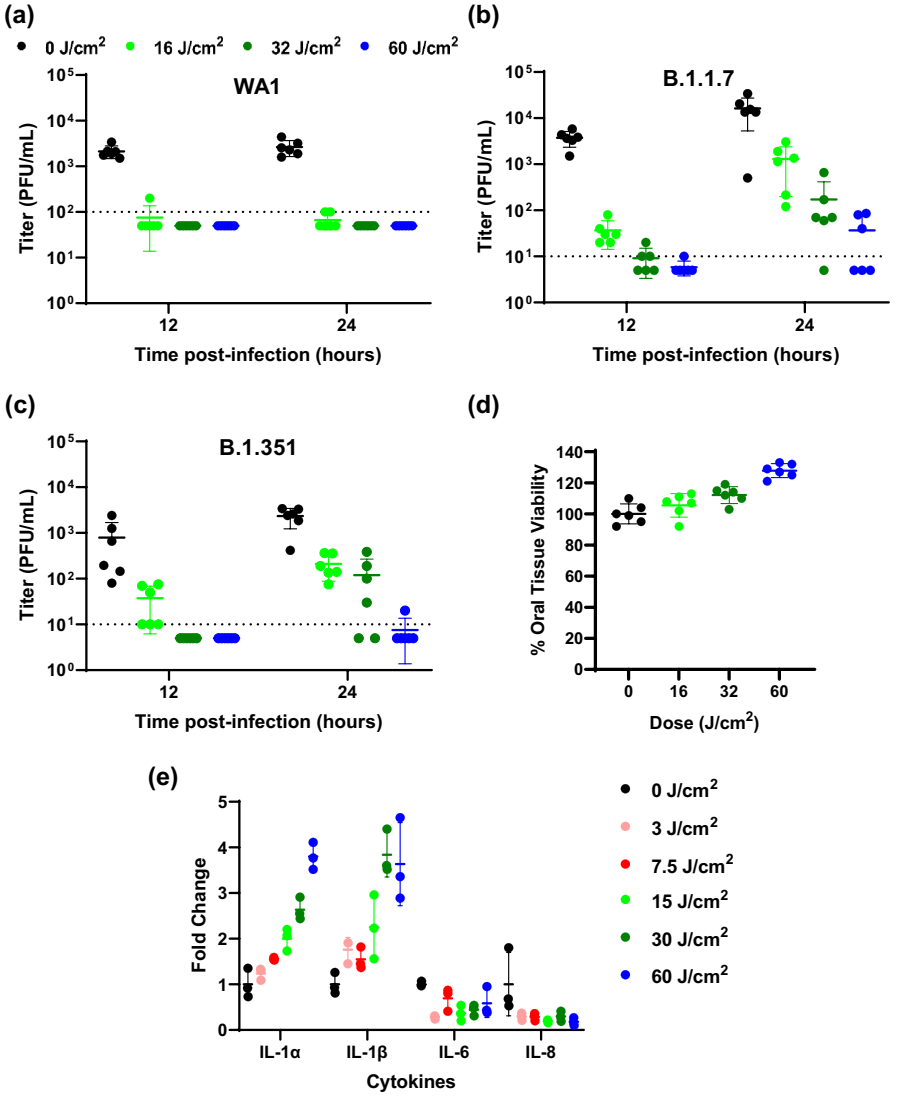

FIGURE 2 Laboratory doses of 425 nm light inhibits SARS-CoV-2 replication in human oral epithelial tissues and induces IL-1 cytokine gene expression. Reduction in SARS-CoV-2 viral titer assessed at 12 and 24 h following a single exposure of 425 nm blue light at doses of 16 J/cm^2 (light green), 32 J/cm^2 (dark green), and 60 J/cm^2 (blue) compared to untreated infected ORL-200 tissue cultures (0 J/cm^2). (a) WA1 parental strain, (b) Alpha – B.1.1.7, and (c) Beta – B.1.351. Dotted line represents the limit of detection for each SARS-CoV-2 strain. Mean ± SD, $n = 6$ independent tissue replicates for each assessment. (d) Tissue viability of uninfected ORL-200 cultures assessed at 24 hours post exposure to light. Mean ± SD, $n = 6$ independent tissue replicates for each assessment. (e) Dose dependent fold change in cytokine RNA expression over mock illuminated tissues (0 J/cm^2) 24 h after light exposure for a range of 425 nm blue light doses. Mean ± SD, $n = 3$ independent tissue replicates for each assessment. SARS-CoV-19, severe acute respiratory syndrome-coronavirus 2

(95% CI, −6.0 to −2.2) for sham represents a 10-fold difference in viral shedding between the treatment groups with some subjects achieving large reductions in SARS-CoV-2 viral load following RD-X19 treatment (−3.5 ΔCt, nominal $p = 0.180$).

