FDA Briefing Document

EUA Request 000113

Drug name: Sabizabulin (VERU-111)

Applicant: Veru Inc.

Pulmonary-Allergy Drugs Advisory Committee Meeting

11/09/2022

Division of Pulmonology, Allergy, and Critical Care (DPACC)

Office of Immunology and Inflammation (OII)

Office of New Drugs (OND)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought Veru's request for Emergency Use Authorization (EUA) 113, for VERU-111, an oral capsule, for treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk for ARDS, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

ACM	all-cause mortality
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	benefit risk framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
COVID-19	Coronavirus disease 2019
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCTD	electronic common technical document
ETASU	elements to assure safe use
EUA	emergency use authorization
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice

GRMP	good review management practice
HFNC	high-flow nasal cannula oxygen delivery devices
ICH	International Council for Harmonization
IMV	invasive mechanical ventilation
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NC	nasal cannula for oxygen delivery
NG	nasogastric tube for enteral delivery
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NiPPV	non-invasive positive pressure ventilation
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update Report

REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
WHO	World Health Organization

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The Food and Drug Administration (FDA) is convening this Advisory Committee (AC) meeting to discuss whether the submitted data support the Emergency Use Authorization (EUA) of VERU-111 (sabizabulin) for the treatment of hospitalized adults with moderate to severe COVID-19 who are at high risk for acute respiratory distress syndrome (ARDS). In addition, we request input/discussion regarding relevant design aspects of an additional trial to be conducted as a condition of authorization.

1.2 Context for Issues to Be Discussed at the AC

1.2.1 VERU-111

VERU-111 is a new molecular entity (NME), that is not approved for any indication. Prior to being developed for COVID-19, it was being studied in castration-resistant prostate cancer. It is proposed as a microtubule inhibitor, but it's mechanism of action in COVID-19 is uncertain. Given that VERU-111 is an NME, and the small size of the study submitted to support the request for authorization, the available clinical information for VERU-111 is limited when compared to the typical efficacy and safety databases available for other products that have been granted EUA.

1.2.2 COVID-19

The 2019 novel coronavirus, first identified in Wuhan China, and now identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes the disease named coronavirus disease 2019 (COVID-19). COVID-19 is a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death.

On March 11, 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. According to the World Health Organization, approximately 614 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported as of September 30, 2022, including ~6.5 million deaths. In the US, according to the Centers for Disease Control and Prevention (CDC), as of September 30, 2022, approximately 96 million cases of COVID-19 had been reported with approximately 1 million deaths.

Patients with symptomatic SARS-CoV-2 infection, or COVID-19, can experience a wide range of clinical manifestations. The VERU-111 development program focuses exclusively on a patient population of subjects hospitalized with severe or critical COVID-19. Severe and critical illness are characterized by worsening pulmonary status due to lower respiratory tract infection with SARS-CoV-2 leading to pulmonary and systemic inflammation, pneumonia, and hypoxemia with peripheral oxygen saturations <94% in the absence of supplemental oxygen, or other markers of respiratory compromise such as respiratory rate >30 breaths per minute or PaO2/FiO2 <300 mm Hg; these patients require

hospitalization, supplemental oxygen, noninvasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or extracorporeal membrane oxygenation (Guidance for Industry 2021; COVID-19 Treatment Guidelines Panel 2022) as the disease process continues to progress. Disease progression can lead to acute respiratory distress syndrome and septic shock involving multiple organ systems.

At this stage of severe or critical disease, standard of care therapy in the US is likely to include dexamethasone, remdesivir, baricitinib (or consideration of other immunomodulators such as tocilizumab, available under EUA) and supportive care. Uptake of these agents as part of local standard of care has been variable outside of the US. The standard of care has evolved and continues to do so over the course of the continuing pandemic as new treatments become available. However, despite these treatments, the CDC continues to report >350 deaths per day and >4,400 new hospital admissions per day in the United States due to COVID-19 (Centers for Disease Control and Prevention). These numbers highlight the continuing unmet medical need for additional safe and effective therapies for COVID-19 that can reduce mortality. Further, while there are no identified shortages currently, available therapies may fall into a shortage situation if the COVID-19 pandemic worsens.

1.3 Brief Description of Issues for Discussion at the AC

Veru Inc. (the Sponsor), submitted an Emergency Use Authorization (EUA) request for VERU-111 for the treatment of SARS-CoV-2 infection in hospitalized adult patients with moderate to severe COVID-19 infection who are at high risk for ARDS. In support of the proposed use, the Sponsor submitted the results of Study V3011902 (Study 902). Study 902 was an international, multicenter, randomized, double-blind, placebo-controlled, parallel group study of 60 days duration that evaluated the efficacy and safety of VERU-111 in hospitalized adult subjects with COVID-19 infection described as being at "high risk for ARDS". Subjects were included if they met criteria for World Health Organization (WHO) ordinal scale category 5 (non-invasive ventilation or high-flow oxygen) or category 6 (mechanical ventilation); or category 4 (oxygen by mask or nasal prongs) with the following comorbidities: asthma, chronic lung disease, diabetes, hypertension, severe obesity (BMI ≥40), 65 years of age or older, primarily residing in a nursing home or long-term care facility, immunocompromised. Study 902 randomized (2:1) 204 patients, with 134 receiving VERU-111 for up to 21 days. The primary endpoint was all-cause mortality at Day 60. At the Day 60 timepoint, 78.4% of the VERU-111 arm remained alive compared to 58.6% of the placebo arm among the 204 subjects randomized 2:1 to VERU-111 versus placebo (risk difference 19.0%, 95% CI (5.8%, 32.2%), odds ratio 2.77, 95% CI (1.37, 5.58)). Secondary endpoints included proportion of patients alive and without respiratory failure at various time points, days on mechanical ventilation, and days in ICU. Because of the influence of the mortality results on these secondary endpoints, and the importance of the all-cause mortality endpoint to the overall regulatory decision-making regarding VERU-111, this briefing document focuses primarily on the analyses of all-cause mortality and the potential uncertainties.

The FDA Review team acknowledges that Study 902 met its prespecified primary endpoint of all-cause mortality at Day 60. We also note that the VERU-111 program is quite small in size compared to other therapeutic programs for patients hospitalized with COVID-19. As detailed in the briefing document, our review has identified a number of uncertainties with the data, which we raise in the context of this small trial in critically ill patients. These include:

- High placebo group mortality rate
- Potential for unblinding events with enteral tube administration
- Baseline imbalances in standard of care therapies
- Differences in hospitalization duration prior to trial enrollment
- Uncertain effects of goals of care decisions on all-cause mortality

- Negative studies with other microtubule disruptors in COVID-19
- Uncertainty in identification of a clinically relevant patient population

Based on our review, none of these uncertainties or imbalances alone invalidate the mortality benefit observed in Study 902, but all of these issues together in a small trial which is more vulnerable to imbalances raise questions about the results. We conducted sensitivity analyses to investigate the potential impact of the noted imbalances. However, these analyses cannot eliminate the concern that certain baseline imbalances across treatment groups may have impacted study outcomes, due to the small study size. In addition, these issues raise concern that, even when using an objective endpoint such as mortality, observed results can be subject to biases in a small trial of short duration in critically ill patients. We ask the AC panel to consider these uncertainties together and how they affect the interpretation of the mortality data.

When considering whether to authorize the emergency use of a product under EUA, the Agency must determine, among other requirements (see section 2.1.3), whether "the known and potential benefits of the product when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product". Evaluation of the potential risks in the VERU-111 development program is limited by the atypically small safety database, comprising a total of 149 subjects who received VERU-111 for the proposed use in COVID-19. While the small safety database limits our ability to identify clinically significant safety signals, potential safety signals identified in our review are urinary tract infections (including serious infections), gastrointestinal motility and defecation conditions (including diarrhea), gastrointestinal signs and symptoms (including nausea/vomiting), anemia, epidermal and dermal conditions (including decubitus ulcer and rash), venous thromboembolism, and hemorrhage (including GI and non-GI hemorrhage terms). We acknowledge that in the face of a potential mortality benefit, there are few safety signals that would contribute to an unfavorable benefit-risk assessment. Therefore, we ask the AC panel to focus their discussion on whether the available data support a mortality benefit with VERU-111 to meet the statutory requirements of an EUA (see section 2.1.3) and to address any residual uncertainties with the mortality results.

With respect to emergency use of an unapproved product, the statutory provisions [564(e)(1)(B)(iii)] state that we may require: *Appropriate conditions with respect to collection and analysis of information concerning the safety and effectiveness of the product with respect to the use of such product during the period when the authorization is in effect and a reasonable time following such period.* Given the uncertainties in the submitted data, but acknowledging the efficacy results, the Agency is considering requiring a trial to be conducted as a condition of authorization (in line with the above statutory provision) if authorization is granted. We propose that there is equipoise in conducting a trial similar to Study 902, to address the uncertainties in the mortality data as well as to expand the safety database. It is important to note that any trial required as a condition to authorization would need to inform the safety and effectiveness of VERU-111 for the use authorized under the EUA. We have presented the outline of such a trial in Section 4. We request that the AC panel discuss relevant design aspects of this trial to be conducted as a condition of authorization.

1.4 Draft Points for Consideration

- Discuss the all-cause mortality data, specifically addressing the extent to which these data could have been affected by the uncertainties raised by the Agency, including the high placebo mortality rate, potential for unblinding, imbalance in standard of care, differences in timing of enrollment, potential differences in goals of care, and the proposed population.
- Discuss your level of concern regarding the limited size of the safety database for this NME.
- Consider whether the known and potential benefits of VERU-111 when used for the treatment of adult hospitalized patients with COVID-19 at high risk of ARDS outweigh the known and potential risks of VERU-111.

  a) If the overall benefit-risk assessment supports authorization:

     i. Are additional data necessary to more fully understand the benefit-risk assessment of sabizabulin for its proposed use?

     ii. If yes, discuss the proposed design aspects of a study to provide this additional data.

  b) If overall benefit risk does not support authorization, discuss what additional data are necessary to further inform the benefit-risk assessment.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

2.1.1 Background of the Condition

COVID-19 is a common, acute, infectious, pandemic disease caused by the novel SARS-CoV-2 that is characterized by pulmonary and systemic inflammatory responses, atypical pneumonia, and hypoxemia in serious cases. The full spectrum of SARS-CoV-2 infection and COVID-19 is broad and spans a wide range of manifestations including asymptomatic infection, mild symptomatic illness with fever and headaches, pneumonia requiring hospitalization, and life-threatening respiratory failure with septic shock and multiple organ dysfunction syndrome. While safe and effective vaccines as well as treatment indicated for ambulatory treatment of mild COVID-19 have decreased the rates of severe illness from SARS-CoV-2, the daily rate of hospitalizations, ICU admissions, and deaths attributable to COVID-19 remain substantial.

The VERU-111 development program focuses exclusively on a patient population of subjects hospitalized with severe COVID-19 or critical COVID-19. Symptomatic COVID-19 includes symptoms of fever, headache, loss of smell or taste, cough, and other symptoms of respiratory infection. Severe COVID-19 is characterized by lower respiratory tract infection with SARS-CoV-2 leading to pulmonary inflammation and systemic inflammation, pneumonia, and hypoxemia with peripheral oxygen saturations <94% in the absence of supplemental oxygen, or other markers of respiratory compromise such as respiratory rate >30 breaths per minute or PaO2/FiO2 <300 mm Hg per NIH guidelines (COVID-19 Treatment Guidelines Panel 2022).

If COVID-19 continues to progress, both pulmonary and systemic inflammation worsen. Worsening systemic inflammation can lead to sepsis physiology, worsening organ function, and hypercoagulability manifested by thrombo-embolic events. Worsening pulmonary inflammation leads to evolving pulmonary edema, worsening ventilation-perfusion mismatching, diffusion impairment, and pathophysiology of early acute respiratory distress syndrome (ARDS). This underlying pathophysiology leads to worsening symptoms of dyspnea and breathlessness, worsening hypoxemia, and critical illness requiring higher levels of supportive care including ICU admission. As systemic inflammation worsens, extrapulmonary manifestations of COVID-19 such as sepsis, shock, myocardial involvement, venous-thromboembolic events, and organ failure also increase in frequency, adding complexity to the patient's prognosis and clinical decision-making. This critical severity of disease also often requires more aggressive forms of oxygen supplementation including delivery by high-flow nasal cannula or noninvasive ventilation.

If the disease continues to progress despite these more aggressive measures, patients show pathophysiology consistent with moderate-to-severe ARDS requiring endotracheal intubation and invasive mechanical ventilation (IMV). Standard of care treatment of ARDS to improve mortality and oxygenation includes elements such as "lung protective ventilation" with low tidal volumes, patient proning among those with PaO2/FiO2 ratio <150 mm Hg, and a conservative fluid management strategy. ARDS physiology often also leads to additional complicating factors such as pulmonary hypertension and pulmonary shunting. This stage of disease may also be complicated with the extra-pulmonary manifestations of COVID-19 noted above.

Extracorporeal membrane oxygenation (ECMO) may also be considered at this stage of disease, either as primary therapy to improve hypoxemic respiratory failure or as salvage therapy for those who are failing mechanical ventilation, although its benefit-risk ratio remains an area of controversy due to mixed results and uncertainties in prior clinical trials. In practice, the limited availability and high resource burden of ECMO has led to ECMO being used more frequently for select patients who have failed standard of care measures for ARDS.

COVID-19-related deaths can result from the viral pneumonia syndrome (e.g., intractable hypoxemia secondary to ARDS), the associated sepsis syndrome (e.g., septic shock and multi-organ dysfunction syndrome), and additional causes attributable to SARS-CoV-2 infection (e.g., thromboembolic events). Additional deaths attributable to COVID-19 may occur due to sequela of critical illness such as secondary infections in the setting of deconditioning and critical illness myopathy. Finally, while some patients die from the directly life-threatening events noted above despite attempts to resuscitate, a substantial number of patients reach thresholds of prognosis/recovery or thresholds of life-sustaining therapies that do not align with their goals of care; in these cases, palliative care measures may be initiated in combination with declination or withdrawal of life-sustaining therapy, allowing death to occur without cardiopulmonary resuscitation attempts.

Despite advances like safe and effective preventative measures such as approved COVID-19 vaccines, our evolving understanding of SARS-CoV-2 and its variants, and evolving COVID-19 standard of care treatment measures, over 1 million people in the US alone have died of COVID-19 since March, 2020. Globally, the World Health Organization (WHO) reports over 6.5 million deaths since December 2019 (World Health Organization 2022), although these counts may underestimate the total due to worldwide differences in reporting measures and requirements. More importantly, despite the positive trends in prevention and treatment, the CDC reports a 7-day moving average of over 300 deaths per day due to COVID-19, over 3,200 new hospital admissions per day due to COVID-19, and over 38,000 COVID-19 cases per day in the US alone as of October 13, 2022 (Centers for Disease Control and Prevention). These numbers highlight both the potential for additional research in COVID-19 and the unmet need for additional safe and effective treatment options for COVID-19 that act upon clinically meaningful endpoints such as all-cause mortality.

2.1.2 Standard of Care

Treatment of serious COVID-19 has been informed by large clinical trials supportive of the efficacy and safety of agents such as remdesivir, dexamethasone, and baricitinib, and multiple agents have been approved to treat COVID-19. While supportive care early in the pandemic was characterized by variable clinical decision-making regarding the timing of intubation, the use of agents with unproven efficacy, the role of anticoagulation, and other sources of uncertainty, increasing knowledge has led to comprehensive and data-driven treatment guidelines (Alhazzani et al. 2020; COVID-19 Treatment Guidelines Panel 2022; Infectious Diseases Society of America 2022; Roche et al. 2022). The currently available products that form the basis of generally accepted standard of care for moderate to severe COVID-19 in the United States are summarized below.

Dexamethasone and COVID-19

Dexamethasone and other corticosteroids – while not authorized for emergency use or approved for a COVID-19 indication – form part of the National Institutes of Health treatment guidelines for patients with COVID-19 (COVID-19 Treatment Guidelines Panel 2022; National Institutes of Health 2022)

requiring supplemental oxygen based primarily on data from the RECOVERY trial (Horby et al. 2021). RECOVERY was a randomized, open-label trial of 2104 patients assigned to receive dexamethasone and 4321 assigned to usual care; results suggested a mortality benefit for the dexamethasone arm compared to usual care (22.9% versus 25.7%, respectively) with an age-adjusted rate ratio of 0.83 (95% CI 0.75 to 0.93). Subsequent subgroup analyses suggested that this overall mortality benefit arose primarily from the higher severity subgroups of those requiring supplemental oxygen or other device support for respiratory failure. Corticosteroids have a well-understood adverse event profile based on decades of use in a broad range of indications in ICU and non-ICU settings that includes risk of secondary infections due to immunosuppression, steroid myopathy, steroid delirium/psychosis, hyperglycemia, hypertension, and other hypothalamic-pituitary axis-related effects.

Baricitinib for the Treatment of COVID-19

Baricitinib is approved in indications spanning rheumatoid arthritis, alopecia areata, and for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. Baricitinib has been studied in these and multiple other indications, with drug labeling[1] (Marconi et al. 2021) describing the risk profile of baricitinib based on baricitinib exposure of 3688 subjects across various indications. Baricitinib's COVID-19 safety profile in the two adequate and well-controlled trials included in labeling alone describe data from 1307 subjects with COVID-19 exposed to baricitinib. The safety profile of baricitinib across these contexts of use include boxed warnings for serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis, as well as Warnings and Precautions describing hypersensitivity reactions, gastrointestinal perforations, and laboratory abnormalities. Adverse events listed in COVID-19-specific drug labeling for baricitinib include increase of liver enzymes, thrombocytosis, creatinine phosphokinase increase, neutropenia, deep vein thrombosis, pulmonary embolism, and urinary tract infection.

Remdesivir for the Treatment of COVID-19

Although available data for remdesivir did not demonstrate a reduction in mortality in COVID-19 compared to placebo[2] (Pan et al. 2021), remdesivir is an approved SARS-CoV-2 nucleotide analog RNA polymerase inhibitor indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 viral testing, who are:

- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death

Remdesivir has been studied primarily in COVID-19, with drug labeling describing the risk profile of remdesivir based on remdesivir exposure in 1592 subjects with COVID-19. The safety profile of remdesivir in COVID-19 includes Warnings and Precautions regarding hypersensitivity- and infusion-related reactions, increased risk of transaminase elevations, and a risk of reduced antiviral activity when co-administered with chloroquine phosphate and hydroxychloroquine sulfate. Adverse events listed in

[1] See OLUMIANT (baricitinib) at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207924s007lbl.pdf
[2] See VEKLURY (remdesivir) at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214787s014lbl.pdf

COVID-19-specific drug labeling for remdesivir include nausea, increase in alanine aminotransferase, and increase in aspartate aminotransferase.

The efficacy of remdesivir among critically ill patients with COVID-19 remains an area of uncertainty, however. Results from trials like SOLIDARITY (WHO Solidarity Trial Consortium 2022), for example, have not provided evidence of the efficacy of remdesivir on all-cause mortality in subjects with COVID-19 who require mechanical ventilation compared to active controls, although subgroup analyses may suggest an improvement in mortality for those not ventilated at baseline.

2.1.3 Eligibility of the Product for an Emergency Use Authorization

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug & Cosmetic Act (FD&C Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus, SARS-CoV-2, that causes COVID-19. On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the FD&C Act (21 U.S.C. 360bbb-3), participant to terms of any authorization issued under that section.

Based on this declaration, FDA may issue an EUA after determining the following statutory requirements are met:

- The chemical, biological, radiological, or nuclear agent referred to in the March 27, 2020, EUA declaration by the Secretary of the U.S. Department of Health and Human Services (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that –
    - the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2; and
    - The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product;
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

As part of its authorization, the FDA will establish, to the extent practicable given the circumstances, conditions in the EUA that it finds necessary or appropriate to protect the public health. This includes, for example, appropriate conditions designed to ensure that health care professionals administering the product, or individuals to whom the product is administered, are informed (e.g., through dissemination of authorized Fact Sheets) of the significant known and potential benefits and risks of the emergency use of the authorized product. Additional examples include, but are not limited to, conditions for the monitoring and reporting of adverse events associated with the emergency use of the product and conditions on the manufacturing of the authorized product.

FDA's authorization of a medical product under an EUA is not the same as the Agency's approval or licensure of a product under its relevant statutory authorities. If authorized, FDA will periodically review the circumstances and appropriateness of the EUA. FDA will also regularly review the EUA Sponsor's progress toward the approval or licensure of the authorized product. The EUA will be effective until the circumstances described in the March 27, 2020, EUA declaration justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic no longer exist, the criteria for issuance are no longer met, or other circumstances make revocation appropriate to protect the public health or safety.

2.2 Pertinent Drug Development and Regulatory History

VERU-111 is a new molecular entity (NME) that is not approved for any indication in the US or globally.

Prior to development in COVID-19, it was being developed for castration-resistant prostate cancer. VERU-111 is a microtubule inhibitor that binds with high affinity to the "colchicine binding site" on tubulin (Chen et al. 2012; Deng et al. 2020), and crosslinks both the α and β tubulin subunits (Chen et al. 2012; Li et al. 2012). VERU-111 has a low micromolar inhibitory concentration in a tubulin polymerization assay and antiproliferative activity at low nanomolar concentrations (Chen et al. 2012). It thereby inhibits tubulin polymerization, induces depolymerization and prevents the formation of dynamic microtubules. Available data suggest that the half-life of VERU-111 is approximately 5 hours for both the powder-in-capsule (PIC, used in study V0211901, Study 901, Phase 2) and formulated capsule (FC, used in V3011902, Study 902, Phase 3) formulations.

