CLINICAL TRIAL PROTOCOL: V3011902

Protocol Number: V3011902

Protocol Date: Original Protocol (Version 1.0)/ 8 March 2021
Protocol Amendment 1 (Version 2.0)/27 April 2021
Protocol Amendment 2 (Version 3.0)/12 May 2021
Protocol Amendment 3 (Version 4.0)/ 3 August 2021
Protocol Amendment 4 (Version 5.0)/ 10 September 2021
Protocol Amendment 5 (Version 6.0)/ 9 January 2022
Protocol Amendment 6 (Version 7.0)/ 18 March 2022

Protocol Title: Phase 3, Randomized, Placebo-Controlled, Efficacy and Safety Study of VERU-111 for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Patients at High Risk for Acute Respiratory Distress Syndrome (ARDS).

IND number: 149282

EudraCT number: 2021-001194-24

Clinical Phase: 3

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1.0 LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic Case report form
ECOG	Eastern Cooperative Oncology Group
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
IMP	Investigational medicinal product
IRB	Institutional review board
IUD	Intrauterine device
IUS	Intrauterine system
LAR	Legally Authorized Representative
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LMWH	Low molecular weight heparin
MedDRA	Medical dictionary of regulatory activities
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over the Counter
PRN	*Pro re nata* – As Needed
RRT	Renal replacement therapy
SAE	Serious adverse event
SAP	Statistical analysis plan

2.0 PHASE 3 PROTOCOL SUMMARY

Study Number:	V3011902
Title:	Phase 3, Randomized, Placebo-Controlled, Efficacy and Safety Study of VERU-111 for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Patients at High Risk for Acute Respiratory Distress Syndrome (ARDS)
Primary Objectives:	To demonstrate the efficacy of VERU-111 in the treatment of SARS-Cov-2 Infection by assessing its effect on the proportion of patients who die on study (prior to Day 60).

<table>
<tr><td>Secondary Objectives:</td><td>The secondary objectives/endpoints on this study are:

1. The proportion of subjects that are alive without respiratory failure at Day 15, Day 22 and Day 29. Day 29 is the key secondary endpoint in this study. Respiratory failure is defined as endotracheal intubation and mechanical ventilation, extracorporeal membrane oxygenation, high-flow nasal cannula oxygen delivery, noninvasive positive pressure ventilation, clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision making is driven solely by resource limitation.
2. Days in ICU
3. WHO Ordinal Scale for Clinical Improvement change from baseline to Day 15, Day 22, and Day 29

<table><tr><th>Patient State</th><th>Descriptor</th><th>Score</th></tr><tr><td>Uninfected</td><td>No clinical or virological evidence of infection</td><td>0</td></tr><tr><td>Ambulatory</td><td>No limitation of activities</td><td>1</td></tr><tr><td></td><td>Limitation of activities</td><td>2</td></tr><tr><td>Hospitalized, Mild disease</td><td>Hospitalized, no oxygen therapy</td><td>3</td></tr><tr><td></td><td>Oxygen by mask or nasal prongs</td><td>4</td></tr><tr><td>Hospitalized, Severe disease</td><td>Non-invasive ventilation or high-flow oxygen</td><td>5</td></tr><tr><td></td><td>Intubation and mechanical ventilation</td><td>6</td></tr><tr><td></td><td>Ventilation + additional organ support – pressors, RRT, ECMO</td><td>7</td></tr><tr><td>Death</td><td>Death</td><td>8</td></tr></table>
4. Days on mechanical ventilation
5. Days in hospital
6. Proportion of subjects that die on study at Day 15, Day 22, and Day 29.
7. Change from baseline in viral load (baseline to Day 9)</td></tr>
<tr><td>Safety Objective:</td><td>To assess the safety, tolerability, and risk/benefit of VERU-111</td></tr>
</table>

Design:	This study is a multicenter, randomized, placebo-control, efficacy and safety study of VERU-111 for the treatment of COVID-19. Subjects will receive either 9 mg of VERU-111 or matching placebo orally or through nasogastric tube daily for up to 21 days or until the subject is discharged from the hospital, whichever comes first. The primary efficacy endpoint of the study will be the proportion of subjects that die prior to Day 60. The total study duration for a subject from screening to follow up visit is planned to be 62 days. In addition to the safety of VERU-111, an evaluation of the efficacy of VERU-111 on SARS-CoV-2 (COVID-19) compared to the placebo control will be evaluated as part of the Independent Data Monitoring Committee (IDMC).
Subjects:	Approximately, 210 subjects are planned to be randomized at a 2:1 ratio into two treatment arms (140 subjects in the VERU-111 treated group and 70 subjects in the Placebo treated group). Randomization will be stratified by baseline WHO Ordinal Scale score of 4, 5 and 6 such that subjects with a WHO Ordinal Scale of 4, 5 and 6 at baseline are approximately equally distributed between the treatment groups. NOTE: Throughout this protocol the terms “patients” and “subjects” are used interchangeably.
Treatments:	Subjects in the VERU-111 treatment groups will receive standard of care, plus oral daily VERU-111 9 mg for 21 days or until released from hospital, whichever comes first. Subjects in the Placebo treatment group will receive standard of care, plus a placebo capsule for 21 days or until released from hospital, whichever comes first.
Procedures:	Potential study participants will undergo a series of screening evaluations, including the collection of demographic information, within 3 days prior to randomization. Subjects who give written informed consent and satisfy the selection criteria will be enrolled into the study. SpO_2 levels will be taken at screening, baseline (Day 1) and on Days 3, 9, 15, 22, and 29.

	Safety evaluations including assessment of adverse events (Days 1-22, Day 29, Day 45, and Day 60), 12-lead electrocardiogram (single) (screening, Day 15, Day 22, and Day 29) and clinical laboratory results: urinalysis (screening, baseline, Day 22, and Day 29), hematology (screening, baseline, Day 3, Day 9, Day 15, Day 22, and Day 29), and serum chemistry (screening, baseline, Day 3, Day 9, Day 15, Day 22 and Day 29).

3.0 INTRODUCTION

3.1 Background

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is an enveloped, nonsegmented, positive-sense, single stranded RNA virus with an unusually large RNA genome, a nucleocapsid, and club-like spikes (S protein) that project from their surface and from which they are named. It belongs to the *betacoronavirus* category which includes SARS-CoV and MERS-CoV. These viruses have been responsible for epidemics with variable severity with both respiratory and extra-respiratory clinical manifestations, highly contagious, and mortality rates between 10-35% (Cascella 2020). The coronavirus superfamily (*Coronaviridae*) includes several human pathogens with large RNA genomes, e.g., influenza and viral encephalitis and they are classified into alpha, beta, delta and gamma coronavirus families and then further divided into Lineages A, B, C and D. SARS-CoV-2 is a Lineage B *betacoronavirus* (Gorbalenya 2020).

Starting in December 2019, SARS-CoV-2 infection resulted in Coronavirus Disease 2019 (COVID-19) and consequently has been declared a global pandemic with 98,050,801 cases and 2,098,174 deaths worldwide as of 22 January 2021 at 1:44 GMT (January 22, 2021; Worldometers.info).

Viruses have efficient mechanisms that take control of their host's cellular machinery to carry out viral replication, assembly and to exit from the cell to spread infectious virions. Given the spatial distances between the point of virion entry at the plasma membrane to the location in the cell where RNA replication (nucleus) and viral assembly occur in the ER and Golgi and then the newly generated virions have to travel back out to the plasma membrane to egress out of the cell, it is no wonder that the virus's most critical task is to hijack the host's internal transportation system, the cytoskeleton (Ward 2011). The cytoskeleton has three major types of protein filaments: microfilaments (actin), microtubules (tubulin), and intermediate filaments. The principal ones involved in viral replication and trafficking (transport) are microtubules and actin since these are the two main filament systems involved in cellular transport (Ward 2011).

Microtubules are important for cell shape, transport, motility, and cell division (Heald 2002). Microtubules are dynamic long polar fibers/filaments that result from the polymerization of α and β tubulin heterodimer subunits with a positive end located at the plasma membrane and a minus end facing the nucleus at the microtubule organizing center (MTOC). From the MTOC, microtubule fibers radiate out from the nuclear area towards the periphery of the cell. Microtubules are dynamic network systems, meaning that, they undergo rapid polymerization (add α and β tubulin subunits heterodimers) to grow, and subsequent rapid depolymerization (remove α and β tubulin subunits heterodimers) to shrink. This "dynamic" growing and shrinking serves the constantly changing transportation requirements of the cell. Large macromolecules, like viruses, engage with specialized motor proteins (kinesins and dyneins) (Dohner 2005; Biswas 2014; Han 2012; Hara 2009). Kinesins and dyneins attach, carry, and move the virus cargo up and down these microtubule tracks to travel long distances to reach the different compartments within the cell (Ward 2011; Simpson 2020; Cooper 2000).