Clinical outcomes

Various clinical outcome assessments were planned to explore the impact of RD-X19 treatment on clinical resolution of COVID-19 signs and symptoms. Key prespecified secondary end points were (1) change in Composite Severity Score from baseline and (2) median time to alleviation of symptoms. On average, subjects treated with RD-X19 experienced a greater reduction of the Composite Severity Score at each assessment during the trial (Table 2) with a larger proportion of subjects achieving sustained resolution of symptoms by day 8.

The Kaplan-Meier analysis for median time to symptom alleviation, the first time point when all symptoms were scored none (0) or mild (1), resulted in a median time to success for RD-X19 of 75.3 h (95% CI, 48.3 to 117.2) compared with 112.7 h (95% CI, 38.0 to 166.2) for

TABLE 1 Demographic and baseline medical characteristics

Characteristic	Category	RD-X19 treatment (*N* = 20)	Sham device (*N* = 11)	Total (*N* = 31)
Demographics				
Age	Median	43	36	40
	Min, Max	20, 65	21, 57	20, 65
Gender, *n* (%)	Male	8 (40%)	8 (73%)	16 (52%)
	Female	12 (60%)	3 (27%)	15 (48%)
Race or ethnic group, *n* (%)[a]	Hispanic or Latino	15 (75%)	7 (64%)	22 (71%)
	White	4 (20%)	3 (27%)	7 (23%)
	Black	1 (5%)	1 (9%)	2 (6%)
Body mass index, kg/m^2	Median	28.8	29.1	28.8
	Min, max	22.3, 35.1	22.1, 35.4	22.1, 35.4
Disease characteristics				
Risk factors for severe COVID-19, *n* (%)[b]	Confirmed	12 (60%)	4 (36%)	16 (52%)
Composite Severity Score @ BL[c]	Mean (SD)	1.26 (0.39)	1.36 (0.28)	1.29 (0.35)
Baseline disease severity[d]	Mild	14 (70%)	8 (73%)	22 (71%)
	Moderate	6 (30%)	3 (27%)	9 (29%)
Baseline viral load in saliva specimen				
Positive at baseline via qRT-PCR	– no. (%)	17/20 (85%)	11/11 (100%)	28/31 (90%)
SARS-CoV-2 cycle threshold[e]	Mean C_t (SD)	28.9 (5.1)	30.4 (4.5)	29.5 (4.8)
Mean SARS-CoV-2 viral load	Log10 copies/ml (SD)	4.10 (2.27)	4.41 (1.37)	4.2 (1.5)
Median SARS-CoV-2 viral load	Log10 copies/ml (range)	4.29 (0.00–8.18)	4.61 (2.18–6.36)	4.3 (0.00–8.18)

Abbreviations: BL, baseline; COVID-19, coronavirus disease 2019; Max, maximum; Min, minimum; qRT-PCR, quantitative reverse-transcriptase-polymerase-chain-reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Race and ethnicity are not mutually exclusive and both are documented for subjects who self-identify as such.

[b]Centers for Disease Control and Prevention (CDC) risk factors of severe disease included medical history of diabetes, chronic kidney or liver disease, cardiovascular disease, chronic respiratory disease, or immunosuppressive disease.

[c]Based on the eight symptom domains (cough, sore throat, nasal congestion, headache, unexplained chills or sweats, muscle pain or joint pain, fatigue, and nausea) that were rated from absent (0) to severe (3), which were added together and divided by eight for an overall composite score (range 0–3; symptom score did not include loss of taste or smell).

