Respiratory application of a novel ultraviolet light delivery device for patients infected with COVID-19: A Pilot Study

NCT04572399
September 30, 2020

PRINCIPAL INVESTIGATOR:
George Chaux, MD

CO-INVESTIGATORS:
Peter Chen, MD
Michael Lewis, MD
Ruchi Mathur, MD
Gil Melmed, MD
Rekha Murthy, MD
Isabelle Pedraza, MD
Mark Pimentel, MD
Ali Rezaie, MD
Will Takakura, MD

STUDY COORDINATOR:
Gillian Barlow, PhD
Shane White

SPONSOR:
Aytu BioScience
373 Inverness Parkway
Suite 206
Englewood, CO 80112

Table of Contents

INVESTIGATOR'S AGREEMENT

This clinical trial shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP)
- Ethical principles that have their origins in the Declaration of Helsinki
- Food and Drug Administration (FDA) Code of Federal Regulation (CFR):
  - Title 21CFR Part 50 and 45 CFR Part 46, Protection of Human Patients
  - Title 21CFR Part 54, Financial Disclosure by Clinical Investigators
  - Title 21CFR Part 56, Institutional Review Boards
  - Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)

As the Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of PI responsibilities to conduct the clinical trial in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

I understand that my signature constitutes agreement and understanding of acceptance of the defined responsibilities of a Sponsor-Investigator as defined by the protocol, applicable FDA Regulations, and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor-Investigator. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol shall be implemented timely with my review and approval prior to implementation.

INVESTIGATOR'S AGREEMENT

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol.

I have read and understand the information in the Instructions for Use (and/or other such pertinent safety information) regarding the risks and potential benefits.

I agree to inform all those who assist/collaborate with me in the conduct of this study of their responsibilities and obligations.

Once the protocol has been reviewed and approved by the Institutional Review Board (IRB) I understand that any change(s) made during the course of the study must also (first) be approved by the IRB prior to implementation, except when such modification is made to remove any immediate hazard(s) to the subject(s).

I certify that I and the study staff responsible, have received the requisite training to conduct this research protocol.

I agree to maintain the confidentiality of all information received and/or developed in connection with this protocol.

_____

Print Name of Physician

_____ _____

Physician's Signature Date

1. BACKGROUND

1.1 Study Disease

Coronaviruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV).

Coronavirus disease (COVID-19) is a new strain that was discovered in 2019 and has not been previously identified in humans. COVID-19 is caused by infection from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus).

Common signs of infection include respiratory symptoms, fever, cough, shortness of breath and breathing difficulties. In more severe cases, infection can cause pneumonia, severe acute respiratory syndrome, kidney failure and even death. On March 11, the COVID-19 outbreak was characterized as a pandemic by the World Health Organization (WHO).[1]

1.2 Study Interventions

The Cedars Sinai UV Respiratory Tract Light Therapy Device consists of a light-emitting diode (LED) catheter intended to provide adjunctive therapy to hospitalized patients with COVID-19, including both ambulatory and intubated patients. The device consists of an array of twelve (12) Ultraviolet Light A (UVA) diodes in the 343 nm (±5 nm) spectrum that is intended to be inserted in standard endotracheal tubes of mechanically ventilated patients for 20 minutes every 24 hours for the reduction in bacterial and viral burden.

The UV Respiratory Tract Light Therapy Device consists of a UVA Light Catheter, Umbilical, and Control Unit. The System has been designed to be used in routine commercially available endotracheal and nasopharyngeal tubes. For endotracheal applications, the UVA Light Catheter will be attached to the Avanos(R) multiaccess port and maintained inside a sealed sheath when not in use.

The UVA Light Catheter sterilized by ethylene oxide [STERILE|EO] sterilization and intended for a single patient for the duration of treatment, and then should be disposed of per hospital policies. The UVA Light Catheter is a medical-grade fluorinated ethylene propylene (FEP) catheter tube that has the light UVA light array fixture mounted inside, which is inserted entirely inside the airway to deliver the light therapy. The UVA Light Catheter is marked with 1 cm markings to ensure that the device is inserted to the correct distance before the UV light is turned on. The UVA Light Catheter is connected to the Umbilical, which is a flexible power and air connector between the Light Catheter and Controller. The Umbilical may be cleaned, disinfected, and reused, with a useful life of up to twenty treatments. The Controller houses the user interface controls, and air compressor, and associated firmware. The Controller may be cleaned, disinfected, and reused, with a useful life of up to five years.

