A Phase 2 Trial to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Intravenous USB002 to Treat Patients with Respiratory Distress due to COVID-19 Infection

Protocol Identifying Number: USB002-2020-001

IND Sponsor: US Biotest, Inc.

Version Number: 6.0

17 February 2022

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LIST OF ABBREVIATIONS

A(1-7)	Angiotensin 1-7
A-II	Angiotensin-II
ABG	Arterial blood gas
ACE	Angiotensin-converting Enzyme
ACE2	Angiotensin-converting Enzyme 2
AE	Adverse event
ALT	Alanine aminotransferase
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AT1R	Angiotensin II receptor type 1
AUC	Area under the curve
BiPap	Bilevel positive airway pressure
BP	Blood pressure
C	Celsius
C_{max}	Maximum concentration
CK	Creatinine kinase
CPAP	Continuous positive airway pressure
CO_2	Carbon dioxide
COVID-19	Coronavirus disease - 2019
C-RP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic Data Capture
EPO	Erythropoietin
FDA	Food and Drug Administration
FiO2	Fraction of inspired oxygen
HR	Heart rate

ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit
ICMJE	International Committee of Medical Journal Editors
ISF	Investigator Site File
IWRS	Interactive Web Response System
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LDH	Lactate dehydrogenase
µg	Microgram
MedDRA	Medical Dictionary of Drug Regulatory Activities
mg	Milligrams
mL	Milliliter
MM	Medical Monitor
mm	Millimeters
mM	Millimolar
mmHg	Millimeters of mercury
MTD	Maximum tolerated dose
MV	Mechanical ventilation
NCI	National Cancer Institute
NDA	New Drug Application
NO	Nitric oxide
NOAEL	No-observed adverse effect level
OA	Oleic acid
OSCI	Ordinal Scale for Clinical Improvement
PaO_2	Arterial partial pressure of oxygen
PBW	Predicted body weight
PEEP	Positive end expiratory pressure
pH	Hydrogen ion concentration

PI	Primary Investigator
PK	Pharmacokinetics
QTc	QT interval corrected for heart rate
QTcB	Correction of QT values using Bazett's Formula
QTcF	Correction of QT values using Fredericia's Formula
RAS	Renin angiotensin system
RBC	Red blood cell
RR	Breaths per Minute
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SBT	Spontaneous breathing trial
SC	Subcutaneous
S-D	Sprague-dawley rats
SHR	Spontaneously hypertensive
SMP	Safety Management Plan
SOB	Shortness of breath
SOC	Standard of care (system organ class also SOC)
SpO_2	Peripheral capillary oxygen saturation
TEAE	Treatment-emergent adverse event
TG+	Renin transgenic
TTP	Time to progression
Vt	Tidal volume
USP	United States Pharmacopeia
WBC	White blood cell
WCG IRB	Western IRB/Copernicus Group
WHO	World Health Organization

SPONSOR SIGNATURE PAGE

Protocol Title:	A Phase 2 Trial to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Intravenous USB002 to Treat Patients with Respiratory Distress due to COVID-19 Infection
Protocol Number:	USB002-2020-001
Version Number:	6.0
Date:	17 February 2022
IND Number:	151166
Investigational Product:	USB002
Sponsor:	US Biotest, Inc. 231 Bonetti Dr., Suite 240 San Luis Obispo, CA 93401-7310 805-595-1300

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Signature of Sponsor's Representative

Mar 8, 2022

Date

INVESTIGATOR SIGNATURE PAGE

I have read the attached protocol and agree to comply with the contents of this document.

I agree to comply with applicable FDA regulations and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

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The signature of the Principal Investigator below constitutes agreement.

Principal Investigator: _____

Institution Address: _____

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Signature of Principal Investigator Date

PROTOCOL SYNOPSIS

Title:	A Phase 2 Trial to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Intravenous USB002 to Treat Patients with Respiratory Distress due to COVID-19 Infection
Sponsor:	US Biotest, Inc.
Study number:	USB002-2020-001
Phase:	Phase 2
Study objectives:	Parts 1 and Part 2: • To determine the safety and tolerability of USB002 in treatment of respiratory distress from coronavirus disease – 2019 (COVID-19) infection; • To identify an early efficacy signal of USB002. Part 1: • To determine the maximum tolerated dose (MTD) of USB002 (up to 900 ug/kg/day). Part 2: • To determine preliminary efficacy of the USB002 MTD following up to 14 days of continuous infusion.
Study Endpoints:	Safety of USB002 will be evaluated by: The rate of occurrence and severity of Adverse Events (AEs) resulting from clinical changes (Day/Visit 1 to Day 28): • Cardiovascular parameters, to include blood pressure (BP), heart rate (HR), 12-lead electrocardiogram (ECG), and requirements for inotropes and vasopressors; • Laboratory parameters, to include kidney and liver function. Preliminary efficacy of USB002 will be determined from start of treatment (Day/Visit 1) by time to peripheral capillary oxygen saturation (SpO_2) $\geq$ 94% on room air, sustained for at least 48 hours, through Day 28. Additional preliminary efficacy assessments include the following, from start of treatment (Day/Visit 1) through Day 28:

	• All-cause mortality at 60 days; • Number of ventilator-free days; • Number and proportion of subjects progressing from non-invasive to mechanical ventilation; • Time of progression from non-invasive to mechanical ventilation; • Proportion of subjects weaned from mechanical ventilation; • Number of days of vasoactive agent usage; • Time (days) to hospital discharge; • Changes in clinical status, as defined by the 7-point ordinal scale.
Study design:	This randomized, double-blinded, placebo-controlled study will be conducted in two parts: Part 1 will escalate through four sequential doses of USB002 to determine the MTD. Part 2 will determine preliminary efficacy of the USB002 MTD dose identified in Part 1. In Part 1, subjects will be randomized to receive Standard of Care (SOC) plus USB002 in up to 4 escalating doses (n=3) or SOC plus placebo (n=3) via continuous intravenous (IV) infusion, for up to 96 hours. Dose escalation, assessment of progress and safety will be determined by a Data Safety Monitoring Board (DSMB) after review of the 96-hour clinical data. If toxicity is identified [evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 criteria] at the lowest cohort level (90 ug/kg/day), DSMB may determine to de-escalate or halt the study. Escalation will continue until Part 1 enrollment is completed and the MTD is determined. In Part 2, subjects will be randomized 1:1 to receive either SOC plus USB002 at the MTD established in Part 1 or SOC plus placebo infusion for up to 14-days. For both Groups, when infusion is stopped/completed, whether prior to 96 hours, at the end of infusion (96 hours in Part 1, Day 14 in Part 2), or earlier, there will be a 24-hour observation period. If a subject stops treatment for any reason after the Visit 1 infusion begins, all attempts will be made to conduct the End of Treatment (Visit 5 in Part 1 and Day 16 in

	Part 2) procedures (See Tables 2 and 3). End of Treatment (Visit 5 or Day 16) procedures may be conducted during the 24-hour observation period. Infusion of USB002/placebo will be discontinued at any time if SpO_2 is $\geq$ 94%, sustained for at least 48 hours, on room air. Visits will continue up to Day 28, if subject is still hospitalized. The Day 28 and Day 60 follow-up visits will be conducted by phone (Telemed) if discharged.
Population:	• 18 years of age or older; shortness of breath (SOB) and respiratory distress requiring oxygen due to COVID-19 infection; • Up to 10 sites in the United States.
Sample size:	Part 1, up to 48 subjects. Part 2, 30 subjects.

1. BACKGROUND INFORMATION

1.1. Investigational Product: USB002

USB002 is pharmaceutically formulated Angiotensin 1-7 [A(1-7)], a non-hypertensive derivative of Angiotensin-II (A-II) and is suspended in a vehicle as a sterile solution of USB002 (22.5 mg/ml) which is stable at room temperature for 90 days.

1.2. Nonclinical Experience with A(1-7)

The proposed treatment of patients with COVID-19-induced respiratory distress with USB002 is supported by animal models of Acute Respiratory Distress Syndrome (ARDS) (ventilator, oleic acid [OA] and sepsis induced), pulmonary hypertension, and fibrosis (Fleming 2005, Ishiyama 2004, Donoghue 2003, Imai 2005, Shenoy 2010, Walther 2011, Yamazato 2009, Zambelli 2015), which demonstrated that an imbalance between the angiotensin converting enzyme (ACE)/Ang-II/angiotensin II type 1 and the angiotensin converting enzyme 2 (ACE2)/Ang-(1–7)/Mas axis of the renin-angiotensin system (RAS) occurs in animals with lung disease.

Imai et al. (2005) showed that ACE2, which converts A-II to A(1-7) by cleavage of one amino acid, protects mice from ARDS induced by acid aspiration or sepsis. Shenoy et al. (2010) in rats showed positive effects in a pulmonary fibrosis model using lentiviral packaged A(1-7)-fusion genes or ACE2 cDNA. Overexpression of A(1-7) significantly prevented the associated negative effects of pulmonary fibrosis. Blockade of the Mas receptor abolished the beneficial effects of A(1-7), confirming the role of the Mas receptor and A(1-7) in protection of the lung. A(1-7) protects against ventilator induced ARDS in mice. A(1-7) attenuated the development of ARDS, as demonstrated by a normalization of the lung wet-to-dry weight ratio and a significant improvement in PaO_2. A(1-7) also protects against OA-induced acute lung injury/ARDS in Sprague-Dawley rats as shown by changes in lung wet-to-dry weight ratio and reduced pulmonary vascular resistance (Yamazato 2009). Importantly, A(1-7) infusion was shown to improve pulmonary function, including prolonged improvement in oxygenation, reduction in inflammatory cells recruitment and reduction in lung fibrosis long term in an animal model of ARDS involving two insults, acid instillation and prolonged injurious ventilation. A(1-7) was effective even after delayed administration (Zambelli 2015).

1.3. Clinical Experience with USB002

The safety of USB002 has been demonstrated in seven clinical trials whose indications include breast cancer and chronic kidney disease. USB002 has also been studied in healthy volunteers. To date, 107 subjects have been treated with USB002 (referred to in studies as TXA127). Doses administered ranged from 2.5 µg/kg/day to 300 µg/kg/day administered as a subcutaneous (SC) dose for up to 28 days. USB002 has been well tolerated with no drug-related serious adverse events (SAEs) noted. A Phase 1/2 randomized, double-blinded, placebo-controlled study of intravenous (IV) USB002 given alone and with erythropoietin (EPO) was conducted in subjects with anemia associated

with end-stage renal disease. The trial had two arms: EPO plus USB002 at one of three (10, 25, or 50 µg/kg) IV doses, and EPO plus placebo three times weekly, administered following each hemodialysis session. No dose limiting toxicity (DLT) was observed in any dosing group. There were no differences between USB002 and EPO in adverse events (AEs) by body system.