[d]Definition for "moderate" based on clinical signs suggestive of moderate illness with a corresponding respiratory rate greater than or equal to 20/min and/or a heart rate greater than or equal to 90/min.[19]

[e]The cycle threshold is the number of polymerase chain reaction cycles required for a viral sample to be detected. Lower numbers indicate higher viral RNA in the sample and an increased burden of disease. Values range between 0 and 40.

the sham treatment group (Figure 5a). This corresponds to RD-X19 yielding a 37-h decrease in median time to symptom alleviation compared with sham (nominal $p = 0.602$ via log rank test). Data from a post hoc analysis conducted on study subjects achieving sustained resolution of symptoms, the time point when all symptoms were scored none (0) or mild (1) and maintained this threshold for the duration of the trial, is shown for both treatment groups in Figure 5b. At the end of the trial, 17 of 20 subjects (85%) in the RD-X19 group had achieved sustained resolution, compared with 6 of 11 subjects (55%) in the sham group. From the Kaplan-Meier analyses, the median time to sustained resolution was 103.8 h (95% CI, 69.0 to 130.8) for RD-X19 compared with 160.7 h (95% CI, 38.0 to NE) for sham. This corresponds to a 57-h decrease in median time to sustained resolution for RD-X19 compared to sham (log rank test, nominal $p = 0.044$). A Cox proportional hazards model of time to sustained resolution (with the single term for treatment) gives a hazard ratio of 0.385 (95% CI, 0.147 to 1.006, nominal $p = 0.051$). When further adjusting for the gender imbalance at baseline, 40% male in the RD-X19 arm versus 73% in the sham arm, the Cox model analysis including a term for sex in the model (in addition to the term for treatment) results in a much lower hazard ratio of 0.259 (95% CI, 0.087 to 0.773, nominal $p = 0.015$). These supportive analyses with hazard ratios less than 0.4 reinforce the RD-X19 treatment benefit observed with the Kaplan-Meier estimates.

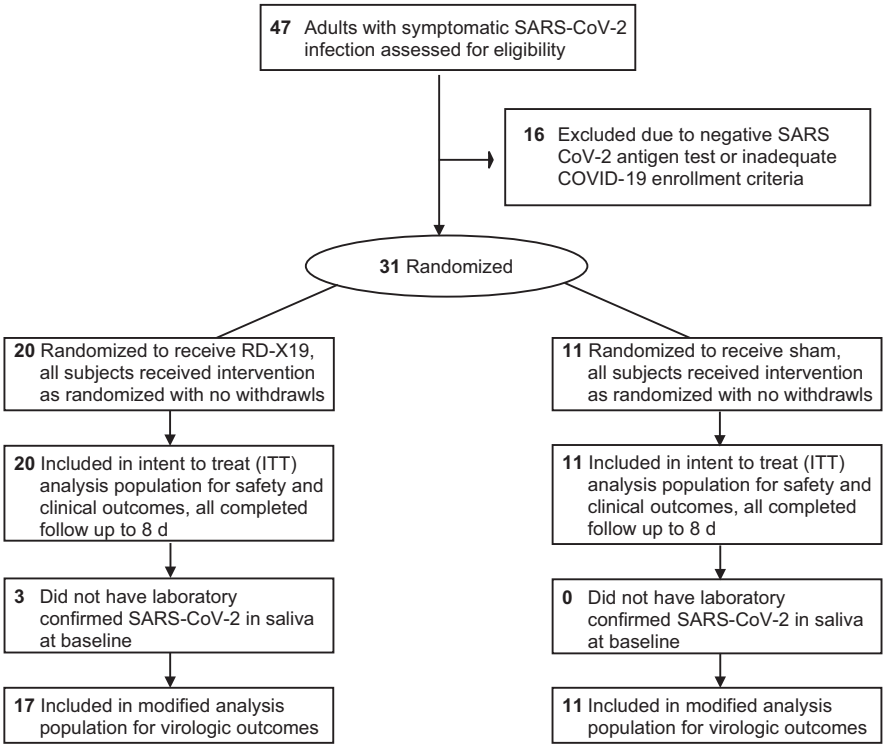

FIGURE 3 Enrollment and treatment assignment. CONSORT Flow diagram illustrating the difference between the intent to treat population randomized with a positive rapid antigen test (ITT, $n = 31$) and the modified analysis population comprising subjects with laboratory confirmed SARS-CoV-2 in saliva via RT-PCR at baseline ($n = 28$). CONSORT, Consolidated Standards of Reporting Trials; COVID-19, coronavirus disease 2019; ITT, intention to treat; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2