As the virus infects the cells on the surface of the airway, acute respiratory viral infection (mainly from SARS-CoV-2, the virus responsible for COVID-19) thought to enter via the nasal passages and pharynx makes its way down the trachea and upper airways. Eventually, the infection results in a cytokine storm affecting the lungs, and subsequent damage to alveoli and lung tissue results in the lethality seen in more severe flu viral infections, especially those fatalities among healthy young adults. In addition, bacteria and fungi can cause a secondary infection in mechanically ventilated patients.

1.3 Study Rationale

The Cedars Sinai UV Respiratory Tract Light Therapy Device is intended to eliminate microorganisms using UV-A light, thereby reducing the viral burden of SARS-CoV-2, and in intubated patients may also reduce the additional risk of ventilator-associated infections, including tracheobronchitis, pneumonia, sepsis, and death.

The Cedars Sinai UV Respiratory Tract Light Therapy Device is intended for salvage of ventilated patients in the ICU with COVID-19 to reduce viral load, reduce ventilator-associated pneumonia, and may reduce ventilator times, and reduce mortality. This is applied in addition to the best practice standard of care treatment for these patients who in some series may have a mortality rate in excess of 70%.

2. STUDY OBJECTIVE

To demonstrate basic safety and proof of principle for Endotracheal UV Light Device.

<u>Primary Endpoint:</u>
Reduction of viral load in upper airway in patients admitted to hospital positive for COVID-19.

<u>Secondary Endpoints:</u>

Overall reduction or change for the following endpoints:

- Bacterial load in upper airway
- Development of ventilated associated pneumonia (VAP)
- Days to extubation
- Days to Discharge
- Inflammatory marker changes
- Clinical Outcomes: death, hospitalized on ventilator or ECMO, hospitalized on non-invasive ventilation, hospitalized on supplemental O_2, hospitalized not on O_2, not hospitalized but with limitations, not hospitalized and no limitations.
- Sampling and microbiologic assessment of endotracheal tube tip from extubated patients

3. STUDY DESIGN

3.1 Accrual goal

Patients newly intubated (within 24 hours) on mechanical ventilation with COVID-19 who meet all other study inclusion criteria and none of the study exclusion criteria.

Target Total: 5 subjects

3.2 Duration of Study Participation

Subjects will be treated for up to 5 days and will be followed until day 30, discharge from hospital or death(whichever comes earlier);; adverse events will be captured throughout study.

Day 0: Enrollment, informed consent, baseline assessment, pre-insertion endotracheal sampling (within 24 hrs of enrollment), device deployment (within 24 hours of enrollment).

Day 1: endotracheal sampling (24h after initial device deployment); ongoing daily UV light treatment while mechanical ventilation is continued.

Days 2 – 4: endotracheal microbiologic assessment, daily UV light treatment while mechanical ventilation is continued (for total of up to 5 doses, day 0 through day 4)

Day 5 – endotracheal and catheter tip sampling

Days 5-30: Assessment of clinical status

4. STUDY ENTRY, ENROLLMENT AND WITHDRAWAL

4.1 Study Entry

For subjects prospectively enrolled, study entry, as used in this protocol, will be defined as a subject (or surrogate) signing informed consent. Study enrollment, as used in this protocol, will be defined as the investigator's confirmation of the subject's eligibility by signing an eligibility checklist. Each study participant, including participants who have screened failed, who sign an informed consent form, should be entered into the study database.

Hospital leadership is closely monitoring the COVID-19 cases and are in communication with investigators running COVID-19 trials. Treating physicians of COVID-19 patients will be made aware of the research offering.