1.4. Known and Potential Risks and Benefits to Human Subjects

A favorable safety profile has been demonstrated with USB002 in preclinical toxicology studies. Single-dose and repeat-dose (4-week) toxicity studies were conducted in rats and dogs utilizing IV USB002 administration. The daily parenteral administration of USB002 to rats and dogs for one month at doses up to 1000 µg/kg/day did not affect clinical condition, body weight, or food intake. No changes in hematology parameters, serum chemistry values, or urinalysis were noted. In addition, there were no treatment-related histopathologic changes in any of the tissues or organs examined. Thus, the maximum no-observed adverse effect level (NOAEL) in rats and dogs following repeat-dosing was 1000 µg/kg/day. An acute IV study evaluated five male and five female mice that were injected with 100 mg/kg USB002. Clinical observations were recorded for 14 days. No treatment-related changes in clinical condition occurred. An acute IV irritation study was performed in 5 groups of three female rats each. The USB002 dose levels were 0.01, 0.1, 1.0, 10, and 100 mg/kg. A concurrent control group of three female rats received placebo. There were no deaths or gross necropsy findings, and no test article-related changes in body weight or clinical findings. An IV one-month study was conducted in rats (Crl:CD(SD)BR VAF/Plus) administered placebo or USB002 by slow bolus injection into a tail vein once daily for 4 weeks at doses of 0 (placebo), 0.01, 0.1, or 1.0 mg/kg. No test article-related effects were found for any toxicological parameter at any dose level. An IV one-month study of USB002 was conducted in beagle dogs by slow bolus IV injection once daily for 4 weeks at doses of 0 (placebo), 0.01, 0.1, or 1.0 mg/kg. No test article-related effects were found for any toxicological parameter at any dose level.

1.4.1. Potential Benefits to Human Subjects

The RAS can be thought of as a hormonal system with 2 axes – the ACE/Ang-II/angiotensin II receptor type 1 (AT_1R) axis (pathological arm) and the counter-regulatory ACE2/A(1-7)/Mas receptor axis (protective arm). The ACE/Ang-II/AT_1R axis has now been implicated in the pathophysiology of the cardiovascular, renal, pulmonary, and central nervous systems (Nehme 2019). *In vivo*, Mas acts as a functional antagonist of the AT_1R, thereby inhibiting these actions of Ang-II (Kostenis 2005). A(1-7) is the endogenous ligand of the Mas receptor and a member of the protective RAS.

COVID-19, like severe acute respiratory syndrome (SARS), binds to the cell surface protein receptor, ACE2, a member of the ACE2/A(1-7)/Mas axis. SARS pathology emerges, in part, due to the reduced ability of ACE2 to cleave A-II, a pro-inflammatory, fibrotic peptide, to A(1-7) (Zhou 2020). Ang-II is a potent vasoconstrictor that can increase lung injury and lung edema (Flemming 2005). A(1-7) counteracts the effects of Ang-II and mobilizes endogenous regenerative processes. Patients in intensive care for ARDS that

do not survive have reduced levels of A(1-7) compared to those that do survive. IV treatment with A(1-7) would not only reduce inflammation and oxidative stress but rebalance the RAS.

In a recent study of intensive care unit (ICU) patients with ARDS, increased serum levels of A(1-10) and reduced serum levels of A(1-7) at the time of admission in patients with this degree of dysregulation of angiotensin peptide metabolism did not survive, despite aggressive ventilator-assisted pulmonary therapy (Reddy 2019). Further, a recent publication showed that circulating Ang-II levels increased with increased COVID 19 viral load and reduced PaO_2/FiO_2 levels (Lui 2020). In SARS-infected animals, increased levels of Ang-II were observed due to reduced ACE2 activity. In this study ACE2 cleaves Ang-II to A(1-7), thereby reducing the pathological activities of Ang-II and increasing the protective arm of the RAS through the ACE2/A(1-7)/Mas axis (Imai 2008).

In a bacterial model of pneumonia, treatment with A(1-7) reduced lung congestion 24 hours after infection (Soto 2020). Finally, in an unpublished study of bone marrow transplant following lethal irradiation, mice began to die due to an unplanned norovirus infection at day 3 after transplant. In mice that received donor cells from the saline treated animals and saline treatment after transplant, there was only 20% survival. In A(1-7) treated mice (both donor and recipient), there was 100% survival. This data show that A(1-7) not only improved sequelae secondary to infection but also prevented multiple organ system failure and death.

1.4.2. Rationale for Clinical Trial

COVID-19 may lead to respiratory distress which progresses from shortness of breath (SOB) requiring hospitalization and supplemental oxygen by nasal cannula, high flow oxygen delivered by a mask with <15 liters/minute of oxygen, bilevel positive airway pressure (BiPAP) with a mask that delivers high pressure 100% oxygen at 5 mmHg peak inspiratory pressure, and ultimately to intubation and assisted ventilation with a respirator. With an increasing number of hospitalized COVID-19 cases in the United States since January of 2020, COVID-19 presents an acute and urgent threat to global health security. Therapeutic interventions capable of reducing pulmonary distress would reduce the fatality rate, improve long-term outcomes, and free up scarce ICU resources.

Respiratory distress in untreated COVID-19 infected patients presents as a progressive continuum from SOB to cardiopulmonary collapse and death. It is diagnosed in symptomatic patients with bilateral lung infiltrates with confirmed positive tests for COVID-19. Without supportive therapy, pulmonary distress rapidly progresses to hospitalization where supplemental oxygen can be given by nasal cannula, high-flow mask, BiPAP mask, and eventually intubation and assisted ventilation. Overall, the physiological damage to cells and structures of the lung can begin within hours of exposure and progress within days (Fahy 2012). The pathologic hallmarks of COVID-19-induced pulmonary distress include neutrophilic alveolitis, hyaline membrane disease secondary to protein transudation and precipitation in the airspace, microthrombi secondary to the generation of procoagulant mediators as well as endothelial and epithelial injury. For these reasons,

there is considerable interest in the use of a A(1-7) to treat patients who have developed respiratory distress from COVID-19 infection (Soto 2020, Piero 2020, NCT 04332666).

1.5. Rationale for Dose Selection

Sponsor US Biotest, Inc. was given permission to proceed with a clinical trial of USB002 (referred to as TXA127) to treat subjects with sepsis-induced ARDS under IND 110550. The study was closed with no enrollment. The doses of USB002 and treatment durations in Parts 1 and 2 of this protocol are the same as those approved by the U.S. Food and Drug Administration (FDA) to treat sepsis induced ARDS.

IV single and repeat-dose (4-week) toxicity studies were conducted in rats, mice, and dogs. The NOAEL in rats and dogs following repeat dosing was 1000 µg/kg/d or higher. Much higher doses of up to 100 mg/kg (100,000 µg/kg) of A(1-7) in mice, produced only reduced body weight gain.

The pharmacokinetics (PK) of 250 µg/kg A(1-7) explored in normal Sprague-Dawley (S-D) spontaneously hypertensive (SHR), and renin transgenic (TG+) rats (Yamada 1998) demonstrated different kinetics depending on the model used. The reported half-life was approximately 10 seconds. Plasma A(1-7) clearance was significantly reduced (39-60%) in the SHR and TG+ rats compared to S-D rats. After four weeks of dosing, the area under the curve (AUC) increased 6-fold and the maximum concentration (C_{max}) increased 10-fold.

In the dog, SC administration of 10 mg/kg/day resulted in a half-life of 30.86 ± 12.59 minutes on Day 0, and a 15% reduction to 27.7 ± 4.02 minutes by Day 28. The AUC and C_{max} decreased by similar amounts.

Preliminary PK data on single doses of SC USB002 at 100 µg/kg body weight are available for 15 breast cancer patients. The mean baseline concentration of A(1-7) was 20.7 pg/mL (range: 6.3-84.5 pg/mL). The mean and standard deviation (SD) of total body weight (used as the dosing weight in this study) were 75.8 and 13.6 kg, respectively, with a range between 55.4 and 301.2 kg. The highest concentration of A(1-7) was observed in the 0.5-hour sample, with an average value (corrected for baseline level) of 1,577 pg/mL (range: 260 - 5086 pg/mL). By 3-6 hours post-dosing, plasma A(1-7) concentrations were at or below baseline levels. The C_{max} and area under the curve for 0-3 hours (AUC^{0-3}) (both corrected for baseline measurements) correlated with dose, but there was variability among patients. Assuming linear kinetics and that 5 half-lives are required to return A(1-7) to baseline, the return to baseline within 3-6 hours would suggest an average half-life of about one hour.

From the above, the initial dose will be $1/10^{th}$ the NOAEL in rats and dogs, and $1/1000^{th}$ the maximum dose administered to mice, *i.e.*, 90 µg/kg/day.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Study Objectives and Endpoints

The objectives of the study are twofold:

- To determine the safety and tolerability of USB002 in treatment of respiratory distress from COVID-19 infection; and
- To identify an early efficacy signal of USB002.

2.1.1 Primary Objectives and Endpoints

The primary objectives of safety and tolerability of USB002 will be evaluated for rate of occurrence and severity of AEs resulting from clinical changes (Visit 1/Day 1 to Day 28): cardiovascular parameters, to include blood pressure (BP), heart rate (HR), 12-lead electrocardiogram (ECG), and requirements for inotropes and vasopressors; laboratory parameters, to include kidney and liver function.

The primary endpoint of preliminary efficacy will be demonstrating the difference between USB002 and placebo groups in time to peripheral capillary oxygen saturation (SpO_2) $\geq$ 94%, sustained for at least 48 hours, on room air through Day 28.

2.1.2 Secondary Objectives and Endpoints

Secondary objectives and endpoints will be assessed from time of start of USB002 or placebo infusion (Visit 1/Day 1) to Day 28.

Secondary endpoints include:

- All-cause mortality at Day 60.
- Number of ventilator-free days (defined as the number of days between Visit 1/Day 1 and Day 28 that subjects are both alive and free of mechanical ventilation [MV]; freedom from MV is further defined as free from MV for at least 48 hours after extubation).
    - In the case of repeated MV, duration of MV will be summed for the purposes of calculation. In the case of tracheostomy, the same criteria apply.
- Proportion of subjects weaned from mechanical ventilation through Day 28 (defined as free from MV for at least 48 hours after extubation. In the case of tracheostomy, the same criteria will apply). This applies only to subjects on mechanical ventilation at baseline.
- Proportion of subjects progressing from non-invasive (at baseline) to mechanical ventilation. This applies only to subjects not on mechanical ventilation at baseline.
- Time to progression (TTP) from non-invasive to mechanical ventilation.

  - In the case of repeat admission to hospital and/or ICU within the first 28-days, the time from first treatment with study medication will be used to calculate TTP to MV;
- Number of days of vasoactive agent usage (defined as use of a vasoactive agent for 6 hours or more within any 24-hour period);
- Time (days) to hospital discharge;
- Changes in Ordinal Scale for Clinical Improvement (OSCI) status (see Appendix 1) from Visit 1/Day 1 to Day 28, defined as 1) time to change and 2) proportions of subjects, with 1-point and 2-point clinical status changes utilizing a time-to-event analysis from time of start of infusion (Visit 1/Day 1) of study medication to Day 28 for the time to change analysis between active and placebo groups.