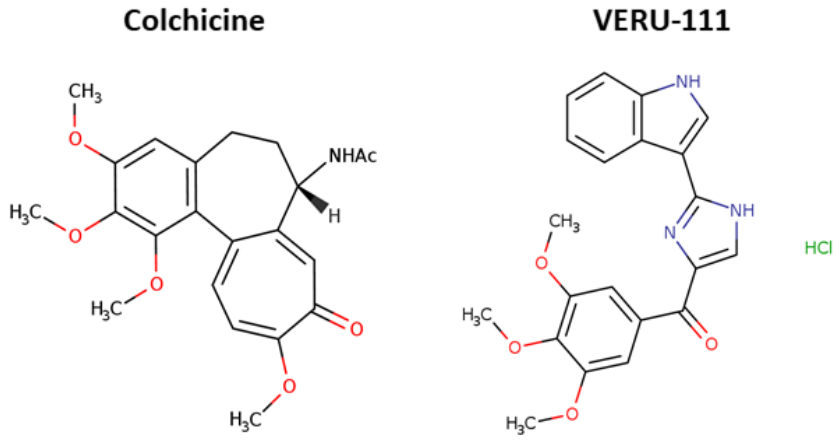
2.2.1 Summary of Mechanism of Action and Nonclinical Development

The mechanism of action of VERU-111 in COVID-19 is not completely determined, although the Sponsor hypothesizes that the microtubules are intracellular transport structures critical for virus trafficking around the cell and for the inflammatory response., and that microtubule disruption will lead to antiviral and anti-inflammatory effects.

Summary of Anti-inflammatory Data for VERU-111

The Sponsor's mechanistic rationale for VERU-111 in COVID-19 relies, in part, on assumptions of downstream anti-inflammatory actions that are similar to the established mechanism of action of colchicine. Actual studies with VERU-111 were limited. Both VERU-111 and colchicine are tubulin inhibitors, although VERU-111 apparently possesses higher potency ("binds more tightly in the colchicine binding site"). VERU-111 inhibited tubulin (microtubule) polymerization in a dose-dependent manner with an IC50 at 3.8 nM. Colchicine is an alkaloid extracted from the colchicum autumnale plant, having molecular formula $C_{22}H_{25}NO_6$, and consists of three rings. VERU-111 is (2-(1H-indol-3-yl)-1H-imidazol-4-yl) (3,4,5-trimethoxyphenyl) methanone hydrochloride, having molecular formula $C_{21}H_{20}ClN_3O_4$, and appears to differ significantly in chemical structure from colchicine (see Figure 1). A number of anti-inflammatory mechanisms are postulated for the efficacy of colchicine in gout that appear to be related to its inhibitory effects on preventing formation of intact microtubule structures. Colchicine was evaluated in large clinical trials with COVID-19 which are reviewed below (see section 3.1.3.6). The mechanism of the potential efficacy of VERU-111 in COVID-19 is unclear.

Figure 1 Chemical Structures of Colchicine and VERU-111



Source: ChemIDPlus (National Library of Medicine). Left structure is colchicine and right structure is VERU-111.

Summary of Antiviral Activity Data for VERU-111

The Sponsor has not provided any direct evidence to support the antiviral activity of VERU-111. Appropriate cytotoxicity controls were not included in their cell culture antiviral activity assessments, antiviral activity was not observed in the NIH ARDS mouse model; and there was no meaningful reduction in viral shedding in study V3011902. These results and the known cytotoxic/cytostatic effects of VERU-111 indicate a mechanism of action based on inhibition of a critical cell processes and not direct-acting antiviral activity.

2.2.2 Proposed Use

The proposed use for EUA is:

For treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 infection:

- with positive results of direct SARS-CoV-2 viral testing, and
- who are hospitalized, and
- who are at high risk for developing ARDS, and
- for whom alternative COVID-19 treatment options authorized by FDA are not accessible or are not clinically appropriate.

2.2.3 Regulatory History

Regulatory history pertinent to Advisory Committee Discussion is summarized below.

A Pre-EUA meeting was held with the sponsor on May 10, 2022. Topics of discussion included:

- The Agency acknowledged that the safety database was sufficient to support an EUA request, but the adequacy of the safety database to support authorization would be a review issue.
- The Sponsor inquired regarding the adequacy of the efficacy/safety data for approval (via a New Drug Application; NDA). The Agency emphasized that the available safety database for

VERU-111, a new molecular entity, was small and strongly recommended a stepwise approach, i.e., to submit an EUA request prior to an NDA submission.

3 Summary of Issues for the AC

3.1 Efficacy Issues

While the pre-specified primary efficacy analysis of Study 902 demonstrated a difference on all-cause mortality at Day 60 in favor of VERU-111, there are several uncertainties in the data that may impact the clinical interpretation of the efficacy results:

- High placebo group mortality rate
- Potential for unblinding events with enteral tube administration
- Baseline imbalances in standard of care therapies
- Differences in hospitalization duration prior to trial enrollment
- Uncertain effects of goals of care decisions on all-cause mortality
- Negative studies with other microtubule disruptors in COVID-19
- Uncertainty in identification of a clinically relevant patient population

3.1.1 Sources of Data for Efficacy

The review of efficacy and safety for the proposed emergency use in COVID-19 relies primarily upon data from Study 902 as a single, randomized, double-blind, placebo-controlled phase 3 trial with the highest number of subjects available for assessment (i.e., 134 randomized to VERU-111, 70 randomized to placebo). The review also evaluated the phase 2, proof-of-concept trial V0211901 (Study 901) as a source of support for conclusions on the efficacy and safety of VERU-111 for the desired use in COVID-19. However, Study 901 is limited in its ability to provide robust support of efficacy and safety conclusions based primarily on its small sample size and lack of statistical power to detect differences on meaningful endpoints.

The focus of the Advisory Committee discussion will be Study 902. Details regarding Study 901 – as well as studies of VERU-111 in prostate cancer studies intended to support product safety (V1011101 and V3011102) - are located in the Appendix for reference.

Table 1. Clinical Trials of VERU-111 for the Treatment of COVID-19

Study Identifier, Design, and Duration	Randomized Treatment	N	Characteristics of Enrolled Population	Primary and Key Secondary Efficacy Endpoints
V0211901 (Study 901) 1:1 R, DB, PC, MC, PG, 60-day duration JUNE 2020 – DECEMBER 2020	VERU-111 18 mg daily via PO/NG + SOC Pbo PO/NG daily + SOC Up to 21 days or hospital discharge	20 19	Hospitalized adult PCR-confirmed SARS-CoV-2 infection WHO Category 5 or 6, or WHO Category 4 plus ≥1 comorbidity of the following: Hypertension, diabetes, BMI ≥ 40 kg/m^2, ≥65 years of age, immunocompromised, resides in a long-term care facility, asthma or chronic lung disease No hepatic or renal impairment	<u>Primary</u> Alive and free of respiratory failure at Day 29 <u>Secondary</u> All-cause mortality at Day 29 Days in ICU Change in mean WHO Ordinal Scale for Improvement at Day 29 Days on Mechanical Ventilation Days in Hospital Effect on CRP Pharmacokinetic Endpoints
V3011902 (Study 902) 2:1 R, DB, PC, MC, PG, 60-day duration MAY 2021 - JUNE 2022	VERU-111 9 mg daily via PO/NG + SOC Pbo PO/NG daily + SOC up to 21 days or hospital discharge	134 70	Hospitalized adult PCR-confirmed SARS-CoV-2 infection WHO Category 5 or 6, or WHO Category 4 plus ≥1 comorbidity of the following: Hypertension, diabetes, BMI ≥ 40 kg/m^2, ≥65 years of age, immunocompromised, resides in a long-term care facility, asthma or chronic lung disease No hepatic or renal impairment	<u>Primary</u> All-cause mortality at Day 60 <u>Secondary</u> Alive and free of respiratory failure at Day 29 Days in ICU Change in mean WHO Ordinal Scale for Improvement at Day 29 Days on Mechanical Ventilation Days in Hospital Change from baseline in viral load

Source: Reviewer.

Note: A formulation change of the drug product from the powder-in-capsule (PIC) to a formulated capsule (FC) formulation occurred between the Phase 2 and Phase 3 studies. Based on the Sponsor's bioavailability analyses of the two formulations, the 18 mg PIC dose in trial V0211901 and the 9 mg FC dose in trial V3011902 can be interpreted to provide clinically comparable doses of VERU-111 for purposes of clinical interpretation of efficacy and safety data.

Abbreviations: BMI, body-mass index; kg/m2: kilograms per meter-squared; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DB, double blind; MC, multicenter; N, number of subjets in linical trial; NG, nasogastric; Pbo, placebo; mg, milligrams; PC, placebo control; PCR, polymerase chain reaction; PG, parallel group; PO, orally; R, randomized; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOC, standard of care; WHO, World Health Organization ordinal scale for clinical severity

3.1.1.1 Study V3011902 (Study 902) Protocol Review

3.1.1.1.1 Administrative Information

Study 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).

Study dates: 18 May 2021 to 06 Jun 2022

Study sites: 56 total sites including 20 US sites

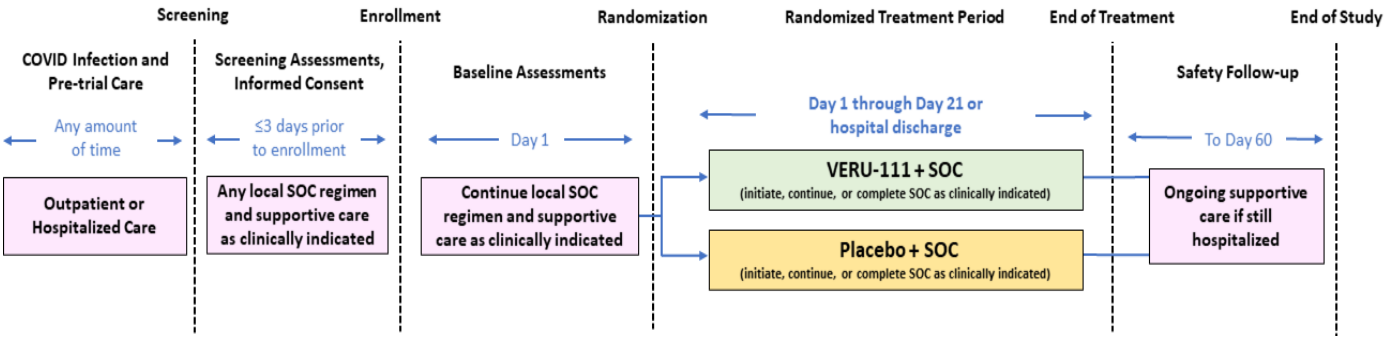
Study report date: Abbreviated clinical study report v1.0, 31 May 2022

3.1.1.1.2 Study Design

Study 902 was a 2:1 randomized, double-blind, parallel-group, placebo-controlled trial that evaluated the efficacy and safety of VERU-111 9 mg oral capsules PO or via NG tube daily for up to 21 days compared to placebo on 60-day all-cause mortality and other critical care endpoints. The study was designed to evaulate 300 subjects hospitalized with SARS-CoV-2 infection with elements of COVID-19 disease severity or comorbidities that placed them at higher risk of poor disease outcomes and ARDS with safety follow-up to Day 60 (see Statistical Analysis for details regarding sample size changes and interim analysis results to result in a final study sample of 204 subjects).

A schematic of the trial is shown in Figure 2 below.

Figure 2. Study 902: Trial Schematic



Source: Reviewer
Abbreviations: COVID, coronavirus disease; SOC, standard of care; VERA-111, sabizabulin

As shown in Figure 2, Study 902 comprised a screening period, baseline assessments, a randomized treatment period of up to 21 days or until hospital discharge (whichever came first), and safety follow-up to Day 60, all with a background of ongoing standard of care interventions for COVID-19 and supportive care of COVID-19 or concomitant conditions as clinically indicated. There was an up to 3-day period between initial screening and baseline assessments on Day 1. Clinical efficacy endpoints were evaluated at Day 15, 22, and 29, and the primary endpoint of all-cause mortality was evaluated based on vital status at Day 60.

3.1.1.1.3 Product Information

The VERU-111 drug substance is described by the Sponsor in the EUA submission as a “white or whitish to yellow-brown powder” and in the Sponsor’s Investigator Brochure edition 10.0 as “yellow solid” and a “yellow solid powder”, which is slightly soluble in water.

The Sponsor supplied placebo in identical capsules to the VERU-111 capsules. Placebo capsules contained only microcrystalline cellulose , an odorless solid white powder, which is slightly soluble in water (no more than 0.25%). Pictures of both the VERU-111 drug product and the placebo powder are provided in section 3.1.3.2).

3.1.1.1.4 Concomitant Medications and Interventions

Medications taken within 30 days prior to the Screening Visit were required to be recorded, in addition to recording of all medications during the course of the study.

The following medications were prohibited during the study:

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

Standard of Care

There were no defined elements to the local standard of care background therapy required by the protocol. Section 5.1 of the protocol states that "All patients will receive standard of care for the treatment of SARS-CoV-2 infection (COVID-19)".

Additional points in the protocol exclude subjects receiving concurrent treatment with other experimental agents against COVID-19 <24 hours prior to study drug dosing except standard of care drugs, and explicitly notes that remdesivir, dexamethasone, and convalescent plasma are allowed.

Additional Supportive Care

The trial did not include a requirement for subjects to agree to a particular level of medical care surrounding specific components of ICU therapy related to severity of disease, respiratory failure, and goals of care.

3.1.1.1.5 Protocol Amendments

The protocol was amended seven times. Protocol amendments relevant to the advisory committee discussion are summarized below:

- January 9, 2022 – the interim analysis was updated to be conducted when 50% of the patients had been enrolled instead of 67% of patients; According to the Sponsor, the change was made to reduce the impact of the interim analysis on the final statistical significance of the study.
- March 18, 2022 – sample size of the study was reduced from 300 to 210; the Sponsor cited enrollment challenges as the reason for this change.

3.1.1.1.6 Enrollment Criteria

The enrollment criteria were intended to enroll adult subjects hospitalized with laboratory-confirmed COVID-19 and one of the following:

- Severe disease with evidence of respiratory failure
- Moderate disease and ≥1 additional comorbidities associated with poor clinical outcomes in COVID-19 (e.g., diabetes)

The protocol was initially designed to enroll 300 subjects (i.e., 200 in VERU-111 arm and 100 in placebo arm), but the final goal enrollment was set at 210 subjects after the amendment on March 18, 2022.

Inclusion

The inclusion criteria provided for the inclusion of hospitalized adult subjects with laboratory confirmed SARS-CoV-2 infection with WHO ordinal scale 5 or 6 severity, or WHO ordinal scale 4 severity with ≥1 additional comorbidities. In addition to providing informed consent and agreement to comply with protocol requirements, enrolled subjects met the following criteria at Baseline (Day 1):

- Age ≥18 years
- Polymerase chain reaction results confirming SARS-CoV-2 infection
- Peripheral oxygen saturation of ≤94% on room air at screening
- Subjects must agree to follow doctor's recommendation for oxygen supplementation
- Agreement to abide by protections regarding contraception for women of child-bearing potential and men with partners of child-bearing potential
- Disease severity commensurate with:
- WHO ordinal scale category 6 (intubation and mechanical ventilation)
- WHO ordinal scale category 5 (non-invasive ventilation or high-flow oxygen)
- WHO ordinal scale category 4 (oxygen by mask or nasal prongs) plus at least one of the following comorbidities:
- Asthma (moderate to severe)
- Chronic lung disease
- Diabetes
- Hypertension
- Severe obesity (BMI ≥40 kg/m^2)
- 65 years of age or older
- Primarily reside in a nursing home or long-term care facility
- Immunocompromised

Exclusion

The exclusion criteria include:

- Severity equal to or greater than WHO ordinal scale 7 (e.g., requiring ventilation plus additional organ support such as pressor support of blood pressure, RRT, ECMO)
- Hepatic impairment including
- ALT or AST > 3 times ULN
- Total bilirubin > ULN
- Documented history of liver disease including hepatitis or any etiology, cirrhosis, portal hypertension, or confirmed or suspected esophageal varices
- Moderate or severe renal impairment, including
- Creatinine clearance < 60 ml/min
- Any comorbid disease or condition that may interfere with the absorption, distribution, metabolism, or excretion of study drug, or would place the subject at increased risk, in the opinion of the investigator
- Known allergy or hypersensitivity to colchicine
- Participation in any other clinical trial of an experimental treatment for COVID-19

- Concurrent treatment with other experimental agents with actual or possible direct-acting antiviral activity against COVID-19 <24 hours prior to study drug dosing other than standard of care therapies
- Participants were excluded if they did not agree to refrain from prolonged sun exposure or did not agree to use sun-protective measures during the study and treatment with VERU-111

3.1.1.1.7 Randomization

The protocol planned 2:1 randomization of screened and enrolled subjects to VERU-111 versus placebo, respectively, using an interactive web response system (IWRS). Randomization was stratified by baseline WHO ordinal scale score of 4, 5, and 6 in order to promote comparable distributions of severity based on WHO ordinal scale in each study arm.

3.1.1.1.8 Blinding

The protocol states that the trial is double-blind using a blinded study intervention, and that both VERU-111 and placebo control study drug products were supplied as bottles containing 21 capsules of VERU-111 or placebo. Capsules were opened and mixed with water for NG tube or other enteral tube administration (see Potential Unblinding Events with Enteral Tube Administration).

In addition to study investigators, the protocol states that the Sponsor would be blinded to interim analysis results conducted by an independent statistician and presented to the Independent Data Monitoring Committee (IDMC).

3.1.1.1.9 Ethics

The protocol states that the study will be conducted in accordance with 21 CFR parts 50, 54, 56, 312, and 314, which are based on the principles of the Declaration of Helsinki. It also notes that Good Clinical Practices should be followed during conduct. The protocol notes that the investigator or institution should have written and dated approval from the appropriate Independent Ethics Committee or Institutional Review Board for the protocols, amendments, informed consent forms, subject recruitment procedures, as well as other study materials.

The protocol notes that the trial was overseen and managed by a contract research organization (CRO) and the Sponsor, with responsibility for the data management, data handling, statistical analysis, quality assurance, and the final study report ceded to the CRO.

The protocol states the following regarding informed consent:

Section 6.2.1, Inclusion Criteria: Provide informed consent from the subject or the subject's Legally Authorized Representative (LAR)

Section 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… 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

3.1.1.1.10 Endpoints

Primary Endpoint

The Sponsor designated all-cause mortality as the primary endpoint of Study 902. All-cause mortality is a clinically relevant endpoint in COVID-19 as described in *FDA Guidance to Industry: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention, February 2021 (available at https://www.fda.gov/media/137926/download)*. The Sponsor defined the primary endpoint as the proportion of subjects that die (up to Day 60). For analyses, the Sponsor chose to compare treatment groups on the proportion of subjects alive at Day 60.

Secondary Endpoints

The Sponsor designated the following secondary endpoints:

- The proportion of subjects that are alive without respiratory failure at Day 15, Day 22, and Day 29. Respiratory failure was defined using the criteria listed below.
- Days in ICU
- WHO Ordinal Scale for Clinical Improvement change from baseline to Day 15, Day 22, and Day 29
- Days on mechanical ventilation
- Days in hospital
- Proportion of subjects that die on study at Day 15, Day 22, and Day 29
- Change from baseline in viral load (baseline to Day 9)

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

The WHO Ordinal Scale for Clinical Improvement used in the study is reproduced below as Table 2.

Table 2. WHO Ordinal Scale for Clinical Improvement

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, renal replacement therapy, extracorporeal membrane oxygenation	7
Death	Death	8

Source: Adapted from Sponsor-submitted materials
Abbreviations: WHO, World Health Organization ordinal scale for clinical severity

Days in ICU and Days on Mechanical Ventilation were included in the multiplicity control procedure. No other secondary endpoints were included in the multiplicity control procedure, though additional clinically relevant outcomes were evaluated.

3.1.1.1.11 Statistical Analysis

Sample Size

The Sponsor initially planned to randomize 300 subjects in a 2:1 ratio to treatment and placebo groups respectively. An interim efficacy analysis was planned after 150 subjects had completed Day 60 assessments. On March 29, 2022, after 198 subjects had already been enrolled into the trial, the sponsor communicated a change of the sample size to 210 subjects. The Sponsor indicated that the decision to change sample size was based on the reduction of COVID cases and considerable slowing of the recruitment of patients into the study. While the Agency cautioned against this change, the Sponsor moved forward with this reduction clarifying that the change was not based on viewing comparative analysis results.

The Sponsor stated that with 210 subjects (140 subjects in the VERU-111 treated group and 70 subjects in the placebo treated group) the study would be sufficiently powered based on Phase 2 study results. Assuming a rate of mortality of 5% in the VERU-111 treated group and 25% in the placebo-treated group, with significance level α=0.05, the Sponsor presented calculations to show that the planned sample size would have >92% power to detect a risk difference of 20% between treatment groups. Additional power calculations in the protocol provided ranges of confidence intervals for the estimated risk difference assuming mortality rate ranges of 5-15% and 15-30% for VERU-111 treated and placebo treated groups, respectively.

Efficacy Analyses

The Intent-to-treat population (ITT) containing all randomized subjects served as the population of primary efficacy analyses. Subjects were analyzed according to the treatment group to which they were randomized for analysis. For the main analyses, all observed information was included regardless of use of rescue medications, protocol violations or investigational product discontinuation, consistent with the treatment policy strategy for handling these intercurrent events.

The main analysis of the primary endpoint was conducted using a logistic regression model analysing the proportion of subjects alive at Day 60. This model included treatment, region, gender, remdesivir use (No/Yes), dexamethasone use (No/Yes) and WHO Ordinal Scale for Clinical Improvement at baseline as covariates. Missing outcome data were imputed via multiple imputation using an imputation model with the same covariates as the primary analysis model and additionally, treatment discontinuation status and discharge status. Odds ratios with 95% confidence intervals and p-values were presented for the treatment comparison. A covariate-adjusted risk difference was also computed by the review team as the sample mean of the difference in predicted risk of outcome under the two treatment arms for each subject, with the predicted risk under each treatment arm derived from a logistic regression model with covariates for region, gender, remdesivir use (No/Yes), dexamethasone use (No/Yes) and WHO Ordinal Scale for Clinical Improvement at baseline (Benkeser et al. 2020). The risk difference, as calculated using this analysis, provides an estimate of the unconditional treatment effect whereas the odds ratio provides an estimate of the conditional treatment effect.

A tipping-point sensitivity analysis considering the full range of possible response rates in patients with missing data was provided to assess the robustness of the primary analysis approach. Additionally, time to death was summarized using Kaplan-Meier survival curves and analyzed using a Cox proportional hazards model with the same covariates as the primary analysis model. Difference in proportions with 95% confidence intervals, calculated using Kaplan-Meier methodology assuming non-informative censoring for patients that withdrew from study early, were also provided.

