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Statistical Analysis Plan

Protocol #:	USB002-2020-001
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
Project Code:	US21TXK
Study Phase:	II
Trial Design:	Randomized, double-blinded, placebo-controlled study with two parts: dose-escalation and dose expansion
Study Drugs:	Part 1, SOC plus USB002 at four sequential cohort doses of 90, 300, 600 and 900 ug/kg/day, or SOC plus placebo. Part 2, SOC plus USB002 at MTD determined in Part 1, or SOC plus placebo.
Patients:	18 years of age or older; shortness of breath and respiratory distress requiring oxygen due to COVID-19 infection. Part 1 – up to 48 subjects; Part 2 – up to 136 subjects.
Treatment Period:	About 74 days including follow-up (telemedicine visit)
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Date:	December 15, 2022
Status:	Final Version

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Date of Final Protocol:	17-Feb-2022
Amendments:	Protocol Version 6.0: 17-Feb-2022 Protocol Version 5.0: 27-Sep-2021
Date of Final Plan	15-Dec-2022

I have reviewed the Statistical Analysis Plan. My signature below confirms my agreement with the contents and intent of this document.

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Signature Approval Page
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15 DEC 2022

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1. List of Abbreviations Definition of Terms

Abbreviation or Term	Definition
ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
CI	Confidence Interval
COVID-19	Coronavirus disease - 2019
CRF	Case Report Form
CRO	Contract Research Organization
DLT	Dose-Limiting Toxicities
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
MedDRA	Medical Dictionary for Regulatory Activities (coding for AEs)
MTD	Maximum tolerated dose
MV	Mechanical Ventilation
NIV	Non-invasive Mechanical Ventilation
QTcB	Correction of QT interval values using Bazett's Formula
QTcF	Correction of QT interval values using Fredericia's Formula
SDLC	Systems Development Lifecycle
SOC	Standard of care
SOC	System Organ Class (from MedDRA coding dictionary)
SOP	Standard Operating Procedure
SpO2	Peripheral capillary oxygen saturation
TTP	Time to progression
WHODD	World Health Organization Drug coding Dictionary managed by the Uppsala Monitoring Centre

2. Background

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 an Angiotensin 1-7 [A(1-7)] to treat patients who have developed respiratory distress from COVID-19 infection (Soto 2020, Piero 2020, NCT 04332666).

This study's investigational product USB002 is pharmaceutically formulated 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.

According to the protocol (see Section 4.1 Study Design), this clinical trial includes two parts (dose escalation phase and dose expansion phase). Due to enrolment difficulty to find subjects meeting the study eligibility criteria, in Dec. 2022, the sponsor decided to stop the enrollment and terminate the trial early, when 21 subjects (all Part 1) have been enrolled: 6 subjects in each of the first three cohorts (90, 300 and 600 ug/kg/day) and 3 subjects in Cohort 4, (900 ug/kg/day).

3. Objectives

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.

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.

3.1. Primary Objective

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.

3.2. Secondary Objective(s)

None

4. Study Design and Endpoints

4.1. 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 (dose escalation phase), 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. The decision to dose-escalate, de-escalate, or increase the number of subjects in any dose level will be made by a Data Safety Monitoring Board (DSMB) based on the safety review of each cohort. Escalation will continue until Part 1 enrollment is completed and the MTD is determined.

In Part 2 (dose expansion phase), 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. Infusion will be discontinued at any time if SpO2 ≥ 94% 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.

4.2. Primary Endpoints

The primary endpoint of the study will be safety and tolerability, as demonstrated by adverse events (AE), changes in laboratory assessments, ECG assessments, vital signs, and concomitant medications (inotropes and vasopressors).

The primary endpoint of preliminary efficacy will be demonstrating the difference between USB002 and placebo groups in time to peripheral capillary oxygen saturation (SpO2) ≥ 94% on room air, sustained for at least 48 hours, through Day 28.

4.3. Secondary Endpoints

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.