Microtubule based transportation is a critical aspect of viral replication (Naghavi 2017; Dohner 2005). In fact, viral infection or expression of viral proteins alters the organization of the microtubular networks to serve their need to replicate and spread infectious virion. Microtubules not only facilitate infection, but microtubules are actively manipulated by viruses (Naghavi 2017). Furthermore, microtubule inhibiting agents that disrupt microtubule networks suppress viral infection (Rudiger 2016).

Virus-cell surface interactions, virus entry and internalization-

Although microtubules are located within the cell, they are able to influence the viral infection from the onset. Viruses utilize specific sites and proteins to attached to the cell surface. The spatial organization of these surface receptors and entry factors are controlled in part by the polarization of the microtubular array (Naghavi 2017). When added early, nocodazole, a microtubule depolymerizing drug, decreased mouse hepatitis coronavirus virus infection by affecting plasma membrane entry by endocytosis (Burkard 2014). There are apparently other ways that entry and internalization may occur as human coronavirus NL63 internalization and vesicle entry was not affected by nocodazole (Milewska 2018).

In the case of SARS-CoV, the first stage of interaction with the microtubule cytoskeleton occurs when the Spike (S) protein mediated attachment to the cell surface (Ren 2015). After binding, the virus particles actively rearrange the cytoskeleton by regulating the FAK/Cofilin/Rac/Cdc42 pathway (Lv 2019).

Virus intracellular transport via microtubules to the perinuclear region-

Many viruses require microtubules at cell entry for efficient nuclear targeting (Dohner 2005). Vesicular transport occurs via microtubule trafficking and the corresponding specialized motor proteins. In the case of the Mouse Hepatitis Coronavirus Virus, the early secretory pathway is important in the formation of the replication complex (Knoops 2010; Oostra 2007). Intracellular transport of the endocytosed vesicles containing coronavirus utilizes S-protein bound to β- tubulin on microtubules to locate to the perinuclear region of the cell. Viruses can also modulate microtubular dynamics to promote rapid transport to nucleus (Naghavi 2017; Suomalainen 2001). Coronaviruses may also have interactions of S proteins with the specialized motor proteins like kinesins and dyneins (Rudiger 2016).

Virion replication and assembly and egress of infectious viral particles out of the cell-

Virus particle assembly occurs in the ER-Golgi intermediate compartment (ERGIC) and is orchestrated by the M protein. M provides the scaffold for virion morphogenesis and M-S and M-N interactions facilitate the recruitment of structural components to the assembly site. Coronavirus particles budding into the ERGIC are transported in smooth walled vesicles and trafficked via microtubules for release by exocytosis. Host factors, specifically, the interactions between the cytoskeleton and other structural proteins are essential in this process. Interactions between tubulin and the cytosolic domain of the S protein of human coronavirus-229E, human coronavirus-NL63, and TGEV are required for successful assembly and release of viral particles (Reviewed in Fung 2019). RNA viruses utilize diverse structures within the cytoskeleton for their replication which rely on microtubules to form and function (Naghavi 2017). Nocodazole, a microtubule depolymerizing agent, blocks the movement and

fusion of capsids and nucleoprotein particles to the budding ER/Golgi compartments to form virions as well as the secretory microtubule trafficking to egress new virions resulting in reduced virus yields (Eichwald 2012; Criglar 2014; Dohner 2005).

To evaluate early assembly events, alpha (HCoV-229E, HCoV-NL63, and TGEV) and beta (SARS-CoV) coronaviruses S proteins were treated with nocodazole. The pharmacological action of nocodazole is the inhibition of tubulin polymerization. Untreated cells had long and filamentous tubulin structures (microtubules) and the S protein accumulated near the nucleus (ERGIC) and less S protein distributed in the cytosol, whereas the nocodazole treated cells had dispersed and patchy tubulin fragments and the S proteins were "differentially distributed", or scattered throughout the cytoplasm (Rudiger 2016). Also, following nocodazole treatment, M protein amount was decreased and there was a reduced colocalization of S and M proteins (Rudiger 2016). Nocodazole treatment resulted in both a significant reduction in viral particles and these particles had very little S protein, and thus, the virions were less infectious as well (Rudiger 2016). In fact, nocodazole treatment at all time points resulted in significantly lower virus titers in cell culture supernatant versus untreated infected cells (Rudiger 2016).

In summary, tubulin interacts with the cytoplasmic domain of *alphacoronavirus* and *betacoronavirus* SARS-CoV spike S proteins. Rudiger et al. (2016) conclude that the reduction in infectious virus titer following treatment with a drug that causes microtubule depolymerization is mainly because there is less S protein present at the assembly site due to impaired S protein-microtubule transport and that the incorporation process of S protein itself into virions is tubulin-dependent. Furthermore, disruption of microtubule trafficking impaired the egress of these poorly assembled virions with less surface spike S proteins, less infectious, out of the cell. A microtubule depolymerizing agent may be effective in treating in treating coronavirus infection to disrupt microtubule trafficking critical for virus replication cycle.

Colchicine-like Activity

The central mechanism of colchicine clinical anti-inflammatory and anti-viral activities is based on its ability to bind the "colchicine binding" sites on alpha and beta tubulin which when incorporated into microtubule block subsequent microtubule polymerization (Slobodnick 2018). Inhibition of tubulin polymerization is responsible for the effects of colchicine on cell migration, cytokine release, and intracellular trafficking (antiviral) and disruption of inflammatory cell activities seen for acute gout and familial Mediterranean fever. Colchicine modulates leucocyte mediated inflammatory activities including inhibition of leucocyte production of superoxides and release of various cytokines and pyrogens (Slobodnick 2018). Colchicine-like agents may be useful to treat the "cytokine storm" seen with SARS-CoV 2. IL-18 is a member of the IL-1 cytokine family and unopposed elevated levels of IL-18 concentrations have been associated with macrophage activation syndrome and poor clinical outcomes in severe inflammatory and septic shock conditions (Verweyen 2020). Interestingly, colchicine abrogates IL-1β and IL-18 overexpression by reducing its transcription to reduce severe inflammation and septic shock. Verweyen et al. (2020) also showed that colchicine as well as nocodazole abrogated IL-18 expression confirming that microtubule depolymerization is the mechanism.

3.2 Target Indication and Pharmacologic Activity

VERU-111 is orally bioavailable bis-indole that binds the "colchicine binding site" of α and β tubulin and inhibits tubulin polymerization at low nanomolar concentrations. VERU-111 is neither a substrate for MDRs including P-gp, MRPs, and BCRP, nor CYP3A4. VERU-111 also decreases the transcription of βI, βIII, and βIV-tubulin isoforms (Li 2012). VERU-111 is currently under development for the treatment of metastatic castration resistant prostate cancer in patients who have failed an androgen receptor targeting agent.

3.3 Study Rationale

In a Phase 2, double-blind, placebo-controlled clinical study the safety and efficacy of VERU-111 in the treatment of SARS-CoV-2 in patients at high risk for ARDS was assessed. Thirty-nine (39) hospitalized patients at high risk for ARDS were randomized to 18 mg of VERU-111 (powder in capsule formulation) or matching placebo. The primary efficacy endpoint for the study was the proportion of patients alive without respiratory failure at Day 15, Day 22, and Day 29. The key secondary endpoints in the study were days on mechanical ventilation, days in intensive care unit (ICU), and proportion of patients discharged from the hospital on Day 15, Day 22, and Day 29. The efficacy conclusions in the Intent-to-Treat (ITT) population from a post-hoc analysis from the Phase 2 study are:

- VERU-111 reduced the proportion of patients who died on study (up to Day 60) from 30% (6/20) in the placebo group to 5% (1/19) in the VERU-111 treated group. This is an approximately 82% reduction in mortality in the VERU-111 treated group.
- VERU-111 reduced the proportion of patients that are treatment failures, i.e. death or respiratory failure from 35.0% in the placebo group to 15.8% in the VERU-111 treated group at Day 15 and from 30.0% in the placebo group to 10.5% in the VERU-111 treated group at Day 29. This represents an approximately 55% reduction in treatment failures at Day 15 and a 65% reduction in treatment failures at Day 29 in the VERU-111 treated group compared to placebo.
- VERU-111 reduced the days on mechanical ventilation from an average of 5.4 days in the placebo group to 1.6 days in the VERU-111 treated group. This represents a 3.4-fold increase in the days on mechanical ventilation in the placebo group compared to the VERU-111 treated group.
- VERU-111 reduced the days in ICU from an average of 9.6 days in the placebo group to 3.0 days in the VERU-111 treated group. This represents a 3.2-fold increase in the days in the ICU in the placebo group compared to the VERU-111 treated group.
- There is an imbalance in the gender distribution between the treatment group such that the placebo group is 85% male (17/20) and the VERU-111 treated group is 53% male (10/19). This imbalance was evaluated as a covariate in the analysis but did not have a significant effect on the conclusions of the study.
- The use of remdesivir and dexamethasone did not have a significant effect on patient outcomes in the study.
- In patients with a WHO disease severity score of ≥5 at baseline, the proportion of patients that died on study (up to Day 60) in the placebo group was 46% compared to 10% in the VERU-111 treated group. This represents a 78% reduction in death in the