The Sponsor specified a Holm (Jeppu et al. 2012) step-down procedure to control multiplicity for the selected key secondary endpoints of Days in ICU and Days on Mechanical Ventilation, such that the overall type I error rate would be maintained at 5% across the primary endpoint and these secondary endpoints. No other secondary endpoints were included in the multiplicity control procedure, though additional clinically relevant outcomes were evaluated.

Secondary endpoints of proportion of subjects alive, and, alive and free of respiratory failure at Days 15, 22 and 29 were analyzed using the same logistic regression analysis as the primary endpoint, with missing data imputed similarly.

Secondary endpoints of Days on Mechanical Ventilation, Days in Hospital, and Days in ICU were analyzed using an analysis of covariance model with the same covariates as the logistic regression analysis model for the primary endpoint. Death was handled using a composite strategy with subjects who died being assigned the worst possible outcome of 60 days. There were no missing data in the submitted datasets for these three endpoints.

Clinical Improvement on the WHO Ordinal scale at Days 15, 22, 29 and 60 was analyzed using a logistic regression model to compare the proportion of subjects who improved to a WHO Ordinal Scale score 0 or 1 (responders) to subjects who had a score of 2 or more (non-responders). The analysis model included the same covariates as the main analysis model for the primary endpoint. Missing data on the WHO Ordinal Scale score was handled by carrying forward the last available score. If a subject died, the following time points were set to the worst possible outcome (score = 8).

All primary and secondary endpoints were analyzed in pre-specified subgroups of baseline dexamethasone and remdesivir users, and by baseline WHO Ordinal Scale category and region.

Interim Analysis

The study followed an O'Brien-Fleming group sequential design, allowing for one interim look and with the overall type I error controlled at 5% ($\alpha = 0.05$). The interim analysis was to include the first 150 randomized subjects who had completed all evaluations through Day 60. The criterion for efficacy at the interim analysis was a two-sided p-value of 0.016. If the criterion was not met, that is, if the p-value from the primary analysis of the primary endpoint was greater than 0.016, the trial would have continued and the final analysis including all 210 subjects would have had a criterion for efficacy of a two-sided p-value ≤ 0.0452.

It is worth noting that the final sample size of the study was reduced from 300 to 210 on March 29, 2022 after 198 subjects had already been enrolled. Under the original final sample size of 300 subjects, the statistical boundary for efficacy would have differed at the interim analysis with 150 patients. When the final sample size was reduced from 300 to 210 the information fraction at interim increased from 50% (150/300) as originally planned to 71.4% (150/210) and so, the criterion for efficacy at the interim

analysis changed from a two-sided p-value of 0.003 to 0.016. The interim analysis was conducted on April 8, 2022, once 150 subjects reached the Day 60 timepoint.

3.1.1.1.12 Safety Assessments

The protocol designated a safety objective of assessing the safety, tolerability, and risk/benefit of VERU-111. The safety population included all randomized subjects who received at least one dose of study medication (i.e., VERU-111 or placebo).

Safety assessments in the study included assessments of AEs, SAEs, medical history, clinical laboratory values, vital signs, physical exams, electrocardiogram (ECG), pregnancy testing, and assessment of concomitant medications. While vital signs, concomitant medications, and AEs were assessed daily through Day 22, clinical laboratories, oxygen saturations, and ECG were assessed only on Days 1, 3, 9, 15, 22, and 29.

The timing of study-specific safety evaluations is detailed in Table 3 below.

Table 3. Study 902: Schedule of Safety Assessments

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)

Source: Sponsor, protocol V3011902

Abbreviations: AE, adverse event; CT, computed tomography; ECG, electrocardiogram; HIPAA, Health Insurance Portability and Accountability Act; SpO_2, oxygen saturation; WHO, World Health Organization ordinal scale for clinical severity

Laboratory assessments included hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, platelet count, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphorus, total protein, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase, cardiac troponin, d-dimer, C-reactive protein, and ferritin, among others.

3.1.1.1.13 Study Conduct and Administrative Details

Study Conduct

Conduct of the clinical trial was overseen and managed by a contract research organization (CRO) and the Sponsor; the CRO was ceded responsibility for data management, data handling, clinical monitoring, statistical analysis, quality assurance, and the final study report.

Study Oversight

The study included an IDMC which reviewed unblinded safety data, including all SAEs, approximately every 4 weeks. In addition, the IDMC was responsible for evaluating the results from the planned interim efficacy analysis. This interim efficacy analysis was initially planned for a timepoint corresponding to approximately 50% of the subjects having completed the Day 60 timepoint, but after protocol amendments that lowered the total goal sample size, the interim analysis was conducted on April 8, 2022, once 71.4% (i.e., 150 subjects) reached the Day 60 timepoint. See Statistical Analysis above for details.

Study Sites

The study was planned as multinational, multicenter study, and was conducted at 55 sites across countries in Europe, South America, and North America.

3.1.2 Efficacy Summary for Study 901 and Study 902

3.1.2.1 Study 901 Results Summary

Key efficacy analysis results from Study 901 are presented in the Appendix. At Day 29, 17 of the 19 (89.5%) randomized subjects in the VERU-111 treated group and 14 out of 20 (70%) randomized subjects in the placebo group remained alive and free of respiratory failure. Covariate adjusted analysis favored the treated group on the primary endpoint of alive and free of respiratory failure, but this finding was not statistically significant (odds ratio: 2.58, 95% Confidence Interval: 0.37 to 18.07). Similar trends were seen for key secondary endpoints of mortality, days in ICU, days on mechanical ventilation, days in hospital and change from baseline in WHO ordinal scale for clinical improvement at Day 29.

3.1.2.2 Study 902 Results

3.1.2.2.1 Disposition

Relevant disposition data for the ITT are presented in Table 4. There are small differences between treatment arms in the proportion of subjects who were randomized but not treated and therefore not included in the safety population, with a higher proportion of randomized subjects not included in the VERU-111 arm. The proportion of subjects who discontinued study medication and those who did not complete the study were similar between study arms. Small differences in reasons for discontinuation and noncompletion are noted in the table below. The mean duration of treatment was similar between the VERU-111 and placebo study arms (9.1 days compared to 9.6 days, respectively).

Table 4. Study 902: Subject Disposition (ITT Population)

	VERU-111 9 mg N=134	Placebo N=70	Total N=204
Safety Population – received a least one dose of study drug, n (%)			
Number of Subjects (%)	130 (97.0)	69 (98.6)	199 (97.5)
mITT Population – completed efficacy portion and do not have major protocol violations, n (%)			
Number of Subjects (%)	129 (96.3)	69 (98.6)	198 (97.1)
Discontinued Study Medication prior to Day 21, n (%)			
Number of Subjects (%)	109 (81.3)	58 (82.9)	167 (81.9)
Discontinued Study Medication prior to Day 21, Reason, n (%)			
Consent withdrawn	2 (1.5)	2 (2.9)	4 (2.0)
Death	13 (9.7)	15 (21.4)	28 (13.7)
Discharge from hospital	84 (62.7)	39 (55.7)	123 (60.3)
Investigator decision	2 (1.5)	0	2 (1.0)
Lack of efficacy	1 (0.7)	0	1 (0.5)
Other reason	2 (1.5)	1 (1.4)	3 (1.5)
Significant and unacceptable adverse event	1 (0.7)	0	1 (0.5)
Missing	29	13	42
Time to Discontinuation of Study Medication (days)			
Mean (SD)	9.1 (5.07)	9.6 (4.56)	9.3 (4.89)
Missing	29	13	42
Completers population – completed Day 60 visit or died before, n (%)			
Number of Subjects (%)	125 (93.3)	66 (94.3)	191 (93.6)
Reason for Withdrawal from Study, n (%)			
Lost to follow-up	1 (0.7)	2 (2.9)	3 (1.5)
Physician decision	1 (0.7)	0	1 (0.5)
Withdrawal by subject	6 (4.5)	2 (2.9)	8 (3.9)
Other	1 (0.7)	0	1 (0.5)

Source: Statistical Reviewer Analysis; adsl.xpt

Abbreviations: IQR, interquartile range; ITT, intention-to-treat population; mITT, modified intention-to-treat population; N, number of subjects; n, number of subjects with disposition; SD, standard deviation; VERU-111, sabizabulin

3.1.2.2.2 Demographics

The baseline demographics for Study 902 are presented in Table 5 below. While the treatment arms are relatively balanced, there are some small differences between the VERU-111 and placebo arms in some clinically relevant demographic factors at baseline. Considering factors that might impact mortality in COVID-19 (Centers for Disease Control and Prevention 2022), the CDC notes that age remains the strongest risk factor for severe COVID-19 outcomes. The mean age of subjects in the placebo arm was similar compared to the VERU-111 study arm, but the proportion of subjects ≥65 years of age was higher in the placebo arm.

The small differences in demographic factors observed between the two study arms at baseline are likely due to the relatively small sample size of Study 902. However, the cumulative clinical impact of these multiple small imbalances on study outcomes (e.g., mortality) in this small study is difficult to predict.

Table 5. Study 902: Subject Demographics (ITT Population)

	VERU-111 9 mg N=134	Placebo N=70	Total N=204
Age			
Mean (SD)	61.3 (14.14)	62.7 (13.90)	61.8 (14.04)
Pooled Age Group 1, n (%)			
<65 years	67 (50.0)	29 (41.4)	96 (47.1)
>=65 years	67 (50.0)	41 (58.6)	108 (52.1)
Sex, n (%)			
Female	44 (32.8)	26 (37.1)	70 (34.3)
Male	90 (67.2)	44 (62.9)	134 (65.7)
Race, n (%)			
American Indian or Alaska Native	3 (2.2)	2 (2.9)	5 (2.5)
Asian	3 (2.2)	0	3 (1.5)
Black or African American	6 (4.5)	2 (2.9)	8 (3.9)
Other	8 (6.0)	2 (2.9)	10 (4.9)
White	114 (85.1)	64 (91.4)	178 (87.3)
Ethnicity, n (%)			
Hispanic or Latino	58 (43.3)	28 (40.0)	86 (42.2)
Not Hispanic or Latino	76 (56.7)	42 (60.0)	118 (57.8)
BMI at Baseline (kg/m2)			
Mean (SD)	31.8 (7.63)	32.1 (7.24)	32.0 (7.36)

Source: Statistical Reviewer Analysis; adsl.xpt

Abbreviations: BMI, body-mass index; kg/m2: kilograms per meter-squared; IQR, interquartile range; ITT, Intention-to-treat population; N, number of subjects; n, number of subjects within specific demographic; SD, standard deviation; VERU-111, sabizabulin

3.1.2.2.3 Baseline Disease Characteristics

The baseline disease characteristics of the ITT population of Study 902 are detailed in Table 6. There are small numerical imbalances between treatment groups seen in some important baseline disease characteristics including WHO severity, acute respiratory failure, ARDS, diabetes, hypertension, and heart failure – all of which occurred in a slightly higher proportion of placebo-treated patients. Dexamethasone and remdesivir use at baseline was slightly higher in the placebo group as well. Conversely, asthma, COPD, and cancer occurred in a higher proportion of VERU-111 treated patients.

While the inclusion criteria listed “immunocompromised” and “primarily resides in a nursing home or long-term care facility” as parameters that could qualify subjects who had WHO severity, the CRF did not include data collection on these parameters for analysis. There were numerical differences in several clinically relevant disease characteristics between the two study arms at baseline, likely due to the relatively small sample size of Study 902. Higher WHO category is directly linked to worsening clinical severity and poor prognosis. Available data from a large, open-label trial suggests that dexamethasone may improve mortality in populations of COVID-19 subjects who require supplemental oxygen compared to usual care (Horby et al. 2021), and available data from a large, active-controlled trial may suggest that remdesivir may improve mortality in populations of COVID-19 subjects who are not intubated and mechanically ventilated at baseline compared to lopinavir, hydroxychloroquine, or interferon beta-1a (WHO Solidarity Trial Consortium 2022). In addition, the CDC (Centers for Disease Control and Prevention 2022) cites evidence linking the following risk factors with higher risk of adverse clinical outcomes with COVID-19: diabetes, heart conditions (including heart failure), cancer, asthma, and chronic obstructive pulmonary disease. While the differences for each individual baseline

characteristic are small, whether these baseline imbalances when considered together influence the interpretation of the efficacy results is a topic of discussion for the Advisory Committee.

Table 6. Study 902: Baseline Disease Characteristics (ITT population)

Characteristic	VERU-111 9 mg N=134	Placebo N=70	Total N=204
Oxygen Saturation at Baseline (%)			
Mean (SD)	91.9 (3.99)	92.6 (3.62)	92.1 (3.87)
Baseline WHO Ordinal Scale, n (%)			
4*. Hospitalized, Moderate disease: Oxygen by mask or nasal prongs	59 (44.0)	29 (41.4)	88 (43.1)
5. Hospitalized, Severe disease: Non-invasive ventilation or high-flow oxygen	63 (47.0)	33 (47.1)	96 (47.1)
6. Hospitalized, Severe disease: Intubation and mechanical ventilation	12 (9.0)	8 (11.4)	20 (9.8)
Standard of Care Agents at Baseline (Day 1)			
Remdesivir, n (%)	40 (29.9)	17 (24.3)	57 (27.9)
Dexamethasone, n (%)	108 (80.6)	54 (77.1)	162 (79.4)
Tocilizumab, n (%)	8 (6.0)	7 (10.0)	15 (7.4)
Baricitinib or Tofacitinib, n (%)	9 (6.7)	8 (11.4)	17 (8.3)
Baseline Comorbidities, n (%)			
Number of comorbidities, Mean (SD)	1.7 (1.17)	1.7 (1.12)	1.7 (1.15)
Subjects with no comorbidities, n (%)	22 (16.4)	9 (12.9)	31 (15.2)
Subjects with 2 or more comorbidities, n (%)	72 (53.7)	36 (51.4)	108 (52.9)
Diabetes, n (%)	45 (33.6)	28 (40.0)	73 (35.8)
Hypertension, n (%)	85 (63.4)	46 (65.7)	131 (64.2)
Heart Failure, n (%)	8 (6.0)	7 (10.0)	15 (7.4)
Asthma, n (%)	14 (10.4)	3 (4.3)	17 (8.3)
COPD**, n (%)	13 (9.7)	3 (4.3)	16 (7.8)
Interstitial Lung Disease, n (%)	8 (6)	5 (7.1)	13 (6.4)
Cancer, n (%)	11 (8.2)	1 (1.4)	12 (5.9)
Resides Primarily in Nursing Home***	***	***	***
Immunocompromised****	****	****	****
Pneumonia, n (%)	81 (60.4)	46 (65.7)	127 (62.3)
Acute Respiratory Failure, n (%)	28 (20.9)	18 (25.7)	46 (22.5)
Acute Respiratory Distress Syndrome, n (%)	3 (2.2)	3 (4.3)	6 (2.9)
COVID-19 Vaccination Prior to Baseline, n (%)			
Y	47 (35.1)	27 (38.6)	74 (36.3)

Source: Statistical Reviewer Analysis; adsl.xpt; adapted with additional Sponsor information provided as Responses to Information Request
Notes: *All subjects randomized with WHO 4 COVID-19 were required to also have ≥1 comorbidity from the list noted in the inclusion criteria of Study 902.
**Per the Sponsor: "Veru notes that 'chronic obstructive pulmonary disease' is the only preferred term in the database for "Chronic Lung Disease."
***Per the Sponsor: "Veru notes that the CRF does not collect any information about "primarily reside in a nursing home or long-term care facility."
****Per the Sponsor: "Veru notes that the CRF does not collect any information about 'immunocompromised.' Veru did not collect all the comorbidities by which a subject qualified for the study and only required that the patient be eligible for the study"
Standard of Care Medications for COVID-19 includes corticosteroids or remdesivir for COVID-19.
Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; ITT, Intention-to-treat population; N, number of subjects; n, number of subjects within specific characteristics; SD, standard deviation; WHO, World Health Organization ordinal scale for clinical severity; VERU-111, sabizabulin

Additional data on the timing of care prior to randomization are presented in Table 7, and these data suggest some clinical differences in the clinical courses of the study arms prior to randomization. Notably, 6.7% of the VERU-111 arm had received >14 days of standard of care medications for COVID-19

prior to randomization compared to 0% of the placebo arm. Similarly, 4.5% of the VERU-111 arm had been admitted to the hospital for >14 days prior to randomization compared to 0% of the placebo arm, and the mean time from hospital admission to randomization was numerically higher in the VERU-111 arm compared to placebo. The clinical implications of the differences in clinical course prior to randomization are discussed in section 3.1.3.4.

Table 7. Study 902: Clinical Care Prior to Randomization (ITT population)

	VERU-111 9 mg N=134	Placebo N=70	Total N=204
Standard of Care Medications for COVID-19, Days Before Randomization, n (%)			
>14 days	9 (6.7)	0 (0.0)	9 (4.4)
7 – 14 days	12 (8.9)	10 (14.3)	22 (10.8)
0 – 7 days	113 (84.3)	60 (85.7)	173 (84.8)
Time from Hospital Admission to Randomization (days)			
Mean (SD)	4.2 (4.45)	3.8 (2.75)	4.1 (3.95)
Min, Max	0, 30	0, 12	0, 30
Time from Hospital Admission to Randomization Group, n (%)			
>14 days	6 (4.5)	0 (0.0)	6 (2.9)
7 – 14 days	11 (8.2)	10 (14.3)	21 (10.3)
0 – 7 days	117 (87.3)	60 (85.7)	177 (86.8)

Source: Statistical Reviewer Analysis; adsl.xpt

Standard of Care Medications for COVID-19 includes corticosteroids or remdesivir for COVID-19.

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; ITT, intention-to-treat population; N, number of subjects; n, number of subjects within specific time frame; SD, standard deviation

3.1.2.2.4 Analysis of the Primary Endpoint: All-Cause Mortality at Day 60

The analysis of the proportion of subjects alive at Day 60 (i.e., all-cause mortality) is presented in Table 8 and a Kaplan-Meier plot of the time-to-death endpoint is presented in Figure 3. At the Day 60 timepoint, 78.4% of the VERU-111 arm remained alive compared to 58.6% of the placebo arm among the 204 subjects randomized 2:1 to VERU-111 versus placebo (risk difference 19.0%, 95% CI (5.8%, 32.2%), odds ratio 2.77, 95% CI (1.37, 5.58)). The proportion of subjects who died in the VERU-111 arm was not higher than placebo at any point during the evaluation period. The separation of the Kaplan-Meier curves in Figure 3 suggests that death events in the placebo arm compared to the VERU-111 arm increased in frequency between study days 10-15 and between study days 30-45. The unadjusted difference in risk of mortality at Day 60 calculated using the Kaplan Meier survival estimates was 20.2% (95% CI: 6.8 – 33.3%).

The study met the pre-specified success criterion at interim analysis, indicating a statistically significant improvement in mortality in the VERU-111 arm compared to placebo and allowing for the study to stop early for efficacy. The p-value (p = 0.0045) at the pre-specified interim analysis that involved 150 subjects was lower than the threshold p-value of 0.016, indicating that the statistical boundary for efficacy was crossed. An additional 54 subjects were already enrolled at the time of this stopping and these subjects were allowed to complete the study period. Thus, while significance testing was based on the 150 subjects at the interim analysis, information is available on 204 randomized subjects and is provided in the analyses below.

As discussed above, the Sponsor reduced the final planned sample size from 300 to 210 subjects prior to the interim analysis and after 198 subjects had been enrolled. The statistical boundary for efficacy would not have been crossed at the interim analysis with 150 patients had the final sample size been 300.

When the final sample size was reduced from 300 to 210 the information fraction at interim increased from 50% (150/300) to 71.4% (150/210) and so, the criterion for efficacy at the interim analysis changed from a two-sided p-value of 0.003 to 0.016. The p-value at interim analysis was 0.0045, which, on account of being lower than 0.016 indicated that the statistical boundary for efficacy was crossed.

Table 8. Study 902: Primary Efficacy Analysis, Proportion of Subjects Alive / Dead at Day 60 (ITT population)

	VERU-111 9 mg	Placebo
Interim Analysis[1]		
Number of subjects (N)	98	52
Alive at Day 60, n (%[2])	75 (76.5)	28 (53.9)
Dead at Day 60, n (%[2])	19 (19.4)	23 (44.2)
Difference (95% CI)[3]	23.1 (7.2, 38.9)	-
Odds Ratio (95% CI)[4]	3.20 (1.43, 7.16)	-
Missing[5], n (% of ITT population)	4 (4.1)	1 (1.9)
All 204 randomized subjects		
Number of subjects (N)	134	70
Alive at Day 60, n (%[2])	105 (78.4)	41 (58.6)
Dead at Day 60, n (%[2])	25 (18.7)	27 (38.6)
Difference (95% CI)[3]	19.0 (5.8, 32.2)	-
Odds Ratio (95% CI)[4]	2.77 (1.37, 5.58)	-
Missing[5], n (% of ITT population)	4 (3.0)	2 (2.9)

Source: Reviewer generated analysis based on applicant submitted data aden.xpt for EUA000113 (V3011902).