2.1.3. Exploratory Endpoints

For any subject that is taken off assisted ventilation and study treatment is terminated earlier than planned (96 hours in Part 1 and Day 14 in Part 2), the re-initiation of assisted ventilation will be assessed as an exploratory endpoint. In the event of re-initiation of assisted ventilation, subjects who continued receiving USB002/placebo infusion will be assessed separately to those who discontinued treatment.

3. STUDY DESIGN

The study is designed as a randomized double-blind study. All staff at the site will be blinded to the treatment allocation, including Pharmacy staff, and all Sponsor personnel will also be blinded. The randomization and allocation of kits will be managed by the data management group via an interactive web randomization system (IWRS).

Part 1

Dose escalation will be randomized, double-blinded and placebo-controlled in 24 subjects (up to 48 if DLT occurs). Up to six subjects will receive either SOC plus USB002 (n=3) or SOC plus placebo (n=3) in up to 4 escalating doses.

COVID-19 diagnosed patients in pulmonary distress requiring supplemental oxygen will be eligible for enrollment once consent has been obtained from the subject or legal representative and eligibility has been confirmed. Screening assessments obtained prior to consent and within 72 hours of infusion start will be used to assess eligibility and will not require repeating, unless determined by the Investigator as needed.

Study registration (subject number assignment) will be conducted through the IWRS upon enrollment. The Investigator will confirm eligibility and notify the pharmacy so designated study pharmacy staff can request cohort assignment and a drug kit identification randomization number through IWRS system. The pharmacy will receive dosage instructions directly from the IWRS system.

Starting at Visit 1/0 hours, subjects will receive a continuous IV infusion of USB002 or

placebo for up to 96-hours. Safety will be assessed by changes in physical examination findings, changes in vitals and laboratory parameters. AEs will be collected from the time of informed consent; those occurring between informed consent and start of infusion will be designated as medical history, and those occurring after start of infusion will be designated as AEs. Baseline assessments are defined as those conducted on Visit 1, prior to start of infusion.

Visit 5 will serve as the End of Treatment visit for Part 1. Additional visits will be conducted on Days 7, 9, 12, 14, 16, 18, 21, 24 and 28 (if/while still hospitalized). The follow-up visits on Days 28 and 60 will be conducted by phone (Telemed) upon discharge. If the subject is discharged earlier than Day 28, Telemed visits will be conducted once a week until Day 28, with the first occurring 7 days after discharge. The Day 28 Telemed visit and Day 60 Telemed visit will occur on Days 28 and 60, respectively, regardless of when the subject is discharged from hospital and the timing of their previous weekly Telemed visits.

The decision to dose-escalate, de-escalate, or increase the number of subjects in any group will be made by a Data Safety Monitoring Board (DSMB) as described in Section 6.6. Dose escalation will use the traditional 3+3 design to assess dose-response as described in Section 3.2. Assessment of progress and safety will be conducted by the DSMB, per the Safety Management Plan (SMP). If the DSMB determines there is a reasonable safety concern, enrollment may be delayed or halted. If toxicity is identified (graded according to NCI-CTCAE v5.0) at the lowest cohort level (90 ug/kg/day), DSMB may determine to de-escalate or halt the study. Escalation will continue until Part 1 enrollment is completed and the MTD is determined.

Part 2

30 subjects will be randomized at the MTD, as determined in Part 1, to either SOC plus USB002 (n=15) or SOC plus placebo (n=15). Subjects will be treated on a continuous infusion for up to 14 days. Infusion will be discontinued at any time if $SpO_2 \geq 94\%$ on room air is sustained for at least 48 hours. Additional visits will be conducted on Days 16 (End of Treatment visit), 18, 21, 24 and 28 (if still hospitalized). The follow-up visit on Days 28 and 60 will be conducted by phone (Telemed) upon discharge. If the subject is discharged earlier than Day 28, Telemed visits will be conducted once a week until Day 28, with the first occurring 7 days after discharge. The Day 28 Telemed visit and Day 60 Telemed visit will occur on Days 28 and 60, respectively, regardless of when the subject is discharged from hospital and the timing of their previous weekly Telemed visits.

Parts 1 and 2

For both groups, there will be a 24-hour observation period, after infusion stop time, regardless of when this occurs and regardless of reason.

If a subject's treatment is terminated after the Visit 1/Day 1 infusion begins, for any reason, all attempts will be made to conduct all remaining study visits and assessments,

as applicable (See Tables 2 and 3). End of Treatment (Part 1 – Visit 5; Part 2 – Day 16) procedures may be conducted during the 24-hour observation period. Missed End of Treatment assessments due to disease progression or early discharge, will be considered deviations.

Respiratory evaluations will be determined by recovery landmarks of time to acceptable spontaneous breathing efforts (up to 30 minutes), termination for the need of oxygen (see Spontaneous Breathing Trial [SBT]: Appendix 2), and time to discontinuation of ventilatory assistance, if applicable. Clinical status will be evaluated using the OSCI and physical examination findings.

Follow-up for AEs with a start prior to Day 28 will be followed to resolution, stabilization, or to Day 60. Survival will be captured during the follow-up period through to Day 60, regardless of treatment or hospitalization status. AEs with a start date after Day 28 will not be captured. Any SAE that occurs at any time, through to Day 60, will be collected.

Participation will terminate for all subjects on Day 60 or at early termination due to death, consent withdrawal or lost to follow-up.

3.1 Study drug(s) and Control Description

3.1.1. Formulation and Appearance

USB002 is formulated as a sterile, preservative-free, non-pyrogenic solution for injection. Formulated solution for injection consists of (Table 1):

Table 1. USB002 Formulated Solution	
Angiotensin 1-7	22.5 mg/mL
Glacial Acetic Acid, *USP*[3]	0.90 mg/mL (15 mM[1])
Sodium Acetate Trihydrate, *USP*[3]	4.76 mg/mL (35 mM)
Mannitol, *USP*[3]	40.0 mg/mL (4%)
Sterile Water for Injection, *USP*[3]	quantity sufficient to 100%
Sodium Hydroxide, *NF*[2]	to pH 5
Glacial Acetic Acid, *USP*[3]	to pH 5

[1]Millimolar[mM] [2]National Formulary [3] United States Pharmacopeia

The parenteral formulation is produced as a hydrogen ion concentration (pH) buffered solution, adjusted for the proper osmolality with the addition of 4% mannitol to provide a final osmolality of 295-415 milliosmole for the dosing concentrations of A(1-7). Sterilization of USB002 is achieved via 0.22-micron filtration of the final bulk solution into the appropriate number of vials filled under aseptic conditions.

The placebo formulation will be the USB002 formulated solutions (see Table 1) without the addition of A(1-7).

3.1.2. Packaging and Labeling

USB002 is packaged in a 22.5 mg/ml, single-use, stoppered 2.0 mL vial with a 2.1-mL fill.

USB002 and placebo vials will be identically labelled as 'For Investigational Use Only,' volume, kit #, and sponsor address.

3.1.3. Storage and Accountability Procedures

The Investigator (or delegate) will maintain adequate records showing the receipt, dispensing, return, or other disposition of USB002/placebo, including the date, quantity, kit number, vial number and identification of subjects (number, initials as allowed) receiving study medication.

USB002/placebo will be stored securely in the institution pharmacy, where it will be prepared and provided to the study staff for infusion. USB002/placebo will be labeled with the date of preparation, subject ID#, and final dose concentration in addition to institution-required labelling.

Used vials and empty kit boxes will not be kept for accountability purposes; they will be disposed of according to the institution destruction procedures.

3.1.4. Dosage and Administration

A new, unused vial will be used for each dose. The total dose administered will be dispensed per kg of body weight. USB002 or placebo will be diluted (see pharmacy manual) in saline and infused continuously by a dedicated line.

Pharmacy will prepare USB002 or placebo and provide the final product for infusion to the study team in a 100 mL sodium chloride (0.9%) Injection, *USP* bag(s). USB002 or placebo should not be administered with other medications in the same IV line and require a dedicated line. The infusion of study medication (USB002/placebo) may be piggy-backed on a 0.9% saline infusion if it is being used specifically and solely for the purpose of keeping vascular access open i.e. TKVO.

If possible, no other procedures should be performed within 90 minutes of the start of infusion; procedures or medication which may induce hypotension (BP decrease by 20% mmHg systolic) should be avoided during the same period.

3.1.5. Route of Administration

USB002 or placebo will be administered by IV. The infusion rate of the reconstituted study medication/solution supplied by the pharmacist is fixed at 4.167 ml/hour (0.069 ml/min) for all dose levels and all subjects when a 100 ml infusion bag is used. The daily dose required for each subject is calculated and dispensed according to the instructions in the pharmacy manual.

3.2. Dose Regimen and Escalation

Part 1: Dose Escalation

During dose escalation, the study will follow a traditional “3+3” design with three subjects in each cohort receiving SOC plus USB002 and three subjects in each cohort receiving SOC plus placebo. Cohorts will be enrolled sequentially for USB002 dose, with subjects receiving active drug at four sequential cohort doses of 90, 300, 600 and 900 ug/kg/day.

DSMB escalation decisions will be conducted on unblinded data. In Part 1, data review to determine dose escalation, de-escalation and study stop will be conducted by the DSMB after the last subject in each cohort has completed infusion (96-hour timepoint). Recruitment will be halted during DSMB data review for dose escalation decisions. Notification of changes in dose concentrations (escalation or de-escalation) will be issued through the IWRS.

The first 6 subjects (3 SOC plus USB002 subjects and 3 SOC plus placebo subjects) will be treated at the lowest dose. If one subject experiences an AE that is determined by the DSMB to be a potential DLT, an additional 6 subjects (3 SOC plus USB002 and 3 SOC plus placebo) will be treated at the same cohort dose. If DLTs are experienced in the new cohort at the same dose, the study may be stopped, or dose de-escalated.

DLT of hypotension (systolic BP < 90 mmHg) is a possibility, which may require the administration of fluid boluses or IV pressor agents.

At the time of a DSMB safety review, if no DLTs are identified in the first cohort, approval will be issued to treat the next 6 subjects (3 SOC plus USB002 and 3 SOC plus placebo) at the next dose. The DSMB safety reviews will be repeated between cohorts until the MTD or top dose of 900 µg/kg/day is reached.

Part 2: Dose Expansion

30 subjects will be randomized to either SOC plus USB002 at the MTD established in Part 1 (n=15) or SOC plus placebo (n=15). Subjects will be treated on a continuous infusion for up to 14 days.

3.3. Randomization

Randomization codes will be generated based on a central randomization schema, and the appropriate code assigned to the study kit will be issued to the Pharmacy via IWRS. Subjects will be randomized in a 1:1 ratio to receive either SOC plus USB002 or SOC plus placebo. Detailed instructions for the IWRS (enrollment/randomization/unblinding) will be provided separately.