4.4. Exploratory Endpoint

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.

4.5. Study Timeline and Schedule of Events

Table 1: Schedule of Assessments (Part 1)

Assessments	Screening (72 hours)	Timepoint																				
		Visit 1					Visit 2			Visit 3	Visit 4	Visit 5 End of Treatment[4]	Day									
		0 hrs[2]	4 hrs	8 hrs	12 hrs	24 hrs	32 hrs	40 hrs	48 hrs	72 hrs	96 hrs		7[5]	9[5]	12[5]	14[5]	16[5]	18[5]	21[5]	24[5]	28[5,6]	+/- 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	
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 2: 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. Data Management

5.1. Data Management

Most data will be collected at the sites via an electronic data capture (EDC) system. The study-specific application will be developed based on the protocol requirements and following the full Systems Development Lifecycle (SDLC). The development and management of the trial application, including security and account administration, will adhere to the Standard Operating Procedures (SOPs) at McDougall Scientific (a division of Alimentiv Inc.), in Toronto, Canada, the CRO retained by US Biotest to perform the statistics and data management functions for the trial.. All participants will be trained in the use of the application, and the training documented prior to each site being initiated.

The application design will, where appropriate, provide choice fields in the form of checkboxes, buttons and lists to aid in ensuring high quality standardized data collection. In addition Data Logic Checks (or data Edit Checks) will be built into the application based on variable attributes (e.g. value ranges), system logic (e.g. sequential visit dates) and variable logic (e.g. onset date must be before cessation date). Visual review and data responses will be overseen by a trained data manager.

The database will be locked when all the expected data has been entered into the application, all query responses have been received and validated, the designated data has been noted as monitored in the system and each investigator has signed off the casebook for each of their study subjects. The data coding must be accepted by the Sponsor and any Serious Adverse Events (SAEs) reconciled with the pharmacovigilance data base working with the Medical Monitor.

The data management processes are outlined in the project specific Data Management Plan (DMP); this and all related documentation are on file at McDougall Scientific and are identified by the project code US21TXK.

5.2. Coding

The medical history and adverse events were coded in MedDRA version 24 and signed off by US Biotest. All concomitant medication was coded using WHO Drug (version 2021 March) and reviewed and signed off prior to data base lock.

5.3. Missing Data

All missing data from CRF will not be imputed. Missing data will be considered missing at random.

5.4. Data Conversion for Analysis

To summarize quantitative endpoints, e.g., lab test results, some data collected as text values need to be converted to numeric values for analysis. Following conventional rules will be applied for this study.

- All "< xx" lab results will be converted to 0.99 * xx. The adjustment is -1% of xx.

All "> xx" lab results will be converted to 1.01 * xx. The adjustment is +1% of xx.

Above data conversions are only applied to data descriptive summaries. In by-subject data listings, original reported data "< xx" or "> xx" will be presented.

For this study's data submission and analysis, all EDC and external data will be converted to SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model) datasets. In the creation of SDTM and ADaM datasets, original lab test results from different sites (laboratories) need to be converted to results in SI units (the International System of Units). For some tests, data rounding may be applied during the conversion. The details will be provided in SDTM and ADaM's define.xml files and their support documents.

6. Change to Analysis as Outlined in the Protocol

6.1. Analysis of Part 2 Data

Due to the early termination of the study, no Part 2 (dose expansion phase) subject is enrolled. All analyses for Study Part 2 (dose expansion phase) will not be performed.

6.2. Time to Achieving 1-point and 2-point OSCI Score Decreases

According to the Protocol, time from Study Day 1 to achieving 1-point and 2-point OSCI decreases will be analyzed using time-to-event method.

Due to the early termination of the study and the small number of subjects in each treatment group, the outcomes will only be summarized descriptively. No time-to-event (Kaplan-Meier) estimates or curves will be provided. See section 8.3.8 for details.