[1]Statistical boundary was crossed for efficacy at interim analysis in N = 150 patients with p-value 0.0045 (compare with an allocated α of 0.016)

[2]Percentages are of number of subjects in ITT population within treatment group

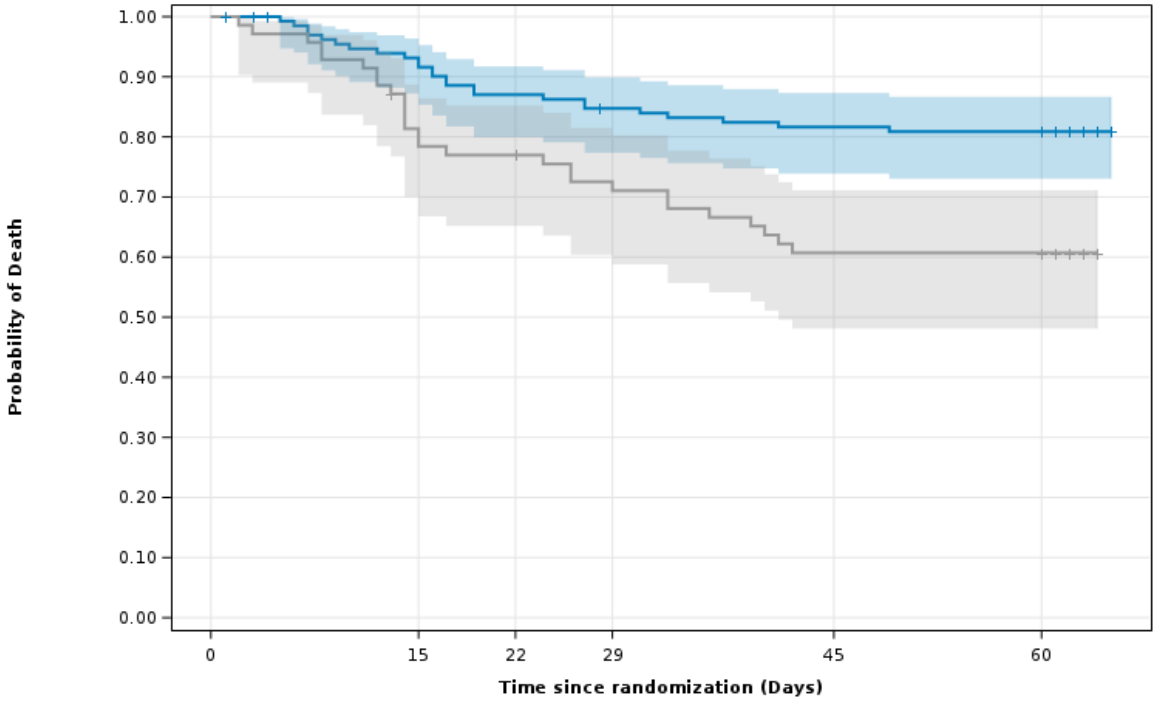
[3]Risk difference is estimated as the sample mean of the difference in predicted risk of outcome under the two treatment arms for each subject, with the predicted risk under each treatment arm derived from a logistic regression model with covariates for region, sex, baseline WHO category, remdesivir use and dexamethasone use at baseline (Benkeser et al. 2020)

[4]Odds ratio for being alive at Day 60, 95% CI and p-value are calculated using logistic regression model with covariates for treatment group, region, sex, baseline WHO category, remdesivir use and dexamethasone use at baseline

[5]Imputation model for missing data included same covariates as logistic regression analysis model and additionally, treatment discontinuation status and discharge status

Abbreviations: CI, confidence interval; ITT, intention-to-treat population; LR, logistic regression; N, number of subjects; n, number of subjects in ITT population within treatment group; VERU-111, sabizabulin

Figure 3. Study 902: Kaplan-Meier Plot: Time to Death (ITT population)



Abbreviations: CI = confidence interval, ITT = intentention-to-treat
Source: Reviewer analysis using Applicant submitted data: adtte.xpt
Abbreviations: VERU-111, sabizabulin

3.1.2.2.5 Sensitivity Analyses of the Primary Endpoint

Missing Data Sensitivity Analysis

To assess the robustness of the primary analysis findings, the Sponsor conducted a tipping point analysis that considered the full range of possible response rates in the subjects with missing data, with a response being defined as being alive at Day 60. Specifically, the assumed response rate (percentage of patients alive) in each treatment group was systematically changed from 0% to 100% in a stepwise manner on each treatment arm. Multiple imputation incorporating the same covariates as used in the primary analysis was used for each pair of response rates under consideration. Imputations were performed independently within the two treatment groups so that, in the most extreme unfavorable case for VERU-111, the imputed response rate in subjects with missing data in the VERU-111 arm was 0% and in the placebo arm was 100%, and in the most extreme favorable case for VERU-111, the imputed response rate in subjects with missing data in the VERU-111 arm was 100% and in the placebo arm was 0%. The primary analysis conclusion remained robust even to missing data assumptions, with the treatment comparison in the most extreme unfavorable case (odds ratio: 2.63, 95% CI: (1.27, 5.44); risk difference: 17.7%, 95% CI: (4.3%, 31.4%)) and the most extreme favorable case (odds ratio: 3.92, 95% CI: (1.84, 8.32); risk difference: 22.6%, 95% CI: (9.8%, 36.4%)) being similar to that seen in the primary analysis.

Revised Models Including Additional Baseline Factors

As discussed above and shown in Table 6 and Table 7, imbalances were observed in the distribution of comorbidities, number of days hospitalized, and start date of standard of care therapies across the treatment arms at baseline. The potential effect of these imbalances on study findings were explored using sensitivity analyses that adjusted for these baseline factors in the primary analysis of the primary endpoint of proportion of subjects alive at Day 60. The results of these analyses are presented in Table 9. Adjusting for imbalance in the distribution of subjects with at least one comorbidity had minimal impact on the primary analysis results (odds ratio: 2.74, 95% CI: (1.36, 5.52)). The estimated treatment effect was slightly lower than that reported in the primary analysis after adjusting for days hospitalized prior to randomization (odds ratio: 2.58, 95% CI: (1.30, 5.14)) and days of SoC therapies prior to randomization (odds ratio: 2.65, 95% CI: (1.32, 5.33)). Adjusting for these imbalances did not seem to affect the estimates of the risk difference summary measure.

These sensitivity analyses were simplistic explorations of the impact of adding additional baseline factors into a logistic regression analysis model and may not have accurately captured the relationship between the imbalanced factors and the outcome. Further exploration of the effect of imbalances in individual comorbidities and interaction of imbalanced factors was not possible due to the limitations of the sample size. As such, these exploratory analyses do not entirely eliminate the concern that certain baseline imbalances across treatment groups may have impacted the study findings. A larger study where such imbalances are less likely to occur after randomization would be needed to confirm the lack of influence of baseline imbalances on study findings.

Table 9. Study 902: Sensitivity Analyses: Proportion of Subjects Alive at Day 60 Adjusting for Baseline Imbalances (ITT population)

Analysis Model[1]	Odds Ratio (95% CI)[2]	Risk Difference (%) (95% CI)[3]
Primary Analysis Model	2.77 (1.37, 5.58)	19.0 (5.8, 32.2)
Primary Analysis Model + Days Hospitalized before Randomization	2.58 (1.30, 5.14)	19.5 (6.9, 32.1)
Primary Analysis Model + Days from SoC[4] Start to Randomization	2.65 (1.32, 5.33)	18.7 (5.6, 31.9)
Primary Analysis Model + Comorbidities (Any vs none)	2.74 (1.36, 5.52)	19.7 (7.3, 32.2)

Source: Reviewer generated analysis based on applicant submitted data aden.xpt, adcm.xpt for EUA000113 (V3011902).

[1]Primary Analysis model was a logistic regression model with covariates for treatment group, region, sex, baseline WHO category, remdesivir use and dexamethasone use at baseline

[2]Odds ratio, 95% CI are calculated using corresponding logistic regression model

[3]Risk difference is estimated as the sample mean of the difference in predicted risk of outcome under the two treatment arms for each subject, with the predicted risk under each treatment arm derived from a logistic regression model with covariates for region, sex, baseline WHO category, remdesivir use and dexamethasone use at baseline (Benkeser et al. 2020)

[4]Standard of Care defined as Corticosteroids for COVID-19 or Remdesivir started 10 days before randomization

Imputation model for missing data (4 subjects in VERU-111 9 mg group and 2 subjects in Placebo group) included same covariates as covariate adjustment model and additionally, treatment discontinuation status and discharge status

Abbreviations: CI, confidence interval; ITT, intention-to-treat population; LR, logistic regression; SoC, standard of care; WHO, World Health Organization ordinal scale for clinical severity; VERU-111, sabizabulin

3.1.2.2.6 Subgroup Analyses of the Primary Endpoint

Efficacy results for various clinical or demographic subgroups of interest in Study 902 are presented in Table 10. In general, individual subgroup analyses should be interpreted with caution due to a lack of statistical power and multiplicity control. While the confidence intervals for some subgroups are wide due to the small size of the subgroups the numerical trend for mortality in favor of VERU-111 seems to be present for subgroups defined by baseline WHO ordinal scale category, dexamethasone and remdesivir use, age, vaccination status and region. The numerical efficacy trend for mortality was also

maintained in the following subgroups defined by the timing of enrollment into the study with respect to clinical course and receipt of standard of care: < 10 days and < 5 days hospitalized prior to randomization, < 10 days and < 5 days of standard of care therapy prior to randomization.

Table 10. Study 902: Subgroup Analyses: Proportion of Subjects Alive at Day 60 by Subgroups (ITT population)

Subgroup at Baseline	VERU-111 9 mg (n/N, %)[1]	Placebo (n/N, %)[1]	Difference (95% CI)[2]	Odds Ratio (95% CI)[3]
Baseline WHO Ordinal Scale Category				
4	55/58 (94.8)	21/29 (72.4)	22.4 (5.2, 39.7)	6.11 (1.56, 23.8)
5	40/60 (66.7)	16/31 (51.6)	14.5 (-6.6, 35.7)	1.61 (0.66, 3.90)
6	10/12 (83.3)	4/8 (50)	33.3 (-7.2, 73.9)	3.58 (0.49, 26.3)
Background Standard of Care - Dexamethasone				
Yes	80/104 (76.9)	31/53 (58.5)	18.2 (2.8, 33.7)	2.11 (1.05, 4.27)
No	25/26 (96.2)	10/15 (66.7)	28.9 (4.1, 53.6)	17.5 (1.85, 165.8)
Background Standard of Care – Remdesivir				
Yes	29/38 (76.3)	7/17 (41.2)	35.7 (8.8, 62.6)	3.90 (1.16, 13.13)
No	76/92 (82.6)	34/51 (66.7)	15.4 (0.5, 30.4)	2.10 (0.97, 4.55)
Age				
< 65 years	56/65 (86.2)	17/28 (60.7)	24.9 (5.1, 44.7)	2.57 (0.86, 7.64)
>= 65 years	49/65 (75.4)	24/40 (60.0)	15.2 (-3.2, 33.6)	2.27 (0.87, 5.96)
Vaccination				
Vaccinated (at least 1 shot)	37/47 (78.7)	18/27 (66.7)	12.1 (-9.2, 33.3)	1.88 (0.65, 5.45)
Unvaccinated	68/83 (81.9)	23/41 (56.1)	25.1 (8.0, 42.3)	2.89 (1.29, 6.48)
Region				
North America	30/44 (68.2)	10/24 (41.7)	26.1 (2.1, 50.1)	2.13 (0.77, 5.94)
South America	45/55 (81.8)	17/27 (63.0)	18.9 (-2.0, 39.7)	3.37 (1.03, 10.99)
Europe	30/31 (96.8)	14/17 (82.4)	14.4 (-4.7, 33.6)	3.45 (0.58, 20.54)
Days of Hospitalization Prior to Randomization				
< 10 Days	97/121 (80.2)	40/66 (60.6)	19.3 (5.6, 33.0)	2.51 (1.25, 5.04)
< 5 Days	73/90 (81.1)	28/46 (60.9)	20.2 (4.0, 36.4)	4.18 (1.63, 10.70)
Timing of SoC Prior to Randomization				
< 10 Days	89/110 (80.9)	39/63 (61.9)	18.8 (4.8, 32.8)	2.38 (1.15, 4.92)
< 5 Days	74/91 (81.3)	32/49 (64.3)	15.8 (0.3, 31.3)	2.88 (1.19, 6.99)

Source: Reviewer generated analysis based on applicant submitted data aden.xpt for EUA000113 (V3011902).

[1] Missing data were excluded from numerator and denominator

[2] Risk difference is calculated using risk estimates obtained from a Kaplan-Meier analysis of time-to-event data

[3] Odds ratio, 95% CI are calculated using logistic regression model with covariates for treatment group, region, sex for subgroups formed by WHO Ordinal Scale category; covariates for treatment group, sex, baseline WHO Ordinal scale category, remdesivir use and dexamethasone use at baseline for subgroups by region; covariates for treatment group and sex for subgroups of vaccinated, unvaccinated, dexamethasone users and remdesivir users. Imputation model for missing data included same covariates as logistic regression analysis model and additionally, treatment discontinuation status and discharge status

Abbreviations: CI, confidence interval; ITT, Intention-to-treat population; LR, logistic regression; N, number of subjects in subgroup; n, number of subjects alive at Day 60 in subgroup; SoC, standard of care; VERU-111, sabizabulin; WHO, World Health Organization ordinal scale for clinical severity

3.1.2.2.7 Analysis of Secondary Efficacy Endpoints

The secondary endpoints of Study 902 that are considered clinically relevant to the discussion of the EUA request comprise the following:

- Proportion of Subjects Alive and Free of Respiratory Failure at Day 29
- Days in ICU through Day 60
- Days in Hospital through Day 60
- WHO Ordinal Scale Clinical Improvement through Day 60

The FDA Guidance to Industry referenced above (Guidance for Industry 2021) includes the proportion of subjects alive without respiratory failure and clinical status using an ordinal scale as clinically relevant endpoints, although the optimal timeframe of evaluation for both of these endpoints (e.g., Day 29 versus Day 60) is an area of uncertainty for a trial that recruits a mixture of critically ill and non-critically ill subjects. In addition, the calculation of each of the listed secondary endpoints is influenced by the mortality results, since each secondary endpoint contains a component of mortality or provides a numerical penalty for mortality events.

Because of this relationship, the interpretation of the secondary endpoints relies on the interpretation of the mortality result. In the case of the composite endpoint of alive and free of respiratory failure at Day 29, mortality is directly represented in the composite. In the case of days in ICU or days in the hospital, mortality led to a numerical penalty that set the value for that subject to 60 days, the maximum number of on-study days. Finally, WHO category 8 is equivalent to death on the scale implemented by the Sponsor for Study 902. Because of the influence of the mortality results on these secondary endpoints, and the importance of the all-cause mortality endpoint to the overall regulatory decision-making regarding VERU-111, this briefing document focuses primarily on the analyses of all-cause mortality and their potential uncertainties. However, the secondary endpoint results are presented and summarized below for reference.

3.1.2.2.7.1 Alive and Free of Respiratory Failure at Day 29

Results for the secondary endpoints of proportion of subjects alive at Day 29, and alive and free of respiratory failure at Day 29 are presented in Table 11. At Day 29, 110 (82.1%) and 48 (68.6%) subjects remained alive in the VERU-111 and placebo arms, respectively, and 96 (71.6%) and 38 (54.3%) subjects in the VERU-111 and placebo arms, respectively, were alive and free of respiratory failure. Thus, the data from Study 902 suggest that the proportion of subjects alive (odds ratio: 2.15, 95% CI: (1.02, 4.56), risk difference: 11.9%, 95% CI: (-0.3%, 24.2%)) and alive and free of respiratory failure at Day 29 (odds ratio: 2.42, 95% CI: (1.17, 5.01), risk difference: 15.3%, 95% CI: (2.4%, 28.3%)) was higher in the VERU-111 arm compared to placebo.

Table 11. Study 902: Secondary Efficacy Analysis: Proportion of Subjects Alive at Day 29 and Alive and Free of Respiratory Failure at Day 29 (ITT population)

	VERU-111 9 mg N=134	Placebo N=70
Alive at Day 29, n (%)	110 (82.1)	48 (68.6)
Odds Ratio (95% CI)[1]	2.15 (1.02, 4.54)	-
Difference (95% CI)[2]	11.3 (-0.3, 24.2)	-
Missing[3], n (%)	4 (3.0)	2 (2.9)
Alive and free of respiratory failure at Day 29, n (%)	96 (71.6)	38 (54.3)
Odds Ratio (95% CI)[1]	2.42 (1.17, 5.01)	-
Difference (95% CI)[2]	15.3 (2.4, 28.3)	-
Missing[3], n (%)	4 (3.0)	2 (2.9)

Source: Reviewer generated analysis based on applicant submitted data aden.xpt for EUA000113 (V3011902).

[1]Odds ratio, 95% CI and p-value are calculated using logistic regression model with covariates for treatment group, region, sex, baseline WHO category, remdesivir use and dexamethasone use at baseline

[2]Risk difference is estimated as the sample mean of the difference in predicted risk of outcome under the two treatment arms for each subject, with the predicted risk under each treatment arm derived from a logistic regression model with covariates for region, sex, baseline WHO category, remdesivir use and dexamethasone use at baseline (Benkeser et al. 2020)

[3]Imputation model for missing data included same covariates as logistic regression analysis model and additionally, treatment discontinuation status and discharge status

Abbreviations: CI, confidence interval; ITT, Intention-to-treat population; LR, logistic regression; N, number of subjects; n, number of subjects within specific proportion; VERU-111, sabizabulin; WHO, World Health Organization

3.1.2.2.7.2 Days in ICU, Days in Hospital, and Days on Mechanical Ventilation

Data from secondary endpoints of Days in ICU through Day 60, Days in Hospital through Day 60, and Days on Mechanical Ventilation through Day 60 are presented in Table 12, below. In each case, these endpoints calculate days from randomization that meet the criteria, however they do not take into account the potential for pre-randomization days for each endpoint (see Section 3.1.3.4). To account for mortality events, any subject who died was assigned the "worst" possible outcome for these endpoints (i.e., 60 days). The number of Days in Hospital through Day 60, on average, was estimated to be lower for subjects receiving VERU-111 than for subjects in the placebo arm, with an estimated difference of -6.3 days (95% CI (-12.4, -0.1)). Similarly, the estimated difference between the VERU-111 and placebo arm subjects in average number of Days in ICU through Day 60 was -9.9 days (95% CI (-16.7, -3.1)), and Days on Mechanical Ventilation through Day 60 was -10.4 days (95% CI (-17.5, -3.4)).

Table 12. Study 902: Secondary Efficacy Analyses: Days in Hospital, Days in Intensive Care Unit and Days on Mechanical Ventilation through Day 60 (ITT population)

	VERU-111 9 mg N=134	Placebo N=70
Days in Hospital through Day 60		
Value at Day 60, adj.[1] mean (SE)	25.6 (2.8)	31.8 (3.3)
Difference from Placebo, adj.[1] mean (CI)	-6.3 (-12.4, -0.1)	-
Days in Intensive Care Unit through Day 60		
Value at Day 60, adj.[1] mean (SE)	16.1 (3.1)	26.0 (3.6)
Difference from Placebo, adj.[1] mean (CI)	-9.9 (-16.7, -3.1)	-
Days on Mechanical Ventilation through Day 60		
Value at Day 60, adj.[1] mean (SE)	13.3 (3.2)	23.8 (3.8)
Difference from Placebo, adj.[1] mean (CI)	-10.4 (-17.5, -3.4)	-

Source: Reviewer generated analysis based on applicant submitted data aden.xpt for EUA000113 (V3011902).

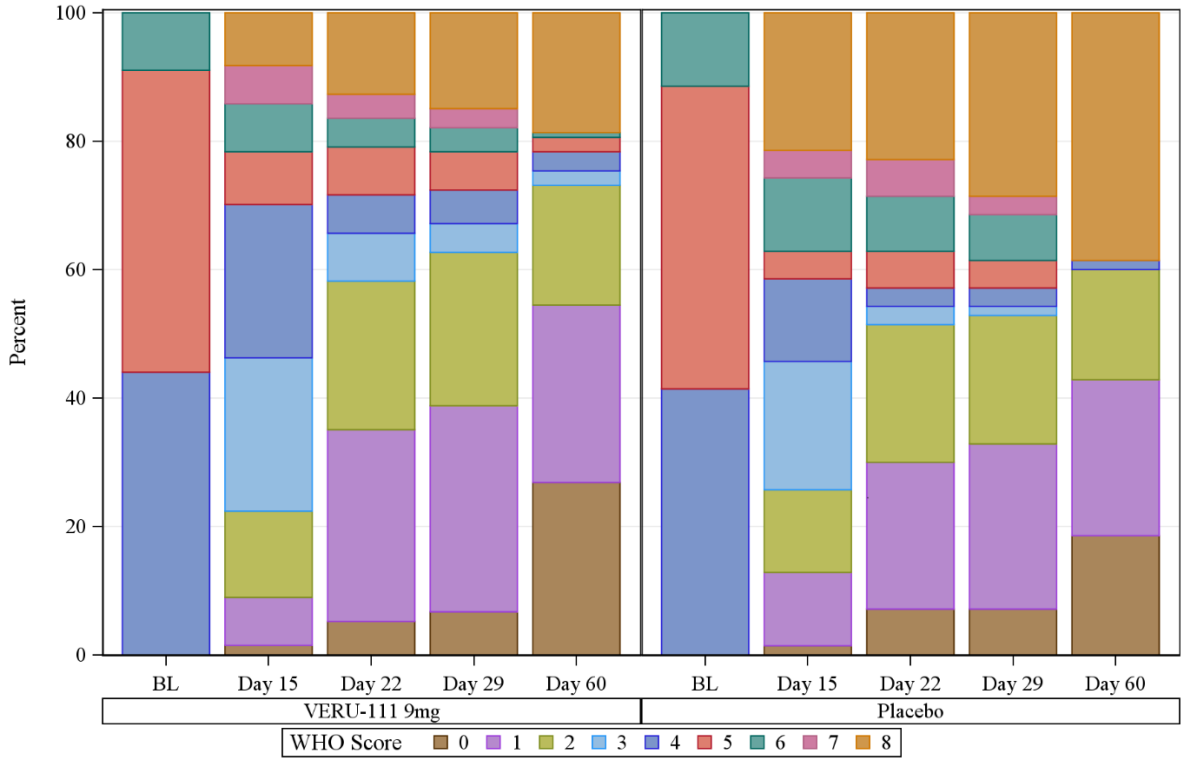
[1] Adjusted mean and mean differences are from an analysis of covariance model adjusting for treatment, treatment group, region, sex, baseline WHO category, remdesivir use and dexamethasone use at baseline, with within-arm means estimated at mean values of the covariates. Death assigned to worst possible outcome of 60 days

Abbreviations: CI, confidence interval; ITT, Intention-to-treat population; N, number of subjects; SE, standard error; ; VERU-111, sabizabulin

3.1.2.2.7.3 WHO Ordinal Scale

At Day 60, 73 (54.5%) subjects in the VERU-111 treated arm and 30 (42.9%) subjects in the placebo treated group had a WHO Ordinal Scale score 0 or 1. The treatment comparison using a logistic regression analysis model with treatment group, sex, WHO Ordinal Scale score at baseline, dexamethasone and remdesivir use yielded an odds ratio of 1.65 (95% CI: (0.87, 3.15)) suggesting a numerical trend favoring the VERU-111 treated group for the odds of attaining a WHO Ordinal Scale score of 0 or 1 at Day 60. The sponsor also provided stacked bar plots for visualizing Clinical Improvement on WHO Ordinal Scale score by treatment arm at baseline, Day 15, Day 22, Day 29, and Day 60 (Figure 4).