DISCUSSION

The oral cavity was originally thought to be a passive conduit for the transmission of SARS-CoV-2 to the lower respiratory tract, but recent findings report multiples lines of evidence for a parallel oral axis in both SARS-CoV-2 infection and transmission.[5,21] Saliva viral load is not only an indicator of local viral shedding in the oral cavity, but it is also a biomarker of total viral bioburden in the respiratory tract and has been shown to be a predictor of COVID-19 disease outcomes.[1–3] As an example, Fajnzylber et al. reported that 1 to 2 logs higher initial oropharyngeal viral load upon hospital admission was associated with increased mortality.[22] It is hypothesized that (1) reductions in saliva viral load coincide with resolution of systemic disease, and (2) that a localized antiviral light treatment targeted to the oropharynx and surrounding tissues may be effective as treatment for COVID-19 in the outpatient setting.

The orally administered RD-X19 device depicted in Figure 1 was devised to exert both direct effects on viral pathogens in the oral mucosa and to stimulate host immune responses through photobiomodulation of barrier epithelial tissue. Epithelial surfaces, including the oral and airway mucosa, are primary portals of entry for viruses and serve as the first line of host defense during infection. The IL-1 family of cytokines produced in epithelial tissue in response to invading microorganisms are apical cytokines that signal multiple downstream processes to affect both innate and adaptive immunity. Specifically, increases in IL-1α and IL-1β can signal key innate immune functions, including triggering neutrophil recruitment, driving emergency myelopoiesis, and altering epithelial barrier permeability.[23] Additionally, IL-1α and IL-1β are biologically active at very low concentrations and have previously been demonstrated to play a critical role in the control of influenza virus-related disease.[24]

Following photobiomodulation of uninfected oral epithelial tissues with 425 nm blue light (Figure 2e), there is preferential upregulation of IL-1 cytokines and simultaneous decline of IL-6 and IL-8 response (IL-6 and IL-8). Given that IL-6 is associated with the development of severe COVID-19, this finding suggests that 425 nm blue light applied to epithelial tissue may contribute to inhibiting the progression of COVID-19.[25] Transcription of inflammatory cytokines is known to be upregulated following oxidative stress induced by UV light through NF-κB pathways.[26] However, the absence of changes in oxidative and cellular stress response biomarkers and the lack of any increase in IL-6 and IL-8 classically expressed as part of NF-κB transcription, suggest that 425 nm visible light is activating transcription pathways contrary and independent from the crosstalk of reactive oxygen species and NF-κB signaling reported for UVB (280–320 nm) and UVA (320–400 nm) wavelengths.[15,26]

Blue light-initiated release of IL-1α and IL-1β can occur before tissue resident immune cells can recognize virus, potentially stimulating the target tissue to a more highly infection resistant state before virions are subsequently introduced to respiratory epithelial tissues. Kagan and

