# Declination of Emergency Use Authorization for Sabizabulin 9 mg Capsules

## Center for Drug Evaluation and Research Review

**Table 1. Identifying Information**

| | |
|---|---|
| Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request. | EUA |
| EUA Application Number(s)[1] | 000113 |
| Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address | Veru, Inc.<br>2916 North Miami Ave<br>Suite 1000<br>Miami, FL 33127<br>Phone: 1-305-509-6897<br><br>POC: Gary Barnette, PhD<br>Chief Scientific Officer, Veru, Inc.<br>2916 North Miami Ave, Suite 1000<br>Miami, FL 33127<br>Mobile: (b) (6)<br>Email: (b) (6) |
| Submission Date(s) | June 6, 2022 (initial), October 11, 2022 (final datasets and clinical study report) |
| Receipt Date(s) | June 6, 2022 (initial), October 11, 2022 (final datasets and clinical study report) |
| OND Division / Office | Division of Pulmonology, Allergy, and Critical Care/Office of Immunology and Inflammation/Office of New Drugs |
| Integrated Review Completion Date | January 31, 2023 |
| Proprietary Name | N/A |
| Established Name/Other names used during development | Sabizabulin (VERU-111) |
| Dosage Forms/Strengths | Oral capsule, 9 mg |
| Therapeutic Class | Oral tubulin inhibitor |
| Intended Use or Need for EUA | Treatment of patients hospitalized with moderate-to-severe coronavirus disease 2019 (COVID-19) |

[1] If a pre-EUA is in existence at the time of the EUA request submission and has been assigned an EUA number, the EUA request should use the same EUA number and electronic archive file.

| | |
|---|---|
| Intended Population(s) | For treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 infection:<br>• with positive results of direct SARS-CoV-2 viral testing, and<br>• who are hospitalized, and<br>• who are at high risk for developing ARDS, and<br>for whom alternative COVID-19 treatment options authorized by FDA are not accessible or are not clinically appropriate. |
| Product in the Strategic National Stockpile (SNS) | No |
| Distributor, if other than Sponsor | N/A |
| Recommendation for Regulatory Action | Decline to Authorize |

Abbreviations: EUA, Emergency Use Authorization; MHT, Maternal Health Team; MO, medical officer; MOV, molnupiravir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ARDS: acute respiratory distress syndrome

# Table of Contents

## Table of Tables

## Table of Figures

# 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 |
| VERU-111 | sabizabulin |
| WHO | World Health Organization |

# 1 Emergency Use Authorization Determination/Declaration

On February 4, 2020, the U.S. Secretary of Health and Human Services (HHS) determined pursuant to section 564 of the federal Food, Drug, and Cosmetic Act that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China, in 2019 (2019-nCoV). The virus is now named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the illness coronavirus disease 2019 (COVID-19).

On the basis of this determination, the U.S. Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the Food, Drug, and Cosmetic Act, subject to the terms of any authorization issued under that section.

# 2 Recommendations

## 2.1 Declination of Emergency Use Authorization

The Division of Pulmonology, Allergy, and Critical Care, Office of Immunology and Inflammation, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA or the Agency) recommends declination of an Emergency Use Authorization (EUA).

The review team recommends that the Agency decline to authorize sabizabulin (VERU-111) for the proposed use, namely for the 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 Basis for Determination to Decline to Issue Emergency Use Authorization for the Product

- COVID-19 is a serious or life-threatening disease or condition caused by the chemical, biological, radiological, or nuclear (CBRN) agent specified in the declaration of emergency.
- Based on the totality of the scientific evidence available to FDA, it is not reasonable to believe that this product may be effective in (1) diagnosing, preventing, or treating the serious or life-threatening disease or condition, or (2) diagnosing, treating, or preventing a disease or condition caused by an EUA product or an FDA-approved product used to

diagnose, treat, or prevent the specified disease or condition caused by the CBRN agent (see Sections 7.2.2, 7.3, 15, and 16).

- Based on the totality of the scientific evidence available to FDA, it is not reasonable to believe that the known and potential benefits outweigh the known and potential risks of the product when used to diagnose, treat, or prevent the serious or life-threatening disease or condition (see Sections 7.2.2, 7.3, 8, 15, and 16).

# 3 Proposed Use and Dosing of the Product Under the EUA

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.

The proposed dosing is VERU-111 capsules 9 mg by mouth daily for 21 days or until hospital discharge

# 4 Background Information on the Disease/Condition and Available Therapeutic Alternatives

## 4.1 Background Information on the Condition

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.

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 2022a).

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 2023). 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.

## 4.2 Therapeutic Alternatives for the Disease

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 2022b; 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 2022a; 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.

**Immunomodulators 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[2] 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 (Marconi et al. 2021). 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.

Similarly, tocilizumab is approved for the treatment of chimeric antigen receptor T-cell cytokine release syndrome, adult rheumatologic indications including rheumatoid arthritis, giant cell arteritis, and systemic sclerosis-associated interstitial lung disease, in addition to its recent approval for the treatment of hospitalized adult patients with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. Tocilizumab received an initial EUA in November 2020 and subsequent approval in December of 2022 on the basis of trial data from the RECOVERY and EMPACTA trials (RECOVERY Collaborative Group 2021b; Salama et al. 2021), among others, that included over 3,016 subjects exposed to tocilizumab. Tocilizumab's overall safety profile includes warnings and precautions regarding serious infections, gastrointestinal perforations, hepatotoxicity, laboratory abnormalities including cytopenias, immunosuppression, hypersensitivity reactions including anaphylaxis, demyelinating disorders, and precautions regarding the use of tocilizumab in patients with active hepatic disease or impairment and the avoidance of live virus vaccinations in patients receiving tocilizumab. Adverse events listed in COVID-19-specific drug labeling for tocilizumab include hepatic transaminases increased, constipation, urinary tract infections, hypertension, hypokalemia, anxiety, diarrhea, insomnia, nausea, as well as laboratory abnormalities of neutropenia and thrombocytopenia.

As of the time of this review, the recent EUA of anakinra for COVID-19 has provided an additional option for immunomodulator therapy for hospitalized patients with COVID-19 who require supplemental oxygen therapy.

**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[3] (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

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

[3] See VEKLURY (remdesivir) at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214787s014lbl.pdf

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 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

# 5 Related Regulatory Submission(s)

VERU-111 9 mg capsules for oral administration are being studied under investigational new drug (IND) 149282 (Table 2) for the treatment of COVID-19. Additional submissions regarding the development of VERU-111 occurred under IND 140406 for the treatment of metastatic, castration-resistant, prostate cancer, under IND 158142 for the treatment of ER+/HER2- metastatic breast cancer, and under IND156530 for the treatment of metastatic triple negative breast cancer. VERU, Inc., is the Sponsor for all four INDs.

## 5.1 Related Master Files

No drug master files were referenced for EUA000113, IND 149282, IND 140406, or IND 158142.

# 6 Summary of Clinical Data

**Table 2. 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<br>(Study 901)<br><br>1:1 R, DB, PC, MC, PG, 60-day duration<br><br>JUNE 2020 – DECEMBER 2020 | VERU-111 18 mg daily via PO/NG + SOC<br><br>Pbo PO/NG daily + SOC<br><br>Up to 21 days or hospital discharge | 20<br><br>19 | Hospitalized adult<br><br>PCR-confirmed SARS-CoV-2 infection<br><br>WHO Category 5 or 6, or WHO Category 4 plus ≥1 comorbidity of the following:<br><br>Hypertension, diabetes, BMI ≥40 kg/m$^2$, ≥65 years of age, immunocompromised, resides in a long-term care facility, asthma or chronic lung disease<br><br>No hepatic or renal impairment | <u>Primary</u><br>• Alive and free of respiratory failure at Day 29<br><br><u>Secondary</u><br>• All-cause mortality at Day 29<br>• Days in ICU<br>• Change in mean WHO Ordinal Scale for Improvement at Day 29<br>• Days on Mechanical Ventilation<br>• Days in Hospital<br>• Effect on CRP<br>• Pharmacokinetic Endpoints |
| V3011902<br>(Study 902)<br><br>2:1 R, DB, PC, MC, PG, 60-day duration<br><br>MAY 2021 - JUNE 2022 | VERU-111 9 mg daily via PO/NG + SOC<br><br>Pbo PO/NG daily + SOC<br><br>up to 21 days or hospital discharge | 134<br><br>70 | Hospitalized adult<br><br>PCR-confirmed SARS-CoV-2 infection<br><br>WHO Category 5 or 6, or WHO Category 4 plus ≥1 comorbidity of the following:<br><br>Hypertension, diabetes, BMI ≥40 kg/m$^2$, ≥65 years of age, immunocompromised, resides in a long-term care facility, asthma or chronic lung disease<br><br>No hepatic or renal impairment | <u>Primary</u><br>• All-cause mortality at Day 60<br><br><u>Secondary</u><br>• Alive and free of respiratory failure at Day 29<br>• Days in ICU<br>• Change in mean WHO Ordinal Scale for Improvement at Day 29<br>• Days on Mechanical Ventilation<br>• Days in Hospital<br>• 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/m$^2$: kilograms per meter-squared; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DB, double blind; MC, multicenter; N, number of subjects in clinical 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

# 7 Human Clinical Efficacy: Assessment of Potential Benefit

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 of 134 subjects randomized to VERU-111 and 70 subjects 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 in COVID-19. However, Study 901 is limited in its ability to provide robust support of efficacy and safety conclusions based on its small sample size and lack of statistical power to detect differences on meaningful endpoints. See Table 2 for summaries of Studies 901 and 902.

The focus of this EUA review is 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.

## 7.1 Trial Design and Review, V3011902 (Study 902)

### 7.1.1 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

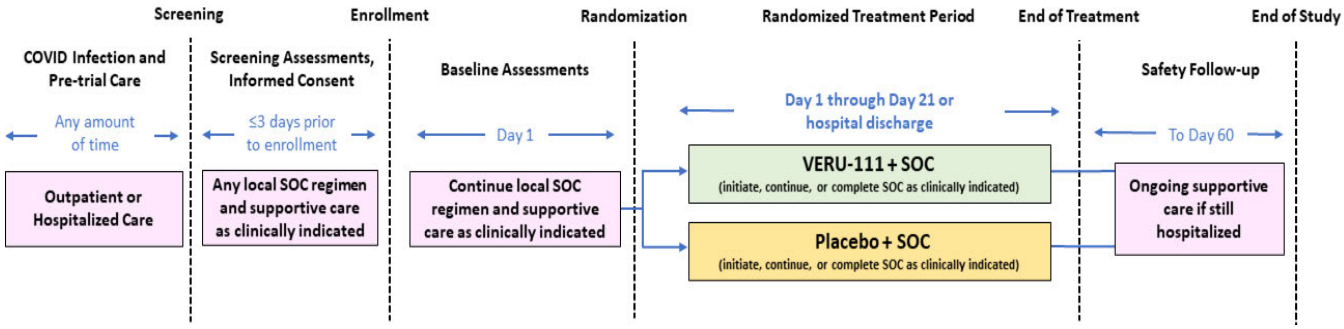
**Study report date**: Abbreviated clinical study report v1.0, 31 May 2022

### 7.1.2 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 evaluate 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 Section 7.1.11 for details regarding sample size changes and interim analysis results that led to a final study sample of 204 subjects).

A schematic of the trial is shown in Figure 1 below.

**Figure 1. Trial Schematic, Study 902**




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

As shown in Figure 1, 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 local 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.

### 7.1.3 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 7.3.1.2.

### 7.1.4 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)". The protocol excludes 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.

### 7.1.5 Protocol Amendments

The protocol was amended seven times. Relevant aspects of the protocol amendments 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.

### 7.1.6 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 (as designated below). 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 or appropriate documentation of previous oxygen saturation ≤94% during the encounter
- 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

### 7.1.7 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.

### 7.1.8 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 Section 7.3.1.2).

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).

### 7.1.9 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

### 7.1.10 Endpoints

**Primary Endpoint**

All-cause mortality was 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). The

Sponsor defined the primary endpoint as the proportion of subjects that died (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 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 3.

**Table 3. 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

### 7.1.11 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. The Agency requested additional information to ensure that the proposed modifications were not influenced by knowledge of comparative results, cautioning that if study modifications may have been influenced by comparative interim results, appropriate statistical methods to control the type I error and produce reliable estimates may not be known, may be challenging to implement, or may greatly reduce the efficiency of the trial. At the Agency's request, the Sponsor clarified that this decision was not based on viewing comparative analysis results and that the planned interim analysis had not yet occurred.

To support the sample size reduction to 210 subjects (140 subjects in the VERU-111 treated group and 70 subjects in the placebo treated group), the Sponsor cited calculations based on assumptions from the Phase 2 study. Assuming a rate of mortality of 5% in the VERU-111 treated group and 25% in the placebo-treated group, with significance level $\alpha=0.05$, 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. The Agency continued to caution against this change, noting that there was considerable uncertainty in the Phase 2 study results relied upon for these calculations. The Agency also raised concerns regarding whether the resulting limited safety database would be sufficient to characterize the known and potential risks associated with VERU-111. However, the Sponsor moved forward with this reduction.