Figure 4. Stacked Bar Plot of WHO Ordinal Scale Score with Last Observation Carried Forward (ITT population)



Source: Sponsor Figure FDA 20221007.Q03.1
Abbreviations: BL, Baseline; ITT, intention-to-treat population; VERU-111, sabizabulin; WHO, World Health Organization ordinal scale for clinical severity

3.1.3 Primary Endpoint Efficacy Issues in Detail

As noted above, consideration of the uncertainties in the all-cause mortality results in Study 902 is influenced substantially by the fact that Study 902 relies on a small dataset of subjects for its efficacy results. Because of the small sample size and the 2:1 randomization scheme, factors that influence the results of even a few placebo subjects' mortality outcomes could have a substantial effect on the overall efficacy estimate.

While all-cause mortality is traditionally considered an objective endpoint that is less subject to biases from knowledge of treatment assignment in long-duration randomized trials of chronic diseases, it is unclear whether results for all-cause mortality are as easily categorized as unimpacted by knowledge of

treatment assignment in short duration trials of critically ill patients, given the potential impact of goals of care decisions, standard of care therapies, and major procedural interventions (e.g., invasive ventilation, renal replacement therapy, ECMO) on duration of life and overall mortality. If systematically unbalanced between study arms, these same factors could present potential uncertainties to the interpretation of all-cause mortality data. In principle, randomization, blinding, and adequate sample size should tend to balance these factors between study arms, so that an observed effect on mortality could be attributed to treatment only. However, studies with smaller sample sizes could be more vulnerable to potential imbalances between study arms (e.g., related to differential site allocation). It is uncertain what effect potential unblinding events may have had upon the medical decision-making regarding therapeutic interventions as well as the timing, tone, content, and outcome of individual goals of care discussions among the 134 subjects in the VERU-111 group compared to the 70 subjects in the placebo groups.

Each of the issues detailed below represent potential limitations in the data supported by observations or conclusions from literature in COVID-19 or other diseases in critical care. Where possible, the review team has conducted exploratory analyses to assess the potential impact of these uncertainties on the findings from Study 902, although further analyses of some areas of uncertainty were limited due to lack of study data collection, as well as study size. While no single issue listed below appears to independently invalidate the mortality benefit observed in Study 902, each raises some degree of uncertainty in the interpretation of the treatment effect. Whether the totality of these uncertainties limits the overall interpretation of the trial results and its ability to provide evidence that VERU-111 "may be effective" to treat the indicated population is a topic for discussion by the Advisory Committee.

3.1.3.1 High Placebo Mortality Rate for Baseline Severity

Based on the planned severity level of patients to be enrolled, the Sponsor utilized a reasonable assumption that the placebo mortality rate would lie between 15% and 30%, consistent with other studies with comparable severity. However, the Day 60 mortality rate at the final analysis in the placebo group in Study 902 was 39.7%. At the interim analysis, the Day 60 mortality rate in the 52 subjects in the placebo group who completed study was 45.1% and among subjects within North America was 63.6%, specifically, 61.9% (13 of 21 subjects) in the US and 100% (1 of 1 subject) in Mexico. Notably, at one site in Bulgaria, 7 patients were randomized to receive VERU-111 and 6 patients were randomized to receive placebo. All patients belonged to the least severe group of randomized patients with a baseline WHO Ordinal Scale score of 4. While all subjects in VERU-111 treated group remained alive, 3 out of 6 subjects (50%) in the placebo group died by Day 60. Randomization was stratified on WHO ordinal scale score, but there were no additional stratification factors to directly address other non-COVID aspects of disease severity or prognosis (e.g., comorbidities), or to account for other potential sources of variability such as clinical site. Randomization will tend to balance these sources of variability between treatment arms given a large enough sample size, however, the small overall sample size raises the possibility of imbalances in unmeasured factors that could affect prognosis.

While it is challenging to make direct comparisons to previous randomized controlled trials due to variability in enrolled severity levels and timing of study enrollment, studies conducted in populations with similar baseline severity have reported much lower Day 60 mortality rates for the placebo arm. For example, the placebo group mortality rate was 15% in the COV-BARRIER study (Marconi et al. 2021), which included subjects with baseline disease severities corresponding to the 8-point WHO Ordinal Scale scores of 3, 4 and 5. The placebo group mortality rate at Day 60 was 25% in the REMDACTA study (Rosas

et al. 2021) and 11% in another study (Lescure et al. 2021), both of which included subjects with baseline disease severity corresponding to WHO Ordinal Scale scores of 4, 5, 6 and 7. All three of these trials concluded before the start of Study 902. In a more recent trial, ACTIV-1 IM, conducted from October 2020 to December 2021, and including subjects with predominantly baseline disease severities corresponding to WHO Ordinal Scale scores of 4, 5, 6, the Day 60 mortality rate in the shared placebo group was reported to be 16.5% (O'Halloran et al. 2022). In another trial, ACTIV-3b, which was conducted in an overlapping time frame with Study 902 in the US and some Brazilian sites, and included subjects with a baseline WHO Ordinal Scale score of 5 and 6, the Day 90 mortality rate in the placebo arm was 35% (Day 60 data not available). Given these data from recent trials, and other trials which were conducted earlier in the pandemic when treatment options were limited and in the presence of variants shown to be associated with a higher mortality rate (Iuliano et al. 2022), the mortality rate observed in Study 902 appears to be higher than what would be expected in the study population during the time frame in which the study was conducted.

We acknowledge that many studies collected Day 29 mortality data that could have been used to compare to the Day 29 mortality in Study 902. We have focused our discussion on Day 60 mortality as this is the primary endpoint for the current study, the results of which were used to justify stopping early for efficacy. While a few studies (RECOVERY Collaborative Group 2021, REMAP-CAP Investigators) had a similar Day 29 mortality rate in the placebo group, we note that these studies were conducted much earlier in the pandemic and had other important differences in terms of study design that make the comparisons hard to interpret. It is also worth noting that, in Study 902, the treatment difference in mortality at Day 29 (odds ratio for staying alive: 2.15, 95% CI: (1.02, 4.56), risk difference: 11.9%, 95% CI: (-0.3%, 24.2%)) was much lower than that observed at Day 60, indicating that much of the differentiation between treatment groups with respect to mortality occured after Day 29.

3.1.3.2 Potential Unblinding Events with Enteral Tube Administration

Differences in Appearance and Physical Characteristics of Drug Product

Both Study 901 and Study 902 were designed as randomized, double blind, matched-placebo controlled trials. Placebo substance for these trials was encapsulated in capsules designed to match the VERU-111 capsules – both the formulated capsule and powder-in-capsule formulations. However, for those subjects who required an enteral access device (e.g., subjects who were critically ill and intubated, or those who may have had a pre-existing percutaneous gastrostomy tube), administration of the study drug required the capsule to be opened and the contents of the capsule to be mixed with water for syringe injection into the enteral access device. This opening of the capsule allowed for potential unblinding events, since the VERU-111 product and the placebo product differed in their physical characteristics and appearance, and the Investigator's Brochure described the drug as a yellow powder.

Pictures of the products in powder form and as they would appear for administration into the enteral access device are shown below. A side-by-side picture of the products in powder form are provided in Figure 5, and a side-by-side picture of the powder/water mixtures for administration are provided in Figure 6. Given the differing composition, color, and solubility characteristics of the capsule contents between placebo and VERU-111, there is uncertainty in whether products with color or solubility

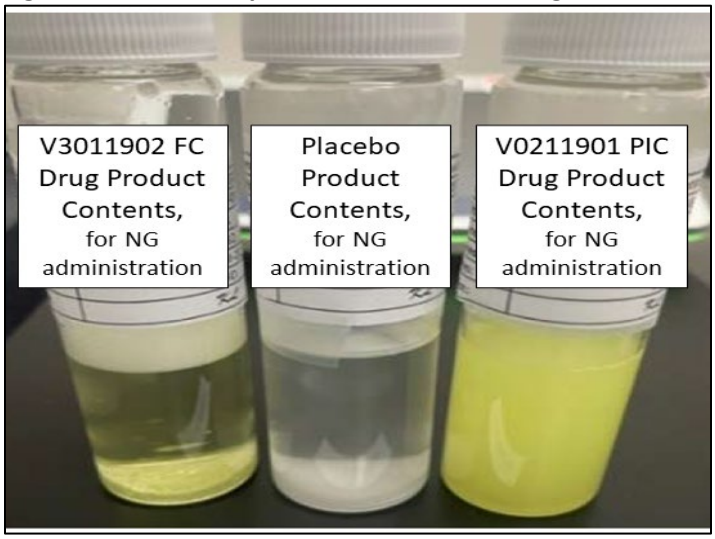
differences would be easily noticed by a medically trained observer such as an ICU nurse, leading to unintentional unblinding events.

Figure 5. Visual Comparison of VERU-111 Drug Product and Placebo Powder

Characteristic	V3011902 FC Drug Product Contents	Placebo Product Contents	V0211901 PIC Drug Product Contents
Formulated Product (as capsule contents/powder)			
Appearance	Yellow powder with some clumping observed	White powder that is free flowing	Light yellow, granular powder

Source: Adapted from screenshots of Sponsor-submitted materials.
Abbreviations: FC, formulated capsule; PIC, powder-in-capsule; VERU-111, sabizabulin

Figure 6. Visual Comparison of VERU-111 Drug Product and Placebo as Administered by Enteral Tube



Characteristic	V3011902 FC Drug Product Contents	Placebo Product Contents	V0211901 PIC Drug Product Contents
Formulated Product Mixed with Water for NG-tube Administration			
Appearance	Yellow transparent solution with many visible yellow particulates present	Clear transparent solution with many visible white particulates present	Pale yellow solution with many yellow particulates present
Dissolution Results	Very little visible drug product dissolved. Many particulates still visible	No visible placebo dissolved. Most particulates still visible.	API visibly dispersed. Fine particulates visible.

Source: Adapted from screenshots of Sponsor-submitted materials
Abbreviations: API, active pharmaceutical ingredient; FC, formulated capsule; NG, nasogastric; PIC, powder-in-capsule; VERU-111, sabizabulin

Scope of Potential Unblinding Events in Study 902

The Sponsor reports that 23.9% of subjects in the VERU-111 arm received at least one dose of study drug via nasogastric (NG) tube, compared to 32.9% of subjects in the placebo arm. However, it is unclear whether subjects may have utilized other enteral access devices such as a Dobhoff tube, percutaneous gastrostomy, or orogastric tube. Additional enteral tube data were not collected and could have led to underreporting.

Prior Human Data Available to Investigators for VERU-111 in COVID-19

As noted above, the Investigator Brochure for VERU-111 described the drug as a yellow powder. The Investigator Brochure for VERU-111 (versions 9 and 10) also contained the following information regarding proof-of-concept efficacy in trial V0211901: "In the ITT population, the mortality rate (proportion of patients who died on study) was 30% (6/20) in the placebo group and 5.2% (1/19) in the VERU-111 treated group. This represents an 82% relative reduction in mortality in the VERU-111 population which is statistically significant at p=0.044". In the context of potential unblinding, the available data on VERU-111 could potentially have subconsciously influenced physician decision-making.

Performance Bias In Unblinded or Inadequately Blinded Trials Evaluating All-Cause Mortality

While the ascertainment of individual death events in clinical medicine is an objective measure, all-cause mortality as a clinical trial outcome may be more vulnerable to biases due to unblinding, specifically in the setting of critical illness. The consideration of all-cause mortality as a predominantly objective endpoint may be reasonable when considering long-term treatment trials of chronic diseases that rely on randomization of large numbers of subjects to provide power for rare death events and might generally be considered to have a low proportion of ICU care and low incidence of goals of care conversations compared to the total study population. In contrast, a short-term treatment trial of an acute illness with a comparatively high proportion of death events and a comparatively high proportion of ICU care that randomized a relatively small number of subjects may be more vulnerable to performance bias, due to the implementation of frequent assessments and interventions. Whether bias arising from potential unblinding events influence the clinical interpretation of the mortality results of study 902 is a topic of discussion for the Advisory Committee.

Blinding in clinical trials is thought to prevent the following types of bias, which may be present in unblinded or inadequately blinded trials: information bias/ascertainment bias and performance bias.

Ascertainment bias arises from differential assessment of outcomes due to knowledge of treatment assignment. An all-cause mortality endpoint is generally considered to be resistant to ascertainment bias because the final assessment of a death event is unlikely to be influenced by the knowledge of treatment assignment.

In contrast, performance bias does have the potential to bias efficacy outcomes of trial endpoints such as mortality in randomized clinical trials. Performance bias is the differential use of post-randomization care and co-interventions (e.g., SoC medications, therapeutic interventions, ancillary services, expectations regarding outcomes, and goals of care decision-making) based on knowledge of treatment assignment (Schulz et al. 2002; Schulz and Grimes 2002) that may occur consciously or subconsciously after unblinding or incomplete blinding. In a trial of an acute illness that can evolve into critical illness and include multiple acute comorbidities and sequelae (e.g., thrombosis, renal failure, ARDS), the

subconscious influence of knowledge of treatment assignment has the potential to bias clinically relevant elements of post-randomization care, communication and recommendations regarding interventions and life-sustaining care, and even mortality outcome measures through performance bias.

While performance bias may affect healthcare providers who are unblinded, similar considerations have the potential to affect the decision-making of patient or family members and could be understood in the context of "nocebo effects" after unblinding of the care team. Nocebo effects have been described in the literature as the negative side of placebo effects or as unfavorable events produced by negative expectations (Colloca and Finniss 2012), and may be produced by expectation and communication including physician-patient communication. At least one source suggests that negative information and prior unsuccessful interventions may influence undesirable outcomes to therapy (Colloca and Finniss 2012). In the setting of potential unblinding events with unclear scope, it is difficult to predict what influence potential performance bias (on the part of the care team) and nocebo effects (by the patient/family decision-makers) may have had on the time-limited all-cause mortality endpoint in Study 902.

Performance Bias in Critical Care Trials and Overestimation of Effect Sizes due to Unblinding

Available data from interventional trials suggest that inadequately blinded clinical trials may overestimate effect sizes of interventions compared to blinded trials (Savović et al. 2012a; Savović et al. 2012b). These data suggest that performance bias due to lack of adequate blinding is not merely a theoretical construct, and that its effects on post-randomization care and interventions may influence outcomes. The literature includes meta-epidemiological evidence of overestimation of effect sizes in critical care trials – and even on mortality outcomes – when comparing blinded and inadequately blinded trials. In a meta-epidemiological study of blinding and mortality results in critical care randomized trials, Martin et al. (2021), suggested that nonblinded critical care trials were associated with statistically significantly larger effect estimate sizes for the intervention compared to blinded trials. This study suggested a 9% overestimation of effect sizes among the included critical care trials (ratio of odds ratios (ROR) 0.91, 95% CI (0.84, 0.99)). The same study reported an effect size overestimation of 12% (ROR 0.88, 95% CI (0.79, 0.99)) from nonblinded critical care trials measuring short-term mortality outcomes compared to blinded critical care trials measuring short-term mortality in their sample. Anthon et al. (2018) observed a statistically significant interaction between the outcome measure of "mortality at longest follow-up" and blinding status in a pooled analysis of ICU interventions (pooled effect estimates of 0.99 versus 0.93 for blinded versus unblinded, respectively). The authors also report that summary effect estimates of mortality in the analyzed unblinded trials were larger than blinded trials for the same intervention in 63% (n = 14). Finally, in an analysis of multiple critical care trials, Landoni et al. (2015) found that nonblinded randomized controlled clinical trials were statistically significantly more likely to report a mortality benefit than blinded trials. This article also notes that – among all the observed articles included in a sensitivity analysis – unblinded trials and trials that enrolled a smaller number of subjects were more likely to show a survival benefit.

In an editorial, Yarnell (2021), implies a particular vulnerability of critical care trials to performance bias. The author makes the observation that critical care medicine involves multiple clinically relevant interventions after randomization and frequent post-randomization reassessment. The author further points to evidence suggesting that many critically ill patients die after care decisions to decline or withdraw life-sustaining therapies, and that performance bias could also influence decisions regarding

life-sustaining therapy. He also suggests that performance bias could potentially be mitigated by "meticulous tracking of cointerventions and adjudication of the clinical status that lead to outcomes" including mortality.

Members of the Care Team and the Potential for Unblinded Product Recognition

It is unclear exactly which members of the care team may have been exposed to potential unblinding events. While the principal investigator is responsible for many aspects of trial conduct at a clinical site, multiple healthcare providers and members of the ICU care team may be involved in clinical care and may influence clinical decision-making. In the US paradigm, ICU nurses form an important and integral pillar of the care team, and communication from nurse to physician and vice-versa drives most medical care. Nurse knowledge of treatment assignment could have important effects on patient care not only through communication with supervising physicians but also through direct performance bias, as well as influencing goals of care (Newman 2016). In academic centers, a nurse's clinical decision-making is already integral to care (addressing or alerting additional team members to clinical change, implementation of medication orders, titration of multiple drugs and interventions, nutrition orders, as well as other general nursing care), and in centers where physicians and trainees have less consistent presence a nurse may play an even larger role in the overall care of the patient.

Potential Impact of Unblinding Events on Interpretation of the All-Cause Mortality Results

Notably, in critical care, the use of an enteral access device is correlated with severity of illness. Patients who have a clinical decline and become critically ill (e.g., septic shock, decreased level of consciousness, intubation and mechanical ventilation due to respiratory failure) are more likely to require an enteral access device. In a clinical trial setting, this implies that the subjects with a higher likelihood of having a potential unblinding event were also those with higher severity and higher likelihood of a death event. This confounding of unblinding and clinical severity – along with the potential for underestimation of the scope of unblinding – makes interpretation of the effects of potential unblinding difficult to disentangle.

The available data from interventional trials suggest that inadequately blinded clinical trials may overestimate effect sizes of interventions. Available data from critical care – even trials with a mortality endpoint – may overestimate effect sizes, potentially due to the influence of performance bias and its effects on post-randomization care and interventions. Sensitivity analyses could have the potential to mitigate these concerns, however, data on additional elements of critical care (e.g., proning, timing and content of goals of care conversations) were not collected. While this lack of data on additional care measures was not unusual in the context of this study conducted during the COVID-19 pandemic, it limited the review team's ability to perform sensitivity analyses to further inform these uncertainties.

3.1.3.3 Application of Standard of Care Therapies

No elements of local standard of care therapy were strictly proscribed by the protocol for study 902. Local standard of care appeared to generally include consideration of corticosteroids for COVID-19, and otherwise reflected regional differences. For example, remdesivir was used predominantly at US sites in Study 902. In addition, the durations of some therapies would be uncommon for US standard of care practices. For example, 30 out of 204 subjects across both arms received >20 days of post-randomization standard of care therapy (defined as remdesivir or corticosteroids for this analysis), which rises to 43 out of 204 subjects across both arms if pre-randomization standard of care therapy is included. Indeed, the data suggest that 6 subjects in Study 902 received over 50 days of standard of care

therapy including pre- and post-randomization care, all in the VERU-111 arm. Given that a decision on EUA is applicable to the US market alone, it is unclear to what degree these measured deviations from US standard of care might be indicative of additional unmeasured elements of standard of care and how these considerations might affect the interpretation/generalizability of the efficacy results. However, available data suggest that numerical imbalances in measured standard of care therapies were present at baseline, prior to randomization, and after randomization in Study 902.

Baseline Imbalances in Standard of Care Therapies

There were numerical imbalances in the proportion of subjects receiving accepted standard of care therapies for COVID-19 at baseline in Study 902 as depicted in Table 6, above. The proportion of subjects receiving dexamethasone on Day 1 and the proportion of subjects receiving remdesivir on Day 1 were numerically higher in the VERU-111 arm compared to placebo. The potential effect of these baseline imbalances on the observed mortality signal in Study 902 is difficult to predict due to additional complicating factors (e.g., baseline severity, comorbidities, pre-randomization course, and post-randomization care). Available evidence for both dexamethasone (Horby et al. 2021) and remdesivir (WHO Solidarity Trial Consortium 2022) in COVID-19 suggest effects on mortality among certain patient populations. Given the small sample size and 2:1 randomization ratio for VERU-111 to placebo in Study 902, factors that influence the predicted mortality of the placebo arm could raise the uncertainty in the efficacy estimate for all-cause mortality attributed to VERU-111. The prespecified primary analysis included an adjustment for baseline dexamethasone and remdesivir use as covariates in a logistic regression model, as noted above. However, it is possible that the adjusted analysis may not have completely and correctly accounted for these observed imbalances.