VERU-111 treated group compared to placebo. It is important to note that in the Phase 2 study, the 6 patients in the placebo group and the 1 patient in the VERU-111 treated group that died on study all had a WHO disease severity score of ≥5 at baseline. Therefore, randomization into the Phase 3 study will be stratified by WHO scale at baseline such that patients who have a WHO disease severity score of 4, 5, and 6 at baseline are approximately equally distributed between the treatment groups. This is a similar population as was used in the Phase 2 study and accounts for patients that move from WHO severity score of 4 to 5 and then from WHO severity score of 5 to 6 to 7 quickly.

The Phase 2 clinical study was hypothesis generating. A 78-82% reduction in mortality, a 55-65% reduction in death or respiratory failure, 3.2-fold higher mean days in ICU and 3.4-fold higher mean days on mechanical ventilation in the Placebo group compared to the VERU-111 treated group are all clinically relevant observations and warrant the continued development of VERU-111 in the treatment of SARS-CoV-2 in patients at high risk for ARDS.

There were no drug related serious adverse events (SAEs) observed in the Phase 2 clinical study of VERU-111 in SARS-CoV-2 infected patients. There were no drug related serious adverse reactions (≥Grade 3).

The relative bioavailability (pharmacokinetics) of the VERU-111 powder in capsule (PIC) formulation has been assessed and compared to a to-be-marketed VERU-111 formulated capsule (FC) formulation. Additionally, the effect of high fat meal (food effect) was also assessed for both formulations. The data are presented in Table 1.

Table 1 The Steady State Pharmacokinetics of VERU-111 Powder in Capsule (PIC) and Formulated Capsule (FC) Under Fasted and Fed Conditions

	63 mg PIC (fasted)	63 mg PIC (fed)	31.5 mg FC (fasted)	31.5 mg FC (fed)
N	6	6	6	6
Cmax (ng/mL)	148.1±64.7	97.8±53.5	182.2±32.6	169.9±104.2
Tmax (hr)	2.17±0.98	7.67±2.66	1.67±1.21	4.08±2.69
$AUC_{0\text{-}24h}$ (ng*hr/mL)	1006.16±376.29	984.80±519.62	973.58±307.87	1011.27±512.54
T½ (hr)	7.38±4.59[a]	5.06±1.53[b]	5.11±1.24	4.89±1.09[c]

AUC = area under the curve; FC = formulated capsule; PIC = powder in capsule.
a. One patient had an aberrant T½ of 16.09 hours. If this value is removed from the analysis, then the T½ is 5.64 hours (±1.90)
b. The terminal T½ was calculable in 3 of 6 subjects in the 63 mg PIC fed group.
c. The terminal T ½ was calculable in 5 of 6 subject in the 31.5 FC fed group.

The conclusions from this study are:

1. The $T_{1/2}$ of VERU-111 is approximately 5 hours and steady state is reached within 5 days of daily dosing.

2. Administration of VERU-111 FC formulation with a high fat meal has minimal effect on the $AUC_{0\text{-}24}$ or Cmax at steady state. However, the shape of the curve appears to be

different with a high fat meal with the Tmax shifted to the right. Based on these data, the instructions for use will be VERU-111 FC may be taken without regard to food.

3. The relative bioavailability of the VERU-111 FC formulation compared to the VERU-111 PIC formulation shows that a 31.5 mg dose of the VERU-111 FC formulation shows similar pharmacokinetics compared to the 63 mg dose of the VERU-111 PIC formulation. The dose of VERU-111 PIC used in the Phase 2 study was 18 mg. Therefore, for the VERU-111 dose for treatment of SARS-CoV-2 in patients at high risk for ARDS, a 9 mg dose of VERU-111 FC will be used.

4.0 STUDY OBJECTIVES

4.1 Primary Objectives

To demonstrate the efficacy of VERU-111 in the treatment of SARS-CoV-2 infection by assessing its effect on the proportion of subjects that die on study (up to Day 60).

4.2 Secondary Objectives

The secondary objectives/endpoints on this study are:

1. The proportion of subjects that are alive without respiratory failure at Day 15, Day 22, and Day 29. Day 29 is the key secondary endpoint. Respiratory failure is defined as endotracheal intubation and mechanical ventilation, extracorporeal membrane oxygenation, high-flow nasal cannula oxygen delivery, noninvasive positive pressure ventilation, clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision making is driven solely by resource limitation.
2. Days in ICU
3. WHO Ordinal Scale for Clinical Improvement change from baseline to Day 15, Day 22, and Day 29

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

4. Days on mechanical ventilation
5. Days in hospital
6. Proportion of subjects that die on study at Day 15, Day 22, and Day 29.
7. Change from baseline in viral load (baseline to Day 9)

4.3 Safety Objective

To assess the safety, tolerability, and risk/benefit of VERU-111

5.0 STUDY DESIGN

5.1 Treatment Groups and Allocation of Subjects

This randomized, placebo-control clinical study consists of two treatment arms: VERU-111 9 mg treated group, and Placebo treated group. Subjects will be randomized in a 2:1 fashion to the VERU-111 treated group and Placebo treated group, respectively.

All patients will receive standard of care for the treatment of SARS-CoV-2 infection (COVID-19).

Randomization will be stratified by baseline WHO Ordinal Scale score of 4, 5 and 6 such that subjects with a WHO Ordinal Scale of 4, 5 and 6 at baseline are approximately equally distributed between the treatment groups.

5.2 Study Duration

The study will require that each subject in the study receive 9 mg daily oral dose of VERU-111 or placebo for up to 21 days (Day 21) or until the patient is discharged from the hospital (whichever comes first) with efficacy and safety follow up continuing to Day 60 of the study. The total duration of the study for a subject in the study from screening to follow-up visit (approximately Day 60 on study) will be approximately 62 days.

5.3 Efficacy Endpoints

5.3.1 Primary Endpoint

The primary endpoint for the study is the proportion of subjects that die on study (up to Day 60).

5.3.2 Secondary Endpoints

The secondary endpoints on this study are:

1. The proportion of subjects that are alive without respiratory failure at Day 15, Day 22, and Day 29. Day 29 is the key secondary endpoint. Respiratory failure is defined as endotracheal intubation and mechanical ventilation, extracorporeal membrane oxygenation, high-flow nasal cannula oxygen delivery, noninvasive positive pressure ventilation, clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision making is driven solely by resource limitation.
2. Days in ICU
3. WHO Ordinal Scale for Clinical Improvement change from baseline to Day 15, Day 22, and Day 29
4. Days on mechanical ventilation

5. Days in hospital
6. Proportion of subjects that die on study at Day 15, Day 22, and Day 29.
7. Change from baseline in viral load (baseline to Day 9)

6.0 SUBJECT POPULATION

6.1 Number of Subjects

Approximately 210 subjects are planned to be randomized at a 2:1 ratio into two treatment arms (approximately 140 subjects in the VERU-111 treated group and approximately 70 subjects in the Placebo treated group).