**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 analyzing 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 to missing data. 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 at the interim analysis, 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.

As discussed above, 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.

### 7.1.12 Safety Assessments

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 4 below.

**Table 4. Schedule of Safety Assessments, Study 902**

| 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.

### 7.1.13 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.

# 7.2 Efficacy Data for Consideration of Clinical Benefit, Study 901 and Study 902

## 7.2.1 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 (CI): 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.

## 7.2.2 Study 902 Results

### 7.2.2.1 Disposition

Relevant disposition data for the ITT are presented in Table 5. 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 5. Subject Disposition, ITT Population, Study 902**

| Subject Disposition | VERU-111 9 mg N=134 | Placebo N=70 | Total N=204 |
|---|---|---|---|
| Safety population – received a least one dose of study drug | | | |
| Number of subjects (%) | 130 (97.0) | 69 (98.6) | 199 (97.5) |
| mITT population – completed efficacy portion and do not have major protocol violations | | | |
| Number of subjects (%) | 129 (96.3) | 69 (98.6) | 198 (97.1) |
| Discontinued study medication prior to Day 21 | | | |
| 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 | | | |
| 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

#### 7.2.2.2 Demographics

The baseline demographics for Study 902 are presented in Table 6 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 6. Subject Demographics, ITT Population, Study 902**

| Demographics | 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 ($kg/m^2$) | | | |
| 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; $kg/m^2$, 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

#### 7.2.2.3 Baseline Disease Characteristics

The baseline disease characteristics of the ITT population of Study 902 are detailed in Table 7. There are small numerical imbalances between treatment groups seen in some important baseline disease characteristics including WHO severity 6, 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 lower in the placebo group as well. Conversely, asthma, COPD, and cancer occurred in a higher proportion of VERU-111 treated patients. In addition to the WHO ordinal scale scores listed below, there was also an observed imbalance in baseline COVID-19 severity in the proportion of subjects in the ICU at baseline (38.1% of subjects in the VERU-111 arm versus 44.3% of subjects in the placebo arm).

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 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 (Centers for Disease Control and Prevention 2022).

While the differences for each individual baseline characteristic are small and statistical analyses with hypothesis testing address the concept of how likely the results could have occurred by chance alone if there were no effect of treatment, when considered together with the small sample size, these baseline imbalances should be examined in the evaluation of the efficacy results.

**Table 7. Baseline Disease Characteristics, ITT Population, Study 902**

| 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

* 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 8, 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 7.3.1.4.

**Table 8. Clinical Care Prior to Randomization, ITT Population, Study 902**

| Clinical Care | 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; VERU-111, sabizabulin

#### 7.2.2.4 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 9 and a Kaplan-Meier plot of the time-to-death endpoint is presented in Figure 2. 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 2 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.

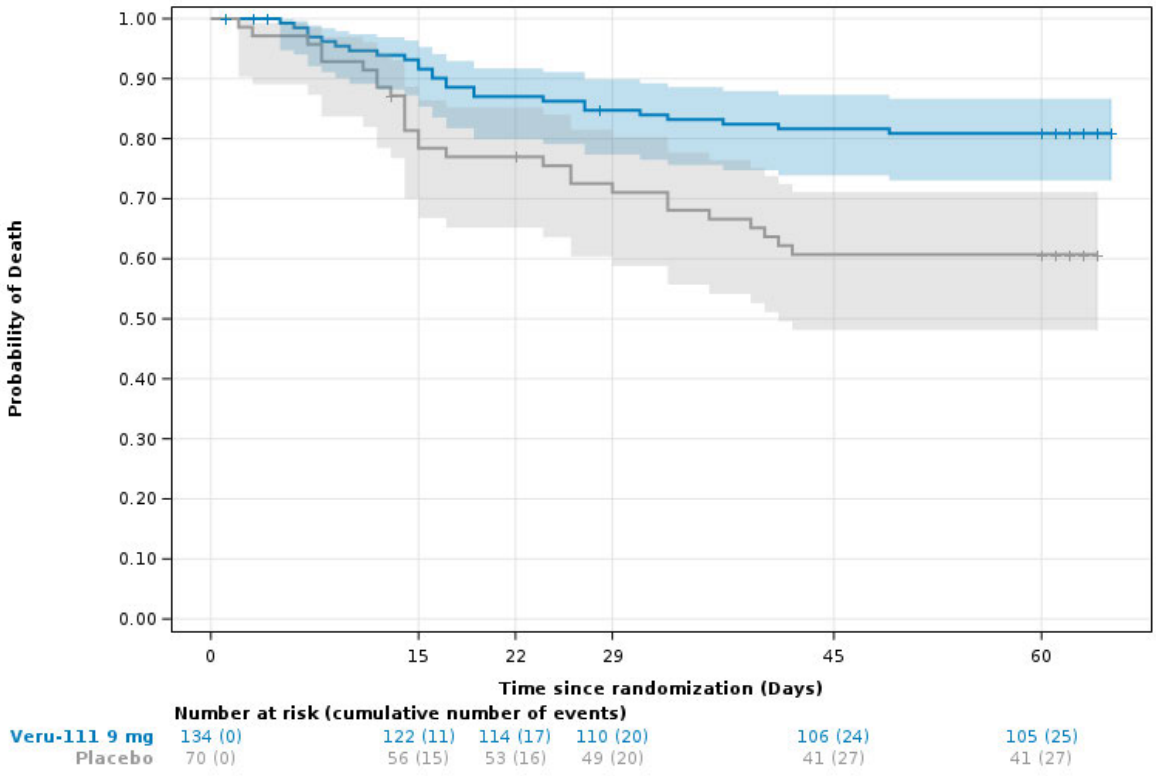
As discussed above, the Sponsor reduced the final planned sample size from 300 to 210 subjects prior to the interim analysis and after 198 subjects had been enrolled. The statistical boundary for efficacy would not have been crossed at the interim analysis with 150 patients had the final sample size 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 9. Primary Efficacy Analysis, Proportion of Subjects Alive / Dead at Day 60, ITT Population, Study 902**

| Analysis | 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 $\alpha$ 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 2. Kaplan-Meier Plot: Time to Death, ITT Population, Study 902**




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

### 7.2.2.5 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 extreme missing data assumptions, with the treatment comparison in the most extreme unfavorable case for VERU-111 (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 for VERU-111 (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 7 and Table 8, 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 defined post hoc 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 10. 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)), days of SoC therapies prior to randomization (odds ratio: 2.65, 95% CI: (1.32, 5.33)) and ICU status at baseline (odds ratio: 2.65, 95% CI: (1.30, 5.39)). Adjusting for these imbalances did not seem to affect the estimates of the risk difference summary measure.

These sensitivity analyses were simplistic and post hoc 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 cannot 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 would be needed to confirm the lack of influence of baseline imbalances on study findings.

**Table 10. Sensitivity Analyses: Proportion of Subjects Alive at Day 60 Adjusting for Baseline Imbalances, ITT Population, Study 902**

| 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) |
| Primary analysis model + ICU at Baseline | 2.65 (1.30, 5.39) | 17.6 (4.6, 30.5) |

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

### 7.2.2.6 Subgroup Analyses of the Primary Endpoint

Efficacy results for various clinical or demographic subgroups of interest in Study 902 are presented in Table 11. 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. Results for the >5 and >10 days hospitalized and of standard of care therapy subgroups are not presented here due to the lack of precision owing to very small sample sizes.

**Table 11. Subgroup Analyses: Proportion of Subjects Alive at Day 60 by Subgroups, ITT Population, Study 902**

| 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 SoC – 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 SoC – 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 assuming non-informative censoring for patients that withdrew from study early

[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

### 7.2.2.7 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 (February 2021) referenced above 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 review 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.

#### 7.2.2.7.1 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 12. 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 12. Secondary Efficacy Analysis: Proportion of Subjects Alive at Day 29 and Alive and Free of Respiratory Failure at Day 29, ITT Population, Study 902**

| Subject Analysis | 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) |

| Subject Analysis | VERU-111 9 mg N=134 | Placebo N=70 |
|---|---|---|
| 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

#### 7.2.2.7.2 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 13 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 7.3.1.4). 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 13. Secondary Efficacy Analyses: Days in Hospital, Days in Intensive Care Unit and Days on Mechanical Ventilation Through Day 60, ITT Population, Study 902**

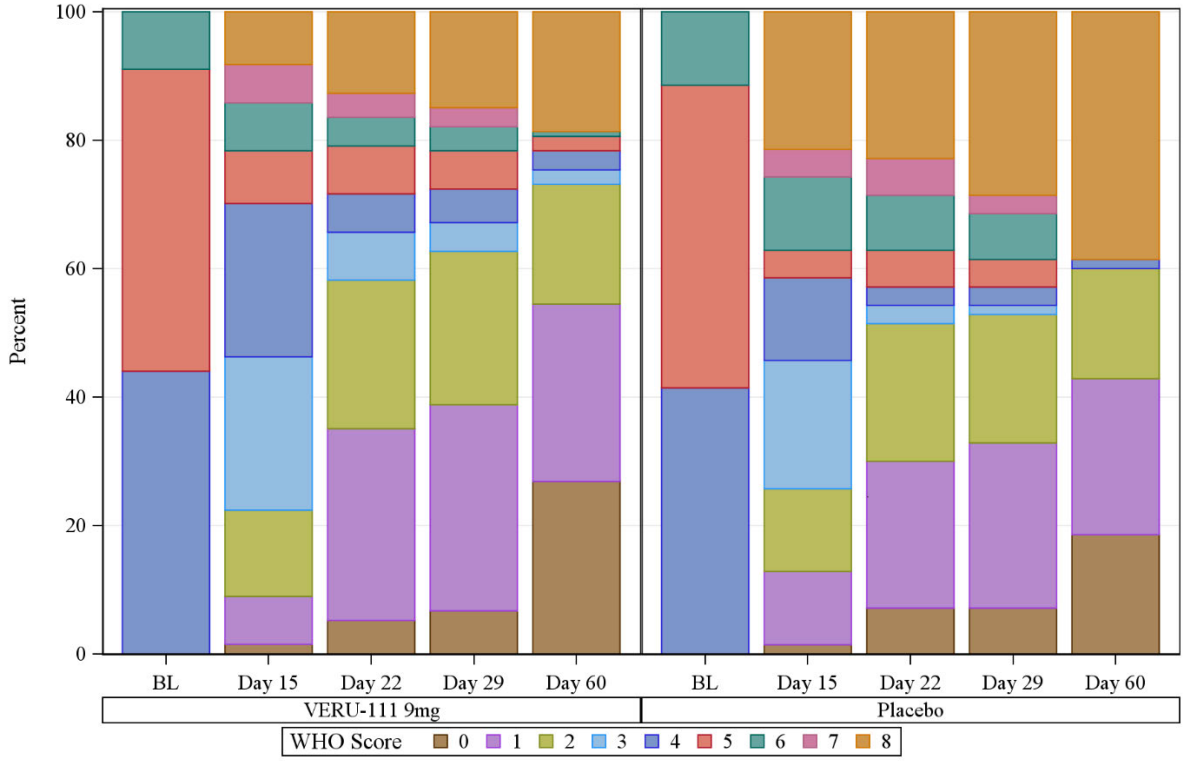
| Analyses | VERU-111 9 mg N=134 | Placebo N=70 |
|---|---|---|
| Days in hospital through Day 60 | | |
| Value at Day 60, adj.[1] mean (SE) | 25.6 (2.8) | 31.8 (3.3) |
| Difference from Placebo, adj.[1] mean (CI) | -6.3 (-12.4, -0.1) | - |
| Days in intensive care unit through Day 60 | | |
| Value at 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

#### 7.2.2.7.3 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. This pre-specified analysis used a logistic regression analysis model to compare the proportion of subjects who improved to a WHO Ordinal Scale score 0 or 1 (responders) at Day 60 in each treatment group. The model including treatment group, sex, WHO Ordinal Scale score at baseline, dexamethasone and remdesivir use as covariates, 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 3).

**Figure 3. 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

## 7.3 Key Review Issues Relevant to Evaluation of Potential Benefit on the Primary Endpoint

### 7.3.1 Overall Key Review Issue Relevant to the Evaluation of Benefit

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). In addition, 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. In the opinion of the review team, 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 proposed population.

#### 7.3.1.1 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.

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 and cross-study comparisons, 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 had a similar Day 29 mortality rate in the placebo group (Gordon et al. 2021; RECOVERY Collaborative Group 2021b), 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 occurred after Day 29.