6.3. Using of Vasoactive Agent

Protocol describes two efficacy endpoints about the using of vasoactive agent:

- The requirements for inotropes and vasopressors
- Total days of using vasoactive agent

These data are not captured by eCRF in separate eCRF form(s). Because of the early termination of the study, Sponsor decides that these endpoints will not be analyzed.

7. Statistical Methods

7.1. Analysis Data Sets

7.1.1. Full Analysis Set (FAS)

Full Analysis Set is defined as all subjects who have received at least one dose of study medication. All safety and efficacy assessments will be analysed based on the analysis dataset.

7.1.2. Per Protocol (PP) Population

All FAS subjects who did not withdraw prior to completing 48 hours in the treatment period will be included in the Per Protocol (PP) population.

All primary and secondary efficacy endpoints will also be analyzed for the PP population.

7.2. Calculated Outcomes

The following are key endpoints derived from data captured at the sites via the EDC system. Complete documentation of the calculations and data manipulation required to go from the CRF database to the analysis database are contained in the companion documents – SDTM Programming Specification File (SDTM Spec) and ADaM Programming Specification File (ADaM Spec).

Outcome	Calculation	Comment
Study Day	= the days from Day 1 (Date of the First Study Infusion) to the event date	
Time in Trial (days)	= Study completion/withdrawal date – date of informed consent date + 1 day	
Time on Treatment	= Date of last infusion – Date of first infusion + 1	
Baseline value	= Value reported prior to the first study treatment	If multiple values collected prior to the first infusion, non-missing value closest to the date/time of the first infusion is considered as baseline value
Change from Baseline	= Value collected at time point (Visit) – Baseline value	
BMI	= 10000 * (Weight in kg) / (Height in $cm)^2$	Value will be rounded to keep one decimal point
Treatment Emergent Adverse Event (TEAE)	= No, if onset date/time AE is before the date/time of the first study infusion = Yes, otherwise	According to conservative rule, all AEs that cannot be determined as started before the first study infusion will be considered as TEAE

Outcome	Calculation	Comment
Time from baseline to achieving $SpO_2 \geq$ 94% on room air	= Date of first achieving SpO_2 >= 94% on room air – Date of first infusion + 1 = null if the subject did not achieve SpO_2 >= 94% till study termination	
Number of ventilator-free days	= the number of days between Day 1 and Day 28 that subjects are both alive and free of mechanical ventilation	
Weaned from MV (Yes/No)	= Yes, if the subject was on MV and then weaned from MV through Day 28 = No, if the subject was on MV and kept using MV till Day 28 = null, if the subject did not use MV from Day 1 to Day 28	
Progressed to MV (Yes/No)	= Yes, if the subject progressed from non-invasive (at baseline) to MV on/before Day 28 = No, if the subject was keeping non-invasive till Day 28	
Time to Progression (TTP)	= First MV date – Date of first infusion + 1 = null, if the subject was keeping non-invasive till Day 28	
Time to hospital discharge	= Hospital discharge date – Study Day 1 + 1 = null if the subject was staying in hospital till Day 28	
Achieving 1-point OSCI Decrease at Visit (Yes/No)	= Yes, if OSCI at visit – OSCI at Day 28 (or End of Treatment) >= 1 = No, OSCI at visit – OSCI at Day 28 (or End of Treatment) < 1 = null, if OSCI at Day 1 and/or at visit were missing	
Time to Achieving 1-point OSCI decreasing	= Date of first achieving 1-point OSCI decreasing – Study Day 1 + 1 = null if never achieving 1-point decreasing	

Outcome	Calculation	Comment
Achieving 2-point OSCI Decrease at Visit (Yes/No)	= Yes, if OSCI at visit – OSCI at Day 28 (or End of Treatment) >= 2 = No, OSCI at visit – OSCI at Day 28 (or End of Treatment) < 2 = null, if OSCI at Day 1 and/or at visit were missing	
Time to Achieving 2-point OSCI decreasing	= Date of first achieving 2-point OSCI decreasing – Study Day 1 + 1 = null if never achieving 2-point decreasing	

7.3. Interim Analysis

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

7.4. Analysis Methods

All calculations and analyses will be performed using SAS version 9.4 or higher under the Windows Server 2012R2 operating system at McDougall Scientific Ltd. in Toronto, Canada. Continuous data will be summarized via PROC MEANS - mean, standard deviation, median, range, and 95% CIs, while categorical data will be presented as counts and percentages (or proportions) via PROC FREQ for the descriptive displays.