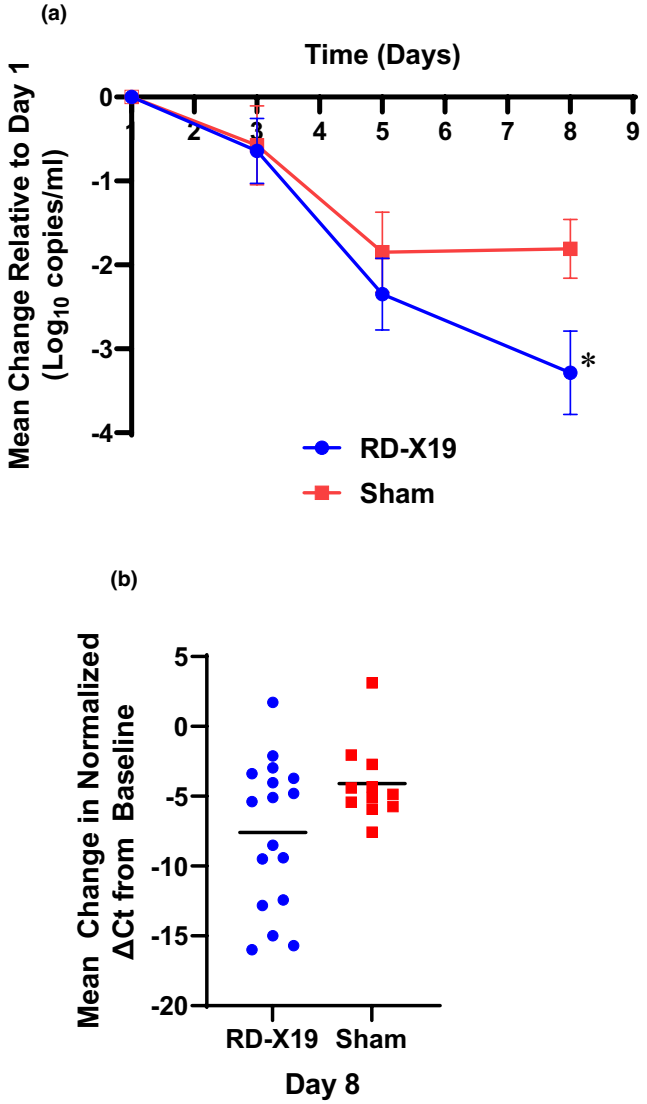

FIGURE 4 Virologic outcome assessments with RD-X19 therapy. (a) Mean change in SARS-CoV-2 saliva viral load (N1 copies/ml) from baseline (day 1) for subjects receiving treatment with RD-X19 (blue) and subjects receiving sham (red), errors represent ± SEM. Asterisk (*) denotes $p < 0.05$. (b) Mean change in ΔCt (N1 Ct – RNase P Ct) from baseline for each subject receiving treatment with RD-X19 (blue) versus sham (red). SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2

coworkers have provided support for the natural function of IL-1 cytokines beyond their fundamental role in innate immune signaling.[27] Mechanistic studies in epithelial cells revealed IL-1 cytokines can induce an antiviral state in surrounding tissue through promotion of interferon-stimulated genes as a backup antiviral mechanism during encounters with immune-evasive viruses. The ineffective antiviral interferon (IFN) responses mounted by the immune system following SARS-CoV-2 infection has been recognized as a signature of COVID-19 disease pathology and contributes to aggressive disease progression.[28] As such, photobiomodulation with 425 nm light of the IL-1 cytokines provides a host defense mechanism against SARS-CoV-2 and its numerous variants that can prime other cells in advance of infection and via a pathway that is insensitive to immune evasion strategies used to prevent IFN gene expression.

In the early feasibility clinical trial, use of the investigational RD-X19 device in the outpatient setting resulted in a reduction in SARS-CoV-2 saliva viral load and a corresponding reduction in time to COVID-19 disease resolution. As summarized in Table 2, numerous outcome assessments resulted in a treatment benefit following 4 days of twice daily dosing with the RD-X19. Whereas the TWAC in the saliva viral load primary end point did not reach statistical significance given the sample size of this study, the −0.47 $\log_{10}$ copies/ml least squares mean difference in SARS-CoV-2 saliva viral load is comparable to the −0.41 $\log_{10}$ copies/ml mean difference reported for the TWAC through day 7 for the pooled doses of casirivimab/imdevimab antibody cocktail via nasopharyngeal sampling.[7] This 0.41 $\log_{10}$ greater improvement over placebo, accompanied by a decrease in medically attended visits, was used in support of Emergency Use Authorization for the 2400 mg dose of the antibody cocktail.[29]

When assessing viral load at a single time point post baseline, the 1.48 $\log_{10}$ greater reduction in saliva viral load for RD-X19 compared to sham at day 8 (Figure 4a, nominal $p = 0.040$) is clinically meaningful given the link established between reduction in SARS-CoV-2 viral load and reduced hospitalizations reported for oral antiviral and antibody therapeutics. Indeed, persistently high viral load at day 7 has been correlated with increased risk of COVID-19-related hospitalization or any-cause death.[30] Dougan et al. reported that in outpatients with COVID-19, a −0.99 $\log_{10}$ reduction in nasopharyngeal viral load by day 7 resulting from the bamlanivimab/etesevimab antibody combo compared to placebo led to a corresponding 86% reduction in hospitalizations and a 2-day reduction in the median time to sustained symptom resolution.[30]