Additionally, we acknowledge that this was a concurrently randomized, controlled trial. Use of a concurrent control arm continues to be strongly recommended precisely because the background mortality rate can vary substantially for many known and unknown reasons. Furthermore, statistical analyses with hypothesis testing address the concept of how likely the results could have occurred by chance alone if there were no effect of treatment. However, with only a single trial, the small overall sample size in Study 902 with an unexpectedly high placebo mortality rate raises the concern about the evidence for a treatment effect.

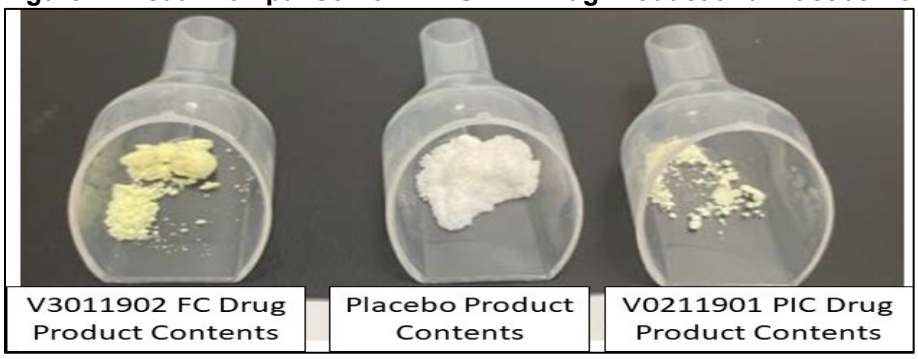
#### 7.3.1.2 Potential Unblinding Events With Enteral Tube Administration

**Differences in Appearance and Physical Characteristics of Drug Product**

Both Study 901 and Study 902 were designed as randomized, double-blind trials, using a matching placebo for the control arm. 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 4, and a side-by-side picture of the powder/water mixtures for administration are provided in Figure 5. 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.

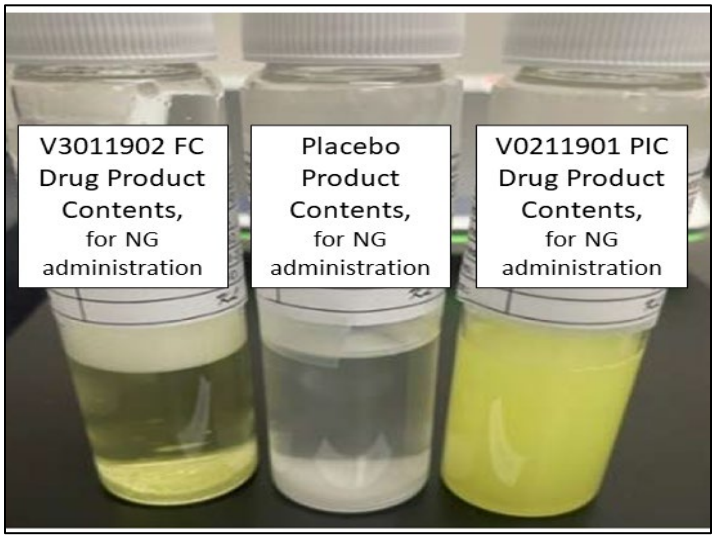
**Figure 4. Visual Comparison of VERU-111 Drug Product and Placebo Powder**




| 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 5. 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 Study 901: “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. 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). 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 (Yarnell 2021). In the opinion of the review team, it is impossible to eliminate the possibility that bias arising from potential unblinding events may have influenced the mortality results of Study 902.

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 not 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 (Anthon et al. 2018; Landoni et al. 2015; Martin et al. 2021). 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) by healthcare providers (Newman 2016) 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.

**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 or supplementary 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 additional analyses to further inform these uncertainties.

#### 7.3.1.3 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. A majority of subjects did not receive remdesivir at international sites or immunomodulators at either international or US sites. While patients did receive corticosteroids, treatment duration was considerably longer than US SOC practices. 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 SOC might have affected the efficacy results.

**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 7, 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. While it is not possible to completely and correctly account for all possible imbalances, the prespecified primary analysis included an adjustment for baseline dexamethasone and remdesivir use as covariates in a logistic regression model and was statistically significant, as noted above.

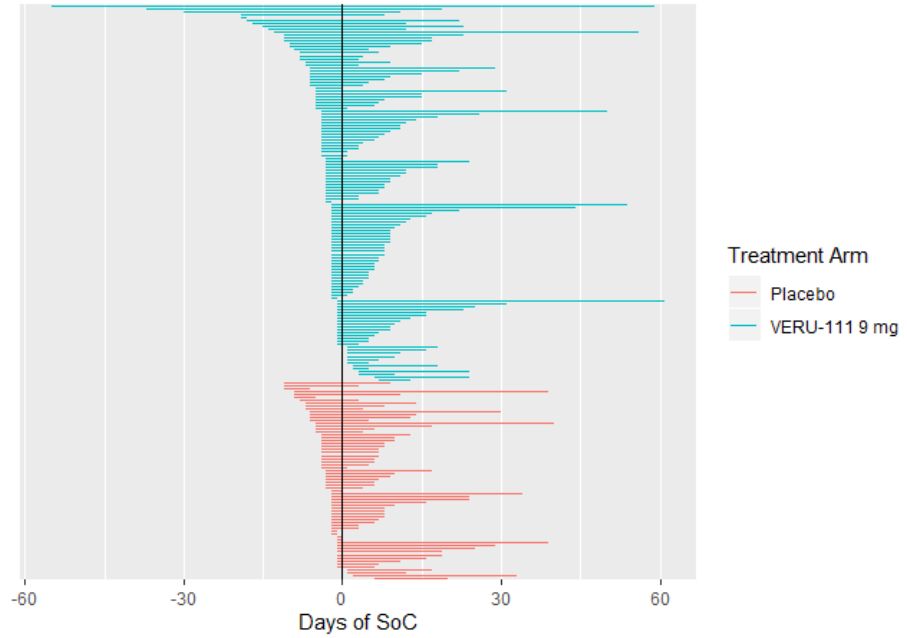
**Timing and Duration of Standard of Care Therapies**

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 6. 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, the top 7% of subjects in each treatment arm with the most extreme (i.e., earliest) values for pre-randomization SoC therapies are depicted in Figure 7.

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 7.2.2.5 and 7.2.2.6. As noted above, although these analyses were simplistic explorations using available data and cannot entirely eliminate the potential impact of random 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.

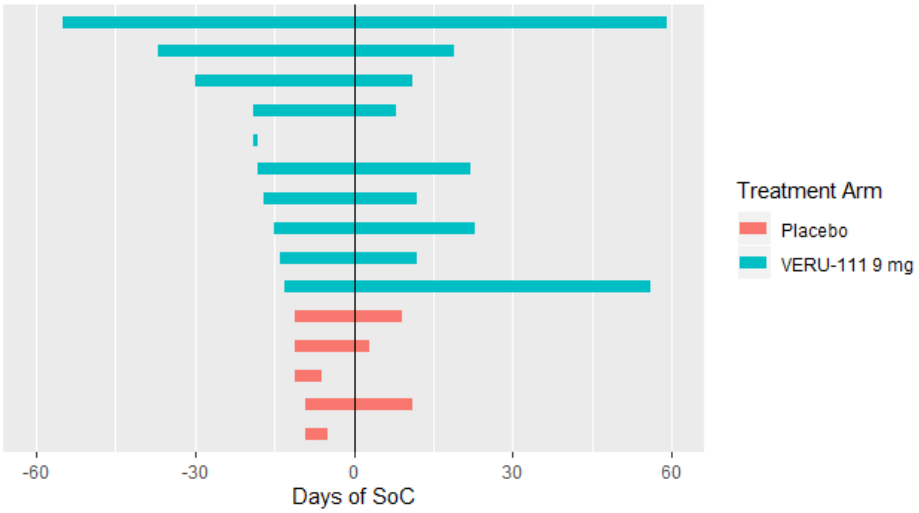
Because the potential use-case of VERU-111 for subjects with COVID-19 under an EUA will likely involve administration of the drug relatively early after the initiation of therapies such as dexamethasone and remdesivir, the subset of subjects with extended durations of standard of care therapy for COVID-19 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 6. Prerandomization and Postrandomization COVID-19 Standard of Care Therapy Days by Treatment Arm (ITT, Sorted by Prerandomization COVID-19 Standard of Care Therapy), Study 902**




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 7. Subjects With the Highest 15 Values of Prerandomization COVID-19 Standard of Care Therapy Days by Treatment Arm (ITT, Sorted by Prerandomization COVID-19 Standard of Care Therapy), Study 902**




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 compared to the VERU-111 group.

Randomization and blinding generally 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 severe 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 unusual 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.

#### 7.3.1.4 Timing of Enrollment Compared to COVID-19 Clinical Course

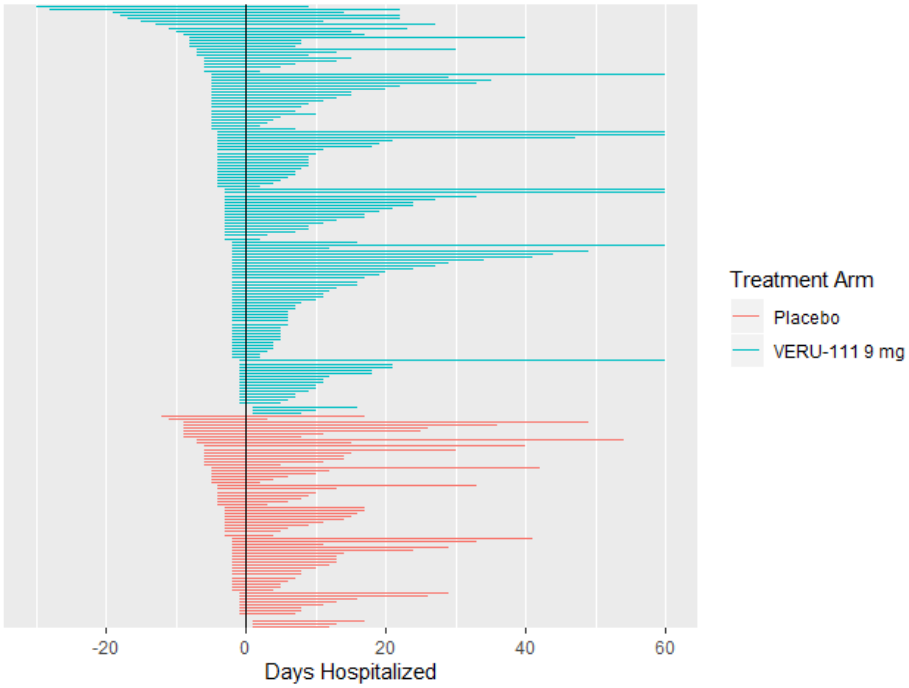
**Prerandomization Length of Hospital Stay**

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 slightly larger proportion of subjects in the VERU-111 arm were hospitalized for over 14 days prior to randomization , as shown in Figure 8. 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 9.

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 7.2.2.5 and 7.2.2.6. As noted above, although these analyses were simplistic explorations using available data and cannot entirely eliminate the potential impact of random 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.

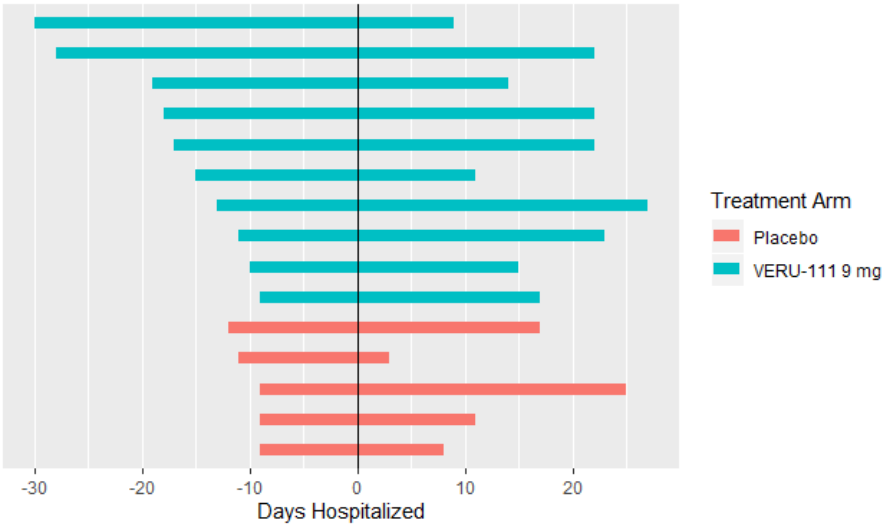
The clinical trajectory and prognosis of subjects who have already been in the hospital for up to 30 days prior to drug administration may differ in clinically relevant ways from those who have been recently admitted. Acknowledging that some patients with COVID-19 experience extended admissions, the 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 8. Prerandomization and Post-randomization Days in Hospital by Treatment Arm (ITT, Sorted by Prerandomization Days in Hospital), Study 902**




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

**Figure 9. Subjects With the Highest 15 Values of Prerandomization Days in Hospital by Treatment Arm (ITT, Sorted by Prerandomization Days in Hospital), Study 902**




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 would 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.