Timing and Duration of Standard of Care Therapies

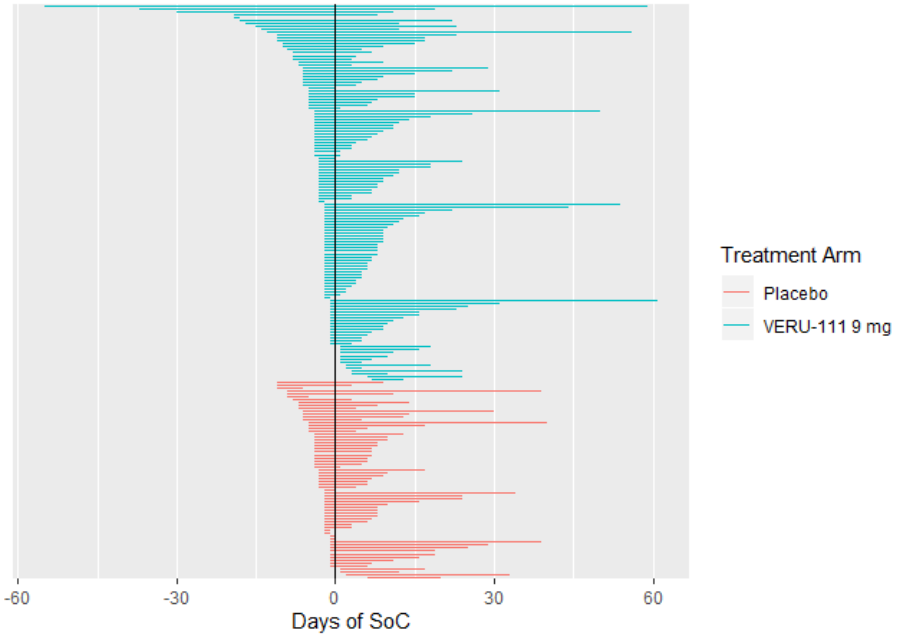
In addition to imbalance in proportion of subjects receiving SoC at baseline, some subjects in the VERU-111 arm of Study 902 began therapy earlier and received a longer duration of standard of care therapies prior to randomization compared to placebo, as depicted in Figure 7. Notably, in Study 902, individual subjects in the VERU-111 arm had received dexamethasone and/or remdesivir for COVID-19 prior to randomization for 55 days, 37 days, and 30 days, and that 6.7% (9 subjects) in the VERU-111 arm received ≥14 days of standard of care medications (i.e., dexamethasone or remdesivir) prior to randomization compared to 0% (0 subjects) in the placebo arm. Illustrating this, subjects with the 15 most extreme (i.e. earliest) values for pre-randomization SoC therapies are depicted in Figure 8.

Sensitivity and subgroup analyses exploring the impact of these differences in duration of SoC therapies prior to randomization between treatment arms on the primary analysis findings are presented above in sections 3.1.2.2.5 and 3.1.2.2.6. As noted above, although these analyses were simplistic explorations using available data and do not entirely eliminate the concern caused by imbalances between treatment arms in the timing and duration of SoC therapies, the addition of covariates had minimal impact on the primary efficacy analysis results and subgroup analyses results were consistent with the primary efficacy analysis.

Because the potential use-case of VERU-111 for subjects with COVID-19 under an EUA will likely involve administration of the drug relatively early after the initiation of therapies such as dexamethasone and remdesivir, the subset of subjects with extended durations of standard of care therapy for COVID-19

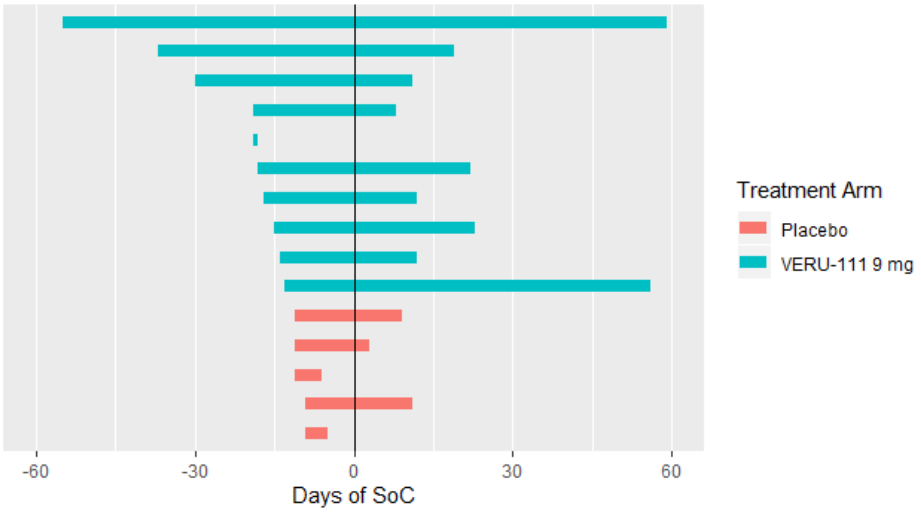
create uncertainty in the role of VERU-111 in the observed outcome data, the clinical interpretation of the all-cause mortality results, and their applicability to clinical practice.

Figure 7. Study 902: Pre-randomization and Post-randomization COVID-19 Standard of Care Therapy Days by Treatment Arm (ITT, Sorted by Pre-randomization COVID-19 Standard of Care Therapy)



Source: Reviewer based on Sponsor-submitted data
Abbreviations: COVID-19, coronavirus disease 2019; ITT, intention to treat population; SoC, standard of care; VERU-111, sabizabulin

Figure 8. Study 902: Subjects With the Highest 15 Values of Pre-randomization COVID-19 Standard of Care Therapy Days by Treatment Arm (ITT, Sorted by Pre-randomization COVID-19 Standard of Care Therapy)



Source: Reviewer based on Sponsor-submitted data
Abbreviations: COVID-19, coronavirus disease 2019; ITT, intention to treat population; SoC, standard of care; VERU-111, sabizabulin

Differences in Standard of Care Application After Treatment Assignment

There were observed numerical differences between study arms in the elements of standard of care used in Study 902. Given the timing and enrollment criteria for Study 902, all subjects had a compelling indication for corticosteroids (e.g., dexamethasone) for COVID-19 at randomization. While some subjects may have had relative contraindications to corticosteroid use, it is unlikely that these would have prevented its use for life-threatening COVID-19. Despite this, and despite baseline imbalances in corticosteroid use for COVID-19 noted above, the proportion of subjects who had not received corticosteroids for COVID-19 by ≥3 days after randomization was numerically higher in the placebo group (5.7%) compared to the VERU-111 group (4.5%).

Randomization and blinding allow for attribution of differences between treatment arms in post-randomization care to the effect of medication on the disease course. However, elements of care occurring after treatment assignment (e.g., ventilation strategies, proning for ARDS, goals of care conversations, and co-interventions) have the potential to influence trial outcomes, and the lack of formal reporting on these co-interventions and their potential influence on outcomes has been noted in critical care studies in septic shock (de Grooth et al. 2018). The potential influence of these differences in care on the efficacy endpoints of Study 902 are difficult to predict, and the data for other elements of clinically relevant standard of care in the critically ill (e.g., for concomitant ARDS or septic shock) were not formally recorded in the data for Study 902. While this is not abnormal for critical care trials, it may be more impactful in a study of this small size. Further, in the setting of potential unblinding events, it limits further evaluation of differences in standard of care after treatment assignment.

3.1.3.4 Timing of Enrollment Compared to COVID-19 Clinical Course

Pre-randomization Length of Hospital Stay

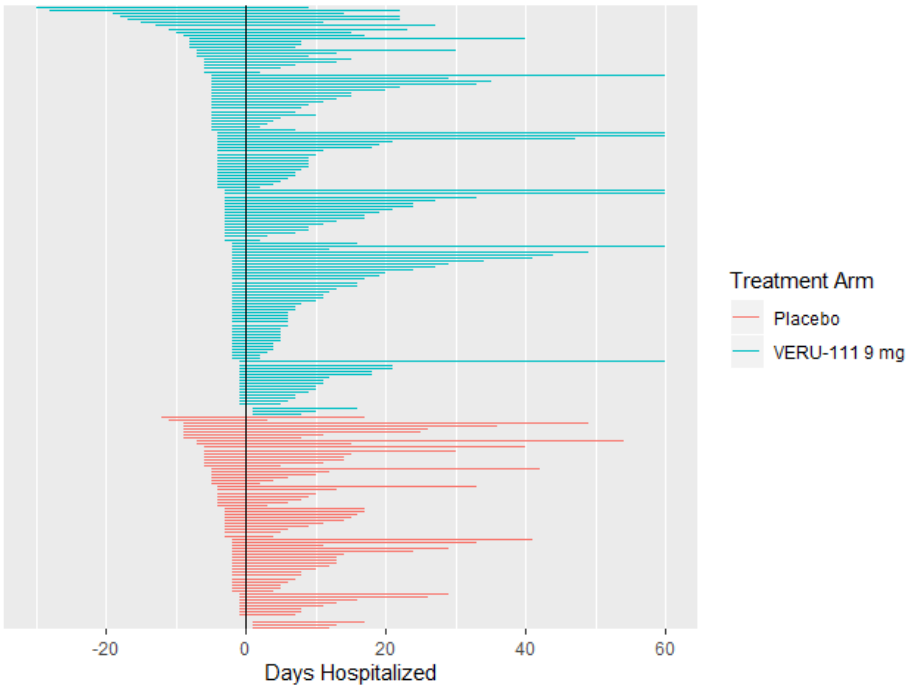
While the mean number of days in hospital prior to randomization was similar across treatment arms (4.2 days for the VERU-111 arm versus 3.8 days for placebo), a larger proportion of subjects in the VERU-111 arm were hospitalized for over 14 days prior to randomization (4.5% vs 0%), as show in Figure 9. Notably, in Study 902, individual subjects in the VERU-111 arm were hospitalized for 30 days, 28 days, 19 days, 18 days, 17 days prior to randomization, while the longest pre-randomization course for a subject in the placebo arm was 12 days. Illustrating this point, subjects with the 15 most extreme values for pre-randomization days in hospital are depicted in Figure 10.

The potential effect of pre-randomization hospitalization on the mortality results of Study 902 is uncertain and difficult to predict due to the complicating factors noted in previous subsections. Sensitivity and subgroup analyses exploring the impact of differences in pre-randomization days in hospital between treatment arms on the primary analysis findings are presented above in sections 3.1.2.2.5 and 3.1.2.2.6. As noted above, although these analyses were simplistic explorations using available data and do not entirely eliminate the concern caused by imbalances between treatment arms in pre-randomization days in hospital, the addition of covariates had minimal impact on the primary efficacy analysis results and subgroup analyses results were consistent with the primary efficacy analysis.

The clinical trajectory and prognosis of subjects who have already been in the hospital for up to 30 days prior to drug administration may differ in clinically relevant ways from those who have been recently admitted. Acknowledging that some patients with COVID-19 experience extended admissions, the

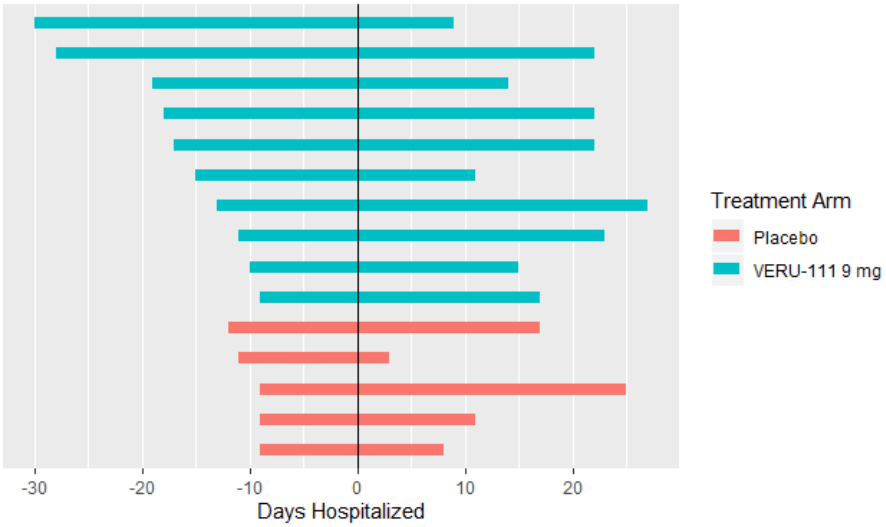
potential use of VERU-111 for subjects with COVID-19 under an EUA would likely involve administration of the drug relatively early in an admission among subjects who require supplemental oxygen and have a trajectory of clinical worsening. Given that potential clinical use of VERU-111 would likely be in this setting, the subset of subjects with extended durations of pre-randomization hospitalization for COVID-19 create uncertainty in the role of VERU-111 in the observed outcome data, the clinical interpretation of the all-cause mortality results, and their applicability to clinical practice. In addition, these uncertainties in pre-randomization hospital length of stay introduce challenges in interpreting secondary endpoints such as Days in Hospital and potentially Days in ICU, since the values measured after randomization do not reflect the total length of stay of the patient. This uncertainty is further complicated by the randomization of subjects who may have been on a clinical trajectory for clinical improvement prior to randomization (see next subsection below).

Figure 9. Study 902: Pre-randomization and Post-randomization Days in Hospital by Treatment Arm (ITT, Sorted by Pre-randomization Days in Hospital)



Source: Reviewer based on Sponsor-submitted data
Abbreviations: ITT, intention to treat population; VERU-111, sabizabulin

Figure 10. Study 902: Subjects With the Highest 15 Values of Pre-randomization Days in Hospital by Treatment Arm (ITT, Sorted by Pre-randomization Days in Hospital)



Source: Reviewer based on Sponsor-submitted data
Abbreviations: ITT, intention to treat population; VERU-111, sabizabulin

Randomization of Subjects Potentially on a Clinical Trajectory of Improvement

In addition to the imbalances in pre-randomization hospital length of stay between study arms, the pre-randomization clinical trajectory of some subjects enrolled in Study 902 may contribute to uncertainty in the interpretation of the efficacy findings.

Available data from enrollment and randomization measurements suggest that at least two subjects met WHO 6 criteria (i.e., intubated and mechanically ventilated) at enrollment and WHO 5 criteria at randomization (i.e., no longer intubated). In addition, one subject met WHO 4 criteria at baseline (Day 1) and was discharged to home meeting WHO 2 criteria on Day 2. These limited data suggest that some subjects were likely on a trajectory of clinical improvement prior to randomization. However, randomized subjects had hospital courses spanning up to 30 days prior to randomization and use of standard of care medications for longer periods (see above), but screening assessments of WHO severity category was only allowed 3 days prior to randomization. As comprehensive data to categorize pre-randomization severity (e.g., prior intubation and mechanical ventilation) and clinical course were not collected in Study 902, we cannot ascertain how many subjects may have been on trajectories of clinical improvement prior to randomization.

Additional uncertainty in clinical trajectory may be suggested by the treatment duration data in Study 902. The protocol rules for duration of treatment imply that VERU-111 treatment could have been given for <21 days in subjects who were discharged. Most subjects in Study 902 completed fewer than 10 days of study drug treatment, and disposition data suggest that 81.3% of the VERU-111 arm discontinued VERU-111 prior to Day 21, with a median time to discontinuation of study medication of 10 days. There is uncertainty – based on the proposed mechanism of action and available clinical data from prior studies – what minimum duration of treatment with VERU-111 would be expected to provide an efficacy benefit in hospitalized subjects with SARS-CoV-2 infection at high risk of ARDS enrolled in Study 902. This uncertainty has the potential to affect the interpretation of individual cases in the VERU-111 arm in the context of improving clinical trajectories.

Potential Impact of Timing of Enrollment and COVID-19 Clinical Course on the Interpretation of All-Cause Mortality

As noted above, the use of VERU-111 for subjects with COVID-19 under an EUA will likely involve administration of the drug early in their clinical course and on a trajectory of hospital admission and disease worsening. The subset of subjects with trajectories of clinical improvement at baseline create uncertainty in the role of VERU-111 in the observed outcome data, the clinical interpretation of the all-cause mortality results, and their applicability to clinical practice. In addition, these uncertainties in pre-randomization clinical trajectory create uncertainty in the clinical interpretation of secondary endpoints such as Days in ICU and Days on Mechanical Ventilation, since some subjects may have potentially completed their ICU course or course of mechanical ventilation prior to randomization.

3.1.3.5 The Effects of Goals of Care on All-Cause Mortality

In the context of a mortality-focused trial of an acute disease with a broad range of baseline severity, age, comorbidities, and a relatively short duration of evaluation, it is notable that there are no enrollment criteria specifying a framework for goals of care or the extent of supportive interventions allowed by participants during the trial. Goals of care decisions such as “do not intubate”, “do not resuscitate”, and withholding or withdrawal of life-sustaining therapy were not formally recorded as data points in Study 902. Considerations of difference in subjects’ goals of care decisions on trial efficacy estimates may be more impactful in small trials.

However, there is evidence from the trial narratives that such decisions were made and documented in some cases, but not all. To present examples of the available information, the narratives include at least one subject who died in the trial with draft narrative notes that document “intubation had been refused” and a separate subject in the final narrative notes that states “he refused intubation”. In contrast, at least one subject who died in the trial had draft narrative notes that document “worsening of respiratory pattern”, “low level of consciousness and hypoactive”, and that “the subject was at high risk of orotracheal intubation within the next few hours”. The same subject died approximately 5 hours later of cardiopulmonary arrest without documentation of intubation and mechanical ventilation or documentation of any goals of care such as a do-not-intubate order, with final narrative notes stating only “the patient received no treatment for the event of cardiorespiratory arrest”.

The lack of formal data collection of goals of care and end-of-life decision-making is not unusual in critical care trials (Messika et al. 2018). Kerever et al. (2019), analyzed the data from 178 critical care trials and found that only 35% of the analyzed trials reported methodologic details of end-of-life decisions, and that those that did reported heterogeneous methodologies for accounting for end-of-life decision-making in the analyses. The authors suggest that this underreporting could lead to a high risk of bias.

Literature supports that goals of care decision-making may play a more direct role in mortality endpoints in critical care trials. Several publications highlight that most subjects in critical care trials die after decisions to withdraw or withhold life-sustaining therapy. Literature also suggests that goals of care decisions may have an independent effect on mortality, that there is high variability in goals-of-care decision-making, that this variability is influenced by factors outside of simple clinical severity/prognosis, and that these decisions may have occurred more frequently during the COVID-19 pandemic. A detailed review of these factors is provided in Appendix 6.3 Study V3011902: Primary Endpoint Efficacy Issues in Detail: End of Life Decision Making and Mortality Outcomes in the Literature.

Potential Impact of Goals of Care on the Interpretation of All-Cause Mortality

There is uncertainty regarding local practice differences in medical decision-making such as goals of care discussions, do-not-intubate decisions, tracheostomy decisions, initiation of renal replacement therapy decisions, do-not resuscitate decisions, and no-escalation-of-care decisions. Both within the US and in non-US sites, there is uncertainty in the interplay of various factors that influence goals-of-care decisions, and that have the potential to impact the timing and proportion of mortality observed in a limited-duration study. These factors would include, but are not limited to, local standards regarding ethical decision-making, avoidance of unnecessary suffering, physician paternalism versus patient autonomy in decision-making, and patient/family-centered care as a component in decision-making. In addition, pandemic-focused concerns such as previous positive/negative experiences with critically ill COVID-19 patients, resource considerations, and local standards for heroic measures in the setting of SARS-CoV-2 infection control measures could also influence medical decision-making. The interplay of these factors is difficult to predict; however, they may represent an important source of variability to the timing of mortality events in the care of critically ill patients in regular ICU care and the proportion of subjects observed to have died in a limited duration study.

Quantifying the potential influence of variation of end-of-life decision-making on all-cause mortality outcomes in Study 902 is not possible, even though end-of-life decision-making may play a significant role in deaths in trials involving critical care. However, Study 902 was a small study with a 2:1 randomization ratio in which a small number of end-of-life decisions had the potential to exert a large influence on the study results. Considering the potential unblinding events noted in Study 902, the variability and urgency of goals of care decision-making during the COVID-19 pandemic, and the reported efficacy results from Study 901, there is uncertainty in whether knowledge of treatment assignment may have influenced goals of care and end-of-life decision-making and mortality outcomes in Study 902. However, it is important to note that the Agency's uncertainties with regard to goals of care and end-of-life decision-making in the context of unblinding events in no way is intended to imply that such decision-making may have been clinically inappropriate, unethical, or inconsistent with local standard of care practice; instead, this uncertainty is limited to the potential effects of subconscious performance bias after unblinding and other elements of practice variation on end-of-life decision-making on the clinical interpretation of the trial's outcome data.

3.1.3.6 Efficacy Results of Other Microtubule Disruptors in COVID-19

Available Evidence for Colchicine in COVID-19

Given that VERU-111 is a new molecular entity that purports a mechanism of action similar to colchicine, it may be informative to consider the available results of randomized controlled trials of colchicine. Both colchicine and VERU-111 are microtubule disruptors that act upon the "colchicine binding site" of tubulin to inhibit tubulin polymerization. However, in contrast to the results of Study 902, multiple randomized controlled trials of colchicine in COVID-19 have failed to provide evidence of the efficacy of this microtubule disruptor on mortality or other clinically relevant outcomes in COVID-19 across multiple levels of baseline severity (e.g., RECOVERY Collaborative Group (2021), Cecconi et al. (2022), Absalón-Aguilar et al. (2022), Tardif et al. (2021), Dorward et al. (2022)). In contrast, an early, small (N = 105), open-label, randomized, controlled trial of colchicine versus usual care in subjects hospitalized with COVID-19 in April 2020 by Deftereos et al. (2020) and the GRECCO Investigators, did suggest efficacy on

a composite endpoint of a 2-point increase in WHO ordinal scale score or death (5 subjects died in the placebo group compared to 1 subject in the colchicine group).

Multiple meta-analyses from different sources have attempted to combine and integrate the available data on colchicine in COVID-19 since the onset of the pandemic. Mikolajewska et al. (2021) performed a meta-analysis of randomized clinical trials of colchicine in COVID-19 under the auspices of the Cochrane Database of Systematic Reviews in 2021 that included 11,525 hospitalized participants from three RCTs and 4488 participants from one RCT with non-hospitalized participants. Their meta-analysis presented a risk ratio for all-cause mortality based on 11,445 hospitalized participants at Day 28 of 1.00 with a 95% CI of 0.93 to 1.08, based heavily on data from RECOVERY (RECOVERY Collaborative Group 2021) supplemented by the relatively small GRECCO-19 trial (Deftereos et al. 2020). The authors conclude that "colchicine plus standard care probably results in little to no difference in all-cause mortality up to 28 days compared to standard care alone" and classify the results as moderate certainty evidence. Similarly, a subsequent meta-analysis of seven randomized controlled trials including 16,024 participants who received either colchicine (N = 7,794) or control (N = 8,230 who received placebo or usual care) published in 2022 by (Lan et al. 2022), found that the colchicine group had a similar risk of mortality compared to control (OR 1.00, 95% CI 0.91 to 1.09) and observed no significant differences on outcomes of length of hospital stay and the need for mechanical ventilation.

Potential Impact of Colchicine Data on the Interpretation of All-Cause Mortality

We acknowledge that these data from randomized clinical trials of colchicine in COVID-19 cannot provide direct evidence to inform a discussion of the effectiveness of VERU-111 in COVID-19, given that colchicine is a different agent. However, whether these data of an agent that shares a similar mechanism of action to VERU-111 may influence the consideration of the robustness of the data provided primarily by a single, small, efficacy and safety trial of VERU-111 is an area of potential discussion for the Advisory Committee.