3.4 Treatment Period

Part 1

Treatment will start during Visit 1/hour 0 and continue for up to 96 hours.

Part 2

MTD treatment will start at Day 1 and continue for up to 14 days.

3.5. Study Participation Duration

Part 1 and Part 2 subjects completing all study assessments will be on study for up to 70 days.

3.6 Study Population

Subjects over the age of 18 with COVID-19 infections and SOB requiring supplemental oxygen to maintain $SpO_2 \geq 94\%$ will be enrolled.

4. PATIENT SELECTION CRITERIA

4.1. Inclusion Criteria

1. Signed informed consent from patient or legal representative;
2. Age 18 or greater;
3. Positive reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 (≤10 days of start of infusion);
4. Respiratory rate > 20 RR;
5. SpO_2 < 94% on room air, requiring supplemental oxygen, on mechanical ventilation for <72 hours (at time of informed consent);

   If screening and infusion occur on the same day, the first SpO_2 taken at the time of screening needs to be <94% to satisfy eligibility (patient will be put onto oxygen immediately); if screening and infusion occur on separate days, confirm sustained SpO_2 <94% on room air prior to infusion –if on supplemental oxygen just prior to infusion and SpO_2 < 94% then patient automatically meets the criteria.

6. Chest X-ray confirming bilateral pulmonary infiltrates;
7. Body mass index of ≤ 40 units/kg/m^2;
8. Adequate method of birth control for subjects of child-bearing potential.*

* *Note: A female patient is considered to be of childbearing potential unless she has had a hysterectomy, is at least one year postmenopausal or has undergone tubal ligation. For the purposes of this study, adequate birth control includes at least one medically*

approved and highly effective method of birth control, defined as those which result in a low failure rate (i.e., < 1% per year) when used consistently and correctly, such as implants, injectables and oral contraceptives combined with the use of double condoms. Only male patients whose vasectomy has been confirmed by semen analysis at least 3 months after the vasectomy are allowed not to use acceptable contraceptive methods.

4.2. Exclusion Criteria

1. Terminally ill patients due to underlying cardiac, cancer or severe debilitating neurological disease including coma;
2. Hospitalization expected to be < 96 hours due to medical improvement;
3. Interstitial lung disease;
4. Patients receiving vasopressors at time of starting infusion;
5. Correction of QTc values obtained by 12 lead EKG using Fridericia's formula (QTcF) > 450 ms;
6. History of hypotension (mean arterial blood pressure < 65 mmHg), unrelated to CoVID-19 infection;
7. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times upper limit of normal;
8. Creatinine >115umol/L (**Part 2 only**);
9. BUN > 8.3 mmol/L (**Part 2 only**);
10. Participating concurrently on another clinical trial for the experimental treatment of COVID-19;
11. Patients who appear to be showing clinical improvement, in the investigator's opinion (and documented in the source), between screening and baseline (infusion);
12. Active chemotherapy use;
13. Pregnant and/or lactating women.

4.3. Subject Withdrawal

Subjects may withdraw from the study at any time without stating a reason and without prejudice to further treatment. Incapacitated subjects may be withdrawn by the legally-authorized representative. The reason for withdrawal will be documented in the source notes and in the Electronic Data Capture system (EDC). Any potential or confirmed drug-related event (clinical AE, laboratory abnormality, or other medical condition/situation) occurring, and/or DSMB determination which may be attributed to the withdrawal, must be documented and followed for the safety of the subject.

Withdrawal of a subject from the study applies to subjects who withdraw their consent; otherwise, all subjects will be followed through Day 60. Subjects who are lost to follow-up (attempts to reach subjects will be documented) will be noted as such, at Day 60, but will not be deemed to have been withdrawn; subjects who do not survive to Day 60 will be noted as such but will not be considered to have been withdrawn.

The sponsor should be notified immediately when a subject withdraws consent from the study after any treatment, as every attempt should be made to capture as much information following treatment as possible. If a subject withdraws consent after the start of infusion, for any reason, all attempts will be made to conduct the End of Treatment (Day 5 or Day 16) procedures (See Tables 2 and 3). End of Treatment (Day 5 or Day 16) procedures may be conducted during the 24-hour observation period.

Following discharge, reasonable and diligent attempts to contact the subject should be documented (dates, phone discussions, emails and registered mail) in the subject's record.

4.4. Study Withdrawal Criteria

The study may be suspended or prematurely terminated at any site if there is sufficient reasonable cause.

Written notification, documenting the reason for the study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the Investigator(s) will promptly inform the Institutional Review Boards (IRBs) and will provide the reasons for the termination or suspension. The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB, and/or FDA.

Circumstances that may warrant termination include, but are not limited to:

- DSMB determination of unexpected, significant, or unacceptable risk to subjects based on safety evaluations and DLTs;
- Insufficient compliance with protocol requirements;
- Data that are not sufficiently complete and/or evaluable;
- Determination of futility.

5. STUDY PROCEDURES AND VISIT SCHEDULE

5.1. Standard of Care Procedures

SOC testing obtained prior to consent and within 72 hours of USB002/placebo infusion start can be used to assess eligibility and will not require repeating, unless determined by the Investigator. SOC tests done on hospital admission may be used to determine patient eligibility.

5.2. Clinical Laboratory Evaluations

Clinical laboratory assessments will be conducted at the local Clinical Laboratory Improvement Amendments certified laboratory routinely used by the Investigator. Laboratory samples will be collected and processed per institution requirements and guidelines.

Laboratory Assessments include:
(Part 1, Screening, Visit 1, 5 and Days 14, 21 and 28)
(Part 2, Screening, Day 1, Days 7, 16 and 28)

- Chemistry: Sodium, potassium, chloride, carbon dioxide (CO_2), calcium, phosphorus, glucose, blood urea nitrogen (BUN), serum creatinine, serum lipase, serum amylase, alkaline phosphatase (ALP), total bilirubin, AST, ALT, lactate dehydrogenase (LDH), LDH isoenzymes, total protein, albumin, triglycerides, uric acid, C-reactive protein (C-RP), creatinine kinase (CK), CK isoenzymes, thyroid stimulating hormone (TSH);
- Hematology: Complete blood count (CBC) to include: Red blood cells (RBC), white blood cells (WBC), complete differential, hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelet count (Plt);
- Urinalysis: Specific gravity, hydrogen ion concentration (pH), RBC, WBC, protein, and glucose;
  (Urinalysis for Part 1 only at Screening, Visit 5 and Day 28)
  (Urinalysis for Part 2 only at Screening and Day 16)
- Coagulation: Activated partial thromboplastin time (aPTT), prothrombin time (PT) and international normalized ratio (INR) and fibrinogen assay.

Laboratory Assessments include:
(Part 1: 24, 48, 72 and 96 hours)
(Part 2: Days 2, 3, 4, 5, 9, 12, 14, 18, 21 and 24)

- Chemistry: Sodium, potassium, chloride, carbon dioxide (CO_2), calcium, glucose, blood urea nitrogen (BUN), serum creatinine, alkaline phosphatase (ALP), total bilirubin, AST, ALT, total protein, albumin;
- Hematology: Complete blood count (CBC) to include: Red blood cells (RBC), white blood cells (WBC), complete differential, hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelet count (Plt);
- Coagulation: Activated partial thromboplastin time (aPTT), prothrombin time (PT) and international normalized ratio (INR) and fibrinogen assay.

5.3 Other Assays or Procedures

Other assays or procedures include:

- Pregnancy test (for females of childbearing potential).
- OSCI (Appendix 1);
  - In addition to study required OSCI status collection, any additional OSCI assessments conducted during the study will also be collected.
- SBT (Appendix 2);
- Chest X-ray (required at screening only);

- 12-lead ECG to include HR and QRS intervals, QT/QTcF/QTcB; Correlation of QT values using Fridericia's formula;
- Vitals to be captured daily; and during the infusion period at a minimum of every 8 hours. Vitals to include systolic and diastolic BP, HR, RR and temperature;
    - If BP changes significantly post start of infusion, mean arterial pressure will be collected at 15-minute intervals, until resolution;
- Weight measured at screening only;
- Study–required respiratory assessments (first and last assessments can be based on 24 hour clock or from infusion time):
    - Arterial Blood Gas (ABG): If multiple assessments are conducted daily, the first and last assessment of the day will be collected; missed ABGs do not qualify as deviations,
    - FiO_2 (%) – The highest value in a 24-hour period to be recorded in the event of multiple daily assessments,
    - PaO_2/FiO_2 ratio, the PaO_2 value to be obtained from the ABG when performed,
    - Respiratory rate (breaths/min) – The highest value in a 24-hour period to be recorded in the event of multiple daily assessments,
    - SpO_2 (%) – The lowest value in a 24-hour period to be recorded in the event of multiple daily assessments.

5.4 Visit Schedule

5.4.1. Screening (Part 1 & Part 2)

The following procedures and assessments must be completed, documented and reviewed by the Investigator within the 72-hour screening period, prior to the first treatment dose (see Tables 2 and 3) unless otherwise indicated:

- Written informed consent, including comprehensive discussion of the study schedule, procedures and protocol requirements with the patient or legal representative;
- Review of demographic data, including date of birth, sex, weight and race;
- Complete medical and surgical history. Any AEs occurring prior to the first USB002/placebo dose will be considered history;
- Medical history to include dates of vaccinations, booster and prior COVID-19 infection(s), if applicable;
- Medical history to include ICU admission date, if applicable;
- Positive RT-PCR for SARS-CoV-2 ($\leq$10 days of start of infusion);
- Chest X-ray;
- Comprehensive physical examination (to include lung auscultation to determine presence or absence of lung crackles (rales), wheezing, dullness to percussion);
- 12-lead ECG;

- Sample collection and processing for clinical laboratory assessments (Section 5.2);
- Urinalysis collection (if patient is producing urine) (Section 5.2);
- Vitals assessments (Section 5.3);
- Respiratory assessments (Section 5.3);
- Pregnancy test for females of childbearing potential;
- OSCI;
- Review and documentation of all concomitant prescription and non-prescription medication.

If a randomized subject eligible to proceed to Visit 1 infusion, suffers an AE and/or if the Investigator deems the subject cannot start the infusion, infusion may be delayed up to 72 hours. If the decision to start infusion is > 72 hours, the subject is considered a screen fail and screening procedures must be repeated. In this situation, a new screening number will be used and a new randomization number provided.

5.4.2. Visit Schedule Part 1

AEs and concomitant medications will be reviewed and documented every day of hospitalization.

Visit 1

Prior to infusion start:

- Conduct final determination of eligibility prior to the start of USB002/placebo infusion;
- If not done in previous 72 hours, repeat within 24 hours prior to start of USB002/placebo infusion:
  - Physical exam (for eligibility only, does not need repeating);
  - Laboratory sample collection per Section 5.2;
  - Respiratory assessments per Section 5.3;
  - Vitals;
  - 12 lead-ECG;
  - Chest X-ray (for eligibility only, does not need repeating);
  - Pregnancy test;
  - OSCI assessment.