#### 7.3.1.5 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. Considerations of differences in subjects' goals of care decisions on trial efficacy estimates may be more impactful in small trials. Goals of care decisions such as "do not intubate", "do not attempt resuscitation", and withholding or withdrawal of life-sustaining therapy were not formally recorded as data points in Study 902.

However, there is evidence from the trial narratives that such decisions were made and documented in some cases, but potentially 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. 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 (Kerever et al. 2019). 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.

**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.

#### 7.3.1.6 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., (Absalón-Aguilar et al. 2022; Cecconi et al. 2022; Dorward et al. 2022; RECOVERY Collaborative Group 2021a; Tardif et al. 2021). 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. 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) (Deftereos et al. 2020).

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. 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 (Mikolajewska et al. 2021). 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 2021a) 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. 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 (Lan et al. 2022).

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

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, these extensive clinical data for an agent that shares a similar mechanism of action to VERU-111 do influence the uncertainty in the data provided primarily by the single, small, efficacy and safety trial of VERU-111. Acknowledging the

limitations of comparing results across agents, the negative results of the colchicine trials do lower the pre-test likelihood that VERU-111 may be effective, and these data must be incorporated when considering whether the results of Study 902 reflect a true positive result.

#### 7.3.1.7 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 Section 7.1.6). 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 treatment-refractory, uncontrolled COPD. Given the lack of data collection on these parameters, it is unclear that Study 902 adequately represented each of these comorbid conditions to provide adequate confidence in the efficacy results across the full scope of these subgroups and comorbidity subsets to apply them to clinical practice.

# 8 Human Clinical Safety: Assessment of Risk and Risk Management

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 authorization, 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.

## 8.1 Adequacy of Clinical Safety Database

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.

**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.

### 8.1.1 Deaths

Refer to Sections 7.2.1 and 7.2.2.4 for discussion of death events in Studies 901 and 902, respectively.

### 8.1.2 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 14, below, are noted due to corresponding signals in the data for AEs (see Section 8.1.3), 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 8.1.3), 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 14. Summary of Treatment-Emergent Serious Adverse Events, Safety Population, Study 902**

| | VERU-111 (N=130) | | | Placebo (N=69) | | |
|---|---|---|---|---|---|---|
| **MedDRA SAE Term** | **Events** | **Number of Subjects** | **Proportion** | **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

### 8.1.3 Common Adverse Events

A summary of adverse events considered clinically relevant in Study 902 are presented in Table 15, 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 15. Summary of Treatment-Emergent Adverse Events, Safety Population, Study 902**

| | 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 |

| MedDRA AE Term | VERU-111 (N=130) Events | Number of Subjects | Proportion | Placebo (N=69) 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

### 8.1.4 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.

### 8.1.5 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 Section 8.1.3, above.

Due to small imbalances noted in common venous thromboembolism adverse events, the review team 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 two 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.

### 8.1.6 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.

## 8.2 Key Review Issues Relevant to Evaluation of Risk

The small safety database raises the issue of uncertainty which must be considered in the assessment of the overall safety profile.

Based on the provided safety data, future trials should consider designating the following as adverse events of special interest:

- Urinary tract infection events
- Secondary (non-COVID) infection events
- Gastrointestinal adverse events (including nausea, vomiting, dyspepsia, abdominal pain, and diarrhea)
- Gastrointestinal bleeding events
- Anemia events
- Skin and dermatologic adverse events including decubitus ulcers
- Venous thromboembolism and pulmonary embolism events

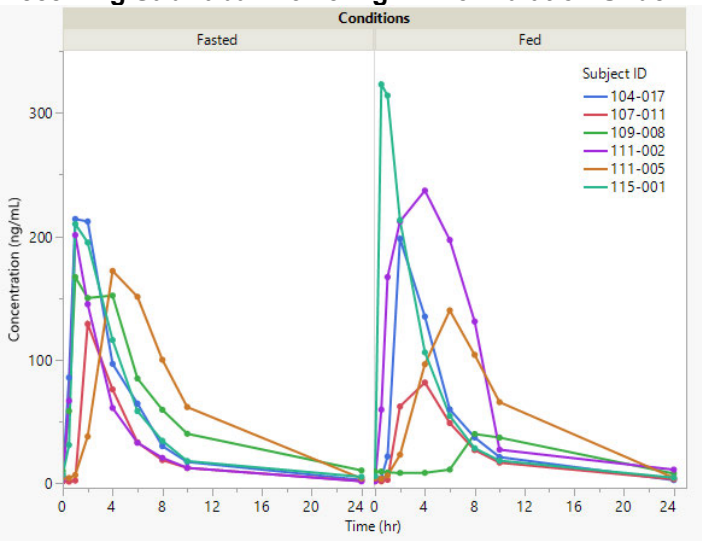
# 9 Human Clinical Pharmacology

The PK information in patients with COVID-19 at the proposed 9 mg dose with the FC formulation is limited given that only sparse PK samples were collected in clinical trials in adult patients with COVID-19. The dosing regimen of Trial V3011902 was 9 mg once daily without regard to meal for up to 21 days until discharge.

However, the PK sub-study of Trial V1011101 in 6 patients with advanced prostate cancer receiving sabizabulin 31.5 mg (FC formulation) once daily provides the steady state PK parameters from intensive sampling scheme as shown in Table 16. Peak plasma concentrations reached approximately at 1 hour and the elimination half-life of sabizabulin is approximately 5 hours after oral administration of sabizabulin 31.5 mg at fasted condition. Nonclinical PK studies in rats (at a range from 1 to 30 mg/kg) and dogs (at 5 and 10 mg/kg) suggest the dose proportionality in PK of sabizabulin from 1 mg/kg to 30 mg/kg (Studies 2649-002 and 2649-006) although the dose proportionality has not been evaluated in humans, neither in FC formulation nor PIC formulation.

When sabizabulin 31.5 mg FC formulation was administered at fed condition, $AUC_T$ were not significantly different from those at fasted condition, but $C_{max}$ decreased 23% [Geometric mean ratio of $AUC_T$ and $C_{max}$ at fed condition to fasted condition, 0.98 (0.67 -1.44) and 0.77 (0.47 - 1.26), respectively, per the reviewer's independent analysis]. The median time to reach $C_{max}$ ($T_{max}$) was delayed from 1 hour to 4 hours (Table 16, Figure 10). In clinical trials in patients with COVID-19, patients took sabizabulin without regard to meal. Comparable $AUC_{inf}$ and slight change of $C_{max}$ values between fed and fasted conditions for the FC formulation from Trial V1011101 supports administration of sabizabulin with or without food.

**Figure 10. Individual Time-Concentration Profiles of Sabizabulin in Patients With Prostate Cancer Receiving Sabizabulin 31.5 mg FC Formulation Under Fasted and Fed Conditions, Trial V1011101**




Source: the reviewer's analysis using the dataset 'V1011101-pk-substudy-data.xlsx' (SDN 3)

**Table 16. Steady State Pharmacokinetics of Sabizabulin in Patients With Prostate Cancer Receiving Sabizabulin 31.5 mg FC Formulation Under Fasted and Fed Conditions, Trial V1011101[a]**

| Parameters | Sabizabulin 31.5 mg at Fasted Condition | Sabizabulin 31.5 mg at Fed Condition |
|---|---|---|
| N | 6 | 6 |
| $C_{max}$ (ng/mL) | 182.2±32.6 | 169.9±104.2 |
| $T_{max}$ (hr) | 1.0 (1.0–4.0) | 4.0 (0.5–8.0) |
| $AUC_{0\text{-}24h}$ (ng·hr/mL) | 1039.07±339.95[b] | 1080.41±522.13[b] |
| $T_{1/2}$ (hr) | 5.11±1.24 | 4.89±1.09[c] |

Source: 2.7.2. Summary of Clinical Pharmacology Studies, Table 1 (SDN 1); the reviewer's analysis using the dataset 'V1011101-pk-substudy-data.xlsx' (SDN 3)
a. $C_{max}$, $T_{max}$, $T_{1/2}$ are presented in arithmetic mean ± SD whereas $T_{max}$ is presented in median (minimum – maximum)
b. Results of the reviewer's independent analysis, whose values are different from the data that the Sponsor provided (i.e., 973.58±307.87 and 1011.27±512.54, respectively)
c. $T_{½}$ was calculable in 5 of 6 subject
Abbreviations: AUC. area under the curve; $C_{max.}$ maximum concentration; $T_{max.}$ time to maximum concentration; $T_{1/2.}$ terminal half-life

In the phase 3 trial in patients with COVID-19 (Trial V3011902), $C_{trough}$ on Day 1, Day 3 and Day 9 were measured following once-daily administration (Table 17) in sabizabulin treatment group. Of note, as Day 1 samples were collected before sabizabulin dosing, the drug concentrations were supposed to be below the lowest limit of quantitation (LLOQ, 0.5 ng/mL). Nonetheless, 5 subjects showed concentrations above LLOQ, which were likely sampled after dosing inadvertently even though the recorded sampling time was all prior to the drug administration time per the submitted dataset.

**Table 17. Descriptive Statistics of $C_{trough}$ of Sabizabulin Following Administration of 9 mg Once Daily, Safety Analysis Set[a], Trial V3011902**

| Parameters | Day 1 | Day 3 | Day 9 |
|---|---|---|---|
| N | 123 | 112 | 75 |
| BLQ (N, %) | 118 (95.9%) | 27 (24.1%) | 16 (21.3%) |
| Mean ± SD (ng/mL) | 0.83±6.24 | 3.88±10.26 | 3.12±7.57 |
| Median (Min–Max) (ng/mL) | 0 (0–54) | 1.54 (0.25–71.6) | 1.6 (0.25–60.7) |
| Age group | | | |
| Age <65 years, N (%) | 56 (45.5%) | 53 (47.3%) | 40 (53.3%) |
| Mean ± SD (ng/mL) | 1.75±9.23 | 4.33±11.18 | 2.80±4.37 |
| Age ≥65 years, N (%) | 67 (54.5%) | 59 (52.7%) | 35 (46.7%) |
| Mean ± SD (ng/mL) | 0.06±0.35 | 3.48±9.44 | 3.49±10.13 |
| Administration method | | | |
| Oral, N (%) | 0 (%) | 100 (89.3%) | 54 (72.0%) |
| Mean ± SD (ng/mL) | - | 4.21±10.81 | 3.33±8.17 |
| NG tube, N (%) | 0 (%) | 12 (10.7%) | 21 (28.0%) |
| Mean ± SD (ng/mL) | - | 1.12±0.68 | 2.57±5.89 |

Source: the reviewer's analysis using the dataset 'adpc.xpt' of Trial V3011902 (SDN 3)
a. BLQ concentrations on Day 1 (pre-dosing) were treated as 0 whereas those on Days 3 and 9 were replaced with 0.25 ng/mL (LLOQ/2).
Abbreviations: BLQ, Below lower limit of quantitation, i.e., <0.5 ng/mL; SD, standard deviation

Distribution, metabolism, and elimination profiles of sabizabulin have not been investigated in humans. Per published literature, in vitro studies using human liver microsomes indicated that CYP enzymes are not much involved in metabolism of sabizabulin (Li et al. 2012).

Nonclinical studies with the radiolabeled drug in rats and dogs (Studies 2649-002 and 2649-032) indicates that biliary excretion is major excretion pathway whereas renal excretion is relatively minor in animals.

## PIC Formulation Vs. FC Formulation

In the phase 2 trial in patients with COVID-19 (Trial V0211901), sabizabulin 18 mg were administered in the powder-in-capsule (PIC) formulation once daily for up to 21 days. The PIC formulation used in the phase 2 trials is different from the product used in Trial V3011908 and the to-be-marketed product, i.e., 9 mg in the FC formulation. No relative bioavailability studies were conducted comparing the 9 mg FC formulation to the 18 mg of PIC formulation.

However, in the PK sub-study of Trial V1011101 in patients with prostate cancer, PK of sabizabulin was compared between 63 mg PIC formulation and 31.5 mg FC formulation (i.e., 50% dose of PIC) at fasted and fed conditions, respectively. It indicated that AUC of PIC formulation was not significantly different from those of 50% dose in FC formulation whereas $C_{max}$ of PIC formulation was 25% and 38% lower than those of FC formulation, at fasted and fed conditions, respectively (Table 18). As such, it is expected that AUC of 18 mg PIC formulation (the phase 2 formulation) is not significantly different from those of 9 mg FC formulation (the phase 3 formulation).