6.2 Selection Criteria

6.2.1 Inclusion Criteria

Subjects accepted for this study must:

1. Provide informed consent from the subject or the subject's Legally Authorized Representative (LAR)
2. Aged ≥18 years
3. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) infection confirmed by polymerase chain reaction (PCR) test
4. Patients with a WHO Ordinal Scale for Clinical Improvement score of 4 at high risk for ARDS, must have at least one of the known comorbidities for being at high risk, such as, Asthma (moderate to severe), Chronic Lung Disease, Diabetes, Hypertension, Severe Obesity (BMI ≥40), 65 years of age or older, primarily reside in a nursing home or long-term care facility, or immunocompromised and patients with a WHO Ordinal Scale for Clinical Improvement score of 5 or 6 regardless of presence of comorbidities.
5. WHO Ordinal Scale for Clinical Improvement score of 4 (Oxygen by mask or nasal prongs), 5 (Non-invasive ventilation or high-flow oxygen) or 6 (Intubation and mechanical ventilation)
6. Peripheral capillary oxygen saturation (SpO_2) ≤ 94% on room air at screening. If patient is on oxygen therapy at the time of presentation for screening and the SpO_2 levels were ≤94% prior to introduction to oxygen therapy with proper documentation example EMT notes or ER/ED notes, then the patient is considered to have met this inclusion criterion. If patient is on oxygen therapy at the time of presentation for screening and the SpO_2 levels prior to introduction to oxygen therapy are unknown, the patient may be considered to have met this inclusion criterion if oxygen therapy is removed and the SpO_2 levels fall to ≤94%, then the patient is considered to have met this inclusion criterion. However, removal of the oxygen therapy should only be done if it is considered medically reasonable.
7. Subjects must agree to follow doctor's recommendation for oxygen supplementation.
8. Subjects must agree to use acceptable methods of contraception:
    - If female of childbearing potential or a male subject's partner could become pregnant, use acceptable methods of contraception from the time of the first administration of study medication until 6 months following administration of

the last dose of study medication. Acceptable methods of contraception are as follows: Condom with spermicidal foam/gel/film/cream/suppository [i.e., barrier method of contraception], surgical sterilization (vasectomy with documentation of azospermia) and a barrier method {condom used with spermicidal foam/gel/film/cream/suppository}, the female partner uses oral contraceptives (combination estrogen/progesterone pills), injectable progesterone or subdermal implants and a barrier method (condom used with spermicidal foam/gel/film/cream/suppository)

- If the female partner of a male subject has undergone documented tubal ligation (female sterilization), a barrier method (condom used with spermicidal foam/gel/film/cream/suppository) should also be used
- If female partner of a male subject has undergone documented placement of an intrauterine device (IUD) or intrauterine system (IUS), a barrier method (condom with spermicidal foam/gel/film/cream/suppository) should also be used

9. Subject is willing to comply with the requirements of the protocol through the end of the study

6.2.2 Exclusion Criteria

Any of the following conditions are cause for exclusion from the study:

1. Known hypersensitivity or allergy to colchicine
2. Pregnant or currently breast feeding
3. Participation in any other clinical trial of an experimental treatment for COVID-19. Convalescent plasma, dexamethasone and remdesivir are allowed in this study.
4. Concurrent treatment with other experimental agents with actual or possible direct acting antiviral activity against COVID-19 is prohibited <24 hours prior to study drug dosing (except standard of care). Remdesivir, dexamethasone and convalescent plasma are allowed in the study.
5. Requiring ventilation + additional organ support – pressors, RRT, ECMO (WHO Ordinal Scale for Clinical Improvement – Score of 7). NOTE: short term (PRN) use of pressors is allowed.
6. Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) >3 X upper limit of normal (ULN)
7. Total bilirubin > ULN
8. Creatinine clearance < 60 mL/min
9. Documented medical history of liver disease, including but not limited to, prior diagnosis of hepatitis of any etiology, cirrhosis, portal hypertension, or confirmed or suspected esophageal varices
10. Moderate to severe renal impairment
11. Hepatic impairment
12. History of hepatitis (Hepatitis B and C) NOTE: treated and controlled hepatitis C is allowed.
13. Any comorbid disease or condition (medical or surgical) which might compromise the hematologic, cardiovascular, gastrointestinal, hepatic, or central nervous system; or in PI's

opinion other conditions that may interfere with the absorption, distribution, metabolism or excretion of study drug, or would place the subject at increased risk.

14. Participants must agree to refrain from prolonged exposure to the sun or agree to use at least SPF 50 on all exposed skin and protective clothing during prolonged sun exposure throughout participation in this study and/or treatment with VERU-111.

7.0 STUDY MEDICATION

7.1 Enrollment and Blinding

The study will be a randomized, double-blind, placebo-controlled study.

Randomization will be stratified by baseline WHO Ordinal Scale score of 4, 5 and 6 such that subjects with a WHO Ordinal Scale of 4, 5 and 6 at baseline are approximately equally distributed between the treatment groups.

An emergency code break will be available to the investigator / pharmacist / investigational drug storage manager. This code break option in IWRS may only be disclosed in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or if required to assure safety of trial participants. If the code break for a patient is opened, the sponsor and CRO will be informed immediately via IWRS notification. The reason for the IWRS unblinding of the subject must be documented on the appropriate eCRF page along with the date and the initials of the person who broke the code.

7.2 Drug Supply

7.2.1 VERU-111 Capsules

VERU-111 9 mg dose will be supplied as capsules containing 9 mg of VERU-111. Capsules will be supplied in bottles containing 21 capsules in each bottle. Patients will take one VERU-111 capsule per day.

The VERU-111 capsules should be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F).

7.2.2 Placebo Control

Placebo capsules containing zero (0) mg VERU-111 drug substance will be supplied in bottles containing 21 capsules each. These capsules are identically appearing to the VERU-111 capsules. Patients will take one Placebo capsule per day.

The Placebo capsules should be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F).

7.2.3 Drug Accountability

Subjects should not take a replacement dose if a dose is missed. Study medication should not be taken more than once a day. If the patient vomits after dosing, the dose will not be replaced.

The pharmacists or other site personnel as delegated by the Investigator are responsible for accountability of all used and unused study drug supplies. A study drug dosing log should be kept current and should contain the dates and times drug dosing the subject, the subject's identification (i.e., subject number), the initials of the dispensing persons. Veru Inc., shall be immediately notified of any unexpected occurrences during the dispensing or dosing of study drug.

7.3 Drug Administration

Study drug should be taken daily at approximately the same time every day with approximately 240 mL (a full glass) of non-alcoholic liquid (drink). Dosing may be taken with or without food. Subjects will take the entire daily dose at once. In subjects with a nasogastric feeding tube, the contents of the capsules may be emptied into the tube and appropriately flushed through the tube.

8.0 STUDY PROCEDURES

8.1 Screening

Potential subjects will be screened for this study in the 3 days prior to enrollment. The following activities will be conducted at screening:

1. Signed informed consent and HIPAA form (or legal documents as directed based on the region outside of the United States) will be obtained prior to any study-specific procedures and a copy of the signed consent form will be given to the subject.
2. Assess subject eligibility for inclusion into this study based on protocol inclusion/exclusion criteria.
3. Pregnancy test (women of childbearing potential only)
4. Medical history will be obtained, including diagnosis of COVID-19 infection (date of diagnosis), details and dates of treatments received, documentation of symptoms related to COVID-19 infection, and COVID-19 vaccination status.
5. WHO Ordinal Scale score assessment
6. The use of any medications will be recorded. This will include medications currently being taken and those taken since COVID-19 symptoms started. Over-the-counter (OTC) medications as well as medications taken on an as-needed basis (PRN) should be recorded.
7. Vital signs (temperature/pulse/supine, if possible, blood pressure)
8. SpO_2 level (%)

9. Physical examination including height and weight
10. Electrocardiogram- 12 lead (single)
11. Clinical Laboratory Tests
    - Hematology (Appendix A)
    - Serum chemistry (Appendix A)
    - Urinalysis

8.2 Enrollment

Enrollment should be done after the subject has completed the screening assessments and after it has been determined that the subject meets all the eligibility criteria.

Subject will be randomized into one of two treatment groups.

8.3 Day 1

The Day 1 visit assessments will serve as the baseline assessments.

1. The medical history should be reviewed and updated to include any changes occurring since the screening visit. This will include the following:
    a. Number of days from onset of COVID-19 symptoms to Day 1
    b. Specific reason for hospitalization
2. Assessment of eligibility - the WHO Ordinal Scale score at Screening will be used as the eligibility criteria for the study. The WHO Ordinal Scale score on Day 1 prior to dosing will be considered the baseline WHO Ordinal Scale score.
3. WHO Ordinal Scale score assessment (prior to dosing)
4. Pregnancy test (women of childbearing potential only)
5. Vital signs (temperature/pulse/supine, if possible, blood pressure)
6. SpO_2 level (%)
7. Physical examination (including weight)
8. Chest X-ray or Computed Tomography (CT) scan
9. Viral load
10. Clinical Laboratory Tests
    a. Hematology (Appendix A)
    b. Serum chemistry (Appendix A)
    c. Urinalysis
11. Record the usage of any concomitant medications and ongoing treatments.
12. Adverse events (ongoing on Day 1)
13. PK sample prior to dosing
14. First dose of study drug

8.4 Day 2 through Day 21 or day of discharge from the hospital (whichever comes first)

The following assessments will be conducted on each of Day 2 to Day 21 or up to the day of discharge from the hospital, whichever comes first:

1. Vital signs (temperature/pulse/supine, if possible, blood pressure)
2. Record the usage of any concomitant medications and ongoing treatments. This should include the following:
    a. Documentation of the standard of care
    b. The clinical rationale for initiation of mechanical ventilation, if necessary
    c. Documentation of supportive measures for ARDS (e.g., proning, paralytics, etc.)
    d. Care decisions that are based on limitations of resources at the clinical site
3. Adverse events
4. Dose study drug
5. At the time of discharge from the hospital, patients should be advised to use refrain from prolonged exposure to the sun or use at least SPF 50 on all exposed skin and protective clothing during prolonged sun exposure until the Day 60 adverse event assessment.