If they have capacity to consent for themselves, treating physicians will ask patients if they are willing to be approached about research options. Researchers may approach potential subjects who indicate they are interested.

If patients do not have capacity to consent for themselves, treating physicians will work with researchers to identify an appropriate surrogate and connect researchers with surrogate decision makers to determine if a research option is appropriate for the patient.

Note: patients may be in isolation units. Therefore, this contact may be made over the phone into the patient's room with visualization from the treating physician and research from the window outside the room to minimize contact.

Research teams may also request to receive a daily list of COVID-19 patients in the hospital or may use Deep6 or reports requested by EIS to identify potentially eligible patients. The research staff can pre-screen the patients by reviewing the EHR and then approach the treating physician if the patient may be an appropriate study candidate.

Process of Informed Consent Considerations:

Given limited supplies of personal protective equipment and isolation requirements, consent may be provided over the phone and, when feasible, with direct visualization through the patient room window or using a video platform to minimize entry into the room. A picture of the consent form with patient signature may be utilized as documentation of informed consent. The signed consent in these circumstances will be photographed and saved electronically. The consenting physician and witness (when the patient is a non-English speaker) will sign a second full copy of the consent and print/attach the photographed patient's signature page.

Given isolation precaution for this population, potential subjects who have capacity to consent and who have access to a smartphone, tablet, or computer with them in their room may be provided a link to a digital version of the consent form using REDCap or DocuSign to avoid the use of paper, which cannot be removed from the containment unit. If the potential subject does not have access to a smartphone/online consent form, then a paper copy will be used. An electronic consent may also be sent by email to a surrogate off site.

While patients may be approached soon after their visit and/or admission begins, they can take time to consider and discuss participation with others before deciding. All questions will be answered by an investigator prior to signing the consent form.

For the enrollment of non-English speaking subjects, certified medical interpreters will be used with the short form consent. A certified medical interpreter will be present (over the phone) to translate the document and interpret the consent discussion following IRB policy. A witness to the consent process must sign the consent form and short form, but the witness does not need to be fluent in both languages. If the interpreter is unable to sign as witness, a chart note should document the identity and involvement of the interpreter.

As a last resort, if the potential subject has capacity to consent, but:

1. a potential subjects' room does not have a window for consent form visualization; thus a paper consent form cannot be used to document consent, AND
2. the potential subject could not use their own device (e.g., are not comfortable enough with the technology to use it for this purpose) and/or there was no other device available, thus an electronic signature or photograph of a hard copy signature cannot be obtained, then the consent process can follow that of subjects who have capacity to obtain consent but cannot physically sign the consent. This consent process is as follows: the consent discussion is over the phone with the consenting investigator, study team member if applicable, translator if applicable, and an independent witness (e.g., the clinical nurse). The witness will sign the consent form for two purposes: 1) to document translation was provided, if short forms were used to enroll a non-English speaker, and 2) to document the patient agreed to participate but could not physically sign the form. There should also be a chart note to describe the process and explain why the subject was physically unable to sign the consent form.

Considerations for the Enrollment of Individuals who Lack Capacity to Consent:

Related to the enrollment of cognitively impaired subjects through a surrogate informed consent process (CA law):
The research relates to life-threatening diseases and conditions of the participants and holds out the prospect of direct benefit. The consenting co-investigators (MDs) will determine the patient's capacity to provide consent. Subjects who lack capacity will be given the opportunity to dissent where appropriate. An individual who has Power of Attorney or who is otherwise authorized to make health care decisions for a potential research subject may not provide consent on behalf of the potential subject if the potential subject has the cognitive capacity to provide consent for themselves. The research will not enroll persons under psychiatric conservatorship or persons on a voluntary or involuntary psychiatric hold. The surrogates will not be paid for providing informed consent. If a subject should regain capacity during their participation, they will be informed of the nature of their participation and given the opportunity to consent to continue to participate in the research or refuse to continue to take part in the study. The study team will document the surrogate decision makers who are involved and available to provide informed consent for the subject, their relationship to the subject, and their respective decisions.