**Table 18. Comparison of Steady State Pharmacokinetic Parameters in Patients With Prostate Cancer Between Sabizabulin 31.5 mg FC Formulation and 63 mg PIC Formulation Under Fasting and Fed Conditions, Trial V1011101**

| Regimens Test vs. Reference | Parameter (units) | Least Square Mean 63 mg PIC | Least Square Mean 31.5 mg FC | Geometric Mean Ratio (90% CI) (N=6) |
|---|---|---|---|---|
| 63 mg PIC vs 31.5 mg FC | $C_{max}$ (ng/mL) | 135.6 | 179.5 | 0.75 (0.46-1.23) |
| At fasting condition | $AUC_t$ (ng·h/mL) | 1164.4 | 992.3 | 1.17 (0.80-1.72) |
| 63 mg PIC vs 31.5 mg FC | $C_{max}$ (ng/mL) | 86.5 | 138.4 | 0.62 (0.38-1.02) |
| At fed condition | $AUC_t$ (ng·h/mL) | 925.2 | 972.6 | 0.95 (0.65-1.40) |

Source: the reviewer's analysis using the dataset 'V1011101-pk-substudy-data.xlsx' (SDN 3)
Fed condition: administration 30 minutes after a high fat/high-calorie meal.
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; $C_{max}$, maximum plasma concentration; FC, formulation in capsule formulation; PIC, powder in capsule formulation

## Drug Interactions (DDI)

No clinical DDI studies were conducted for sabizabulin. Per published literature, in vitro studies indicated that CYP enzymes are not much involved in sabizabulin metabolism and sabizabulin does not inhibit CYP3A4, 2D6, 2C9, 2C19, and 1A2 enzymes (Li et al. 2012). Risk of CYP enzyme-mediated DDI is low.

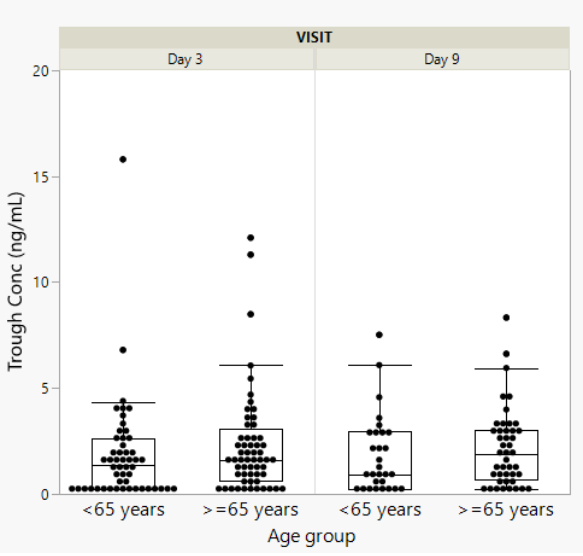
Therefore, it is reasonable to allow coadministration of sabizabulin with the standard of care medications such as dexamethasone, corticosteroids, baricitinib, antiviral drugs (remdesivir, molnupiravir, nirmatrelvir + ritonavir) without dose adjustment. In Trial V3011902, concomitant use of retroviral/antiretroviral medications (except remdesivir), experimental medications (except convalescent plasma), or colchicine were prohibited, and the most commonly (≥25%) reported concomitant medications were dexamethasone, methylprednisolone, paracetamol, and remdesivir in the sabizabulin treatment group.

## PK in Geriatric Population

Geriatric PK is not expected to be different from PK in younger patients. Out of 130 subjects in sabizabulin treatment group in Trial V3011902, 65 subjects (50.0%) were 65 years of age or older. The $C_{trough}$ on Day 3 and Day 9 of sabizabulin were not significantly different between patients <65 years of age and ≥65 years of age in Trial V3011902, (Figure 11); the mean $C_{trough}$

were 3.48 ng/mL and 4.33 ng/mL in patients <65 years of age and ≥65 years on Day3, and 2.80 ng/mL and 3.49 ng/mL on Day 9, respectively (Table 17).

**Figure 11. $C_{trough}$ of Sabizabulin Following Administration of Sabizabulin 9 mg Once-Daily in Patients With COVID-19 by Age Groups (<65 Years and ≥65 years of Age), Trial V3011902**




Source: the reviewer's analysis using the dataset 'adpc.xpt' of Trial V3011902 (SDN 3)
Note: Day 1 concentrations are not presented as pre-dose level; Concentrations below LLOQ (0.5 ng/mL) were replaced with 0.25 ng/mL (LLOQ/2); 6 data points >20 ng/mL were excluded from this plot in order to present the overall data better.

## Renal/Hepatic Impairment

The effect of renal or hepatic impairment on PK of sabizabulin has not been evaluated in clinical trials. In Trials V3011902 and V0211901, patients with CrCL <60 mL/min and/or AST/ALT >3X ULN or total bilirubin >1X ULN were excluded. Given the lack of safety and effectiveness data, the use of sabizabulin in such patients are not recommended.

Considering that patients with mild renal impairment (i.e., CrCL 60 to 90 mL/min) were evaluated in the phase 3 trial and that sabizabulin was mainly excreted through biliary excretion in nonclinical studies in rats and dogs, patients with mild renal impairment (CrCL 60 to 90 mL/min) may use of sabizabulin without dose adjustment.

## Alternative Administration of Sabizabulin Via Nasogastric Tube (NG Tube)

For patients who are unable to take the drug orally, the Sponsor proposed alternative administrations where the mixture of the entire contents of the capsule is dispersed with water and administered via NG tube. Of note, 55 subjects (22.9%) and 5 subjects (12.8%) received drug (either sabizabulin or placebo) via NG tube at least once in Trials V3011902 and V0211901, respectively.

The SD 13 amendment includes preliminary results of an *in vitro* nasogastric (NG) tube study. The study used 9 mg capsules from lot # D22128 for the study with the following NG tube configurations.

**Table 19. In Vitro NG Tube Study: Nasogastric Tube Types**

| Material of Construction | Description | Manufacturer | Product Code | Diameter (Fr[1]) | Catheter Length (In.) |
|---|---|---|---|---|---|
| Polyurethane | Corflo* Nasogastric/ Nasointestinal Feeding Tube with Enfit® Connector | Avanos | 42-1432 | 12 | 43 |
| Silicone | Gastro-Duodenal Long-Term Feeding Tube, Closed Tip, Four Lateral Eyes Latex and DEHP Free | Neomed, Inc | FTM8.0S -NC | 8 | 49 |
| PVC | Argyle Nasogastric Levin Feeding Stomach Tube | Covidien | 460406 | 8 | 42 |

Fr[1] = French size roughly equal to the circumference of the catheter in millimeters

Source: Sponsor
Abbreviations: NG, nasogastric; PVC, polyvinyl chloride

The Sponsor used their assay and related compounds methodology to analyze the stability of the samples prepared for administration by NG tubes. Sample capsules were opened and were weighed to determine the delivered formulation mass and the capsule contents were then transferred using sterile water (20 mL) into 50 mL volumetric flasks. After aging for 0, 1, 2, 4, 6, and 8 hours, these samples of formulation in water were diluted to the 50 mL volume with 70:30 0.1 N HCl: 50:50 Acetonitrile/MeOH and these were sonicated for 15 minutes. Samples were protected from light and aliquots were filtered (0.45 mcm nylon) and analyzed. The results in Table 20 show %LC recoveries of between 90.6 and 95.1% (average 93.3%) and also provide related compounds data.

In order to study the compatibility of the 9 mg capsule contents dispersed in 20 mL of water with the various NG tubes, the solutions were allowed to sit in the tubes for 10 minutes prior to delivery and followed by rinsing with additional water (40 mL). The recovery results are shown in the table reproduced below:

**Table 20. In Vitro NG Tube Study: NG Tube Recovery (% Label Claim)**

| | Argyle (PVC) | Corflo (Polyurethane) | Gastro-Duodenal (Silicone) |
|---|---|---|---|
| 1 | 96.1 | 69.4 * | 91.1 |
| 2 | 92.6 | 92.3 | 89 |
| 3 | 96.5 | 93.6 | 80.3 * |
| 4 | | 95.3 | 92 |
| 5 | | 87 | 92.4 |
| 6 | | 92.7 | 92.4 |
| 7 | | | 90.8 |
| Average | 95.1 | 88.4 (92.2) * | 86.8 (91.3) * |
| % RSD | 2.3 | 11.0 (3.0) * | 6.6 (1.3) * |

* Coreflo (Polyurethane) result 1 and Gastro-Duodenal (Silicone) result 3 were determined to be outliers, and therefore were not included in the Average and %RSD calculations presented in this table.

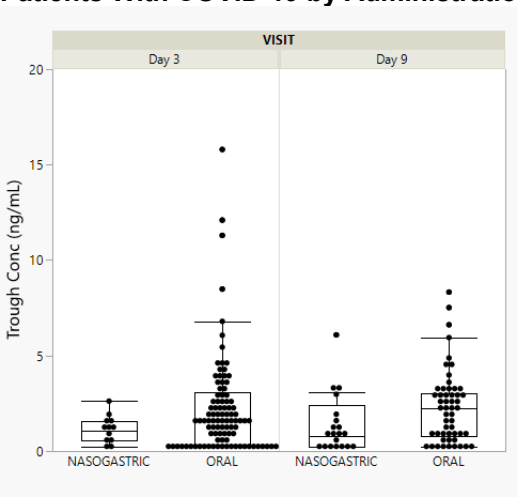
Source: Sponsor
Abbbreviations: NG, nasogastric; PVC, polyvinyl chloride; RSD relative standard deviation.

The Sponsor indicates that the two results in the above Table 20 marked with asterisks (*) are atypical based on a two tailed Dixon's Q-test for outliers. In addition, there was no change in the related compounds profiles of those samples that were held in the various types of tubes for 10 minutes.

In the VERU-111 arm of the phase 3 clinical efficacy study 902, 24% of the subjects had at least one dose of drug via a nasogastric (NG) tube (33% in the placebo arm) at the 55 study sites. The dispersion sample stability results are reasonable with an average of 93.3% of LC content and with no degradation over an 8-hour period. However, for the recovery study (see Table 20 above), the Sponsor did discount two results collected from the Corflo (polyurethane) and the Gastro-Duodenal (silicone) tubes (marked with asterisks) and considered these to be outlying values, based on Dixon's Q-test. With these values rejected, the average recovery exceeded 90% as long as a 40 mL water flush followed the delivery, and the dose was used within 8 hours. Although the number of recovery samples is quite limited, particularly for the PVC NG tube, and the appropriateness of the use of Dixon's Q-test for determining outlying values can be questioned, considering that NG tubes were used for a relatively high percentage of patients, from a risk-benefit standpoint, additional follow-up is not deemed necessary were the EUA to be authorized.

In Trial V3011902, the mean trough concentrations of sabizabulin from the patients who received the drug via NG tube tend to be lower than those from the patients took the drug orally (the mean, 1.12 ng/mL vs 4.21 ng/mL on Day 3; 2.57 ng/mL vs 3.33 ng/mL on Day 9, respectively) (Table 17), though it is within the range from those of patients who took the drug orally (Figure 12). By considering that the sabizabulin $C_{trough}$ values are close to the LLOQ value (0.5 ng/mL) and 23% of $C_{trough}$ samples were BLQ, the observed $C_{trough}$ values generally supports the NG tube administration as an alternative drug delivery method in patients with moderate to severe COVID-19.

**Figure 12. $C_{trough}$ of Sabizabulin Following Administration of Sabizabulin 9 mg Once-Daily in Patients With COVID-19 by Administration Method (Oral or Via Nasogastric Tube), Trial V3011902**




Source: the reviewer's analysis using the dataset 'adpc.xpt' of Trial V3011902 (SDN 3)
Note: $C_{trough}$ on Day 1 are not presented as pre-dose level; $C_{trough}$ levels < LLOQ (=0.5 ng/mL) were replaced with 0.25 ng/mL (LLOQ/2); 6 data points >20 ng/mL were excluded from this plot in order to present the overall data better.

- Bioanalytical methods used to quantify sabizabulin concentrations in human K2EDTA plasma was adequately validated. Sabizabulin was extracted from 50 µL plasma by means of protein precipitation and measured by LC-MS/MS. Quantitation range was 0.5 to 500 ng/mL. The validation results on linearity, selectivity and stability fell within the acceptable criteria. In Trials V1011101 and V0211901, 216 and 28 plasma samples, respectively, were analyzed with the acceptable performance and within in the established long-term stability (i.e., stable up to 246 days at 70℃). However, since the final clinical trial reports of Trial V3011902 is pending, which is expected to include the bioanalysis report, the adequacy of the in-study validation results of Trial V3011902 was not able to be assessed.

# 10 Nonclinical Data to Support Safety

## Executive Summary

VERU-111 is an investigational drug that has been reported to possess pharmacological activity as a tubulin inhibitor. Development of VERU-111 was initiated for the treatment of oncology indications. The Sponsor contends that VERU-111 has potential anti-inflammatory and anti-viral effects that could be beneficial in patients with COVID-19. The nonclinical program was based on the ICH S9 Guidance for development of oncology drugs and consisted of primary pharmacology studies, safety pharmacology studies, in vitro genetic toxicology studies, and oral toxicology studies in rats and dogs up to 28 days.