8.5 Day 3, Day 9, and Day 15

The following additional assessment will be conducted on Days 3, Day 9 and 15:

1. SpO_2 level (%) (or day of discharge if prior to Day 15)
2. Serum Chemistry – (Appendix A) (or day of discharge if prior to Day 15)
3. Hematology – (Appendix A) (or day of discharge if prior to Day 15)
4. Viral load (Day 9 only or day of discharge if prior to Day 9)
5. WHO Ordinal Scale score assessment (Day 15 only or day of discharge if prior to Day 15)
6. Physical examination (including weight) (Day 15 only or day of discharge if prior to Day 15)
7. Pregnancy test (Day 15 only or day of discharge if prior to Day 15) (women of childbearing potential only)
8. 12 lead ECG (single) (Day 15 only or day of discharge if prior to Day 15)
9. Plasma samples for pharmacokinetic assessment will be taken prior to dosing on Day 3 and Day 9.

8.6 Day 22 ± 3 days (these assessments will also be done at Early Termination from the study)

The following assessments will be performed on Day 22 (± 3 days):

1. Vital Signs (temperature/pulse/supine blood pressure)
2. SpO_2 level (%)
3. Physical examination (including weight)
4. 12-lead ECG (single)

5. Chest X-ray or CT scan
6. Clinical Laboratory tests
    a. Hematology (Appendix A)
    b. Serum chemistry (Appendix A)
    c. Urinalysis
7. Adverse events
8. Pregnancy test (women of childbearing potential only)
9. Record the usage of any concomitant medications and ongoing treatments.
10. WHO Ordinal Scale score assessment (at Day 22 or day of discharge if prior to Day 22)

8.7 Day 29 ± 3 days

The following assessments will be performed at approximately Day 29 (± 3 days):

1. Vital Signs (temperature/pulse/supine blood pressure)
2. SpO_2 level (%)
3. Physical examination (including weight)
4. 12-lead ECG (single)
5. Chest X-ray or CT scan
6. Clinical Laboratory tests
    a. Hematology (Appendix A)
    b. Serum chemistry (Appendix A)
    c. Urinalysis
7. Adverse events
8. Pregnancy test (women of childbearing potential only)
9. Record the usage of any concomitant medications and ongoing treatments.
10. WHO Ordinal Scale score assessment (at Day 29 or day of discharge if prior to Day 29)

8.8 Follow up visits at Day 45 (± 3 days) and Day 60 (± 3 days) (conducted via phone/teleconference)

1. Adverse events
2. WHO Ordinal Scale score assessment

8.9 Subject Stopping Rules

If, in the opinion of the investigator, the participation in the study is or is becoming detrimental to the well-being of a particular subject, this issue should be discussed with the Medical Monitor for this study and dosing may be discontinued.

In subjects that experience an adverse event of Grade 4 or greater severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0_2010-06-14_QuickReference_5x7.pdf) that is deemed to be possible, probably or definitely related to study drug dosing with study drug will be discontinued. Prior to discontinuation of study drug, the grading of the event and causal relationship should be discussed with the Medical Monitor for the study.

Subjects will be discontinued from dosing if AST or ALT levels are >5 times the upper limit of normal, or if AST or ALT levels are >3 times the upper limit of normal along with a total bilirubin elevation of >2 times the upper limit of normal.

Subjects will be discontinued from dosing if Grade 3 diarrhea is observed.

Subjects will be discontinued from dosing if Grade 3 neutropenia is observed.

NOTE: These subject stopping rules are related to the discontinuation of study drug, not discontinuation from the study. Subjects should be followed for efficacy and safety even if study drug is stopped based on these stopping rules.

8.10 Early Discontinuation of Study Treatment or Early Termination from the Study

Subjects may prematurely discontinue study treatment for any of the following reasons:

1. Consent withdrawn for further study treatment (specify the reason).
2. Significant and unacceptable adverse event – specify the adverse event leading to discontinuation of study drug
3. Investigator decision (specify the reason), must be approved by the Medical Monitor
4. Non-compliance by subject with protocol requirements, must be approved by the Medical Monitor
5. Lost to follow-up (record the date of last contact)
6. Death (specify the following information)
    a. Date of death
    b. Death due to primary disease? Yes or no
    c. Death due to study drug? Yes or no
    d. Death due to adverse event? Yes or no
7. Lack of efficacy
8. Study terminated by the Sponsor
9. Other reason (specify the reason) should be approved by the Medical Monitor

The reason for discontinuation of study treatment will be documented for each subject. Subjects who discontinue study drug prematurely will not be replaced. At the time of discontinuation, please fill out the End of Study case report forms (eCRFs) and subject disposition eCRF pages.

Every effort will be made for the patient to complete all study related procedures at Day 15, Day 22, Day 29, Day 45, and Day 60. Every effort will be made to determine patient status (alive or dead) at Day 15, Day 22, Day 29, and Day 60. This determination can be made via telephone contact or public search records.

OF NOTE: For subjects who are terminated from the study prematurely, every effort should be made to have the subject complete all Early Termination Assessments (same as day 22 assessments). The reason for early termination from the study will be documented for each subject. Subjects who are early terminations will not be replaced. At the time of early termination, please fill out the Early Termination and End of Study case report forms.

Every effort should be made to determine patient status (alive or dead) at Day 60. This determination can be made via telephone contact or public search records.

8.11 Adverse Events

An adverse event (AE) is any unfavorable or unintended change in body structure (signs) or body function (symptoms), abnormal laboratory result that is associated with symptoms or requires treatment or worsening of a pre-existing condition. This includes all such events regardless of the presumed relationship between the event and the study medication(s).

Any AE that occurs after the informed consent is signed but prior to dosing on Day 1 will be captured as part of the medical history and will be documented on the appropriate eCRF. This would include AEs resulting from concurrent illnesses, reactions to concomitant medications or progressive disease states.

Each subject will be assessed for the development of any adverse events. Adverse events should be assessed daily during the time in the hospital and at each visit to the clinic after discharge. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?") and from signs and symptoms detected during each examination, observations of the study personnel or spontaneous reports from the subjects.

Any AEs such as complaints, signs, or symptoms that occur during the course of the study or designated follow-up periods will be recorded on the subject's case report form (eCRF). This would include AEs resulting from concurrent illnesses, reactions to concomitant medications, or progressive disease states.

Whenever possible, the AE will be described on the case report form using standard medical terminology consistent with Common Terminology Criteria for Adverse Events (CTCAE) version 5 in order to avoid the use of vague, ambiguous or colloquial expressions. The investigator will evaluate all adverse events as to their intensity, relation to test medication, outcome and action taken.

Each AE will be evaluated for duration, intensity, and relationship to (or association with) the study treatment (or other causes). Additionally, the actions taken (e.g., reduction of dosage, discontinuation of study medication, administration of treatment, etc.) and the resulting outcome of the AE will be indicated on the case report form.

Any subject who is withdrawn from the study drug due to an adverse event will be followed until the outcome of the event is determined, and the investigator will prepare a written

summary of the event and document the available follow-up information on the case report form.

8.11.1 Intensity of Adverse Events

The intensity of the AEs will be graded according to CTCAE version 5. For any adverse event that is not specifically covered in CTCAE version 5, the following criteria should be used:

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences: urgent intervention indicated.
5	Death related to AE

If the intensity (Grade) changes within a day, the maximum intensity (Grade) should be recorded. If the intensity (Grade) changes over a longer period of time, the changes should be recorded as separate events (having separate onset and stop dates for each grade).

8.11.2 Test Medication Causality

The relationship (or association) of each AE to the test medication will be assessed by the investigator according to the following definitions:

Unrelated: There is no chance that the study medication caused the AE; other conditions, including concurrent illnesses, progression or expression of the disease state, or a reaction to a concomitant medication best explain the event.

Unlikely: There is little chance that the study medication caused the AE; other conditions, including concurrent illnesses, progression or expression of the disease state, or a reaction to a concomitant medication best explain the event.

Possible: The association of the AE with the study medication is unknown; however, the AE is not clearly due to another condition.

Probable: A reasonable temporal association exists between the AE and treatment administration and, based on the investigator's clinical experience, the association of the AE with the study treatment seems likely.