3.1.3.7 Study Population Uncertainties

The Sponsor proposes treatment with VERU-111 in adult subjects hospitalized with COVID-19 and "at high risk of ARDS". High risk of ARDS was represented in the Sponsor's drug development program as WHO 5 or WHO 6 ordinal scale severity, or subjects with WHO 4 ordinal scale severity with at least one additional comorbid condition (see Enrollment Criteria). There is uncertainty in whether the identified comorbidities adequately define a specific and clinically relevant population for treatment. It is also unclear whether the overall efficacy results would be recapitulated across individual comorbidity subgroups and clinical conditions that might fall within these broad headings in routine clinical practice. This uncertainty is complicated by the fact that Study 902 did not formally collect data on which comorbidity criteria were met by a subject– nor on the specific diagnosis they may have met a criterion – for subjects enrolled with WHO 4 ordinal scale severity or other severities.

For example, immunocompromise in clinical practice is a broad concept and has the potential to represent a broad range of conditions such as CVID, HIV/AIDS, and acute leukemia. In addition, immunocompromise may also represent subjects on a wide array of medications including immunosuppressive monoclonal antibody medications for rheumatologic diseases, cytotoxic chemotherapy for malignancies, and chronic low-dose corticosteroids for uncontrolled COPD. Given the lack of data collection on these parameters, it is unclear that the proposed trial would have the power

to provide adequate confidence in the efficacy results across the full scope of these subgroups and comorbidity subsets to apply them to clinical practice.

3.2 Safety Issues

3.2.1 Sources of Data for Safety

Data from the 199 subjects in the safety population of Study 902 are the primary data used to evaluate safety for VERU-111 for the proposed emergency use, with Study 901 serving to assess for additional support for potential safety signals in Study 902. Study 902's safety population included 130 subjects exposed to VERU-111 compared to 69 subjects who received placebo. Study 901 did not include a dataset-defined safety population, however the study comprised 19 subjects in the VERU-111 arm and 20 in the placebo arm.

In addition to efficacy and safety data for the proposed use in the treatment of COVID-19, the Sponsor also submitted limited safety data from two other studies in unrelated patient populations and indications. Study V1011101 was a non-randomized, unblinded, uncontrolled, single arm clinical study of VERU-111 dose levels in men with advanced metastatic castration-resistant prostate cancer (AMCRPC). Study V3011102 was a randomized, open-label, active-control study in men with AMCRPC who have failed prior treatment with ≥ 1 androgen receptor-targeting agent. The applicability of data from these studies is unclear to the review of safety for VERU-111 in COVID-19. The patient populations enrolled in both of these studies were not critically ill, were receiving active treatment for late-stage cancer (e.g., involving the potential for androgen receptor-targeting agents and radiation), and higher doses of VERU-111 were administered to the majority of the subjects in these prostate cancer studies than in the COVID-19 studies. In addition, the lack of placebo control in either study does not allow for reliable attribution of rates of adverse events or imbalances in adverse events to VERU-111.

Categorization of Adverse Events

Adverse events were coded to MedDRA dictionary version 23 for study 901 and MedDRA version 24 for Study 902. The definition of serious adverse events was adequate. Severity of adverse events was recorded according to the Common Terminology Criteria for Adverse Events version 5.

3.2.2 Safety Summary

The focus of the Advisory Committee discussion is whether the data presented in Study 902 demonstrate that VERU-111 may be effective for the proposed emergency use, based on the mortality data presented. When considering whether to authorize the emergency use of a product under EUA, the Agency must determine, among other requirements (see section 2.1.3), whether "the known and potential benefits of the product when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product". Determination of the potential risks of VERU-111 are limited by the very limited size of the safety database for the proposed use; the limited size precludes definitive identification of significant safety signals, especially when considering rare events. In the face of a potential efficacy benefit on all-cause mortality, there are few safety signals for which risk would outweigh this potential benefit. Therefore, while the Agency has not designated any particular safety signal that requires discussion at the Advisory Committee, the Safety Summary provides an overview of the safety data and potential safety signals to aid in the Committee's overall benefit-risk evaluation (see below).

In this context, the potential risks identified from the safety analysis of Studies 902 and 901 include urinary tract infections (including serious infections), gastrointestinal motility and defecation conditions (including diarrhea), gastrointestinal signs and symptoms (including nausea/vomiting), anemia, epidermal and dermal conditions, venous thromboembolism, and hemorrhage (including GI and non-GI hemorrhage terms). At least three of these adverse event pathologies (i.e., infectious/immune, gastrointestinal, and skin) involve cells with relatively high rates of turnover. There are insufficient mechanistic data to suggest whether VERU-111's mechanism of action of microtubule disruption would be predicted to adversely affect these cell types preferentially.

3.2.2.1 Adequacy of Safety Database and Safety Assessments

The content and frequency of safety assessments in Study 901 and Study 902 were adequate in the setting of trials considered safe to proceed during the COVID-19 pandemic. However, as noted above, a full characterization of the safety profile of VERU-111 is limited by the small safety database in COVID-19 comprising a total of 149 subjects who received VERU-111 for the proposed use in COVID-19 across Studies 901 and 902, with a mean duration until study drug discontinuation of 9.1 days and a total safety follow-up duration of 60 days. Due to the small size of the safety database and short treatment duration, information on prediction/prevention, monitoring, or reversibility of safety issues is difficult to assess. However, clinical care of hospitalized subjects with COVID-19 is characterized by short-term treatment and monitoring labs at a level commensurate with inpatient hospitalized acute care, which may mitigate these limitations.

3.2.2.2 Deaths

Refer to sections 3.1.2.1 and 3.1.2.2.4 for discussion of death events in Studies 901 and 902, respectively.

3.2.2.3 Serious Adverse Events

The small sample size and limited timeframes of Study 902 limit its ability to allow for detection of rare events with confidence, such as some serious adverse events (SAE).

While there were imbalances in the proportion of subjects experiencing some SAEs, few of these SAE terms included a number of events or subjects that would provide a standalone safety signal, and most of the SAEs that are discussed in this section and presented in Table 13, below, are noted due to corresponding signals in the data for AEs (see section 3.2.2.4), providing some support for their overall relevance to the safety of VERU-111. Similar to the imbalance in urinary tract infection AEs suggested in common adverse events (see section 3.2.2.4), there was a small numerical imbalance in the proportion of subjects with serious urinary tract infections as captured by the SAE terms of urinary tract infection, urosepsis, and urinary tract infection bacterial. captured in Study 902.

While the imbalance in urinary tract infection is concordant across both SAEs and AEs (see below), potential safety signals for other serious bacterial infections with VERU-111 are mixed in their interpretation, and likely do not support a clear picture of increased risk with VERU-111.

Finally, while common adverse events and standardized MedDRA queries may suggest a potential safety signal for venous thromboembolic events with VERU-111 (see below), SAE data only captured a single serious event of deep vein thrombosis in subjects receiving VERU-111 (0.8% versus 0% of placebo subjects). In contrast, SAEs of pulmonary embolism were captured in 2.3% of subjects receiving VERU-111 compared to 4.3% of subjects receiving placebo. With so few events, it is unclear whether

proportions of serious venous thromboembolic events in Study 902 meaningfully influence the interpretation of the rates of overall venous thromboembolic events discussed below.

Additional data from Study 901 do not provide sufficient numbers of SAEs to draw meaningful conclusions to increase or decrease confidence in the potential safety signals in Study 902; all but one SAE event terms captured in study 901 comprised 2 or fewer subjects in either study arm.

Table 13. Study 902: Summary of Treatment Emergent Serious Adverse Events (Safety Population)

Treatment Emergent Serious Adverse Events (SAEs)	VERU-111 (N = 130)			Placebo (N = 69)		
MedDRA SAE Term	Number of Events	Number of Subjects	Proportion	Number of Events	Number of Subjects	Proportion
SOC infections and infestations						
Urinary tract infection	2	2	1.5	0	0	0
Urosepsis	1	1	0.8	0	0	0
Bacterial infectious disorders	8	5	3.8	2	2	2.9
Acinetobacter infection	1	1	0.8	0	0	0
Pneumonia acinetobacter	1	1	0.8	0	0	0
Pneumonia bacterial	0	0	0	2	2	2.9
Urinary tract infection bacterial	2	2	1.5	0	0	0
Burkholderia cepacia complex infection	1	1	0.8	0	0	0
Clostridium difficile colitis	1	1	0.8	0	0	0
Enterococcal sepsis	1	1	0.8	0	0	0
Endocarditis staphylococcal	1	1	0.8	0	0	0
SOC Vascular disorders						
Deep vein thrombosis	1	1	0.8	0	0	0

Source: Reviewer using MAED software. Treatment-emergent serious adverse events occurring in the safety population of Study 902.
Abbreviations: MedDRA, Medial Dictionary for Regulatory Activities; N, number of subjects; NEC, not elsewhere classified; SAE, severe adverse event; SOC, System Organ Class; VERU-111, sabizabulin

3.2.2.4 Common Adverse Events

A summary of adverse events considered clinically relevant in Study 902 are presented in Table 14, below. Discussion of each clinically relevant adverse events category in detail precedes the table.

Urinary Tract Infections Adverse Events

The AE data suggest a potential safety signal for urinary tract infections with the use of VERU-111 compared to placebo. The data observed a higher proportion of subjects in the VERU-111 arm of Study 902 compared to placebo for high-level term urinary tract infection (6.2% versus 1.4%, respectively). This potential signal is supported by the smaller imbalances in the separate preferred terms of urinary tract infection bacterial (1.5% versus 0%) and urosepsis (1.5% versus 0%).

Available data from Study 901 are limited in their ability to reinforce the potential safety signal from Study 902. There was only one AE of urinary tract infection recorded in Study 901, an event of urinary tract infection enterococcal in the VERU-111 arm with no AEs of urinary tract infections in the placebo arm (5.3% versus 0%, respectively).

Gastrointestinal Adverse Events

The AE data suggest potential gastrointestinal safety signals with the use of VERU-111 compared to placebo. The proportion of subjects with gastrointestinal system organ class AE terms was higher in

subjects who received VERU-111 compared to placebo in Study 902 (16.2% versus 8.7%, respectively). Clinically relevant imbalances within this system organ classes included:

- A higher proportion of subjects with AE terms gastrointestinal hemorrhages or upper gastrointestinal hemorrhage (2.3% versus 0%, comprising the high level group term gastrointestinal hemorrhages NEC), which is further investigated using a standardized MedDRA Query approach, below.
- The high-level group term gastrointestinal motility and defecation conditions comprising the terms diarrhea, constipation, gastroesophageal reflux disease, and impaired gastric emptying (11.5% versus 8.7%, respectively for the high level group term). More specifically, the proportion of subjects with a recorded AE preferred term of diarrhea was higher in the VERU-111 arm compared to placebo as well (3.8% versus 1.4%, respectively)
- A higher proportion of subjects who received VERU-111 experienced AE terms from the high-level group term gastrointestinal signs and symptoms compared to placebo (6.9% versus 0%, respectively) comprising preferred terms dyspepsia, abdominal pain upper, abdominal pain, dysphagia, nausea, and vomiting. More specifically, the proportion of subjects with a recorded AE terms of nausea or vomiting was 3.1% in the VERU-111 arm compared to 0% in the placebo arm.

Available data in Study 901 may be considered to reinforce the imbalance in gastrointestinal safety signals suggested by Study 902. There was a higher proportion of subjects in the VERU-111 arm compared to placebo who experienced gastrointestinal disorders system organ class AE terms (26.3% versus 20%). Exploration of available AE terms within this system organ class show one adverse event of "rectal hemorrhage" occurred in one subject in each study arm. Similarly, 15.8% of subjects in the VERU-111 arm of Study 901 experienced the AE preferred term of constipation compared to 10% of placebo; it is notable that the imbalance in Study 902 suggested diarrhea in association with VERU-111. Finally, the preferred AE term dyspepsia was experienced by 5.3% of subjects in the VERU-111 arm of Study 901 compared to 0% of the placebo arm.

Anemia Adverse Events

The AE data suggest a potential safety signal of anemia with the use of VERU-111 compared to placebo. The proportion of subjects in Study 902 with high level group term of anemias nonhemolytic and marrow depression was observed to be higher for subjects who received VERU-111 compared to placebo (6.9% versus 4.3%, respectively), comprising AE terms of anemia, blood loss anemia, and pancytopenia.

Data from Study 901 are limited in their ability to contribute to the assessment of the potential safety signal suggested by Study 902. There was only a single AE of anemia recorded in Study 901, in one subject in the placebo arm (0% in the VERU-111 arm versus 5% of the placebo arm). The relevance of this single event is unclear.

Skin Conditions and Dermatologic Adverse Events

The AE data suggest a potential safety signal for skin conditions with the use of VERU-111 compared to placebo. The proportion of subjects in Study 902 with AEs comprising the high-level group term epidermal and dermal conditions was higher in the VERU-111 arm compared to placebo (6.2% versus

2.9%, respectively), with preferred terms including decubitus ulcer, dermatitis allergic, intertrigo, rash, rash erythematous, and rash maculo-papular.

Data from Study 901 do not document any AEs in the epidermal and dermal conditions high-level group term.

Venous Thromboembolism Adverse Events

While there were few events recorded for individual AE terms, the data suggest an imbalance in the proportion of subjects who experienced the venous thrombosis AE terms deep vein thrombosis (2.3% versus 1.4%) and venous thrombosis limb (1.5% versus 1.4%), axillary vein thrombosis (0.8% versus 0%) and thrombophlebitis superficial (0.8% versus 0%). These few events are not sufficient to establish a potential safety signal alone, however this potential signal is further investigated using a standardized MedDRA Query approach, below.

Data from Study 901 records no VTE events in its AE data, and so is limited in its ability to contribute to the assessment of VTE due to VERU-111.

Miscellaneous Adverse Events

There were additional imbalances of unclear clinical relevance due to relatively few events. The AE data suggest that fever/pyrexia was experienced by 3.8% of subjects in the VERU-111 arm compared to 0% in the placebo arm in Study 902. No events of pyrexia were recorded as AE terms in Study 901.

In addition, the terms edema and edema peripheral were recorded for 3.1% of subjects in the VERU-111 arm and 0% of subjects in the placebo arm of Study 902. Data from Study 901 are limited in their ability to contribute to the assessment of edema, since they record only one event in each arm for the term generalized edema in the VERU-111 arm and edema peripheral in the placebo arm (5.3% versus 5%).

Table 14. Study 902: Summary of Treatment Emergent Adverse Events (Safety Population)

Treatment Emergent Adverse Events	VERU-111 (N = 130)			Placebo (N = 69)		
MedDRA AE Term	Events	Number of Subjects	Proportion	Events	Number of Subjects	Proportion
SOC Blood and lymphatic system disorders						
Anaemias nonhaemolytic and marrow depression	9	9	6.9	3	3	4.3
Anemia	7	7	5.4	3	3	4.3
Blood loss anemia	1	1	0.8	0	0	0
Pancytopenia	1	1	0.8	0	0	0

Treatment Emergent Adverse Events	VERU-111 (N = 130)			Placebo (N = 69)		
MedDRA AE Term	Events	Number of Subjects	Proportion	Events	Number of Subjects	Proportion
SOC Gastrointestinal disorders						
Gastrointestinal disorders	32	21	16.2	11	6	8.7
Gastrointestinal hemorrhages NEC	3	3	2.3	0	0	0
Gastrointestinal hemorrhage	1	1	0.8	0	0	0
Upper gastrointestinal hemorrhage	2	2	1.5	0	0	0
Gastrointestinal motility and defecation conditions	16	15	11.5	11	6	8.7
Diarrhea	5	5	3.8	1	1	1.4
Constipation	9	9	6.9	10	6	8.7
Gastroesophageal reflux disease	1	1	0.8	0	0	0
Impaired gastric emptying	1	1	0.8	0	0	0
Gastrointestinal signs and symptoms	11	9	6.9	0	0	0
Dyspepsia	2	2	1.5	0	0	0
Abdominal pain	1	1	0.8	0	0	0
Abdominal pain upper	1	1	0.8	0	0	0
Dysphagia	2	2	1.5	0	0	0
Nausea	2	2	1.5	0	0	0
Vomiting	3	3	2.3	0	0	0
SOC General disorders and administration site conditions						
Pyrexia	5	5	3.8	0	0	0
Edema NEC	4	4	3.1	0	0	0
Edema	2	2	1.5	0	0	0
Edema peripheral	2	2	1.5	0	0	0
SOC Infections and infestations						
Urinary tract infection bacterial	2	2	1.5	0	0	0
Urosepsis	2	2	1.5	0	0	0
Urinary tract infections	8	8	6.2	2	1	1.4
SOC Skin and subcutaneous tissue disorders						
Epidermal and dermal conditions	11	8	6.2	2	2	2.9
Dermatitis allergic	3	1	0.8	0	0	0
Intertrigo	2	2	1.5	0	0	0
Rash	1	1	0.8	0	0	0
Rash erythematous	0	0	0	1	1	1.4
Rash maculo-papular	1	1	0.8	1	1	1.4
Decubitus ulcer	4	4	3.1	0	0	0
SOC Vascular disorders						
Axillary vein thrombosis	1	1	0.8	0	0	0
Deep vein thrombosis	3	3	2.3	1	1	1.4
Thrombophlebitis superficial	1	1	0.8	1	1	1.4
Venous thrombosis limb	2	2	1.5	1	1	1.4

Source: Reviewer using MAED software. Treatment-emergent adverse events occurring in the safety population of Study 902.
Abbreviations: MedDRA, Medial Dictionary for Regulatory Activities; N, number of subjects;NEC, not elsewhere classified; SAE, severe adverse event; SOC, System Organ Class; VERU-111, sabizabulin

3.2.2.5 Laboratory Findings

While there were small imbalances in the proportion of subjects for some laboratory-based adverse event terms (e.g., transaminitis, hyperglycemia), further data analyses did not support a clinically relevant signal for these adverse events.

3.2.2.6 Exploratory Standardized MedDRA Query (SMQ) Analyses

In addition to standard estimates of incidence for adverse event terms, standardized MedDRA queries (SMQ) were used to identify potential safety signals. SMQs group multiple AE terms that are pertinent to identifiable disease processes that may be more difficult to aggregate using a standard MedDRA hierarchy approach, for example pulmonary embolus and deep vein thrombosis (classified under System Organ Classes "Respiratory, thoracic, and mediastinal disorders" and "Vascular disorders", respectively). For the current review, SMQs for treatment emergent adverse events were analyzed to evaluate findings from the Common Adverse Events section, above.

Due to small imbalances noted in common venous thromboembolism adverse events, this reviewer conducted a SMQ to investigate this finding further. In the narrow SMQ of "Embolic and thrombotic events, venous" with adverse events comprising the terms: "venous thrombosis limb, deep vein thrombosis, pulmonary embolism, jugular vein thrombosis, thrombophlebitis superficial, axillary vein thrombosis – a small imbalance was noted (8.5% VERU111 vs. 7.2% placebo)

No adverse events meeting criteria for the "Embolic and thrombotic events, venous" narrow SMQ were recorded in Study 901.

While the narrow SMQ "gastrointestinal hemorrhage" simply reciprocated the imbalance in AE terms gastrointestinal hemorrhages AEs reported above, the SMQ "hemorrhage (excluding laboratory terms) provided additional insight into this potential safety signal. This SMQ also revealed an imbalance comparing VERU-111 versus placebo (14 events in 8.5% of subjects in the VERU-111 arm versus 8 events in 5.8% of subjects in the placebo arm) with adverse event terms encompassing the additional terms pulmonary hemorrhage, blood loss anemia, subarachnoid hemorrhage, hematoma, procedural hemorrhage, hematuria, post procedural hemorrhage, immune thrombocytopenia, hematoma muscle, contusion, epistaxis, tracheal hemorrhage. Only one adverse event in each treatment arm was deemed a serious adverse event these events comprised pulmonary hemorrhage and post-procedural hemorrhage.

As discussed above, available data in Study 901 show that the narrow SMQ "gastrointestinal hemorrhage" captured one adverse event of "rectal bleeding" in one subject in each study arm. The narrow SMQ "hemorrhage terms (excl laboratory terms)" captured 4 events in 10.5% of subjects in the VERU-111 arm compared to 1 event in 1 subject (5%) in the placebo arm, with encompassing the events of rectal bleeding noted above, in addition to 1 adverse event of petechiae and 2 adverse events of epistaxis in one additional subject in the VERU-111 arm.

3.2.2.7 Important Safety Issues With Consideration to Related Drugs

Colchicine

VERU-111 is a microtubule disruptor that binds to the colchicine-binding site. Colchicine is a microtubule disruptor used primarily for its anti-inflammatory properties. While colchicine-containing agents have been recognized and utilized in different formulations as an anti-inflammatory agent since antiquity, colchicine has been approved since 2009 for treatment of gout flares and familial Mediterranean fever. Colchicine has a recognized safety profile as documented in approved drug labeling. Warnings and Precautions for colchicine include the following:

- Risks of fatal overdoses reported in adults and children

- Blood dyscrasias including myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, and aplastic anemia
- Drug interaction with P-gp and/or CYP3A4 inhibitors with an additional warning that such interactions have resulted in life-threatening events and death
- Neuromuscular toxicity and myotoxicity including rhabdomyolysis may occur

Additional labeled adverse events for colchicine in gout flares or familial Mediterranean fever include diarrhea, pharyngolaryngeal pain, abdominal pain, nausea, and vomiting.