Primary pharmacology studies are discussed in Section 11. In the GLP-compliant in vitro hERG assay, VERU-111 showed a dose-dependent inhibition of hERG-mediated potassium currents in HEK293 cells with $IC_{20}$ values calculated as 7.27 mcM (based on actual concentrations) and 9.23 mcM (based on nominal concentrations). However, in the GLP-compliant in vivo cardiovascular safety pharmacology study in Beagle dogs, there was no evidence of QTc prolongation and there were no treatment-related effects on cardiovascular parameters (blood pressure, heart rate, or ECG parameters [QRS duration and the RR, PR, and QT intervals]).

Some evidence of QTc prolongation was evident in the 28-day toxicology study with dogs, although effects were confined to males. Respiratory effects were also assessed in the cardiovascular safety pharmacology study with Beagle dogs, and no effects on respiratory rate, tidal volume, and minute volume were observed. In the GLP-compliant in vivo CNS safety pharmacology study, oral VERU-111 at 30 mg/kg (high dose) resulted in the death of one male CD® [Crl:CD®(SD)] rat. Further, transient changes in several functional observational battery (FOB) parameters were observed after treatment with oral VERU-111 (3, 10, and/or 30 mg/kg), which reversed after 24 hours postdose. Deaths were attributed to the adverse effects of VERU-111 on the gastrointestinal tract.

In the GLP-compliant in vitro Ames assay, VERU-111 HCL was negative for mutagenic potential. In the in vitro micronucleus assay in TK6 cells, VERU-111 HCL was positive for the induction of micronuclei in the non-activated and S9-activated test systems. Subsequent CREST analysis indicated that VERU-111 HCL induced micronuclei predominantly by an aneugenic mechanism of action with adverse effects on the cytoskeletal system that occurred through a concentration-based threshold. As a tubulin inhibitor, VERU-111 could potentially adversely impact rapidly dividing cells in organs and tissues such as the GI tract, bone marrow, and male reproductive organs (of note, such effects were seen in the 28-day toxicity study with VERU-111 in rats). VERU-111 was negative for mutagenic and clastogenic potential; however; it possesses aneugenic potential with adverse effects on the cytoskeletal system that can disrupt the segregation of chromosomes into daughter cells during cell division.

The repeat-dose toxicity of VERU-111 was evaluated in pivotal GLP-compliant 28-day oral toxicity studies in CD® [Crl:CD®(SD)] rats (0, 0.3, 1, 3, 10, or 30/20 mg/kg/day; the 0.3 and 1 mg/kg/day groups were added to the study at a later date) and Beagle dogs (0, 2, 4, and 8 mg/kg/day). In the28-day rat study, oral VERU-111 at ≥10 mg/kg/day was lethal to several rats, with deaths attributed to ulcers, degeneration, and/or necrosis in intestinal tissues. VERU-111-related microscopic findings in several target organs including the gastrointestinal (GI) tract (≥3 mg/kg/day), heart (≥10 mg/kg/day), liver (≥3 mg/kg/day), bone marrow (≥3 mg/kg/day), lymphatic system (≥3 mg/kg/day), male reproductive system (≥10 mg/kg/day), and adrenal glands (≥3 mg/kg/day). The observed findings appeared to be fairly characteristic of tubulin inhibitors (e.g., toxicity to rapidly dividing cells in the bone marrow and GI tract, lymphoid depletion in several organs, etc.). The no observed adverse effect level (NOAEL) was determined to be 3 mg/kg/day based on mortality and adverse histopathology findings at higher doses (≥10 mg/kg/day). Only animals in the ≤3 mg/kg/day groups completed 28 days of treatment. At 3 mg/kg/day, the average combined $C_{max}$ =81 ng/mL and $AUC_{0\text{-}24h}$ =1100 ng*hr/mL. In the 28-day dog study, oral VERU-111 at ≥4 mg/kg/day resulted in adverse decreases in absolute body weight (≥10%) and body weight gain, which corresponded with lower food consumption. Adverse increases (≥10%) in PR, QT, and QTc (males only) intervals were noted at Week 4 in the 8 mg/kg/day groups. VERU-111-related microscopic findings included depletion of hematopoietic cells in the sternal bone marrow and depletion of lymphocytes in thymus at 8 mg/kg/day. The observed findings were generally characteristic of tubulin inhibitors (e.g., clinical signs of vomiting/emesis, depletion of hematopoietic cells in the sternal bone marrow, and lymphoid depletion in the thymus). The NOAEL was identified as 4 mg/kg/day based on the adverse bodyweight loss, lengthening of the PR, QT, and QTc intervals, and histopathology findings in animals in the 8 mg/kg/day group. At 4 mg/kg/day, average combined $C_{max}$ =23 ng/mL and $AUC_{0\text{-}12h}$ =74 ng*hr/mL ($AUC_{0\text{-}24h}$ =148 ng*hr/mL). The findings at the high dose of 8 mg/kg/day might be considered monitorable.

The clinical safety margins for the proposed clinical dose of VERU-111 (i.e., 9 mg sabizabulin for 21 days) compared to the NOAELs from the pivotal 28-day toxicity studies in rats and dogs are 2.4x and 0.32x, respectively (on a plasma drug exposure [AUC] basis) and 20x and 27x,

respectively (on a mg/kg basis). The findings in the dog study at 8 mg/kg/day could be considered monitorable in the clinical setting, resulting in clinical safety margins of 0.63x (on an exposure basis) and 53x (on a mg/kg basis). Safety margins were calculated on a mg/kg basis to account for the local toxicity observed in the GI tract after oral dosing to rats and dogs. Of note, based on the significant differences in the exposures between rats and dogs, and more severe toxicities including death in rats, the rat was identified as the most sensitive animal species.

There are no reproductive and developmental toxicology studies with VERU-111 (either conducted by the Sponsor or identified from the literature). Per the Sponsor, given similar mechanism of actions between VERU-111 and colchicine as microtubule destabilizing agents, and the potential to induce micronuclei via an aneugenic mechanism of action based on the in vitro micronucleus assay, it is highly likely that the use of VERU-111 in a pregnant woman will result in impairment in the growth of the developing fetus and may result in birth defects in and/or death of the developing fetus.

In the in vitro neutral red uptake phototoxicity assay using BALB/c 3T3 mouse fibroblasts, VERU-111 (0.562 to 31.6 mcg/mL in the definitive study) was found to be phototoxic. The $IC_{50}$ for VERU-111-mediated phototoxicity in the presence of UVR exposure was estimated at 0.237 mcg/mL.

The details of nonclinical toxicology studies can be found in the Section 19.4.

# 11 Nonclinical Data to Support Efficacy

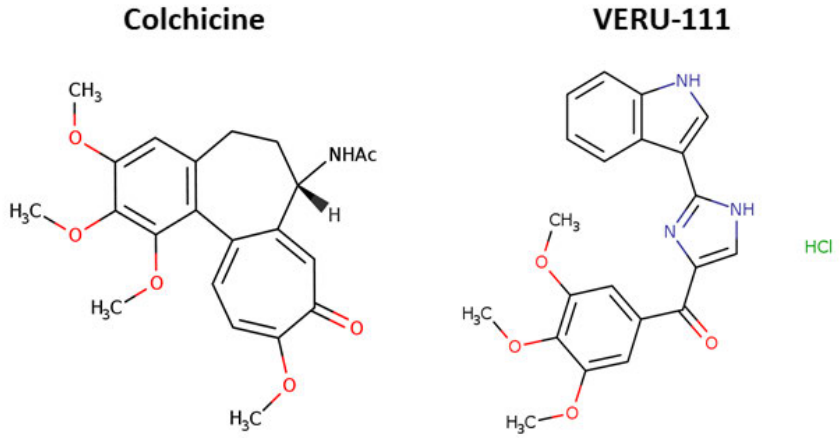
## 11.1 Mechanism of Action

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. 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 13). 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 7.3.1.6). The mechanism of the potential efficacy of VERU-111 in COVID-19 is unclear.

**Figure 13. Chemical Structures of Colchicine and VERU-111**




Source: ChemIDPlus (National L brary of Medicine). Left structure is colchicine and right structure is VERU-111.
Abbreviations: VERU-111, sabizabulin

## Primary Pharmacology

The primary pharmacology of VERU-111 has been evaluated both in vitro and in vivo. The in vitro assays assessed the effect of VERU-111 on tubulin binding (Chen et al. 2012; Li et al. 2012; Wang et al. 2019), anti-viral activity against SARS-CoV-2, and lipopolysaccharide (LPS)-mediated cytokine release. The in vivo assessment evaluated the ability of VERU-111 to prevent and treat severe COVID-19 disease in an aged mouse model of SARS-CoV-2 infection including ARDS. These studies were not GLP-compliant, which is typical of primary pharmacology studies.

Based on these studies, which are described below, the Sponsor indicated that VERU-111 targets, binds, and crosslinks the α and β tubulin subunits to inhibit polymerization and to induce depolymerization of microtubules. At equimolar concentrations, VERU-111 appeared to be more potent than colchicine, by approximately 3-fold, in terms of inhibiting tubulin polymerization. The concentrations of VERU-111 used in these in vitro studies to evaluate inhibition of tubulin polymerization were orders of magnitude (approximately 50- to 100-fold) higher than the $C_{max}$ of 0.138 mcM (138nM or 57.5 ng/mL) achieved with a clinical dose of VERU-111 at 9 mg/day in COVID-19 patients. The Sponsor has conducted pharmacology studies purported to demonstrate that VERU-111 possesses anti-viral activity against SARS-CoV-2 and can suppress the excessive inflammatory activity in response to SARS-CoV-2 infection (e.g., decreased release of cytokines in an in vitro setting and decreased levels of histopathological injury in the lungs of mice following SARS-CoV-2 infection) that were attributed to VERU-111 effects on α and β tubulin subunits.

This review was limited to an evaluation of the potential anti-inflammatory activity of VERU-111 in nonclinical studies.

- In the in vitro mouse septic shock model, VERU-111 reduced LPS-stimulated production of all the inflammatory cytokines tested (TNFα, IL-1α, IL-1β, IL-6, and CXCL1/KC [IL-8]) in isolated mouse spleen cells, providing proof of concept that VERU-111 can suppress cytokine production in this in vitro model. The concentrations of VERU-111 used in the study were reasonably comparable to the $C_{max}$ of 138nM achieved with a clinical dose of VERU-111 at 9 mg/day in COVID-19 patients. The fetal bovine serum used in the study might bind VERU-111 in similar manner as occurs with circulating albumin (or plasma

proteins) in the blood. However, it is unclear how this in vitro model translates to an in vivo setting and an inflammatory response after viral infection. In general, dose-response relationships were not evident with VERU-111.

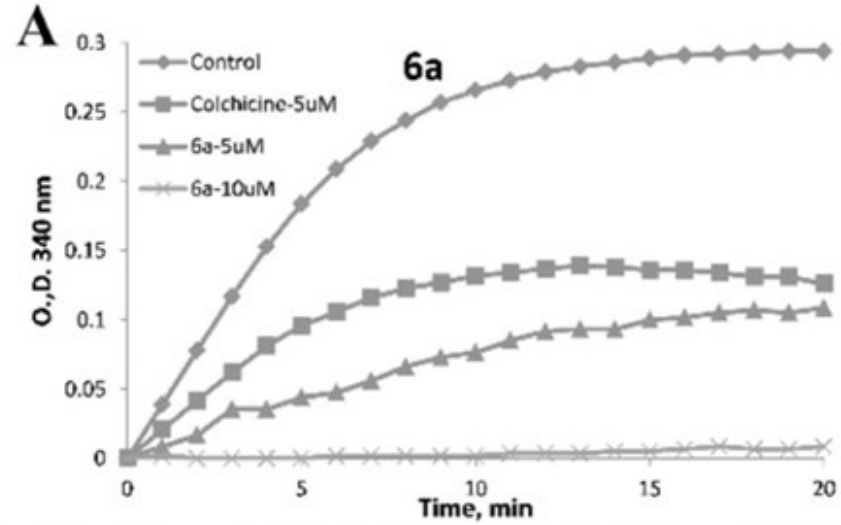
- In an aged mouse model of acute respiratory distress syndrome, BALB/c mice infected with mouse-adapted SARS-CoV-2 and simultaneously administered once daily oral gavage doses of VERU-111 (3 mg/kg or 9 mg/kg) displayed a decrease in deaths and global pneumonia severity score. Of note, the number of mice on Day 5 was low compared to Day 2, which limited the confidence in the results (i.e., mice that died during the study were not submitted to histopathology examinations of the lungs). The decreases in bronchointerstitial inflammation and/or lung congestion were less convincing. There were no comparable studies with colchicine to allow a comparison between VERU-111 and colchicine.
- Any connection to VERU-111 effects on α and β tubulin subunits seemed remote.