Visit 1 – 0 hours

- Infusion start: as soon as possible once deemed eligible.

Visits 1 – 4 (4, 8, 12, 24, 32, 40, 48, 72 and 96 hours)

- Blinded Dosing
- Vitals (If no continuous vitals monitoring, collect vital signs per Section 5.3 during the infusion period);
- Respiratory assessments per Section 5.3;

- Laboratory (chemistry, hematology and coagulation per Section 5.2) at approximately 24, 48, 72, 96 hours;
- 12 lead-ECG at approximately 48, 72, 96 hours;
- For mechanically ventilated subjects, SBT at approximately 24, 48, 72, and 96 hours, if weaning criteria met;
- AEs;
- Concomitant medications.

Visit 5 (End of Treatment or Early Termination of Treatment)

- Laboratory (chemistry, hematology, coagulation and urinalysis per Section 5.2);
- 12 lead-ECG;
- Vitals;
- Respiratory assessments per Section 5.3;
- SBT and at any time that weaning criteria is met;
- OSCI assessment;
- AEs;
- Concomitant medications.

Days 7, 9, 12 and 14

- Laboratory (chemistry, hematology and coagulation per Section 5.2) (Day 14);
- 12 lead-ECG (Days 7, 9, 14);
- Vitals;
- Respiratory assessments per Section 5.3;
- SBT at Days 7, 9 and 14 and at any time that weaning criteria is met;
- AEs;
- Concomitant medications.

Day 16

- Vitals;
- Respiratory assessments per Section 5.3;
- SBT and at any time that weaning criteria is met;
- OSCI assessment;
- AEs;
- Concomitant medications.

Days 18, 21, 24, 28

- OSCI assessment (Day 28);
- AEs;
- Laboratory (chemistry, hematology, coagulation and urinalysis per Section 5.2) (Day 21 and Day 28 with urinalysis at Day 28)
- Concomitant medications;
- Follow-Up (Telemed) (Day 28).

Day 60

- AEs
- Follow-Up (Telemed).

5.4.3. Visit Schedule Part 2

AEs and concomitant medications will be reviewed and documented every day of hospitalization. Monitoring is to be conducted daily if no continuous monitoring is available, unless specified below.

Day 1

Prior to infusion start

- Conduct final determination of eligibility prior to the start of USB002/placebo infusion.
- If not done in previous 72 hours, repeat within 24 hours of start of infusion:
    - Physical exam (for eligibility only, does not need repeating);
    - Laboratory sample collection per Section 5.2;
    - Respiratory assessments per Section 5.3;
    - Vitals;
    - 12 lead-ECG;
    - Chest X-ray (for eligibility only, does not need repeating);
    - Pregnancy test;
    - OSCI assessment.

Day 1 - 0 hours

- Infusion start: As soon as possible once deemed eligible.

Days 1-14

- Blinded Dosing
- Vitals;
    - If no continuous vitals monitoring, collect vital signs per Section 5.3 during the infusion period.
- Respiratory assessments per Section 5.3;
- Laboratory (chemistry, hematology, coagulation and urinalysis [Day 1 only] per Section 5.2);
- 12 lead-ECG (Day 1);
- SBT and at any time that weaning criteria is met;
- OSCI (Day 7);
- AEs;
- Concomitant medications.

Day 16 (End of Treatment or Early Termination of Treatment)

- Laboratory assessments (chemistry, hematology, coagulation and urinalysis per Section 5.2);
- 12 lead-ECG;
- Vitals;
- Respiratory assessments per Section 5.3;
- SBT and at any time that weaning criteria is met;
- OSCI assessment;
- AEs;
- Concomitant medications.

Days 18, 21, 24, 28

- Laboratory (chemistry, hematology, coagulation per Section 5.2);
- OSCI assessment (Day 28);
- AEs;
- Concomitant medications;
- Follow-Up (Telemed) (Day 28).

Day 60

- AEs;
- Follow-Up (Telemed).

5.4.4 End of Treatment or Early Termination of Treatment

Subjects completing the study up to Visit 5 (in Part 1) or Day 16 (in Part 2) will have End of Treatment procedures completed at Visit 5 (in Part 1) or Day 16 (in Part 2). For subjects discharged prior to Visit 5 (in Part 1) or Day 16 (in Part 2) or where treatment is terminated early, for any reason, all attempts will be made to conduct the End of Treatment (Visit 5 or Day16) procedures (See Tables 2 and 3). End of Treatment (Visit 5 or Day16) procedures may be conducted during the 24-hour observation period.

See Section 5.4.2 Visit 5 (Part 1) and Section 5.4.3 Day 16 (Part 2).

5.4.5 Hospital Discharge Prior to Day 28

If a subject is discharged from hospital earlier than Day 28, Telemed visits will be conducted once a week until Day 28, with the first occurring approximately 7 days after discharge. The Day 28 and Day 60 Telemed visits will occur on Days 28 and 60, respectively, regardless of when the subject is discharged from hospital and the timing of their previous weekly Telemed visits. Part 1 subjects discharged prior to Day 28 will not return to the site for visits (may apply to any of Days 7, 9, 12, 14, 16, 18, 21, or 24, depending on day of discharge) or undergo the procedures regularly scheduled for those visits. Part 2 subjects discharged prior to Day 28 will not return to the site for visits (may apply to Days 18, 21, or 24, depending on day of discharge) or undergo the procedures regularly scheduled for those visits.

Data from the Telemed visits post-discharge will be captured in the EDC.

Table 2. Schedule of Assessments: Part 1

		Timepoint																				
Assessments	**Screening** (72 hours)										**Visit 5**	Day										+/- 7 days
		Visit 1					**Visit 2**			**Visit 3**	**Visit 4**	End of Treatment[4]	**7[5]**	**9[5]**	**12[5]**	**14[5]**	**16[5]**	**18[5]**	**21[5]**	**24[5]**	**28[5,6]**	
		0 hrs[2]	4 hrs	8 hrs	12 hrs	24 hrs	32 hrs	40 hrs	48 hrs	72 hrs	96 hrs											**60**
Informed Consent	X																					
Medical and Surgical History[1]	X																					
Demographics	X																					
Physical exam[3]	X	X																				
Chemistry	X	X				X			X	X	X	X				X			X		X	
Hematology	X	X				X			X	X	X	X				X			X		X	
Coagulation	X	X				X			X	X	X	X				X			X		X	
Urinalysis	X	X										X									X	
Pregnancy test	X	X																				
12-lead ECG	X	X							X	X	X	X	X	X		X						
Chest X-ray	X	X																				
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X					
SBT Assessment						X			X	X	X	X	X	X		X	X					
Respiratory assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Blinded Dosing		X	X	X	X	X	X	X	X	X	X											
OSCI Status	X	X										X					X				X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Follow-Up[5,6](Telemed)																					X	X

1. History to include but not limited to any significant, ongoing, or controlled with treatment, medical condition; date of hospital admission; date of ICU admission; start time of supplemental oxygen therapy; start time of nasal high-flow oxygen therapy; start time of non-invasive mechanical ventilation or mechanical ventilator via intubation.
2. If screening assessments are not completed prior to start of infusion, conduct within 24 hours of infusion start. If performed as part of screening and within 72 hours, do not repeat unless required by the Investigator. Chext X-ray and Physical Exam do not need repeating within 24 hours.
3. Physical exam to include lung auscultation.
4. Visit 5 is also End of Treatment – all End of Treatment assessments are to be conducted at Visit 5 for all subjects or for any discharge prior to Visit 5.
5. If subject is discharged from hospital, Telemed visits will be conducted once a week until Day 28, with the first occurring approximately 7 days after discharge. Day 28 and Day 60 Telemed visits will occur on Days 28 and 60, respectively, regardless of discharge date and timing of previous Telemed visits. Discharged subjects will not attend the site for visits (Days 7, 9, 12, 14, 16, 18, 21, or 24, as applicable to discharge day) or undergo procedures scheduled for those visits.
6. Telephone follow-up, if discharged. Day 28 phone call window = +/- 3 days; window not applicable if still hospitalized.

Table 3. Schedule of Assessments: Part 2

Assessments	Timepoint (Days)															
	Screening (72 hours)	**1**[2]	**2**	**3**	**4**	**5**	**7**	**9**	**12**	**14**	**16**[5] End of Treatment	**18**[6]	**21**[6]	**24**[6]	**28**[6,7]	+/- 7 days **60**
Informed Consent	X															
Medical and Surgical History[1]	X															
Demographics	X															
Physical exam[3]	X	X														
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X									X					
Pregnancy test	X	X														
12-lead ECG	X	X									X					
Chest X-ray	X	X														
Vital signs	X	X	X	X	X	X	X	X	X	X	X					
SBT Assessment		X	X	X	X	X	X	X	X	X	X					
Respiratory assessments	X	X	X	X	X	X	X	X	X	X	X					
Blinded Dosing[4]		X	X	X	X	X	X	X	X	X						
OSCI Status	X	X					X				X				X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Follow-Up[6,7](Telemed)															X	X

1. History to include but not limited to any significant, ongoing, or controlled with treatment medical condition; date of hospital admission; date of ICU admission; start time of supplemental oxygen therapy; start time of nasal high-flow oxygen therapy; start time of non-invasive mechanical ventilation or mechanical ventilator via intubation.
2. If screening assessments are not completed prior to start of infusion, conduct on Day 1, prior to infusion. If performed as part of screening and within 72 hours, do not repeat unless required by the Investigator. Chest X-ray and Physical Exam do not need repeating within 24 hours.
3. Physical exam to include lung auscultation.
4. Continuous infusion of USB002 or placebo for up to 14 days.
5. Day 16 is also End of Treatment – all End of Treatment assessments are to be conducted at Day 16 or for any discharge prior to Day 16.
6. If subject is discharged from hospital, Telemed visits will be conducted once a week until Day 28, with the first occurring approximately 7 days after discharge. Day 28 and Day 60 Telemed visits will occur on Days 28 and 60, respectively, regardless of discharge date and timing of previous Telemed visits. Discharged subjects will not attend the site for visits (Days 18, 21, or 24, as applicable to discharge day) or undergo procedures regularly scheduled for those visits.
7. Telephone follow-up, if discharged. Day 28 phone call window = +/- 3 days; window not applicable if still hospitalized.

5.5. Concomitant Medication

Any treatment or medication for respiratory distress associated with COVID-19 infection, underlying medical conditions, or prophylaxis, to include, but not limited to prescribed medication, anticoagulants, corticosteroids, convalescent plasma, or VEKLURY® (remdesivir) is allowed on this study. For this study, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

All concomitant medications will be recorded on the case report forms (eCRFs), to include concomitant prescription medications, over-the-counter medications, and non-prescription medications taken by, or administered to the subject while on study (ongoing at baseline, changed from baseline (frequency and/or dose), started after baseline) until discharge. Medication started after discharge will be collected only if administered for the treatment of a Serious Adverse event. Any medication continuing after discharge will be recorded as ongoing in the eCRF.