Surrogate Consent obtained remotely: REDCap or DocuSign may be used for remote consent of surrogate decision makers, as there are restrictions in place that preclude in-person visitors. The remote consent process may take place over the phone or via a video visit to allow the consent conversation and process, and signature may be obtained either through REDCap or DocuSign, or the surrogate may scan/email their signed copy for the investigator to either print and sign, or add an Adobe digital signature. If need be, the surrogate could fax their signature page instead of scanning/emailing.

Review the surrogate consent section in the consent process policy (starting on page 18 of the policy), including the decision tree for who can serve as surrogate decision maker per California

law in non-emergency and emergency settings (starting on page 20 of the policy). If a surrogate decision maker is not able to sign (e.g. spouse), then the study team can continue down the priority list of surrogate decision makers.

Note: In some instances a surrogate decision maker is able to provide verbal consent, but unable to use REDCap or other technology needed for the documented consent process to take place. Given the limitations to visitors and widespread nature of the risks of COVID-19, in these instances, obtain the surrogate's permission to contact another surrogate decision maker who will be able to provide the documented consent. Record a note in the research record of this consent conversation and the process used to subsequently obtain written/documented consent from a surrogate decision maker.

4.2 Enrollment Procedure

Completed and signed protocol-specific eligibility checklist;

All pages of the original signed informed consent forms (ICFs), including HIPAA Form B;
Relevant source documents or medical records such as: subject medical history and physical exam, admission or discharge notes, diagnostic reports, pathologic confirmation of diagnosis, and relevant subject-specific written communication.

Documentation from the Investigator that he/she has determined the subject meets eligibility criteria.

4.3 Cancellation Guidelines

The following are reasons for withdrawal of subjects from the study:

- A subject does not meet the eligibility criteria; (the subject will be considered a screen failure).
- A subject withdraws consent,

Regardless of reason for withdrawal, an intention to treat analysis will be performed.

5. PATIENT SELECTION / ELIGIBILITY CRITERIA

5.1 Inclusion (Eligibility) Criteria

1. Patients over 18 years of age
2. Confirmed positive test result for SARS-CoV-2
3. Mechanically ventilated

4. Endotracheal tube inner diameter at least 7.5 mm

5.2 Exclusion (Eligibility) Criteria

1. Unable to provide informed consent (or surrogate)
2. Enrolled in a therapeutic clinical trial for same condition that does not allow recruitment in other trials.
3. Pregnant women.

While not an exclusion criterion, special care should be exercised in treating patients who are receiving concomitant therapy (either topically or systemically) with known photosensitizing agents such as anthralin, coal tar or coal tar derivatives, griseofulvin, phenothiazines, nalidixic acid, fluoroquinolone antibiotics, halogenated salicylanilides (bacteriostatic soaps), sulfonamides, tetracyclines, thiazides and certain organic staining dyes such as methylene blue, toluidine blue, rose bengal, and methyl orange.

5.3 Study Population

5 confirmed positive subjects with SARS-CoV-2, of whom have been newly (within last 24 hours) intubated with an ETT size 7.5 or greater, on mechanical ventilation.

Target enrollment: 5

5.4 Setting

Subjects will be identified from those individuals whom have presented themselves to hospital/department of health/doctor's office as exhibiting signs and symptoms of COVID-19. If they meet the inclusion criteria , the subjects (or their surrogate) will receive an explanation of the study. Subject (or surrogate) will be informed both verbally and in written form of the study and procedures involved. The PI, co-investigators and/or the study coordinator will obtain a signed/dated Informed Consent Document (ICD) before enrolling each subject. Study data will be safely stored in a physical central file database, and additionally digitized onto a HIPAA secure server.

6. STUDY DESIGN, CLINICAL, AND LABORATORY EVALUATIONS

6.1 Study Design

The Ultraviolet (UV) Respiratory Tract Light Therapy Device is a novel delivery device for patients infected with COVID-19 whom have been mechanically intubated. The purpose of this

study is to demonstrated basic safety and proof of principle for the Endotracheal UV light device in reducing SARS-CoV-2 viral load.