**In Vitro Microtubulin Binding (Based on Published Studies From Chen et al. 2012, Li et al. 2012, and Wang et al. 2019)**

Published studies have shown that VERU-111 exerts its mechanism of action by binding the "colchicine binding site" of α and β tubulin to inhibit tubulin polymerization and to induce depolymerization of microtubules (Chen et al. 2012; Li et al. 2012; Wang et al. 2019)

Based on Chen et al., VERU-111 (referred to as ABI-III 6a; 5mcM or 10mcM) inhibited tubulin (microtubule) polymerization in a dose-dependent manner with 100% inhibition of tubulin polymerization after 20 minutes of treatment with 10mcM VERU-111 and 70% inhibition with 5mcM VERU-111 (Chen et al. 2012). In comparison, the positive control colchicine (5mcM) inhibited tubulin polymerization by 47% at 10 minutes. See Figure 14 (Figure 3a from Chen et al. (2012)). At equimolar concentrations, VERU-111 appeared to be more potent than colchicine, by approximately 3-fold, in terms of inhibiting tubulin polymerization.

**Figure 14. Effect of VERU-111 (ABI-III 6a) on Tubulin Polymerization In Vitro**

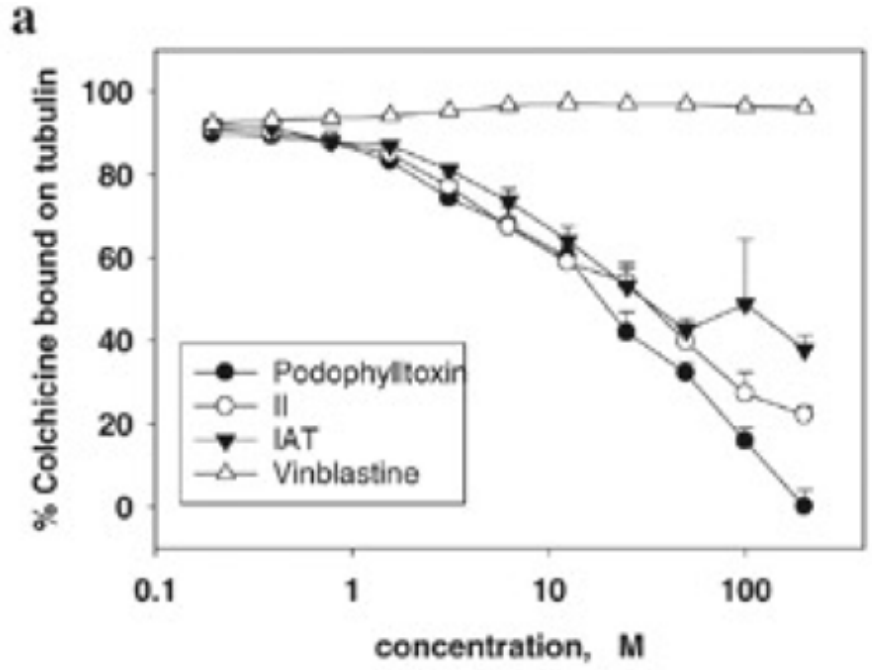



Tubulin (0.4 mg) was exposed to sabizabulin (compound 6a; 5 µM and 10 µM), vehicle control or 5µM colchicine (positive control). Absorbance at 340nm was monitored at 37°C every minute for 20 minutes.

Source: Figure 3a from Chen, J, S Ahn, J Wang, Y Lu, JT Dalton, DD Miller, and W Li, 2012, Discovery of Novel 2-Aryl-4-benzoyl-imidazole (ABI-III) Analogues Targeting Tubulin Polymerization As Antiproliferative Agents, Journal of Medicinal Chemistry, 55(16):7285-7289.
Abbreviations: VERU-111, sabizabulin

As described by Li et al., in a competitive mass spectrometry binding assay, VERU-111 (identified as Compound II in the publication) competed effectively with colchicine for tubulin binding, with potency similar to podophyllotoxin (Li et al. 2012). See Figure 15 (Figure 1a from Li et al. (2012)).

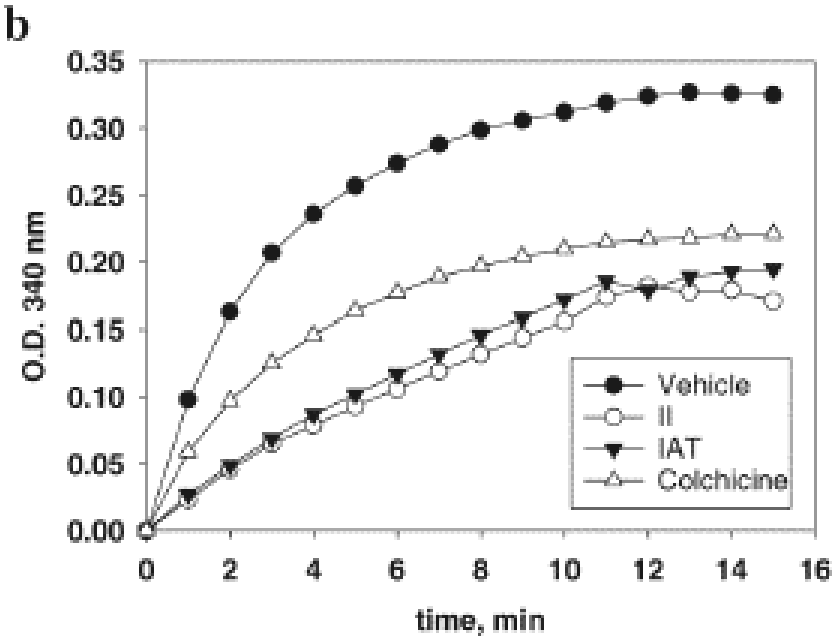
**Figure 15. VERU-111 (Compound II) Displaces Colchicine by Binding to the Colchicine Binding Site**




Source: Figure 1a from Li, CM, Y Lu, J Chen, TA Costello, R Narayanan, MN Dalton, LM Snyder, S Ahn, W Li, DD Miller, and JT Dalton, 2012, Orally bioavailable tubulin antagonists for paclitaxel-refractory cancer, Pharm Res, 29(11):3053-3063
Abbreviations: VERU-111, sabizabulin

As reported by Li et al., VERU-111 (identified as Compound II in the publication) inhibited tubulin polymerization by 47% at 15 minutes compared to a 32% inhibition of tubulin polymerization with colchicine (5mcM) (Li et al. 2012). See Figure 16 (Figure 1b from Li et al. (2012)).

**Figure 16. Effect of VERU-111 (Compound II) on Tubulin Polymerization In Vitro**




Source: Figure 1b from Li, CM, Y Lu, J Chen, TA Costello, R Narayanan, MN Dalton, LM Snyder, S Ahn, W Li, DD Miller, and JT Dalton, 2012, Orally bioavailable tubulin antagonists for paclitaxel-refractory cancer, Pharm Res, 29(11):3053-3063.
Abbreviations: VERU-111, sabizabulin

As described by Wang et al., compared to colchicine, VERU-111 has more hydrogen bonds within the “colchicine binding” pocket of β tubulin and reaches across the interface between β tubulin and α tubulin to form two more hydrogen bonds with α tubulin indicating that VERU-111 tightly crosslinks α and β tubulin subunits (Wang et al. 2019).The concentrations of VERU-111 used in these studies were orders of magnitude (50- to 100-fold) higher than the $C_{max}$ of 0.138 mcM (138nM or 57.5 ng/mL) achieved with a clinical dose of VERU-111 at 9 mg/day in COVID-19 patients.

**Title: Evaluation of the Ability of Sabizabulin (VERU-111) to Suppress Cytokine Release from Endotoxin (LPS) Shocked Mouse Spleen Cells (Report No. UT-SCS)**

**Objective:** To evaluate whether VERU-111 can suppress release of key inflammatory cytokines from mouse spleen cells in an in vitro mouse model of septic shock

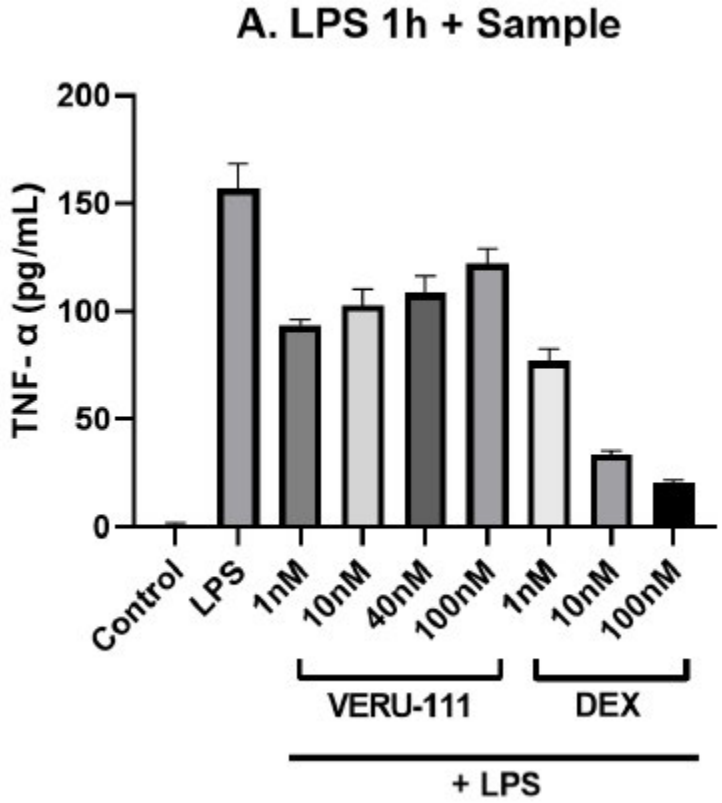
**Methods:** Spleen cells were isolated from 10-week-old tight skin 1 Vitamin D deficient (TSK1 D-) female mice, cultured with RPMI-1640 medium with 10% fetal bovine serum, plated into 24-well plates, and subsequently stimulated with LPS (5 mcg/mL) for 1 hour. The spleen cells were then treated for about 21 hours with nothing (control), dexamethasone (1, 10, or 100nM; positive control), or different concentrations of VERU-111 (1, 10, 40, or 100nM). Cell culture supernatants were then harvested and analyzed for levels of mouse TNF-α, IL-1α, IL-1β or IL-6, and CXCL1/KC (IL-8) cytokines by enzyme-linked immunosorbent assay (ELISA).

Based on the study report, 40nM VERU-111 represents a concentration similar to blood concentrations of VERU-111 with oral daily doses of 9 mg VERU-111 in phase 2 clinical trials (i.e., 50nM).

**Results:** As shown in Figure 17 (Sponsor’s Figure), levels of TNF-α were slightly lower in cell culture supernatants from LPS-stimulated mouse spleen cells treated with VERU-111 (1, 10, 40,

or 100nM) compared to the control group. Further, there was no evidence of a dose-response. In comparison, levels of TNF-α were even lower in cell culture supernatants from LPS-stimulated mouse spleen cells treated with dexamethasone (1, 10, or 100nM) and there was evidence of a dose-response relationship.

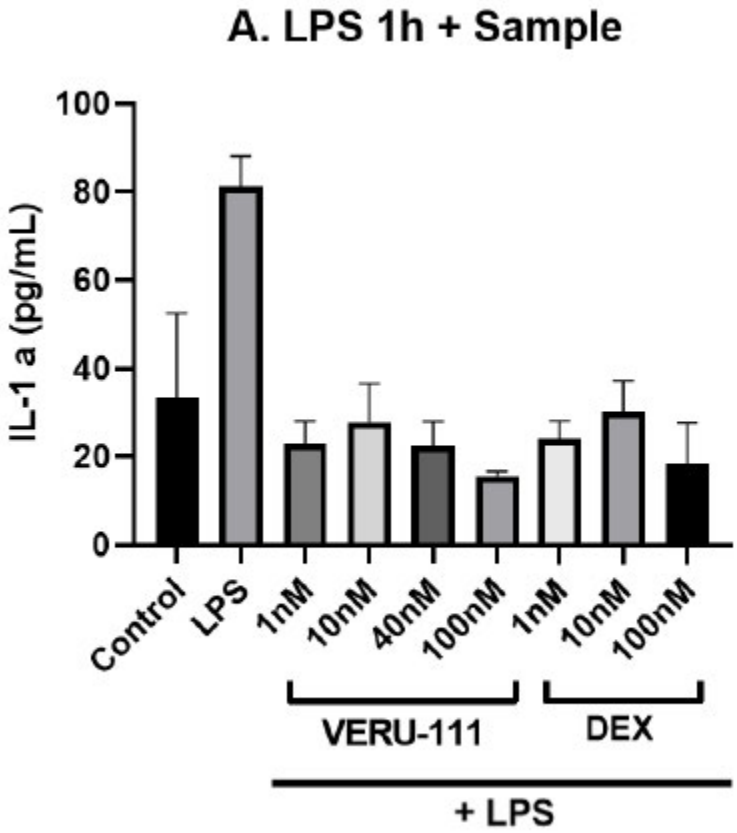
**Figure 17. TNF-α Release From LPS-Stimulated Mouse Spleen Cells in an In Vitro Mouse Model of Septic Shock**




Source: Sponsor's figure from Report No. UT-SCS
Abbreviations: DEX, dexamethasone; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor alpha

As shown in Figure 18 (Sponsor's Figure), levels of IL-1α were lower in cell culture supernatants from LPS-stimulated mouse spleen cells treated with VERU-111 (1, 10, 40, or 100nM) compared to the control group, although there was no evidence of a dose-response. The decrease in the levels of IL-1α in cell culture supernatants from LPS-stimulated mouse spleen cells treated with dexamethasone (1, 10, or 100nM) was comparable.