Medications that are needed for the purpose of mechanical ventilation i.e. any induction agents, muscle relaxants, or sedative agents are not needed to be captured. Medication administered for other procedures that might be performed while in ICU e.g. opiates/analgesics for tracheostomy, local anesthetics for chest tubes or other procedures, oral hygiene care, etc. are not needed to be captured. Anything that is administered for the treatment of COVID should be captured, as well as any vasopressors that might be required post infusion, (since there is the potential BP affect with USB002). Medication for complications of COVID e.g. prophylactic anticoagulation, DVTs, strokes, MIs, AKI, stroke, hemorrhage, etc. are captured. In addition, antibiotics used prophylactically or as treatment for any infection, and use of nephrotoxic agents, including any imaging agents, should be captured.

5.6. Prohibited Medication

Ongoing treatment of cancer with chemotherapy is not allowed while enrolled in the study. Use of vasopressors at time of infusion is not permitted.

6. ASSESSMENT OF SAFETY

6.1. Safety Parameters

Safety assessments to be conducted in this study include:

- AEs collected at all study visits from the time of first study drug dose;
- Changes in concomitant medications;
- Findings from physical examinations;
- Changes in laboratory parameters;
- Changes in respiratory and cardiovascular assessments.

Safety and tolerability will be assessed by the DSMB (see Section 6.6).

Any AE that is considered definitely, probably, or possibly related to USB002 is potentially a DLT. DLT will be defined per the DSMB SMP.

6.1.1. Definition of Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended change in structure, function, sign, or symptom temporally associated with the use of a medicinal product, whether related to the product. Undesirable changes in laboratory values should not be considered AEs unless they are considered symptomatic of a clinical condition or diagnosis, are evaluated as clinically significant, or require therapy. Worsening of a pre-existing condition is also considered an AE, as is the discovery of an abnormal finding during a physical exam (done per SOC) that was not included in the medical history. Clinical conditions attributable to disease progression will be considered AEs.

6.1.2. Definition of Serious Adverse Events (SAE)

An SAE is any AE that meets at least one of following criteria:

- Is fatal;
- Is life-threatening; in the opinion of the Investigator, the subject was at substantial risk of dying at the time of the adverse event, or use or continued use of the medical product might have resulted in the death of the patient;
- Is a persistent or significant disability or incapacity;
- Requires hospitalization or prolongs an existing hospitalization. Hospitalization will be defined as such if > 24 hours, or a hospitalization that requires an intervention to treat emergent symptomatology (non-diagnostic);
- Exposure prior to conception or during pregnancy may have resulted in a congenital anomaly or birth defect in the child;
- Other important medical events not noted in events above, but may be considered a serious experience when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes as listed in #1-5 in this definition.

6.2 Classification of an Adverse Event

6.2.1. Severity of Event

Signs and symptoms will be graded by the Investigator as mild, moderate, severe, life-threatening, or fatal according to the following definitions:

- **Mild:** The AE is transient and does not interfere significantly with the subject's normal functioning level. The AE resolves spontaneously or may require minimal

therapeutic intervention;
- **Moderate:** The AE produces limited functional impairment and may require therapeutic intervention. The AE produces no sequelae;
- **Severe:** The AE results in significant impairment of function and may lead to temporary inability to resume the subject's normal life pattern. The AE produces sequelae which require prolonged therapeutic intervention;
- **Life-Threatening:** The AE results in life-threatening consequences, urgent intervention is indicated, urgent operative intervention is indicated, or the patient is at risk of death at the time of the event if immediate intervention is not undertaken;
- **Fatal:** The AE results in death.

Further, toxicities should be evaluated according to the NCI-CTCAE v5.0 criteria.

6.2.2. Relationship to Study Drug

The following five-point scale will be used by the Investigator to rate the relationship of the AE to the study drug:

- **Definitely related:** A clinical event (including laboratory test abnormality) occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitively associated pharmacologically, using a satisfactory re-challenge procedure, if necessary;
- **Probably related:** A clinical event (including laboratory test abnormality) with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition;
- **Possibly related:** A clinical event (including laboratory test abnormality) with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear;
- **Unlikely to be related:** A clinical event (including laboratory test abnormality) whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments);
- **Not related:** An event for which sufficient information exists to conclude that the etiology of the event is unrelated to the study drug. An alternative definitive etiology should be documented by the Investigator.

6.2.3. Expectedness

Expectedness determination will be related to the study drug specifically. An event may be unexpected in the subject but that in itself does not qualify as unexpected; review against information available and provided for the study drug is what will determine expectedness.

Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study drug, in the protocol and within the Investigator Brochure.

6.3. Adverse Event Follow-Up

AEs will be recorded throughout the study and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs ongoing at the final study visit or early termination, must be followed until resolution or until the Investigator determines them to be stable and/or adequately managed.

Date and time of onset and resolution (if applicable) of all AEs will be documented.

All SAEs must be followed until the event resolves or, in the opinion of the Investigator, become stable.

The Sponsor will report any serious, unexpected and drug-related AE to applicable regulatory agencies and provide these reports to the clinical trial sites. The Investigator must promptly inform the IRB of such events and retain a copy of the notification in the Investigator Site File (ISF).

6.4. Reporting Procedures

6.4.1 Adverse Event Reporting

AEs will be captured from the start of USB002/placebo infusion until Day 28 or hospital discharge, whichever occurs last. Any AEs ongoing at Day 28 (or discharge) will be followed/assessed up to the Day 60 Telemed visit. No new AEs will be collected following discharge. SAEs (new or ongoing) will be followed and/or collected until Day 60.

All AEs (whether attributable to the study drug) occurring during the study observed by the Investigator or reported by the subject will be recorded on the eCRF. The following information will be recorded for all AEs:

- Event: name/condition/diagnosis/description;
- Onset and resolution time and/or date;
- Severity;
- Relationship to study drug (assessment by staff trained and authorized to

diagnose);
- Action taken;
- Seriousness.

6.4.2 Serious Adverse Event Reporting

All SAEs are to be marked in EDC as an SAE. However, sites are not expected to complete the SAE forms if the event occurs while subject is in the ICU. If an event is serious while not in the ICU, regular reporting of SAEs will occur (SAE forms completed and forwarded to MM immediately).

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24-hour Emergency Contacts:

Medical Monitor Tony Verco, MD 805-235-9193 or Medical Director Gere diZerega, MD 805-630-2800

SAEs occurring during the study period, from the initiation of USB002/placebo infusion up to Day 60, will be recorded.

SAEs experienced by subjects enrolled into the study, who are not transferred to the ICU, will be reported according to standard regulatory requirements and guidelines.

For all patients enrolled outside ICU but progress and end up in ICU: all SAEs that occur prior to ICU admission should be recorded and reported per usual requirements, any SAE that occurs after ICU admission will be recorded as an SAE in the EDC but no SAE form will be required to be submitted. Should the Medical Monitor require further information that will be requested directly.

For all patients enrolled when already in ICU, all events are to be recorded as an SAE in the EDC but will not require reporting on an SAE form unless the Investigator feels the event was not a consequence/progression of COVID, in which case the event should be reported on an SAE form per standard practice.

For all those patients discharged from ICU, all SAEs that occur after discharge are to be recorded and reported per standard practice.

The Sponsor will request additional information or documentation as required. As applicable, the Investigator should provide the following documentation at the time of notification if available:

- SAE Report Form;
- Concomitant medication (supporting documents);
- Relevant diagnostic reports;
- Relevant laboratory reports;
- Hospitalization notes;
- Hospital discharge summary (if available).

Due to the high rate of expected clinical deterioration in the ICU group of patients, the following anticipated adverse events/interventions associated with COVID-19 infection will be reported to the Sponsor immediately via email:

- Abnormal pathology results from presentation (including inflammatory markers related to a hyperinflammatory response)
- Secondary infection
- Renal failure
- Cardiac disease e.g., arrythmias, right heart failure
- Intubation and ventilation
- Venous thromboembolism/arterial thrombosis
- Other clinically significant end organ damage, either biochemical e.g., acute kidney injury, liver impairment, or clinical e.g., stroke
- Death from COVID-19

6.4.3 Reporting of Pregnancy

A female patient is of childbearing potential unless she has had a hysterectomy, is at least one year postmenopausal, or has undergone tubal ligation. All sexually active patients must use a reliable method of birth control until Day 60. Any pregnancy occurring in a subject or a subject's sexual partner during the study must be reported to US Biotest as soon as the Investigator is aware of it. The pregnancy will not be considered an SAE; however, information on the event will be collected and the outcome followed to birth or termination of pregnancy.

Any pregnancy complication or premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as an SAE, as described in Section 6.4.2. Should the pregnancy result in a congenital anomaly or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality. In addition, any infant death that occurs after the 30-day reporting period that the Investigator suspects is related to the in-utero exposure to the study treatment should also be reported.

6.5 Study Halting Rules

This study is a Phase 2 dose escalation study. Dose escalation will be determined following review of the safety and tolerability data in a cohort by the DSMB (see Section 6.6). Following review, at any time point, the study may be terminated. Should this occur,

all subjects who have received treatment will be followed for safety up to Day 60. The Sponsor is responsible for notifying FDA of any temporary halt to the study or when the study is terminated. The Investigator will be required to notify the IRB accordingly.

6.6. Safety Oversight

Safety will be overseen by the MM and the DSMB. The DSMB will be comprised of three medical experts, at least one of whom is an infectious disease specialist, and will be supported by a Statistician, who will not be a voting member. The DSMB will be independent and external to the Sponsor and study personnel. DSMB meetings will be conducted per the DSMB charter.

All subject study data will be captured in an EDC system, allowing real-time access to safety and tolerability data and prior to proceeding to dose escalation.

Prior to dose escalation, the DSMB will convene to review the cohort data, and generate a report outlining safety concerns from the subjects' EDC data. This review will be conducted prior to proceeding with either addition of more subjects to a current cohort or proceeding to dose escalation in the next cohort. Assessment of progress and safety, as well and decision to dose-escalate, de-escalate, or increase the number of subjects in any group will be made by a DSMB and recorded in the DSMB meeting minutes as described in the SMP.

The DSMB will evaluate data for each cohort after all 6 subjects in the cohort have completed 96-hours of the USB002/placebo infusion. During the safety review, DSMB members will review all EDC safety data available; provided as reports generated directly from the EDC system and by the Data Management group. Emphasis will be placed on emerging safety trends or events which may constitute DLT (See Section 6.1).

Enrollment will be halted during the cohort data review. If the DSMB determines there is a reasonable safety concern, further enrollment and dose escalation may be delayed or halted. Escalation will continue until Part 1 enrollment is completed and the MTD is determined for Part 2.