6.1.1 Study Calendar

Subjects will be treated for up to 5 days and will be followed for 30 days, or until extubation or death (whichever comes earlier); adverse events will be captured throughout study.

Day 0: Enrollment, informed consent, baseline assessment, pre-insertion endotracheal sampling (within 24 hrs of enrollment), device deployment (within 24 hrs of enrollment)

Day 1: endotracheal sampling (24h after initial device deployment, primary endpoint); ongoing daily UV light treatment while mechanical ventilation is continued.

Days 2 – 4: endotracheal microbiologic assessment, daily UV light treatment while mechanical ventilation is continued

Day 5 – endotracheal and light catheter sampling

Days 5-30: Assessment of clinical status

6.2 Specimen Collection

- Aspirate collection
- Viral qPCR
- Bacterial load

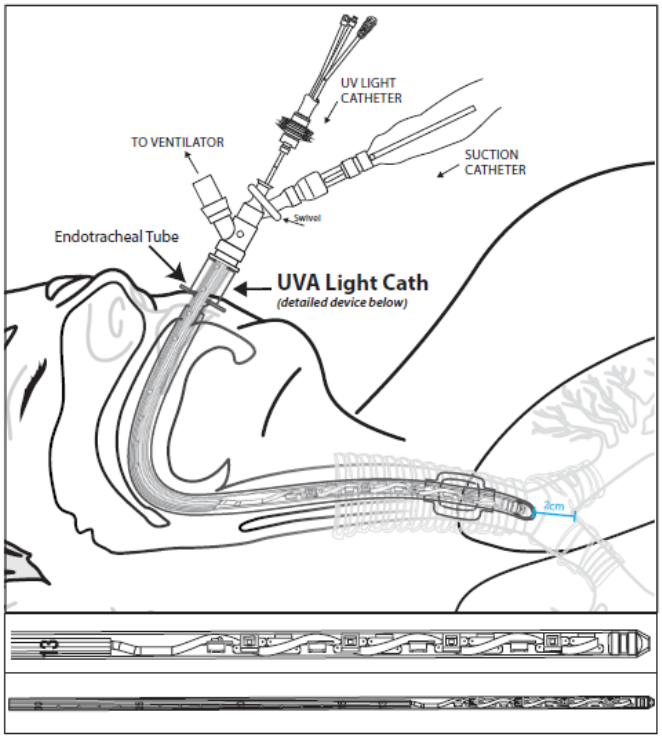
6.3 Ultraviolet (UV) Respiratory Tract Light Therapy Procedure

The UV Respiratory Tract Light Therapy Device should be used by physicians trained on the procedure for which the device is intended. The techniques and procedures described do not represent all medically acceptable protocols, nor are they intended as a substitute for the physician's experience and judgment in treating any specific patient. All available data, including the patient's signs and symptoms and other diagnostic test results, should be considered before determining a specific treatment plan.

Mechanically Ventilated Patients

1. Ensure bite block is inserted
2. Ensure that patient has ETT size 7.5mm or greater, attached to the Avanos(R) mutliaccess port
3. The device can be inserted with the patient in either the supine or the prone position

4. Ensure FIO2 is at 100% for at least 30 minutes prior to device deployment
5. Perform routine respiratory suctioning of the endotracheal tube to ensure no mucous plug inside the tube. Please refer to sampling protocol for tracheal sample retrieval.
6. The procedure needs to be performed in a manner that minimizes the likelihood of breaking the ventilatory circuit and exposing the circuit contents to ambient surroundings. The catheter will be enclosed in a plastic sleeve with a port that connects to the Y-port in the ventilatory circuit at or near the patient mouth.
7. One of the study investigators must be present during the time period that the catheter is inserted in ETT.
8. Inspect tubing and catheter device for damage.
9. By holding the tubing, advance the catheter device approximately 13cm into the ventilatory circuit and the endotracheal tube, towards the carina, until the catheter marking aligns with the endotracheal tube entrance.