Definite: The association of the AE with the study medication has a direct relationship.

For the purpose of safety analyses, all AEs which are classified as "Possible," "Probable" or "Definite" will be considered treatment-related events.

8.11.3 Serious Adverse Events

A **serious adverse event (SAE)** is defined as any experience that suggests a significant clinical hazard, contraindication, side effect, or precaution. This includes any event which:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity.
- Results in congenital abnormality/birth defect.
- Requires intervention to prevent permanent impairment or damage

An SAE also may include other events, based on medical judgment, which jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above.

Any SAE, including death due to any cause, which occurs during the study or within 60 days following initiation of dosing on study medication, whether or not related to the study medication, must be reported immediately via telephone (within 24 hours) to Veru Inc. Drug Safety.

In addition, the investigator must immediately complete a Serious Adverse Event eCRF report form and electronically submit the form. The investigator will promptly notify the Institutional Review Board (IRB).

If additional information regarding a previously submitted SAE is obtained, a follow-up SAE eCRF report should be completed and submitted as indicated above. Supporting source documentation should be provided to [redacted] Drug Safety at the contact information below.

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

8.11.4 Initial Reports

SAEs will be collected from the time of first study drug administration through 60 days after first study drug administration. SAEs and events of clinical interest must be reported to the Sponsor (or designee) within 24 hours of the knowledge of the occurrence.

In the event an SAE is observed or reported, the SAE report will be completed as thoroughly as possible including all available details about the event and the signature of the Investigator. If the Investigator does not have all information about an SAE, the Investigator will not wait to receive additional information before notifying the Sponsor of the event and completing the form. The form will be updated when additional information is received.

8.11.5 Precautions

Adverse events should be treated in accordance with standard medical practice. During the course of the study, the overall safety, and tolerability of all study treatments will be reviewed by the sponsor and the investigator.

8.11.6 Reporting of Adverse Events Associated with Study Drug Overdose, Misuse, Abuse or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose: Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose

Misuse: Intentional and inappropriate use of study drug not in accordance with the protocol

Abuse: Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error: Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as non-serious on the SAE form and the Adverse Event eCRF.

8.12 Concomitant Medications and Concomitant Therapies

Any medication (including OTC medications) taken by a subject within 30 days prior to the Screening Visit and during the course of the study and the reason for use of the medication will be recorded on the eCRF. Upon entering the study, each subject will be instructed to report the use of any medication (including OTC medications) to the investigator.

8.13 Prohibited Medications

The following medications are prohibited with the appropriate washout period, if any, for each prohibited medication:

- Retroviral/antiretroviral medications, except for remdesivir
- Any experimental drug/clinical trial, except for remdesivir and convalescent plasma
- colchicine

8.14 Pharmacokinetic Sampling and Handling

The limited sampling schedule is used due to limitations on study personnel entering the patient's room during the day.

The blood sample should be collected in a 6 mL K_2EDTA blood collection tube at each collection time.

Immediately after collection, the tube will be gently inverted several times to mix the anticoagulant with the blood sample. The blood sample should be kept at room temperature until processed. The blood samples should be processed within 60 minutes after collection. The plasma fraction will be separated by placing the collection tube into a centrifuge for 10 minutes at 1,500 x g (at room temperature). The plasma fraction will be withdrawn by pipette and divided into two polypropylene freezing tubes (with each tube receiving approximately equal aliquots). All plasma samples will be placed into a freezer at -20ºC (or below) within 90 minutes after collection. (NOTE: A flash freezing in dry ice or liquid nitrogen is NOT required under this protocol but may be used.)

8.15 Plasma Sample Labels for Pharmacokinetic Samples

The plasma freezing tube labels will contain the following information:

- Subject Number
- Study Number
- Site Number
- Prior Dosing time (hour and minute)
- Sample time (hour and minute)
- Aliquot Number: Aliquot A or B
- Species and Matrix: Human Plasma
- Sample Sequence Number
- Barcode Number

Labels will be fixed to freezing tubes in a manner that will prevent the label from becoming detached after freezing.

All plasma samples will be stored frozen (-20°C or below). Details of the method validation and sample analysis will be included with the final report.

9.0 STATISTICAL ANALYSIS

9.1 Sample Size Calculation

In the Phase 2, the VERU-111 treated group showed a 5.3% mortality rate compared to a 30% mortality rate in the Placebo group in the same patient population.

Approximately, 210 subjects are planned to be randomized at a 2:1 ratio into two treatment arms (140 subjects in the VERU-111 treated group and 70 subjects in the Placebo treated group). Randomization will be stratified by baseline WHO Ordinal Scale score of 4, 5 and 6 such that subjects with a WHO Ordinal Scale of 4, 5 and 6 at baseline will be approximately equally distributed between the treatment groups. Assuming a rate of mortality of 5% in the VERU-111 treated group and 25% in the Placebo treated group, the above sample sizes will yield 95% confidence interval of [--0.308, -0.092] for the risk difference between treatment groups. Other scenarios are shown in the table below.

Confidence interval = $(p1 - p2) +/- z^*\sqrt{(p1(1-p1)/n1 + p2(1-p2)/n2)}$

where:

- p_1, p_2: sample 1 proportion, sample 2 proportion
- z: the z-critical value based on the confidence level
- n_1, n_2: sample 1 size, sample 2 size

Table of Alternative 95% Confidence intervals for the difference between Treatment Groups: Mortality at Day 60

VERU-111	Placebo	Difference	LOWER 95% CI	UPPER 95% CI
0.05	0.15	-0.1	-0.191107629	-0.008892371
0.05	0.2	-0.15	-0.250420118	-0.049579882
0.05	0.25	-0.2	-0.307672652	-0.092327348
0.05	0.3	-0.25	-0.363261644	-0.136738356
0.1	0.15	-0.05	-0.147297482	0.047297482
0.1	0.2	-0.1	-0.206067903	0.006067903
0.1	0.25	-0.15	-0.262958399	-0.037041601
0.1	0.3	-0.2	-0.318297929	-0.081702071
0.15	0.15	0	-0.102449012	0.102449012
0.15	0.2	-0.05	-0.160812454	0.060812454
0.15	0.25	-0.1	-0.21742487	0.01742487
0.15	0.3	-0.15	-0.27256998	-0.02743002

With significance level α=0.05, and a 2:1 ratio of enrollment into the VERU-111 and Placebo arms respectively, the sample size is adequate to achieve >92% power assuming the treatment estimates stated above.

NOTE: The IDMC will monitor efficacy and safety and may make a recommendation to stop the study based on treatment success according to the statistical analysis plan and IDMC charter for this study.

9.2 Analysis Sets

Intent-to-Treat (ITT) population: All randomized subjects will be included in this population.

Modified Intent-to-Treat (mITT) analysis set: All randomized subjects who do not have any major protocol violations will be included in the mITT population.

Safety (SAF) analysis set: All randomized subjects who received at least one dose of study medication (VERU-111 or Placebo) will be included in this population The SAF population will be used as the safety population.

9.3 Analysis Scope

The Intent-to-Treat (ITT) analysis scope will include all data collected from randomization to the end of the study at Day 60. This will be considered the primary analysis scope for the primary analysis.

9.4 Efficacy Analyses

A statistical analysis plan will be written for this Phase 3 clinical study. A detailed description of the analyses that will be conducted will be included in that document.

9.4.1 Primary Endpoint

The primary endpoint for the study will be the proportion of subjects that die on study (up to Day 60).

The number and percentage of deaths will be summarized by treatment group. Mortality rates will be analyzed using a logistic regression model. This model will include treatment as a factor and study site, gender, remdesivir use (No/Yes), dexamethasone use (No/Yes) and WHO Ordinal Scale for Clinical Improvement at baseline as a covariates. The model will be fitted using logit link function. Odds ratios, standard errors, 95% confidence intervals and p-values for the treatment difference will be presented.

The primary analysis will be performed on the ITT analysis set and the ITT data scope regardless of patient's use of rescue medications, protocol violations or investigational product discontinuation consistent with the treatment policy strategy. Every effort will be made to collect vital status up to the end of the study period. Missing data for subjects who are lost to follow up will be imputed using multiple imputation methods. Details for the imputation will be given in the Statistical Analysis Plan (SAP).

9.4.2 Secondary Analyses of the Primary Endpoint

The primary endpoint, mortality rate, will also be assessed in the subset of mITT patients.

To obtain risk differences between treatment groups, the same analysis as described above will be fitted except identity link function will be used.