In Part 2, DSMB safety reviews will be conducted every 6 weeks. As with Part 1, the DSMB may decide to halt or delay enrollment at any time during Part 2.

7. STATISTICAL CONSIDERATIONS

7.1 Statistical and Analytical Plans

Formal Statistical Analysis Plans (SAP) will be prepared for each part (1 and 2) of this trial and will be signed off prior to study database lock and prior to any unblinding procedures. Part 1 will detail parameters and interpretation of safety and efficacy signals for dose escalation randomization groups (SOC plus USB002 and SOC plus placebo). Part 2 will detail parameters and interpretation of preliminary efficacy outcomes of the

randomized groups. Any deviations to the planned analyses specified within the SAP will be justified in writing and presented in the final clinical study report.

In Part 1, the data summaries, which will be supported with by-subject listings, will focus on the dose group for SOC plus USB002 as compared to the SOC plus placebo as well as time in trial.

In Part 2, preliminary efficacy assessments will compare the endpoints for the two treatment groups for a signal of efficacy including: time without mechanical ventilation, all-cause mortality, survival at discharge, absence of respiratory failure, responders according to OSCI (see Appendix 1). Data relating to efficacy response will be listed and summarized by dose cohort and time point, as appropriate. On each measurement day, the worst OSCI score will be recorded. Since the efficacy objective of this study is to assess the preliminary efficacy signals, statistical inference (e.g. p value) from the efficacy analyses will be used to assess the strength of the efficacy signals, and will not be adjusted for multiple comparisons. Unless specified in the analyses of efficacy endpoints (see Section 7.2.1), missing data will not be imputed.

7.2 Description of Statistical Methods

7.2.1 Analysis of the Efficacy Endpoint(s)

Efficacy assessments will be based on the safety analysis set, which is defined as all subjects who have received at least one dose of study medication. Data relating to efficacy response will be listed and summarized by treatment group and time point, as appropriate. Any efficacy related outcomes in Part 1 will be present descriptively and will be detailed in the SAP.

Summary statistics (mean, median, standard deviation, minimum, and maximum) and change from baseline to each scheduled study assessment for ventilator readings will be presented by treatment group. Baseline is defined as the latest non-missing assessment prior to the first study drug infusion.

The primary efficacy outcome, time to peripheral capillary oxygen saturation (SpO_2) $\geq$ 94% on room air, sustained for at least 48 hours, through Day 28, will be estimated and compared between the two treatment groups using Kaplan-Meier (KM) analysis. Subjects who do not achieve $SpO_2 \geq 94\%$, sustained for at least 48 hours, or die by Day 28 will be censored at Day 28. As a supplemental analysis, an analysis using a Cox proportional hazards model incorporating the baseline covariates: age, baseline severity, and comorbidity, will be performed.

The secondary efficacy outcome of proportion of subjects with all-cause mortality within 60 days from start of treatment, will be compared between the two treatment groups using Fisher's exact test. In addition, as a supplemental analysis, a logistic regression analysis will also be performed to adjust for the same baseline covariates in the primary efficacy outcome analysis: age, baseline severity, and comorbidity.

The secondary efficacy outcomes that are binary, e.g., subjects weaned from mechanical ventilation within the 28-day, subjects progressing from non-invasive (at baseline) to mechanical ventilation, the proportions will be compared using Fisher's exact test. Death will be considered unfavorable outcome for these analyses, i.e. death prior to Day 28 will be considered as on mechanical ventilation. In addition, analysis of subjects weaned from mechanical ventilation will be conducted on those who were on mechanical ventilation at baseline, and analysis of subjects progressing from non-invasive to mechanical ventilation will be conducted on those who were not on mechanical ventilation at baseline. Time to hospital discharge will be analyzed using Kaplan-Meier method. Subjects who are not discharged by Day 28 or die will be censored at Day 28 for the analysis.

All other secondary outcomes will be presented descriptively.

7.2.1.1. Sub-Group Analyses

The primary efficacy outcome and key secondary outcome will be analyzed for the Per Protocol population. Subjects who withdrew prior to completing 48 hours in the treatment period will be excluded from the PP population. Details will be described in the SAP.

7.2.1.2. Baseline Descriptive Statistics

Complete demographic and baseline data will be tabulated. The medical history, which will be coded in MedDRA, will be presented. The disease history data, with a focus on the previous treatment and current staging, and the information collected on the procedure to apply the treatment will also be summarized.

7.2.1.3. Concomitant Medication

All medication taken during the trial will be, at a minimum, listed with the start and stop dates. Concomitant medications will be coded using the World Health Organization (WHO) drug dictionary and summarized by anatomical therapeutic chemical (ATC) level 2 (pharmacological or therapeutic sub-group) and ATC level 4 (chemical sub-group).

7.2.1.4. Interim Analyses

There are no formal interim analyses planned. Safety and tolerability review will be conducted by the DSMB.

7.2.2. Extent of Exposure

A summary of exposure to study drug including the total exposure to USB002 and the duration of exposure, will be provided.

7.2.3 Safety Analyses

All subjects who are enrolled and infusion dose of study drug/placebo was started will be included in the descriptive analysis. All safety and tolerability assessments will be based on the safety analysis set, which is defined as all subjects who have been randomized into the study. All subjects will be included in the analyses irrespective of protocol deviations or discontinuation from the study. No formal statistical analysis will be performed on safety data. Part 1 and Part 2 will be presented separately.

7.2.3.1. Adverse Events

The number of subjects reporting, and number of events reported will be presented in frequency tables (overall, by intensity, by relationship and by outcome) for each dose cohort in each group. AEs of special interest will be presented separately. No specific AEs of interest are prospectively defined for the purposes of this study. AEs will be coded according to MedDRA (Vn. 23.1). All AE and abnormal laboratory variables will be assessed according to the CTCAE v5.0 grading system. Treatment-emergent adverse events (TEAEs) (events not present at baseline and worsened in severity following the start of treatment) will be presented. The following summaries will be provided at a minimum (the SAP will provide further details of summaries that will be provided):

- A summary of the number and percentage of patients reporting any TEAE/SAE;
- A summary of the number and percentage of patients reporting TEAEs according to severity;
- A summary of the number and percentage of patients reporting related TEAEs/SAE;
- A summary of the number and percentage of patients reporting TEAE/SAE by treatment group, preferred term, and system organ class;
- A summary of the number and percentage of patients reporting TEAE/SAE by treatment group, severity, and system organ class;
- A summary of the number and percentage of patients reporting TEAE/SAE by treatment group, by relationship to study drug, and system organ class; and
- A summary of the number and percentage of patients reporting a TEAE leading to withdrawal from study treatment by treatment group, preferred term, and system organ class.

Listings of the above will also be presented for the DSMB reviews on an ongoing basis; for each subject and for each TEAE, the worst severity recorded will be attributed and used in the by-severity summaries.

7.2.3.2. Laboratory Analytes

Summary statistics (mean, median, standard deviation, minimum, and maximum) and change from baseline to each scheduled study assessment will be presented for all

continuous laboratory parameters. Baseline is defined as the latest non-missing laboratory assessment prior to the first study drug infusion.

For continuous laboratory parameters, shift tables of the number and percentage of patients with normal, low, or high results (as defined by the normal ranges) will be presented from baseline to the most extreme post baseline value by group and treatment group. For categorical urinalysis parameters, shift tables of the number and percentage of patients by classification at baseline and each post baseline visit will be presented. Abnormal laboratory values will be graded according to the latest version of the CTCAE (v5.0). All laboratory assessments will be listed.

7.2.3.3. Vital Signs

Summary statistics (mean, median, standard deviation, minimum, and maximum) and change from baseline to each scheduled study assessment for systolic and diastolic BP, HR, RR, SpO_2, and body temperature will be presented by treatment group. Baseline is defined as the latest non-missing vital sign value prior to the first study drug infusion. By-patient listings of all vital signs will be presented flagging the notable values.

7.2.3.4. ECG Evaluation

Summary statistics (mean, median, standard deviation, minimum, and maximum) and change from baseline to each scheduled study assessment for all ECG parameters will be presented by treatment group. Baseline is defined as the latest non-missing value prior to the start of the first treatment infusion.

A shift table from baseline to maximum post baseline ECG result of the number and percentage of subjects with normal, clinically insignificant abnormalities and clinically significant abnormalities will be presented. The number and percentage of subjects meeting threshold criteria for QTcF and QTcB will be presented by treatment group. The threshold criteria for QTcF and QTcB interval prolongation are as follows: [International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E14]: >450 ms, >480 ms, >500 ms, and interval increases from baseline of >30 ms and >60 ms.

By-patient listings of notable abnormal changes in ECG parameters will be presented along with the overall interpretation of ECGs for Part 1 at visits 1 (0, 48, 72, 96 hrs), 5, 7, 9 and 14 and Part 2 at Days 1 and 16.

7.2.3.5. Physical Examination

Results from the physical examinations (to include lung auscultation) will be summarized, as available, based on categories “normal” and “abnormal”. Baseline is defined as the latest non-missing PE value prior to the first study drug infusion. By-patient listings of physical examination data will be listed.

7.3. Sample Size

Given the dose escalation nature of this study, no specific sample size calculations were performed for Part 1. The number of subjects for each escalation was chosen to provide reasonable confidence in safety to inform the dose for Part 2. For Part 2, sample size is determined not based on statistical power; 15 subjects per group are planned to be enrolled, which is expected to provide sufficient data to evaluate the efficacy signals for this study.

7.4. Measures to Minimize Bias

7.4.1 Enrollment/Randomization/Masking Procedures

Study registration (subject number assignment) will be conducted through an IWRS system upon enrollment. The Sponsor, Investigator, pharmacy, and all study staff will be blinded.

7.4.2 Evaluation of Success of Blinding

Not Applicable

7.4.3 Breaking the Study Blind/Participant Code

The requirements for unblinding (to include emergency unblinding) will be controlled with immediate notifications transmitted to key stakeholders and recorded in the audit trail. All procedures will be detailed in the IWRS Procedure Manual.

8. CLINICAL MONITORING

US Biotest monitors, or delegates, will conduct scheduled site visits to the investigational centers or remotely, for the purposes of monitoring the study. The Investigator agrees to allow monitors and other authorized sponsor personnel or designees, access to the subject's complete and comprehensive medical and research study records, ISF, pharmacy document and any other applicable documents as needed to assure that the conduct of the study and the safety of the study subject is maintained and within compliance. In addition, FDA or other government agencies may request an inspection, following notification to the site. In such an event, the Investigator agrees to notify the Sponsor immediately, or at the earliest possible opportunity of the request. The clinical trial site will allow access to the inspectors to review requested records.

US Biotest will conduct the site initiation visit to provide the Investigator and study staff with a comprehensive overview of the protocol and study procedures and to review mutual obligations and requirements of regulatory authorities. The ISF (may be identified as regulatory file or binder) containing required documentation will be up to date throughout the life of the study and maintained at the site for reference and inspection.