10. Check the Controller for the green light to turn on, indicating that the Device catheter is sufficiently inserted into the airway.
11. Turn on the compressor and the UV light using the Controller. The 20-minute timer will begin automatically.
12. Upon completion of the 20-minute treatment, the timer will be at zero, and the light will automatically shut off. The catheter can be safely withdrawn from the endotracheal tube back into the plastic sleeve until reuse in 24 hrs.

6.3.1 Securement for Endotracheal Use

Ensure the catheter device is withdrawn into the plastic sleeve and is no longer in continuity with the ventilator circuit. Secure the catheter device/plastic sleeve and disconnect the controller.

6.3.2 Treatment Procedure

1. Once the UVA Light Catheter has been placed, and the position has been confirmed, connect the umbilical to the LED Control Panel.
2. Turn on the compressor.
3. Turn ON the Power switch. The Green Power Indicator will be illuminated. The timer will indicate 20 minutes.
4. Push the Blue START Button to light up the LED array and to start the treatment.
5. After treatment, the LED light array will automatically shut off.
6. Removal of the UVA Light Catheter
7. When therapy is complete, unplug the connection to the Control Unit.
8. Turn off compressor
9. Carefully grasp catheter hub and remove slowly with a constant steady pull into the polypropylene sleeve.
10. Inspect catheter to ensure complete removal.
11. Place catheter near the patient for use in the next 24-hour treatment.

6.3.3 Monitoring patient during the UV treatment and termination criteria

Subjects will be monitored closely by the study investigator during the treatment. This includes close monitoring of O2 saturation, minute ventilation,PEEP,peek inspirator pressure, pulse rate, blood pressure every 5 minutes. A procedure report will be prepared. Procedure will be terminated if oxygen saturation drops below 88% or clinical instability as per investigators discretion.

6.3.4 Disinfecting the UV Respiratory Tract Light Therapy Device Control Unit and Umbilical

1. Use a clean wipe with an intermediate sanitizing solution (e.g., isopropyl alcohol or CaviWipes towelette) to disinfect the control unit and umblical surface, ensuring to wet the surface thoroughly.
2. Repeated use of another towelette may be required to ensure that the surface remains visibly wet for three minutes at room temperature (69°F/20°C). This will confirm viricidal activity and effectiveness against HIV-1, HBV and HCV applications, and effectiveness against *Clostridium difficile* (vegetative cells only), Methicillin-Resistant *Staphylococcus aureus* (MRSA), Vancomycin-Resistant *Enterococcus faecalis* (VRE)

and *Staphylococcus aureus* with reduced susceptibility to vancomycin, and tuberculocidal activity and effectiveness against *Staphylococcus aureus*, and *Pseudomonas aeruginosa*.

3. Do not reuse towelette. Dispose of used towelette in accordance with Federal, State, and local regulations for infectious materials disposal.
4. Cleaning materials used that may contain blood, or other body fluids should be autoclaved and disposed of in accordance with Federal, State, and local regulations for infectious materials disposal.
5. Place a large equipment bag on the controller and the umbilical.

6.4 Treatment Schedule

Subjects will be treated for up to 5 days and will be followed for 30 days, or until discharge from hospital or death (whichever comes earlier); adverse events will be captured throughout study.

Day 0: enrollment, informed consent, baseline assessment, pre-insertion endotracheal assessment (within 24 hrs of enrollment), device deployment (within 24 hrs of enrollment)

Day 1: endotracheal microbiologic assessment (24h after initial device deployment, primary endpoint); ongoing daily UV light treatment while mechanical ventilation is continued.

Days 2 – 4: endotracheal microbiologic assessment, daily UV light treatment while mechanical ventilation is continued

Day 5: Endotracheal and light catheter sampling

Days 5-30: Assessment of clinical status

6.5 Results Documentation

- Viral qPCR Results
- Bacterial assessment/load
- Days until extubation
- Days to discharge
- Inflammatory markers
- Clinical Outcomes: death, hospitalized on ventilator or ECMO, hospitalized on noninvasive ventilation, hospitalized on supplemental O2, hospitalized not on O2, not hospitalized but with limitations, not hospitalized and no limitations
- Microbiologic assessment of endotracheal tube tip from extubated patients