Additionally, mortality rates will be summarized using Kaplan-Meier (KM) survival curves and equality of treatment groups will be tested using log-rank test. Hazard ratios will be calculated using the Cox proportional hazards model including terms for treatment, study site, gender, remdesivir use (No/Yes), dexamethasone use (No/Yes) and WHO Ordinal Scale for Clinical Improvement at baseline. Any subjects that are lost to follow-up or terminated early prior to death will be censored at the day of their last observed assessment or last captured event.

9.4.2.1 Sensitivity Analyses

A sensitivity analysis using the tipping-point approach will be conducted to assess the robustness of the primary analysis approach.

Missing endpoints will be re-assigned in a series of analyses that are progressively more in favor of placebo.

The tipping point analysis will consider the full range of possible response rates in the subjects with missing data in the primary analysis. This will be done by systematically changing assumed response rates from 0% to 100% in a stepwise manner. The imputation will be performed independently within the two treatment groups so that, in the most extreme case, the imputed response rate in the VERU-111 arm will be 0% and 100% in the placebo arm.

Multiple imputation will be used for each pair of response rates under consideration. Both the imputation model and the analysis model will incorporate the covariates as used in the primary analysis.

Details for the imputation will be given in the SAP.

9.5 Secondary Endpoint

Primary analysis of secondary endpoints will be performed on the ITT analysis set and the ITT data scope regardless of patient's use of rescue medications, protocol violations or investigational product discontinuation consistent with the treatment policy strategy.

Full details for the handling of missing data, and consideration of subjects that die during the study for those endpoints that do not directly incorporate death, will be included in the Statistical Analysis Plan.

9.5.1 Proportion of patients alive and free of respiratory failure at Day 29, Day 15 and Day 22

Respiratory failure is defined as endotracheal intubation and mechanical ventilation, extracorporeal membrane oxygenation, high-flow nasal cannula oxygen delivery, noninvasive positive pressure ventilation, clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision making is driven solely by resource limitation.

This analysis will compare the percentage of subjects that are alive without respiratory failure (responder) on Day 29 and on Day 15 and on Day 22.

Proportion of subjects alive and free of respiratory failure will be analyzed separately at each timepoint using the same logistic regression methodology as primary endpoint (section 9.4.1).

9.5.1.1 Days in ICU

Days in ICU will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) by treatment group.

For subject who die, days in ICU will be set to the worst possible outcome (29 days) to give deaths unfavorable value in the analysis.

Treatment comparison will be based on analysis of covariance (ANCOVA) model including treatment as a factor and study site, gender, remdesivir use (No/Yes), dexamethasone use

(No/Yes) and WHO Ordinal Scale for Clinical Improvement at baseline as covariates. Treatment difference, standard error, 95% confidence interval and p-value will be presented.

9.5.1.2 Change from baseline in WHO Ordinal Scale for Clinical Improvement at Day 15, Day 22 and Day 29

Baseline for WHO Ordinal Scale for Clinical Improvement will be the last available record prior to first dose of study medication.

For subject who die, WHO Ordinal Scale for Clinical Improvement will be set to the worst possible outcome (8 – death) for the following planned timepoints to give deaths unfavorable value in the analysis. For subjects who are discharged early, or are otherwise having missing values, following timepoints use data from multiple imputation. Details for the imputation will be given in the SAP.

WHO Ordinal Scale for Clinical Improvement will be summarized using frequencies and percentages by treatment group and timepoint. Also change from baseline will be summarized.

Change from baseline will be analyzed as ordinal response using proportional odds logistic regression. Analysis will be performed separately for each timepoint (Day 15, Day 22, Day 29). Proportionality of odds will be tested and if the proportionality assumption does not hold, then non-proportional odds model will be fitted. Model will include treatment as fixed effect and study site, gender, remdesivir use (No/Yes), dexamethasone use (No/Yes) and WHO Ordinal Scale for Clinical Improvement at baseline as covariate. Odds ratio, 95% confidence interval and p-value for the treatment difference will be presented. Distribution of change from baseline will be plotted in stacked bar plot by treatment group and time point.

Proportional (or non-proportional) odds model will be performed only using the imputed data to include all subjects in the analysis.

Additionally, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be summarized for absolute values and change from baseline by treatment group and visit.

Additionally, change from baseline will be analyzed using mixed model for repeated measures (MMRM) including treatment, visit and treatment-by-visit interaction as fixed effects and study site, gender, remdesivir use (No/Yes), dexamethasone use (No/Yes) and WHO Ordinal Scale for Clinical Improvement at baseline as covariate. The resulting F-tests will be based on Kenward-Roger's adjusted degrees of freedom. Least squares means, standard errors, 95% confidence intervals and p-values for treatments and treatment differences at each visit will be presented.

MMRM analysis will be performed only using the imputed data to include all subjects in the analysis.

9.5.1.3 Days on mechanical ventilation

Days on mechanical ventilation will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum and maximum) by treatment group.

For subject who die, days on mechanical ventilation will be set to the worst possible outcome (29 days) to give deaths unfavorable value in the analysis.

Days on mechanical ventilation will be analyzed using the same methodology as for Days in ICU (section 9.5.1.2).

9.5.1.4 Days in hospital

Days in hospital will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum and maximum) by treatment group.

For subject who die, days in hospital will be set to the worst possible outcome (29 days) to give deaths unfavorable value in the analysis.

Days in hospital will be analyzed using the same methodology as for Days in ICU (section 9.5.1.2).

9.5.1.5 Mean change from baseline in Viral load to Day 9

The mean change in viral load from baseline to Day 9 will be assessed.

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be summarized for absolute values, and change from baseline by treatment group.

Change from baseline will be analyzed using the same methodology as for change from baseline in WHO score (section 9.5.1.3).

9.6 Pharmacokinetic Analysis

The pharmacokinetic samples for assessment of VERU-111 levels will be taken at baseline (prior to dosing on Day 1) and then prior to dosing on Days 3 and 9.

An evaluation of baseline levels versus effectiveness of VERU-111 will be conducted.

Pharmacokinetic concentration data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum and maximum). CV%, geometric mean, geometric SD and geometric CV% will be presented.

All PK data will be listed.

9.7 Safety Analysis

The frequency of adverse events (AEs) will be tabulated by MedDRA term and system organ class. The incidence of AEs and the maximum intensity and frequency of AEs will be

summarized. A new onset AE is defined as an AE that was not present prior to treatment with study medication but appeared following treatment or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the subject was on treatment is a new-onset AE (regardless of the intensity of the AE when the treatment was initiated).

All laboratory results, vital sign measurements, and other safety variables will be summarized using appropriate descriptive statistics. Changes from baseline will be computed and will be summarized using appropriate descriptive statistics.

A summary of the number of subjects developing treatment emergent values of ALT and AST ≥3x ULN, 5x ULN, and 10x ULN, respectively and a shift table for individual subjects shifts from baseline to maximum observed value by category: <3x ULN, ≥3x ULN, ≥5x ULN and ≥10x ULN will be provided. Additionally, a summary of patients that develop Drug Induced Liver Injury by Hy's Law will be provided.

Safety data will be summarized utilizing the SAF analysis set.

9.7.1 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will review the unblinded safety data from this Phase 3 study, including all SAEs, approximately every 4 weeks. The efficacy data will be reviewed at the specified timepoint for the interim efficacy analysis when approximately 50% of the subjects have completed Day 60.

The recruitment of this Phase 3 study is expected to be completed within 9 months of first patient, first dose.

9.7.2 Interim Analysis

An efficacy interim analysis of the primary endpoint, all-cause mortality at Day 60, will be conducted when approximately 71.4% of the subjects (~150 subjects) have completed Day 60, died or withdrawn for other reasons. The first 150 patients randomized into the study will be included in the planned interim analysis. The interim and final analyses will follow an O'Brien-Fleming group sequential design, with a plan of stopping the trial at the interim analysis if the results are statistically significant in favor of VERU-111. The criterion for efficacy at the interim analysis will be a two-sided 0.0160 p-value (a one-sided p-value <=0.0080 in favor of VERU-111). If the criterion is not met, the trial will continue, and the final analysis will have a criterion for efficacy of a two-sided p-value <=0.0452 (one-sided 0.0226 in favor of VERU-111).

In addition, an estimate of the conditional power that the trial will be positive (statistically significant difference for final analysis) will be provided to the IDMC at regular intervals. If the conditional power is below 0.30 this may suggest termination for futility. However, this would not be a binding rule. Factors other than the conditional power will be considered by the IDMC when weighing the futility of the study as a whole after carefully evaluating various factors, including among others, enrolment rate and safety.

The interim analyses will be conducted by an independent statistician and provided to the IDMC. The sponsor will not be unblinded to the data and will only be notified of the recommendation of the IDMC to stop or continue the trial for futility. The sponsor will make such a decision after carefully evaluating various factors, including among others, enrolment rate and safety.