No statistical inference will be made for all outcomes.

8. Results

8.1. Study Subjects

All enrolled and treated subjects will be the analysis population for all analyses. All data collected in EDC will be at a minimum listed.

All outcomes will be summarized between the total treated subjects and total placebo subjects.

All safety and subject level outcomes will also be summarized by cohort (assigned dose level). All placebo groups will be combined as one group.

For all efficacy outcomes, see 8.2.1 and 8.2.2, the difference between treatment and placebo groups within each cohort (dose level) will also be presented, if data applicable.

All available data of screen failures will be provided in a separate listing.

8.1.1. Patient Disposition

All subjects will be accounted for. All early withdrawals will be summarized by primary reason for discontinuation; these will be summarized by treatment group.

Treatment exposure (time in trial and time on treatment) will be summarized by cohort for all subjects in the analysis dataset.

8.1.2. Baseline Characteristics

Demographic (age, sex, ethnicity, and race) and baseline body measurements and vital signs (height, weight, BMI, heart rate, blood pressure, and ECG assessments) will be summarized.

Ordinal Scale for Clinical Improvement (OSCI) score at screening will be summarized.

8.1.3. Medical History

Medical history will be coded in MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT).

8.1.4. USB002 Administration

USB002 administration data, including dose of administration, infusion start/end date, start/end time, start rate of infusion, and all information of infusion rate changes, infusion incompletion reason, and related AEs, if applicable, will be listed.

8.1.5. RT-PCR SARS-CoV-2 Test

RT-PCR SARS-CoV-2 Test at screening will be listed.

8.2. Primary Outcomes

The primary endpoint of the study will be safety and tolerability, as demonstrated by adverse events (AE), changes in laboratory assessments, ECG assessments, vital signs, and concomitant medications (inotropes and vasopressors). These outcomes will be summarized by cohort. See details in sections 8.2.1 to 8.2.6.

Co-primary endpoint is the difference between USB002 and placebo groups in time to peripheral capillary oxygen saturation (SpO2) ≥ 94% on room air, sustained for at least 48 hours, through Day 28. All peripheral capillary oxygen saturation (SpO2) results from baseline to Day 28 will be listed (and summarized if applicable). See section 8.2.7.

No statistical inference will be made for primary endpoint.

8.2.1. Adverse Events

Only treatment emergent adverse events (TEAEs) will be summarized. Summaries will be provided by dose level cohort with all placebo groups combined. Following summaries will be provided:

- Overview of TEAEs - include the total number of TEAEs, serious TEAEs, DLT, and TEAE leading to death
- TEAEs by MedDRA System Organ Class (SOC) and Preferred Term (PT)
- TEAEs by MedDRA SOC, PT, and severity
- TEAEs by MedDRA SOC, PT, and relationship to treatment
- TEAEs by MedDRA SOC, PT, and outcome
- Serious TEAES by MedDRA SOC, and PT
- TEAE leading to death
- DLT.

All these summaries will include the counts and frequencies of events, and of subjects who had events.

All TEAEs will be listed by subject. Serious TEAEs, TEAEs leading to death, and DLTs will be listed separately.

8.2.2. Respiratory Results

All respiratory data, including all assessments, Non-invasive Mechanical Ventilation (NIV) data, and Mechanical Ventilation Status (MVS) data, will be listed.

8.2.3. Laboratory Assessments

Laboratory assessments with quantitative results, including raw assessments at each visit and change from baseline at post-baseline visits, will be summarized by dose level cohort, and visit for each test.