7. ADVERSE EVENTS

7.1 Possible Risk Associated with the Device (i.e. Treatment Emergent Adverse Eevent)

- Heat/thermal injury to nasal passages/pharynx (nasopharyngeal insertion) or trachea/vocal cords (endotracheal insertion)
    - This risk is mitigated by cooling the LEDs within the device via the chilled and compressed air pumped through the device during deployment. In addition, a thermistor will automatically shut off the device if the temperature of the device exceeds 43 degrees C.
- Decreased ventilation/oxygenation due to partial airway occlusion in mechanically ventilated patients
    - This risk is mitigated through experimental determination that airway pressures and tidal volumes are not affected when the device is deployed in an ETT size 7.5mm or greater. Therefore, patients with ETT sizes smaller than 7.5mm are excluded.
- Trauma to the carina (due to over-insertion in mechanically ventilated patients)
    - This risk is mitigated by alignment of external cm markings on the device, intended to be inserted until the cm markings of the device align with markings of the ETT.
- Allergic reaction to device materials
    - With proper use of the device, there is no physical contact between the device and the patient as the device is inserted within the ETT and never makes contact with external or internal airways.

7.2 Expected Adverse Events

Expected Adverse Events with this test procedure are unknown.

7.3 Serious Adverse Events

Serious injury or death

Any adverse event and eventual complication must be recorded at any time during the treatments and the follow up visits, and throughout the entire study duration. Patients will be instructed to alert the study investigator by telephone of any side effects occurring in the period after the treatment and until the study end.

For Reporting of adverse events see section 8.

8. DATA AND SAFETY MONITORING PLAN

The study will be monitored by an independent data safety monitoring board. This board will be comprised of a pulmonologist/intensivist, clinical trial specialist, and biostatistician. The members will not be faculty or staff at CSMC. The DSMB will meet to review the safety and outcomes of the 5 patients, and no further study of the device will be conducted until the DSMB has concluded its review. The DSMB will convey any safety concerns to the investigators and the sponsor.

During the study, the investigators will conduct continuous reviews of the data and subject safety, keeping track of the number of subjects, significant toxicities in accordance with the protocol and observed responses. All grade 3-5 adverse events (CTCAE v4.0) will be entered into study database and reviewed at research committee meetings. In addition, all adverse reactions considered "serious" will be entered into research database and reviewed by the monitor on an ongoing basis. All adverse events will also be reported to 1-855-AYTU-BIO (1-855-298-8246). Additionally, all serious events will also be reported to the supervising IRB in the same timely manner.

9. STATISTICAL CONSIDERATIONS

9.1 Primary Study Endpoints

The primary objectives of the study are to evaluate the effectiveness and saftey of UV Light treatment on hospitalized patients with COVID-19.

Primary endpoint:

1- Change in viral load from the ETT aspirate on day 0 to the last day of treatment.

9.2 Secondary Study Endpoints

- Bacterial load in upper airway
- Development of ventilated associated pneumonia (VAP)
- Days to extubation
- Days to Discharge
- Inflammatory marker changes
- Clinical Outcomes: death, hospitalized on ventilator or ECMO, hospitalized on non-invasive ventilation, hospitalized on supplemental O_2, hospitalized not on O_2, not hospitalized but with limitations, not hospitalized and no limitations.
- Sampling and microbiologic assessment of endotracheal tube tip from extubated patients

9.3 Exploratory endpoints

- Change in inflammatory and COVID-prognosticating markers day 0-7 (for those drawn for clinical care)
    - Ferrtin
    - Interleukin-6

    - CRP
    - White blood cells
    - Procalcitonin
    - Lymphocyte count
    - D-dimer
    - CPK
    - Troponin
- Percentage of Covid-related complications after treatment
    - Deep vein thrombosis
    - Pulmonary embolus
    - Cardiac event
    - cerebrovascular event
    - Renal failure
    - Increased liver enzymes

9.4 Sample size, accrual and study duration

TOTAL SAMPLE SIZE: 5
TOTAL ACCURAL: 5
STUDY DURATION: 4 weeks

We are conducting a first-in-human open-label pilot study of the safety and effectiveness of Endotracheal UV light in patients with COVID19. Given that this is a pilot study, it is not powered to any specific endpoint.