As suggested by FDA guidance for the development of therapeutics for COVID-19, a post hoc analysis was conducted on symptom scores using a "sustained resolution of symptoms" definition.[19] The 57-h reduction in median time to sustained symptom resolution shown in Figure 5b demonstrates the clinical benefit from the RD-X19 treatment regimen. For comparison purposes, if confirmed in a subsequent trial with a larger sample size, this level of treatment benefit exceeds the clinical benefit demonstrated for approved drugs to treat otherwise healthy subjects with acute uncomplicated influenza (e.g., baloxavir marboxil and oseltamivir phosphate).[31,32] The reduction of SARS-COV-2 viral load at day 8 and the large proportion of study participants with sustained resolution of all COVID-19 illness (85% for RD-X19 compared to 55% for

TABLE 2 Summary of key virologic and clinical outcomes

	RD-X19	SHAM
Virologic outcomes	*N* = 17	*N* = 11
Time-weighted average change (N1 Log10 copies/ml)		
Least squares mean ,95% CI	−1.69 (−2.27, −1.12)	−1.23 (−1.94, −0.52)
Difference versus sham at day 8, 95% CI	−0.47 (−1.39, 0.45)	–
Saliva viral load over time (N1 Log10 copies/ml)		
Mean change from baseline at day 3	−0.64	−0.57
Mean change from baseline at day 5	−2.35	−1.85
Mean change from baseline at day 8	−3.29	−1.81
Difference versus Sham at day 8	−1.48	–
Median SARS-CoV−2 viral load on day 8 (Log_{10})	0.00	3.17
Proportion of subjects achieving clearance of viral infection on day 8	59%	36%
Clinical outcomes	*N* = 20	*N* = 11
Composite Severity Score		
Mean change from baseline at day 3	−0.63	−0.44
Mean change from baseline at day 5	−0.82	−0.75
Mean change from baseline at day 8	−1.04	−0.96
Kaplan-Meier time to event symptom analyses		
Median time to alleviation - all none (0) or mild (1) 95% CI	75.3 h (48.3, 117.2)	112.7 h (38.0, 166.2)
Proportion of subjects achieving success	85%	82%
Median time to sustained resolution - all none (0) or mild (1) without rebound of any score >1 for the remainder of the trial 95% CI	103.8 h (69.0, 130.8)	160.7 h (38.0, NE)
Proportion of subjects achieving success	85%	55%

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

sham) in this study demonstrate that a reduction of viral load in the saliva can lead to a clinically meaningful improvement in subject outcomes.

Although the overall mortality rate for COVID-19 has declined in the United States due to better care for hospitalized patients, the number of deaths and global cases propagated from variants of concern continues to climb. Over a year ago, officials within the National Institutes of Health concluded that the availability of therapeutics as a complement to vaccines, especially those administered easily at home and widely available, "would have significant implications for the ability to end this pandemic."[33] Monoclonal antibody cocktails and oral antivirals have been granted Emergency Use Authorization that allows healthcare providers to administer these therapies to non-hospitalized patients with confirmed COVID-19 who are experiencing mild to moderate symptoms and are at high-risk for severe symptoms and hospitalization. Currently, there are no FDA authorized/approved treatment options indicated for the 75% of all outpatients diagnosed with COVID-19 that have no underlying risk factors.[9] The potential advantages of RD-X19 for outpatient treatment is supported by the absence of device-related TEAEs observed to date, ease of administration in an at-home setting, and variant-agnostic mechanism of action.

Predictive data generated from a preclinical human tissue model was useful in the design of the hypothesis generating, proof-of-concept study described herein. Although future trials are needed to confirm the results obtained from the small sample size, this feasibility study evaluating RD-X19 as an early intervention (≤3 days from symptom onset) for symptomatic adult outpatients with COVID-19, irrespective of the presence of risk factors for disease progression, was a successful translation of the preclinical data. The study provided a first demonstration that visible light (16 J/cm^2, twice daily, 128 J/cm^2 total dose) applied at home to the oropharynx and surrounding tissues may present a potential treatment for COVID-19. At its December 22, 2020, meeting, the SMC reviewed summary listings and recommended that device power could be increased by 100% for further investigations. Future trials will aim to further evaluate the safety and efficacy of RD-X19 at higher doses with a larger sample size and may examine other clinical outcomes of cardiopulmonary function in targeted patient populations.