Routine monitoring visits will be conducted on-site or remotely to assure compliance with the study protocol and regulatory requirements, to review and verify the subject's eCRF by comparing with source documents, to ensure adequate records of clinical supplies are maintained, and to assess the continued suitability of the investigational site. On completion of the study, the monitor will conduct a final visit to assess the conduct of the study, inform the Investigator of ongoing and final regulatory obligations and perform a final inventory of all clinical supplies to be either returned to US Biotest, destroyed or retained at the site.

9. QUALITY CONTROL AND QUALITY ASSURANCE

9.1. Electronic Data Capture

Data required by the protocol will be collected and entered into a validated data management system that is compliant with all regulatory requirements. The eCRF is an electronic document designed to record all protocol-required information to be reported to the Sponsor on each study subject.

Data recording must follow the instructions described in the CRF Completion Guidelines. The Primary Investigator (PI) has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The PI or designee, as identified on form FDA 1572, must electronically sign the completed eCRF for each participating subject to attest to its accuracy, authenticity, and completeness.

The EDC application being used in this study will be TrialMaster® version 5.0 from Anju Life Sciences software. TrialMaster studies are hosted from a state-of-the-art data center with rigorous physical and electronic security. All data is backed up daily to Iron Mountain, in Ohio and is also backed up to a hurricane-proof bunker in Fort Lauderdale, Florida. Anju Life Sciences is certificated with European "Safe Harbor" regulations (all necessary measures are in place to protect patient confidentiality even with the data being stored in a US data center). The data management and statistical CRO, McDougall Scientific Ltd., ensures that the development of the eCRF follows their SOPs which are based on the Systems Development Life Cycle methodology. Access to the system is restricted by username and password; these are controlled by the Data Management CRO. All personnel using the system will be trained and the training documented. All changes to the database are recorded in an audit trail. The database will be locked when all outstanding queries have been addressed, all agreed-to data is marked as source-verified, and the PI has signed off on the eCRF contents.

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements.

10. ETHICAL STANDARD

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki. Sponsor and Investigator will comply with their responsibilities as defined in 21 CFR 312.50-312.70.

10.1. Institutional Review Board (IRB)

Regulatory oversight will be conducted by Western IRB/Copernicus Group (WCG IRB) services. Before the start of the study, the sponsor will be responsible to submit the study protocol, informed consent form, and/or other appropriate documents to WCG IRB in accordance with local legal requirements. It is the responsibility of the Sponsor and Investigator to assure that all aspects of the IRB review are conducted in accordance with current regulations. The Sponsor and the Investigator must inform each other in writing that all ethical and legal requirements have been met before the first subject is enrolled in the study. Amendments to the protocol will be subject to the same requirements as the original protocol. All changes to the consent form will be IRB-approved; a determination will be made regarding whether previously consented participants need to be re-consented by the IRB.

10.2 Informed Consent Process

10.2.1. Subject Information and Consent

Subjects being considered for participation in this study will be provided an informed consent form (ICF) to read and sign before being permitted to participate, by the subject or by legal representative if subject is incapacitated and unable to consent. The ICF will describe the study drug and any prior findings from previous studies; study procedures including the timing of study clinic visits and responsibility to adhere to those timelines; any risks which may be associated with the study drug or the procedures being carried out in the study; and all other items required under 21 CFR Part 50.25.

10.2.2. Consent Procedures and Documentation

The Investigator will obtain informed consent from each subject enrolled in the study, in accordance with the FDA regulations 21 CFR 50.20 - 50.27 and the laws and regulations of the states and countries in which the investigation is being conducted. The IRB must approve the ICF to be used at the study site. Written IRB approval must be provided to the Investigator, before permitting subject enrollment into the study.

It is the responsibility of the Investigator to ensure that informed consent is obtained from the subject or legal representative before any activity or treatment is undertaken which is not part of routine care; consent will be obtained prior to participation in Part 1 or Part 2 of the study. This includes, but is not limited to, the performance of diagnostic or therapeutic procedures and the administration of the first dose of study drug.

In the event a protocol is amended, the consent form may be revised to reflect those changes; in which case, it is the responsibility of the Investigator to ensure that an amended consent is approved by the IRB and signed by all subjects currently on study, as well as those subsequently entered in the study, if required by the IRB. The terms of the consent and when it was obtained must also be documented in the eCRF. The original, signed informed consent document must be maintained on file at the study site and be made available for review during monitoring visits and site audits.

10.3. Confidentiality

All local legal requirements regarding data protection will be enforced. All study findings and documents will be regarded as confidential. The Investigator and members of the research team must not disclose such information without prior written approval from the Sponsor. The anonymity of participating subjects must be maintained to the extent required by law. Throughout documentation and evaluation, the subjects will be identified in the eCRFs and other documents submitted to the Sponsor by their initials (if allowed by institution, local and/or state requirements), birth date, and subject number. Documents are not to be submitted to the Sponsor which identify the subject and must be maintained in confidence by the Investigator. The subjects will be informed that all study findings will be stored and handled in the strictest confidence, according to local requirements, and that authorized research Investigators and agents of the FDA, the NCI, and authorized personnel or delegates of the Sponsor have the right to inspect their medical records.

11. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial site staff under the supervision of the site PI. The Investigator is responsible for ensuring the data is attributable, legible, contemporaneous, original, accurate, and complete (ALCOA+) compliant.

For electronic source, the institution must provide a secure, validated electronic medical record (EMR) data management system that is 21 CFR Part 11 compliant and meets all regulatory requirements, regulations and quality standards.

For paper source, documentation is expected to be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies.

Source documents will be maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents. Any discrepancies should be explained and captured in a progress note and maintained in the subject’s official electronic study record.

11.1 Study Records Retention

The Investigator must retain a copy of all study documents in accordance with FDA or local regulations, whichever are the more stringent.

The Investigator must maintain study documents:

- For a minimum of two years following the date the marketing application (NDA) is approved for the indication for which the drug was investigated;
- For a minimum of two years following the release date of the final report, if no marketing application is to be filed, or if the marketing application is not approved for the indication of which the drug was investigated or is discontinued, and FDA has been notified.

If the Investigator relocates, retires, or withdraws from the study for any reason, the study records may be transferred to an acceptable designee, such as another Investigator, another institution, or the Sponsor. The Investigator must obtain the Sponsor's written permission before transferring or disposing of any records.

11.2 Source Documents

An eCRF is required and must be completed for each consenting and enrolled subject by qualified and authorized personnel. Any correction to eCRF entries must be reflected in a validated audit trail. Only data required by the protocol for the purposes of the study should be collected within the EDC. The Investigator must maintain adequate and accurate source documents on which the eCRFs for each subject are based. They will be separate and distinct from the eCRFs. These records should include detailed notes on:

- The medical history prior to the subject's involvement in the study;
- Date of informed consent;
- Basic identifying information that links the subject medical record with the eCRFs;
- Screening, enrollment, treatment visits, End of Treatment and follow-up visit details including dates and reasons for early termination;
- Results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject;
- All AEs;
- The subject's exposure to the study medication;
- The subject's exposure to any concomitant therapy;
- All relevant observations and data on the condition of the subject throughout the trial;
- Justification for all entries in the subject's eCRF.

11.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice, or FDA or IRB requirements. The noncompliance may be on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are required and expected to be implemented promptly by the site.

These practices are consistent with ICH E6(R2):

- 4.5: Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3 and 4.5.4;
- 5.1: Quality Assurance and Quality Control, Section 5.1.1;
- 5.20: Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations as soon as possible after occurrence. All deviations must be addressed in study source documents, and reported to the Sponsor, the Data Management group and to the local IRB, per guidelines. The site PI/study staff is responsible to adhere to any IRB reporting requirements.

Serious site non-compliance and an inability of the Sponsor to bring the site back into compliance, will be reported to FDA in accordance with their requirements.

12. PUBLICATION AND DATA SHARING POLICY

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. The Sponsor will prepare an integrated clinical/statistical report. Publication/presentation of data is not allowed without explicit permission from The Sponsor. Submission of data for publication/presentation will be coordinated and approved by The Sponsor in collaboration with the Investigator.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in subjects, including AE. The ICMJE policy, and the Section 801 of the FDA Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Data entered to the ClinicalTrials.gov website will be in accordance with FDA requirements for this registration and for publication of study results on that site.

13. LIABILITY AND INSURANCE

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all local legal requirements. This insurance will cover all parties involved in the trial including, but not necessarily limited to, the PI, clinical trial site, and subjects. As a precautionary measure, the Investigator, the persons instructed by him and the hospital, practice or institute are included in such coverage in regard to work done by them in carrying out this study, to the extent that the claims are not covered by their own professional indemnity insurance.

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APPENDIX 1: ORDINAL SCALE FOR CLINICAL IMPROVEMENT (OSCI)

Score	Patient State	Descriptor
0	Uninfected	No clinical or virological evidence of infection
1	Ambulatory	No limitation of activities
2		Limitation of activities
3	Hospitalized; Mild Disease	Hospitalized, no oxygen therapy
4		Oxygen by mask or nasal prongs
5	Hospitalized; Severe Disease	Non-invasive ventilation or high-flow oxygen
6		Intubation and mechanical ventilation
7		Ventilation + additional organ support – pressors, renal replacement therapy, ECMO
8	Dead	Death

WHO R&D Blueprint novel Coronavirus: COVID-19 therapeutic trial synopsis. 2020 Feb 18.

APPENDIX 2: SPONTANEOUS BREATHING TRIAL (SBT)

Daily SBT will be conducted (as appropriate) to determine terminating oxygen needs. Daily monitoring of weaning criteria will be performed as per institutional standard and recorded.

Weaning Criteria for initiating SBT:

- $SpO_2 \geq 0.88$ with $FiO_2 \leq 0.40$ and PEEP ≤ 8 cm H_2O;
- PEEP and $FiO_2 \leq$ values of previous day;
- Acceptable spontaneous breathing efforts. (May decrease vent rate by 50% for 5 minutes to detect effort);
- BP ≥ 90/60 mmHg without vasopressor support.

If all above criteria are met, initiate trial with **up to** 30 minutes of spontaneous breathing with $FiO_2 < 0.5$ and PEEP < 5, as follows:

1. Place on T-piece, tracheostomy collar, or CPAP ≤ 5 cm H_2O with Pressure Support < 5 cm H_2O
2. Assess for tolerance for up to 30 minutes:
    a. $SpO_2 \geq 90$;
    b. Spontaneous $V_t \geq 4$ mL/kg predicted body weight (PBW);
    c. Respiratory rate ≤ 35/min;
    d. pH ≥ 7.3;
    e. No respiratory distress (distress = 2 or more).
        - HR > 120% of baseline
        - Marked accessory muscle use
        - Abdominal paradox
        - Diaphoresis
        - Marked dyspnea
3. If tolerated for at least 30 minutes, consider removal of endotracheal tube.
4. If not tolerated, resume pre-weaning settings.