Each no-missing lab result's normal/abnormal status (e.g., normal/low/high for quantitative results, and normal/abnormal for qualitative results) will be calculated based on the normal reference ranges provided by the lab. The status will be summarized using shift tables from baseline to each post-baseline time point.

All lab data will be presented in by-subject data listing.

8.2.4. ECG Assessments

ECG assessments (heart rate, PR interval, QRS duration, QT interval, QTcF and QTcB intervals, and overall assessments (Normal /Not clinically significant abnormal /Clinically significant abnormal) will be summarized by dose level cohort and visit.

Change of ECG values from baseline values will be summarized for all post-baseline visits.

8.2.5. Vital Signs

Vital Signs (weight, BMI, systolic and diastolic blood pressure, heart rate, and temperature) will be summarized by dose level cohort and visit.

Change of vital signs (weight, BMI, systolic and diastolic blood pressure, heart rate, and temperature) from baseline values will be summarized for all post-injection visits.

Unscheduled vital signs will only be presented in by-subject listing.

8.2.6. Time to peripheral capillary oxygen saturation (SpO2) ≥ 94% on room air

The time from baseline to achieving SpO2 ≥ 94% on room air will be calculated for each subject. Two summaries will be provided:

- All subjects treated with USB002 vs. all placebo subjects
- USB002 subjects vs. placebo subjects by cohort. That is, comparing between two treatment groups within each cohort (dose level)

All data will be listed.

8.3. Secondary Outcomes

8.3.1. All-cause mortality at Day 60.

All death data will be listed. If data applicable, the death rate at Day 60 will be summarized by total treatment groups, and by cohort and treatment group.

8.3.2. Number of ventilator-free days

The number of ventilator-free days (defined as the number of days between Day 1 and Day 28 that subjects are both alive and free of mechanical ventilation) will be summarized by total treatment groups, and by cohort and treatment group, if data applicable.

All Mechanical Ventilation Status data will be listed.

Total MV duration days will be listed and summarized.

8.3.3. Proportion of subjects weaned from mechanical ventilation through Day 28

The number of subjects who were on MV and then weaned from MV through Day 28 will be counted and the proportion of those subjects out of all subjects applied MV will be summarized.

8.3.4. Proportion of subjects progressing from non-invasive (at baseline) to mechanical ventilation.

The number of subjects who progressed from non-invasive (at baseline) to MV will be counted and the proportion of those subjects out of all subjects were not on MV at baseline will be summarized.

8.3.5. Time to Progression (TTP) from non-invasive (at baseline) to mechanical ventilation.

Time to Progression (TTP), i.e., time from first treatment with study medication to MV will be calculated. If enough data applicable, the outcome will be summarized.

8.3.6. Time to hospital discharge

Total days from Day 1 to hospital discharge will be listed and summarized.

8.3.7. Change of OSCI status from Day 1 to Day 28

For each subject, following outcomes will be calculated:

- Days from baseline to the date with OSCI score decreased 1-point from baseline
- Days from baseline to the date with OSCI score decreased 2-point from baseline
- OSCI score change from baseline to Day 28
- Achieving 1-point decrease of OSCI score at Day 28 (Yes/No)
- Achieving 2-point decrease of OSCI score at Day 28 (Yes/No)

These outcomes will be summarized.

All OSCI data will be listed.

8.4. Other Outcomes

8.4.1. Prior and Concomitant Medications

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.

A summary of all concomitant medications taken during the course of the study will be presented in tabular form by therapeutic drug class (ATC Level 2 code) and generic drug name (ATC Level 4 code) using the World Health Organization (WHO) Drug Dictionary (WHODD). The summaries will be provided for medications prior to and following the first infusion separately.

8.4.2. Pregnancy Test

Pregnancy test will be conducted at Screening Visit and Day 1, if not within 72 hours of Screening test. For female subjects, the childbearing potential data and all pregnancy test data will be listed.