9.5 Statistical Analysis

Demographic and baseline characteristics will be summarized for all the subjects. Demographics and baseline characteristics include: age, gender, race, ethnicity, height, weight, and body mass index (BMI).

- Height (in cm)=height (in inches)*2.54
- Weight (in kg) = weight (in lbs)*0.4536
- BMI = weight/height^2 (Kg/m^2)

Both primary and secondary endpoints will be presented using descriptive statistics. For continuous variables, descriptive statistics will include the number of subjects with data to be summarized (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). The same number of decimal places as in the raw data will be presented when reporting min and max, one more decimal place than in the raw data will be presented when reporting mean and median, and two more decimal places than in the raw data will be presented when reporting SD.

If the raw data have three decimals or more, three decimals will be presented for mean, median, min and max, and SD.

All the categorical data will be presented by counts and percentages. The denominator for each percentage will be the number of subjects within the population treatment group unless otherwise specified. All percentage will be presented with one decimal point.

All analyses and summary outputs will be generated using SAS version 9.3.

10.INVESTIGATORS RESPONSIBILITIES

10.1 Investigator Responsibility/Performance

The investigator (or a person designated by the investigator) should inform the patient (or surrogate) of all pertinent aspects of the study, including the written information.

The investigator should provide the patient ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the patient (or surrogate). Neither the investigator, nor the study staff, should coerce or unduly influence a patient to participate or to continue to participate in a study.

10.2 Confidentiality

The identity of the patients in this study will be treated as confidential. Patients eligible to participate in the study following the pre-treatment visit will be assigned a unique patient code. The results of the study, including any other data, may be published for scientific purposes but will not give the patients' name or include any identifiable references to them.

However, any records or data obtained as a result of the patient participation in this study may be inspected by the sponsor, by any relevant governmental agency, by the Hospital Ethics Committee, or by the persons conducting this study, provided that such inspectors are legally obligated to protect any identifiable information from public disclosure, except where disclosure is otherwise required by law or a court of competent jurisdiction. These records will be kept private in so far as permitted by law.

10.3 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator to obtain written informed consent from each subject (or surrogate) participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to

study participation, each subject (or surrogate) will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate).

The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

10.4 Source Documentation and Investigator Files

The investigator will maintain adequate and accurate records to document the conduct of the study and to ensure that study data can be subsequently verified. These documents will be classified into two separate categories: (1) investigator study file and (2) subject clinical source documents that corroborate data collected on the CRF's. Subject clinical source documents would include hospital/clinic patient records; physician's and nurse's notes; original laboratory, radiology, pathology, and special assessment reports; QOL forms, signed informed consent forms. When the CRF or any form is used as the source document, this will be clearly stated in the investigator study file.

At a minimum, the following be documented in source documents:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify protocol entry criteria.
- Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed notes on the day of entry into the study)
- Progress notes for each subject visit.
- Laboratory test results.
- Condition and response of subject upon completion of or early termination from the study.

10.5 Recording and Processing of Data

Physical CRFs will be utilized at first and will be stored in a secure location at each investigation site. Additionally, physical CRFs will be digitized, and sent to the sponsor's HIPAA compliant server for analysis and long-term storage. A CRF is required for every patient who received any study intervention. The investigator will ensure that the CRF's are accurate, complete, legible and timely. Separate source records are required to support all CRF entries. All corrections to study data will be made by drawing a single line through the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary. **Do not use "white-out" or obscuring correction tape.**

10.6 Non-Protocol Research

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

10.7 Ethics

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics.

10.8 Essential Documents for the conduct of clinical trial

Essential documents are those documents with individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

The following documents will be on file:

- CV's and license of all investigators.
- IRB documentation/correspondence.
- Documentation of IRB certification.

11.REFERENCES

1. CDC Website. https://www.cdc.gov/coronavirus/2019-ncov/index.html