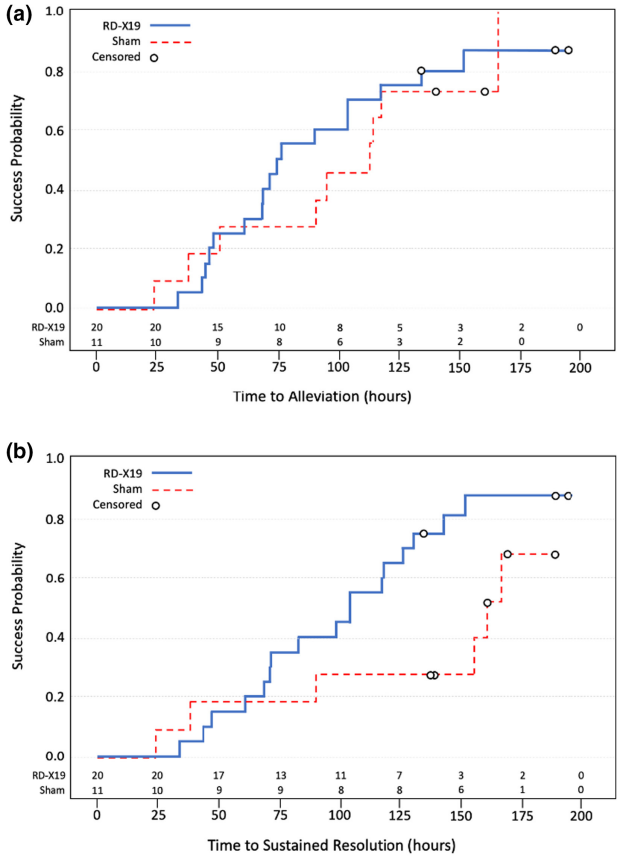

FIGURE 5 Kaplan-Meier time to event analyses of COVID-19 symptoms. (a) Kaplan-Meier time to alleviation of symptom analysis with success defined as the first instance subjects achieved symptom scores of all none (0) or mild (1) post baseline. Median time to resolution of symptoms was 75.3 and 112.7 for RD-X19 and sham treatment arms, respectively; a difference of ~ 1.5 days faster for RD-X19. (b) Kaplan-Meier time to sustained resolution of symptoms analysis with success defined as the first instance subjects achieved symptom scores of all none (0) or mild (1) post baseline, without rebound of any score greater than one for the remainder of the trial. Median time to resolution of symptoms was 103.8 and 160.7 for RD-X19 and sham treatment arms, respectively; a difference of more than 2 days faster for RD-X19. COVID-19, coronavirus disease 2019

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CONFLICT OF INTEREST

Stasko, Cockrell, Kocher, Emerson, Henson, McNeil report having/had employment relationships with EmitBio, Inc. (which may include equity-based compensation in either EmitBio, Inc. or ownership in parent company KnowBio, LLC). Stasko, Cockrell, Kocher, and Emerson report being coinventors of patents broadly relevant to the disclosed work. Wang, Henderson, Wood, and Bradrick report employment by entities that provided services to EmitBio for compensation. Smith reported consulting fees from EmitBio during the conduct of the study. Drs. Jones and Santander reported investigator fees from EmitBio during the conduct of the study. No other disclosures were reported.

AUTHOR CONTRIBUTIONS

Drs. Stasko and McNeil had full access to all of the data for the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Wrote Manuscript*: Stasko, McNeil; *Designed Research*: Stasko, Cockrell, Emerson, McNeil; *Performed Research/Data Acquisition*: Jones, Santander, Henderson, Wood, Bradrick, Kocher, Henson; *Data analysis and interpretation*: Wang, Smith, Stasko, Cockrell, Emerson, McNeil.

ROLE OF THE FUNDER/SPONSOR

EmitBio Inc. was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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