10.0 ADMINISTRATION PROCEDURES

10.1 Study Conduct and Compliance

The study will be conducted in accordance with the Code of Federal Regulations (21 CFR parts 50, 54, 56, 312, and 314), which originates from the ethical principles laid down in the Declaration of Helsinki. Good Clinical Practices (GCPs) and the policies and procedures of the Sponsor and/or its authorized representative will also be followed. This clinical trial will be overseen and managed by a contract research organization (CRO) and the Sponsor. The CRO will be responsible for data management, data handling, clinical monitoring, statistical analysis, quality assurance and the final study report. The Sponsor will be responsible for project management of the CRO.

Sponsor Emergency Contact Info:

[redacted]

Before initiating a trial, the Investigator/Institution should have written and dated approval/favorable opinion from the Independent Ethics Committee (IEC)/IRB for the trial protocol/amendment(s), written informed consent form, any consent form updates, subject recruitment procedures (e.g., advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

10.2 Informed Consent

Prior to study entry, the Investigator, or a person designated by the Investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's LAR or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the

investigational medicinal product (IMP). Sufficient time will be allowed to discuss any questions raised by the subject.

The Sponsor will provide a sample informed consent form. The final version-controlled form must be agreed to by the Sponsor and the IEC/IRB and must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's LAR, and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed informed consent.

The consent form may need to be revised during the trial should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments. In this instance approval should always be given by the IEC/IRB. It is the Investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The Investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical trial.

10.3 Protocol Amendments

In the event that an amendment to this protocol is required, it will be classified into one of the following three categories:

- **Non-Substantial Amendments** are those that are not considered 'substantial' (e.g., administrative changes) and as such only need to be notified to the IECs/IRBs or Competent Authorities (CA) for information purposes.

- **Substantial Amendments** are those considered 'substantial' to the conduct of the clinical trial where they are likely to have a significant impact on:

  - the safety or physical or mental integrity of the subjects;
  - the scientific value of the trial;
  - the conduct or management of the trial; or
  - the quality or safety of the IMP used in the trial.

  Substantial amendments must be notified to the IECs/IRBs and CA. Prior to implementation, documented approval must be received from the IECs/IRBs. In the case of the CA in the EU member states, approval or 'favorable opinion' can be assumed if the CA has raised no grounds for non-acceptance during an allocated time period (to be confirmed with the Sponsor's Regulatory Affairs (RA) representative) following acknowledgment of receipt of a valid application to make a substantial amendment.

- **Urgent Amendments** are those that require urgent safety measures to protect the trial subjects from immediate hazard and as such may be implemented immediately by the Sponsor with subsequent IECs/IRBs and CA notification, forthwith.

10.4 Protocol Deviations

It is the responsibility of the Investigator and Sponsor to ensure compliance with the study protocol. When the protocol is not followed, it can put the safety of study subjects at risk as well as jeopardize the accuracy and reliability of the study results which could lead to a rejection of the data by regulatory authorities.

All identified deviations from the protocol must be documented and reported to the Sponsor using the appropriate electronic form to be supplied by the Sponsor. Deviations will be categorized into minor deviations or major deviations; definitions and examples of deviations will be provided by the Sponsor. The Sponsor will be reviewing all deviations on an ongoing basis.

10.5 Data Handling and Recordkeeping

10.5.1 Data Handling

Data will be recorded at the site on the eCRF and reviewed by the clinical research associate (CRA) during monitoring visits. The CRA will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for and electronically signed by the Investigator or assignee.

Data will be processed using a validated computer system conforming to regulatory requirements.

10.5.2 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.5.3 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of MedDRA (version 18.1 or higher) for medical history and AEs, and
- World Health Organization Drug Dictionary Enhanced (Sept. 2015 or later) for prior and concomitant medications.

10.5.4 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator in order to be considered complete.

10.5.5 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study drugs, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.6 Data Quality

Monitored eCRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the Investigator by the monitor for clarification/correction. The Investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

Clinical site personnel must make themselves available for any potential audit by the Sponsor or Sponsor representative and regulatory authorities, such as, but not limited to, United States Food and Drug Administration. The clinical site personnel must be completely responsive and cooperative during these audits.

10.7 Regulatory Approval

As required by local regulations, the Sponsor’s Regulatory Affairs group will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

10.8 Publication Policy

The Sponsor encourages acknowledgement of all individuals/organizations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the Sponsor.

The results of this study may be published or communicated to scientific meetings by the Investigators involved in the study. For multicenter studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study Investigators or a Steering Committee. The Sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The Sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the Sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or authors' institution) after receipt of the proposed publication by the Sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the Sponsor's request for delay to the proposed publication should the Sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

10.9 Clinical Study Report

A final clinical study report will be prepared according to the ICH guideline on structure and contents of clinical study reports. A final clinical study report will be prepared where any subject has signed informed consent, regardless of whether the trial is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

10.10 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital/institution authorized representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included subject, based on the calculated costs of performing the study assessments and other activities in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe

whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly.

10.11 Insurance and Indemnity

The Sponsor will obtain Product Liability insurance providing coverage relating to the clinical study and subjects participating therein.

11.0 REFERENCES

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12.0 APPENDICES

12.1 Appendix A: Clinical Laboratory Tests (local laboratory)

Hematology:	***Serum Chemistry:***
Hemoglobin	Sodium
Hematocrit	Potassium
Red Blood Cell Count	Chloride
White Blood Cell Count	Bicarbonate[a]
White Blood Cell Differential	BUN
Platelet Count	Creatinine
Reticulocyte Count	Calcium
Cardiac Troponin	Phosphorus
	Total Protein
Urinalysis:	Albumin
pH	Total Bilirubin
Specific Gravity	SGOT (ALT)
Protein	SGPT (AST)
Glucose	Alkaline phosphatase
Leucocytes	LDH
Nitrates	GGT
Ketones	Glucose
Blood	Ferritin
Microscopic Examination (only if urinalysis results are abnormal)	D-dimer

[a] Bicarbonate will be collected only if it is part of the standard local panel.

12.2 Appendix B: Schedule of Study Evaluations

Day	Screen[a]	Day 1	Days 2-21	Days 3, 9, & 15	Days 22[d] and 29	Days 45 and 60
Informed Consent and HIPAA	X					
Medical History	X	X				
Assessment of Eligibility	X	X				
Physical Exam	X	X		X[f]	X	
Pregnancy test	X	X		X[f]	X	
Vital signs	X	X	X		X	
12-lead ECG (single)	X			X[f]	X	
WHO Ordinal Scale score	X	X		X[f]	X	X
Chest X-ray or CT		X			X	
Clinical Laboratory Tests						
Hematology	X	X		X	X	
Urinalysis	X	X			X	
Serum Chemistry	X	X		X	X	
SpO_2	X	X		X	X	
Dosing[b,c]		X	X			
Pharmacokinetic assessment		X		X[e]		
Assessment of conmeds	X	X	X		X	
Assessment of AEs		X	X		X	X
Viral load		X		X[g]		

a Screening evaluations are to be conducted within 3 days prior to Day 1.
b Subjects will be treated for 21 days OR until discharged from hospital, whichever comes first
c Subjects can be discontinued from treatment if they are not responding to therapy, however patients should continue to be followed on study and have the study assessments as outlined herein.
d Early termination assessments are the same as Day 22 assessments
e Days 3 and 9 only
f Day 15 only
g Day 9 only (or day of discharge if prior to Day 9)

PROTOCOL SIGNATURE PAGE

Protocol Number: V3011902

Protocol Date: Protocol Amendment 6 (Version 7.0)/ 18 March 2022

Protocol Title: Phase 3, Randomized, Placebo-Controlled, Efficacy and Safety Study of VERU-111 for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Patients at High Risk for Acute Respiratory Distress Syndrome (ARDS)

SIGNATURE:

DocuSigned by:
[redacted]
AEC03E934851435E...

3/18/2022

Sponsor Date

[redacted] Chief Scientific Officer

Name and Title of Sponsor Representative

This signature of the Sponsor Representative constitutes approval of this protocol.

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number:	V3011902
Protocol Title:	Phase 3, Randomized, Placebo-Controlled, Efficacy and Safety Study of VERU-111 for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Patients at High Risk for Acute Respiratory Distress Syndrome (ARDS)
Protocol Date:	Protocol Amendment 6 (Version 7.0)/ 18 March 2022

SIGNATURE:

Principal Investigator: Date

Name of Principal Investigator *(Please Print)*

Address of Principal Investigator

The signature of the Principal Investigator constitutes approval of this protocol and an assurance that this study will be conducted according to all requirements of this protocol and according to Good Clinical Practices (GCP).