4 Considerations for Additional Trials

With respect to emergency use of an unapproved product, the statutory provisions [564(e)(1)(B)(iii)] state that FDA may require: *Appropriate conditions with respect to collection and analysis of information concerning the safety and effectiveness of the product with respect to the use of such product during the period when the authorization is in effect and a reasonable time following such period.* Per this statutory authority, FDA may require the conduct of additional trials within the same population and emergency use for which the product is authorized. As part of its discussion, DPACC requests that the AC consider whether additional trials are warranted to characterize the safety and efficacy of VERU-111 for the proposed indication and population in COVID-19. Such trials would allow for further characterization of the safety profile of VERU-111 as well as providing additional confidence in the all-cause mortality results seen from Study 902. When considering additional trials to provide efficacy and safety data in the COVID-19 population, the following should be considered:

- The ability of the trial to provide additional clinically interpretable safety data
- The ability of the trial to provide clinically interpretable efficacy data and how the new data would impact the available data
- Choice of primary endpoint (e.g., mortality at Day 60, alive and free of respiratory failure at Day 29)
- Placebo control, active control, or combinations of both
- Superiority versus non-inferiority
- Additional design elements and consideration of uncertainties raised by FDA in Study 902
- Elements of current standard of care for COVID-19, including recommended time courses, US and worldwide
- Blinding and methods to prevent unblinding events
- Time of enrollment and COVID-19 clinical course
- Standards or data recording for goals of care decision-making
- Stratification of randomization by site
- Representation of baseline severity class and comorbidities between arms
- Ethical aspects of the trial
- Equipoise between study interventions

FDA has considered the feasibility and utility of multiple trial designs in conjunction with the Sponsor in order to inform the Committee's discussion, and asks the Committee to provide its input on the following trial design specifically:

- A randomized, double-blind, fully matched placebo-controlled superiority design of VERU-111 + standard-of-care versus placebo+standard of care among subjects with WHO 5 and 6 severity, or WHO 4 severity with additional selected comorbidities.

In discussion with the Sponsor about the conduct of an additional trial as a condition to the EUA, an option proposed was to conduct another placebo-controlled superiority trial in the same patient population. This approach has major advantages of a clear demonstration of efficacy and enhancement of a safety database of VERU-111 when compared to placebo. Given the multiple uncertainties presented with the results of Study 902, the Agency considers there to be equipoise in conducting an additional trial. We ask the committee to discuss and provide comments on the proposed trial as a condition of authorization.

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6 Appendix

6.1 Studies of VERU-111 for the Treatment of Prostate Cancer

The Sponsor submitted additional study data from two studies in castration-resistant prostate cancer to support the safety of the proposed EUA (see Table 15). Limitations in these data to the proposed indication – including study design and study population – create uncertainty in their ability to inform the safety or efficacy of VERU-111 in patients with COVID-19. It is uncertain whether the safety data provided by these studies is relevant in the overall benefit-risk assessment of VERU-111 in COVID-19. In contrast to the hospitalized and/or critically ill subjects in the presented COVID-19 trials, subjects in studies V1011101 and V3011102 were exclusively men who were enrolled based on a diagnosis of metastatic prostate cancer resistant to multiple therapies who had an ambulatory and independent self-care performance status as measured by the ECOG scale. In addition, the lack of placebo control in either study does not allow for reliable attribution of rates of adverse events or imbalances in adverse events to VERU-111.

Table 15. Human Studies of VERU-111 for the Treatment of Prostate Cancer Indications

Study Identifier, Design, and Duration	Randomized Treatment	N (planned)	Characteristics of Enrolled Population	Primary and Key Secondary Efficacy Endpoints
V1011101 (Study 101) Nonrandomized, Open-label, multiple ascending dose study Study Ongoing	VERU-111 4.5 to 45 mg daily for up to four 7- to 21-day cycles PO VERU-111 4.5 to 45 mg daily for up to four 7- to 21-day cycles PO + SOC secondary androgen-blocking agent Up to four 21-day cycles	33 6	Adult male with histo- or cytologically proven metastatic castration-resistant small cell prostate cancer Prior treatment with ≥1 novel androgen receptor blocking therapy ECOG performance status ≤2 No clinically relevant anemia, creatinine elevation, hepatic dysfunction, neutropenia, thrombocytopenia	Primary Safety: Incidence of Grade 3 to 5 toxicities Efficacy: Radiographic Progression-free Survival Secondary PSA Progression-free Survival Progression-free Survival PSA_{50} Response Rate Objective Response Rate
V3011102 (VERACITY) Randomized, open-label, active control, duration Study Ongoing	VERU-111 32 mg daily PO VERU-111 26 mg daily PO Androgen receptor targeting agent (Abiraterone or enzalutamide) Until evidence of progression	82 82 82	Adult male with histo- or cytologically proven metastatic castration-resistant adenocarcinoma of the prostate (excluding small cell carcinoma) Prior treatment with ≥1 novel androgen receptor blocking therapy ECOG performance status ≤2 No clinically relevant anemia, creatinine elevation, hepatic dysfunction, neutropenia, thrombocytopenia	Primary Radiographic Progression-free Survival Secondary Overall Survival Objective Response Rate Duration of Objective Response Others

Source: Reviewer

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N, number of subjects; PO, orally; PSA, progression-free survival; SOC, System Organ Class, VERU-111, sabizabulin

6.2 Study V0211901 (Study 901) Protocol Review And Efficacy Review

6.2.1 Study V0211901 (Study 901) Protocol Review

Administrative Information

Study title: V0211901: Randomized, placebo-controlled, phase 2 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)

Study dates: 18 Jun 2020 to 09 Dec 2020

Study sites: 5 US sites

Study report date: 13 August 2021

Objectives

The primary objective was:

- To demonstrate the efficacy of VERU-111 in the treatment of SARS-CoV-2 infection by assessing its effect on the WHO Ordinal Scale for Clinical Improvement change from baseline to Day 15, Day 22, and Day 29

Secondary objectives included assessing the efficacy of VERU-111 on the following:

- The proportion of subjects with normalization of fever and oxygen saturation through Day 15, Day 22, and Day 29
- Days on mechanical ventilation
- Percentage of subjects discharged from hospital by Day 15 (and Day 22)
- All-cause mortality at Day 15, Day 22, and Day 29
- Proportion of patients alive and free of respiratory failure at Day 15, Day 22, and Day 29
- Proportion of patients alive and discharged from the ICU at Day 15, Day 22, and Day 29
- Proportion of patients with objective measures of improvement at Day 15, Day 22, and Day 29
- Days in ICU
- Days in hospital
- Proportion of subjects on mechanical ventilation at Day 15, Day 22, and Day 29
- Time to objective measure of improvement

Safety objective:

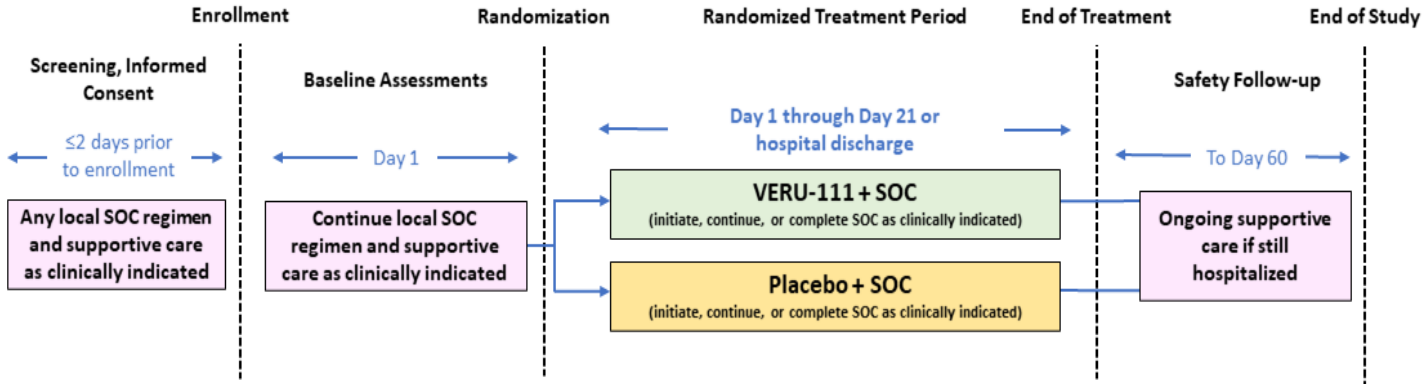
- To assess the safety and tolerability of VERU-111

6.2.2 Study Design

Trial V0211901 was a 1:1 randomized, double-blind, parallel-group, placebo-controlled trial that evaluated the efficacy and safety of VERU-111 18 mg oral capsules PO or via NG tube daily for up to 21 days compared to placebo on 60-day all-cause mortality and other critical care endpoints among 40 subjects with safety follow-up to Day 60.

A schematic of the trial is shown in Figure 11, below.

Figure 11. Study 901: Trial Schematic



Source: Reviewer
Abbreviations: SOC, standard of care; VERU-111, sabizabulin

Trial Duration and Clinical Visits

As shown in Figure 11, Study 901 comprised a screening period, baseline assessments, a randomized treatment period of up to 21 days or until hospital discharge (whichever came first), and safety follow-up up to Day 60, all with a background of ongoing standard of care interventions for COVID-19 and supportive care of COVID-19 or concomitant conditions as clinically indicated. There was an up to 3-day period between initial screening and baseline assessments on Day 1. Clinical efficacy endpoints were evaluated at Day 15, 22, and 29, and the primary endpoint of all-cause mortality was evaluated based on vital status at Day 60.

6.2.3 Dose and Duration

VERU-111 versus placebo were administered in the following dosages and durations during Study 901:

- VERU-111 18 mg daily PO or via NG tube for 21 days or until hospital discharge, whichever came first
- Placebo daily PO or via NG tube for 21 days or until hospital discharge, whichever came first

6.2.4 Concomitant Medications

Concomitant medications taken within 30 days prior to the Screening Visit were required to be recorded, in addition to recording of all medications during the course of the study.

The following medications were prohibited during the study

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

Standard of Care

There were no defined elements to the local standard of care background therapy required by the protocol. Section 5.1 of the protocol states that “All patients will receive standard of care for the treatment of SARS-CoV-2 infection (COVID-19)”.

Additional Supportive Care

The trial did not include a requirement for subjects to agree to a particular level of medical care surrounding specific components of ICU therapy related to severity of disease, respiratory failure, and goals of care.

6.2.5 Enrollment Criteria

Study 901’s enrollment criteria were intended to enroll adult subjects hospitalized with laboratory-confirmed COVID-19 and one of the following:

- Severe disease with evidence of respiratory failure
- Moderate disease and ≥1 additional comorbidities associated with poor clinical outcomes in COVID-19 (e.g., diabetes)

The protocol was designed to enroll 40 subjects (i.e., 20 in VERU-111 arm and 20 in placebo arm). The inclusion criteria provided for the inclusion of hospitalized adult subjects with laboratory confirmed SARS-CoV-2 infection with WHO ordinal scale 5 or 6 severity, or WHO ordinal scale 4 severity with ≥1 additional comorbidities. In addition to providing informed consent and agreement to comply with protocol requirements, enrolled subjects met the following criteria at Baseline (Day 1):

- Age ≥18 years
- Polymerase chain reaction results confirming SARS-CoV-2 infection
- Peripheral oxygen saturation of ≤94% on room air at screening
- Subjects must agree to follow doctor’s recommendation for oxygen supplementation
- Agreement to abide by protections regarding contraception for women of child-bearing potential and men with partners of child-bearing potential
- Disease severity commensurate with:

– WHO ordinal scale category 6 (intubation and mechanical ventilation)
– WHO ordinal scale category 5 (non-invasive ventilation or high-flow oxygen)
– WHO ordinal scale category 4 (oxygen by mask or nasal prongs) plus at least one of the following comorbidities:

  - Asthma (moderate to severe)
  - Chronic lung disease
  - Diabetes
  - Hypertension
  - Severe obesity (BMI ≥40 kg/m2)
  - 65 years of age or older
  - Primarily reside in a nursing home or long-term care facility
  - Immunocompromised

The exclusion criteria include:

- Severity equal to or greater than WHO ordinal scale 7 (e.g., requiring ventilation plus additional organ support such as pressor support of blood pressure, RRT, ECMO)
- Hepatic impairment including

– ALT or AST > 3 times ULN
– Total bilirubin > ULN
– Documented history of liver disease including hepatitis or any etiology, cirrhosis, portal hypertension, or confirmed or suspected esophageal varices

- Moderate or severe renal impairment, including

– Creatinine clearance < 60 ml/min

- Any comorbid disease or condition that may interfere with the absorption, distribution, metabolism, or excretion of study drug, or would place the subject at increased risk, in the opinion of the investigator
- Known allergy or hypersensitivity to colchicine
- Participation in any other clinical trial of an experimental treatment for COVID-19
- Concurrent treatment with other experimental agents with actual or possible direct-acting antiviral activity against COVID-19 <24 hours prior to study drug dosing other than standard of care therapies
- Participants were excluded if they did not agree to refrain from prolonged sun exposure or did not agree to use sun-protective measures during the study and treatment with VERU-111

6.2.6 Ethics

The ethical statements for Study 901 included in the protocol are substantively similar to those included for Study 902. See Section Ethics, above, for additional details. These statements include study conduct in accordance with 21 CFR parts 50, 54, 46, 312, and 314, based on the principles of the Declaration of Helsinki, and a statement regarding Good Clinical Practice during study conduct. Local IEC or IRB approval was required for protocols, amendments, informed consent forms, and other study materials.

6.2.7 Endpoints

The Sponsor designated mean change from baseline in the WHO Ordinal Scale for Clinical Improvement as the primary endpoint of Study 021. Mean change in an appropriate ordinal scale for clinical improvement assessed at a clinically relevant timepoint is considered a clinically relevant endpoint in COVID-19 trials. The Sponsor defined the primary endpoint as:

- Mean change from baseline in the WHO Ordinal Scale for Clinical Improvement at Day 15

The Sponsor designated the following secondary endpoints, each assessed at Day 15, 22, and 29:

- Proportion of subjects that progress to Grade 5, 6, 7, or 8 on the WHO Ordinal Scale for Clinical Improvement
- Change in mean WHO Ordinal Scale for Clinical Improvement
- Proportion of subjects with normalization of fever and oxygen saturation

– This composite endpoint comprised fever normalization maintained for at least 24 hours AND peripheral capillary oxygen saturation (SpO2) >94% sustained for 24 hours.

- Days on mechanical ventilation
- All-cause mortality
- Proportion of patients alive and free of respiratory failure
- Proportion of patients alive and discharged from the ICU
- Proportion of patients alive and discharged from hospital
- Proportion of patients with objective measures of improvement
- Proportion of subjects on mechanical ventilation

In addition, the Sponsor designated additional secondary endpoints of

- Days in ICU
- Days in hospital
- Time to objective measure of improvement

6.2.8 Safety Assessments

The protocol designated a safety objective of assessing the safety, tolerability, and risk/benefit of VERU-111.

Safety assessments in the study included assessments of AEs, SAEs, medical history, clinical laboratory values, vital signs, physical exams, electrocardiogram (ECG), pregnancy testing, and assessment of concomitant medications (see Table 16). While vital signs, concomitant medications, and AEs were assessed daily through Day 22, clinical laboratories and oxygen saturations were assessed only on Days 1, 3, 9, 15, 22, and 29.

Table 16. Study 901: Schedule of Safety Assessments

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	
Vital signs	X	X	X		X	
Pregnancy test (female subjects only)	X					
12-lead ECG (single)	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	
Temperature/SpO_2	X	X	X[e]		X	
Dosing[b,c]		X	X			
Assessment of primary and secondary efficacy endpoints				X[f]	X	
Assessment of conmeds	X	X	X		X	
Assessment of AEs		X	X		X	X

a Screening evaluations to be conducted within 2 days prior to Day 1.
b Subjects will be treated for 21 days OR until discharged from hospital
c Subjects can be discontinued if they are not responding to therapy
d Early termination assessments the same as Day 22 assessments
e Temperature and SpO_2 will be taken every 4 hours on these days
f Day 15 only

Source: Sponsor, protocol V0211901

Laboratory assessments included hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, platelet count, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphorus, total protein, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase, cardiac troponin, d-dimer, C-reactive protein, and ferritin, among others

6.2.9 Study 901 Results in Detail

Key efficacy analyses for Study 901 are presented in Table 17, below.

Table 17. Key Efficacy Analyses – ITT Set, Trial V0211901

	VERU-111 18 mg N=19	Placebo N=20
Alive and free of respiratory failure at Day 29, n (%)	17 (89.5)	14 (70.0)
Odds Ratio (95% CI)[1]	2.58 (0.37, 18.07)	-
Alive at Day 29, n (%)	1 (5.3)	4 (20.0)
Odds Ratio (95% CI)[1]	1.96 (0.22, 17.19)	-
Days in Intensive Care Unit through Day 29		
Value at Day 29, adj.[2] mean (SE)	3.25 (2.65)	9.31 (2.96)
Difference from Placebo, adj.[2] mean (CI)	-6.07 (-12.7, 0.62)	-
Days on Mechanical Ventilation through Day 29		
Value at Day 29, adj.[2] mean (SE)	1.76 (2.28)	3.45 (2.54)
Difference from Placebo, adj.[2] mean (CI)	-1.69 (-7.42, 4.04)	-
Days in Hospital through Day 29		
Value at Day 29, adj.[2] mean (SE)	8.5 (2.29)	11.69 (2.56)
Difference from Placebo, adj.[2] mean (CI)	-3.18 (-8.94, 2.59)	-
Change from Baseline in WHO Ordinal Scale through Day 29		
Value at Day 29, adj.[3] mean (SE)	-1.87 (0.56)	-1.29 (0.61)
Difference from Placebo, adj.[3] mean (CI)	-0.59 (-2.05, 0.87)	-

Source: Reviewer generated analysis based on applicant submitted data aden.xpt for EUA000113 (V0211901).

[1] Odds ratio, 95% CI are calculated using logistic regression model with covariates for treatment group, study site, baseline WHO category, remdesivir use and dexamethasone use at baseline

[2] Adjusted mean and mean differences are from an analysis of covariance model adjusting for treatment, study site, baseline WHO category, remdesivir use and dexamethasone use at baseline, with within-arm means estimated at mean values of the covariates.

[3] Adjusted mean and mean differences are from a mixed model repeated measures analysis adjusting for treatment, study site, baseline WHO category, remdesivir use and dexamethasone use at baseline, with within-arm means estimated at mean values of the covariates.

Abbreviations: CI, confidence interval; ITT, Intention-to-treat population; LR, logistic regression

6.3 Appendix 6.3 Study V3011902: Primary Endpoint Efficacy Issues in Detail: End of Life Decision Making and Mortality Outcomes in the Literature

As noted above, Study 902's lack of formal data collection on goals of care and end-of-life decision-making is not unusual based on review of the literature. However, literature also suggests that variability in goals of care decision-making could contribute to uncertainty in the clinical interpretation of mortality and related endpoints in clinical trials of critical care.

End-of-Life Decision-Making and Mortality Events

While data on end-of-life decision-making is not often collected, prospective data from 1,698 subjects by Azoulay et al. (2003) suggests that goals of care decisions and decisions to forgo or withdraw life-sustaining therapies may not simply codify poor prognosis and reflect an otherwise-expected death event, but may be an independent predictor of death in hospital even after controlling for comorbidities, severity at ICU admission, and severity within the first week. Additional evidence from Lautrette et al. (2015) examined observational data from 10,080 subjects and reinforced the contention that withholding or withdrawal of life-sustaining therapies were independently associated with mortality. Finally, Quill et al. (2014) made the observation that an ICU's risk-adjusted propensity to withdraw life support is directly associated with its standardized mortality ratio.

Further highlighting the importance of goals-of-care decision-making for trial endpoints in trials of acute and critical illness such as COVID-19, available evidence suggests that the majority of subjects who die in trials of ICU-related conditions die after decisions to forgo life-sustaining therapy. The ETHICUS trial

(Sprung et al. 2003) summarized by Anthon et al. (2018), suggests that decisions to withhold or withdraw life-sustaining therapies and similar goals of care decision-making precedes approximately 75% of deaths in European ICUs, highlighting the impact of these decisions on mortality in critical care trials. Similarly, Mehter et al. (2014) presented evidence from a randomized ARDS trial that showed that 79% of subjects who died during the trial had a "do not resuscitate" order.

High Variability in End-of-Life Decision-Making Practices

While end-of-life decision making may independently influence a majority of deaths in clinical trials, evidence suggests that end-of-life decision-making practices are variable. Multiple studies suggest that certain patient factors – both disease-related and demographic-related – influence goals of care decision-making. These factors include age, race, sex, severity of illness, preadmission function status, and comorbidities (Hakim et al. 1996; Quill et al. 2014; Kim et al. 2016; McPherson et al. 2019; Barnato et al. 2022) However, other studies – including some of the same studies – suggest that goal-of-care decision-making is also affected by non-patient factors including treating physician, local ICU practices, and hospital (Azoulay et al. 2009; Hart et al. 2015; Chen et al. 2019), and that there is wide variability in physician and ICU-related practice regarding goals-of-care (Hakim et al. 1996) that may be influenced by factors including personality factors and religious belief (Ntantana et al. 2017). The variability in goals-of-care decision-making due to non-patient-related factors is perhaps best exemplified in a statement of results by Mark et al. (2015), from a systematic review including 56 studies that recorded data on withholding and withdrawal of life-sustaining therapy, which states "substantial variability was found between world regions, countries, individual ICUs within a country, and individual intensivists within one ICU". This review reported that the mean prevalence of withdrawal of life-sustaining therapy for patients who died varied from 0% to 84.1% between studies, that the mean prevalence of withholding life-sustaining therapy varied between 5.3% and 67.3% between studies, and that similar results were seen in sensitivity analyses of ICU patients.

While evidence suggests that physician- and hospital-related factors may influence goals-of-care decision-making, more recent evidence from the COVID-19 pandemic era suggest that such decisions may have occurred more frequently during the pandemic (Briedé et al. 2021; Moin et al. 2022) and been influenced by additional pandemic-related factors. Recent data also suggest that these pandemic-era goals of care decisions may have differed from pre-pandemic decision-making with a trend towards less aggressive care choices . Moin, et al, present evidence that reinforces these idea using data from three ICUs in Massachusetts (Moin et al. 2022). The authors state that 421 (91.7%) of 459 subjects admitted to the ICU with COVID-19 were "full code" at hospital admission, but that 140 (95.2%) of the 147 patients who died during the hospitalization died with do-not-resuscitate code status, and 86.4% of those patients died within two days of their final code status change. Kramer et al. (2020) suggest that the COVID-19 pandemic may have been responsible for heightened significance and more importance attached to goals of care conversations due to resource limitations and possible staff exposure to COVID-19.