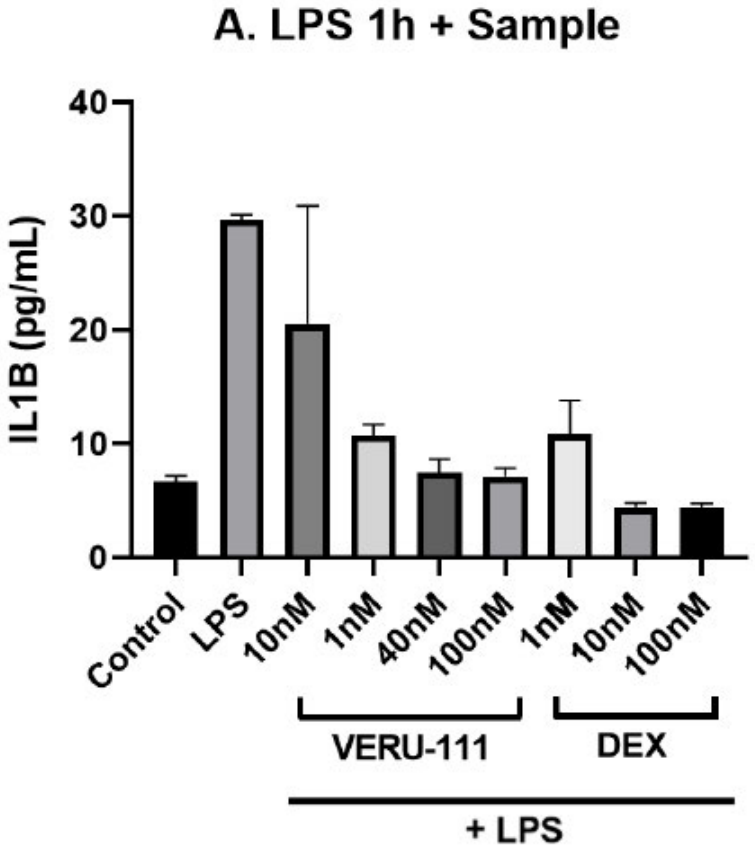
**Figure 18. IL-1α Release From LPS-Stimulated Mouse Spleen Cells in an In Vitro Mouse Model of Septic Shock**




Source: Sponsor's figure from Report No. UT-SCS
Abbreviations: DEX, dexamethasone; IL, interleukin; LPS, lipopolysaccharide

As shown in Figure 19 (Sponsor's Figure), levels of IL-1β were lower in cell culture supernatants from LPS-stimulated mouse spleen cells treated with VERU-111 (1, 10, 40, or 100nM) compared to the control group. There was some evidence of a dose response up to 100nM. The decrease in the levels of IL-1β in cell culture supernatants from LPS-stimulated mouse spleen cells treated with dexamethasone (1, 10, or 100nM) was comparable.

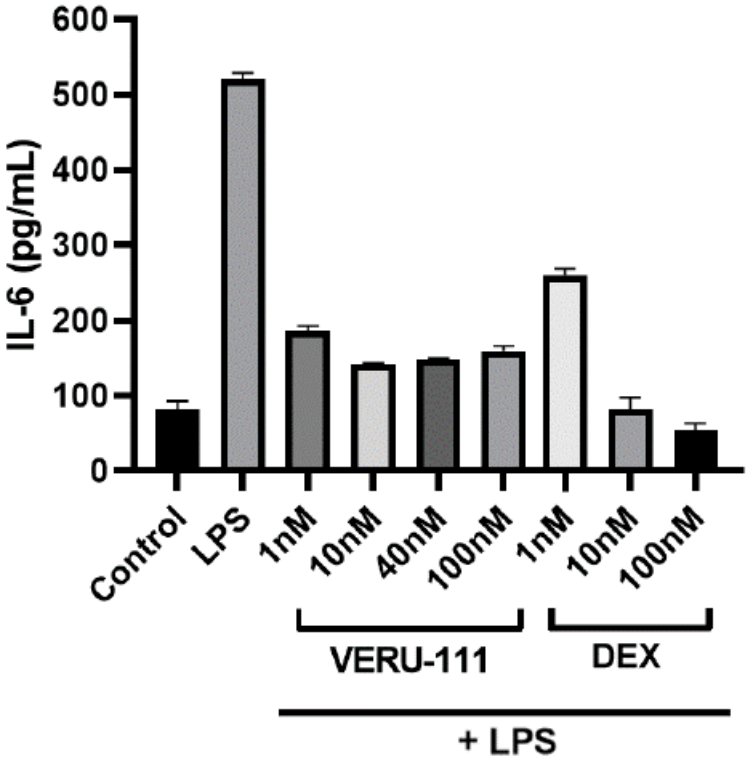
**Figure 19. IL-1β Release From LPS-Stimulated Mouse Spleen Cells in an In Vitro Mouse Model of Septic Shock**




Source: Sponsor's figure from Report No. UT-SCS
Abbreviations: DEX, dexamethasone; IL, interleukin; LPS, lipopolysaccharide

As shown in Figure 20 (Sponsor's Figure), levels of IL-6 were lower in cell culture supernatants from LPS-stimulated mouse spleen cells treated with VERU-111 (1, 10, 40, or 100nM) compared to the control group, although there was no evidence of a dose-response. The decrease in the levels of IL-6 in cell culture supernatants from LPS-stimulated mouse spleen cells treated with dexamethasone (1, 10, or 100nM) was comparable and dose-dependent.

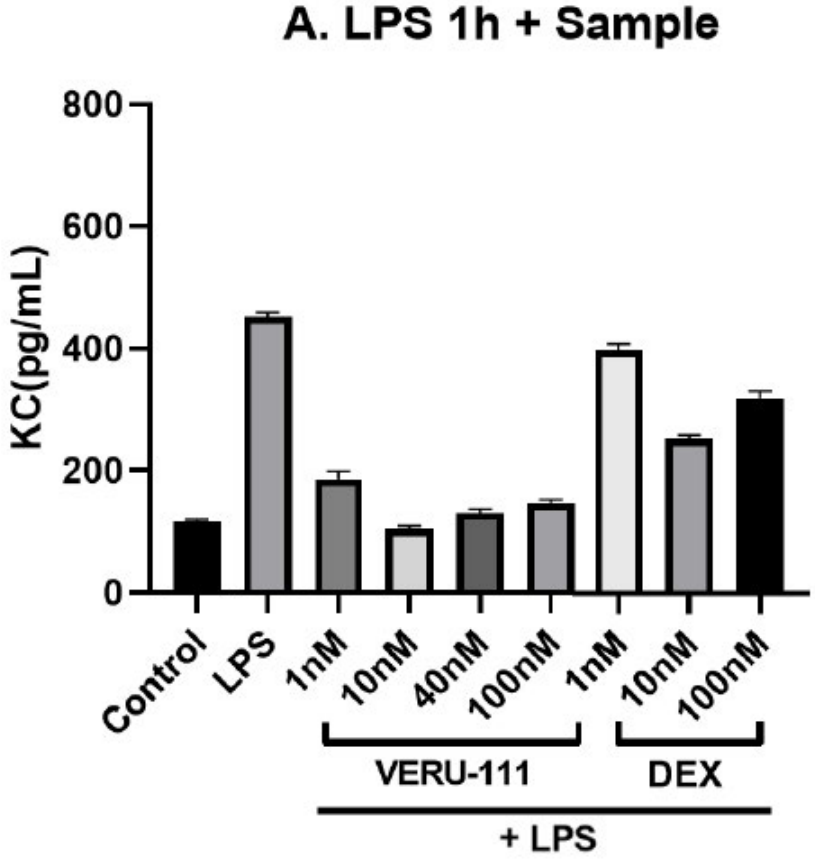
**Figure 20. IL-6 Release From LPS-Stimulated Mouse Spleen Cells in an In Vitro Mouse Model of Septic Shock**




Source: Sponsor's figure From Report No. UT-SCS
Abbreviations: DEX, dexamethasone; IL, interleukin; LPS, lipopolysaccharide

As shown in Figure 21 (Sponsor's Figure), levels of CXCL1/KC (IL-8) were lower in cell culture supernatants from LPS-stimulated mouse spleen cells treated with VERU-111 (1, 10, 40, or 100nM) compared to the control group, although there was no evidence of a dose-response. In comparison, there was a less robust decrease in the levels of CXCL1/KC (IL-8) in cell culture supernatants from LPS-stimulated mouse spleen cells treated with dexamethasone (1, 10, or 100nM).

**Figure 21. CXCL1/KC (IL-8) Release From LPS-Stimulated Mouse Spleen Cells in an In Vitro Mouse Model of Septic Shock**




Source: Sponsor's figure from Report No. UT-SCS
Abbreviations: CXCL1, chemokine ligand 1; DEX, dexamethasone; IL, interleukin; KC, cytokine-induced neutrophil-attracting chemokine; LPS, lipopolysaccharide

Based on the study report, 40nM VERU-111 represents a concentration similar to blood concentrations of VERU-111 with oral daily doses of 9 mg VERU-111 in phase 2 clinical trials (i.e., 50nM). As summarized in Table 21 (Sponsor's Table), 40nM VERU-111 had -31%, -97%, -123%, -85%, -96% decreases relative to the LPS control in TNF-α, IL-1β, IL-1α, IL-6, and CXCL1/KC (IL-8) cytokine levels. In most cases, except for TNFα, the decrease in cytokine levels with VERU-111 (40nM) was similar to the decrease seen with dexamethasone (10nM) or greater than the decrease seen with dexamethasone (10nM). Dose-response relationships were generally not evident with VERU-111.

**Table 21. Fold Change in Effect of VERU-111 on LPS-Induced Cytokine Release in Isolated Mouse Spleen Cells Comparison to LPS Alone (Sponsor's Table)**

| | TNF-α | IL-1β | IL-1α | IL-6 | KC/IL-8 |
|---|---|---|---|---|---|
| VERU-111 (40nM) | -31% | -97% | -123% | -85% | -96% |
| Dexamethasone (10nM) | -79% | -110% | -106% | -100% | -59% |
| p-value* | 0.006 | 0.0003 | 0.0005 | <0.00008 | <0.0000007 |

* p-value calculations were based upon the response of VERU-111 40 nM compared to LPS stimulated spleen cells
Source: ut-sabizabulin-cytokine-study

Abbreviations: IL, interleukin; KC, cytokine-induced neutrophil attracting chemokine; TNF-α, tumor necrosis factor alpha

**Conclusion(s):** In the in vitro mouse septic shock model, VERU-111 reduced LPS-stimulated production of all the inflammatory cytokines tested (TNFα, IL-1α, IL-1β, IL-6, and CXCL1/KC [IL-8]) in isolated mouse spleen cells, providing proof of concept that VERU-111 can suppress cytokine production in this in vitro model. The concentrations used in the study were reasonably comparable to $C_{max}$ of 138nM achieved with a clinical dose of VERU-111 at 9 mg/day in COVID-19 patients. The fetal bovine serum used in the study might bind VERU-111 in similar manner as occurs with circulating albumin (or plasma proteins) in the blood. However it is unclear how this in vitro model translates to an in vivo setting and an inflammatory response after viral infection. In general, dose-response relationships were not evident with VERU-111.

**Title: Assess the** Ability of Sabizabulin (VERU-111) to Prevent and Treat Severe COVID-19 Disease in SARS-CoV-2-Infected Aged Mice (Report No. ARDS-MM)

**Objective:** To evaluate the ability of VERU-111 to prevent and to treat severe COVID-19 in an aged mouse model of SARS-CoV-2 infection including acute respiratory distress syndrome

**Methods:** BALB/c female aged mice (11 to 12 months old) were infected with mouse-adapted SARS-CoV-2 and treated at the time of infection with daily oral gavage doses of vehicle or VERU-111 (3 mg/kg and 9 mg/kg) for up to 5 days. There were also a sham-infected (intranasal phosphate buffered saline) group. Mice were assessed on Day 2 and Day 5 postinfection for 1) weight loss post-viral infection, 2) congestion score of the lung at the terminal endpoints post-infection, 3) viral titers at the terminal endpoints, 4) lung histopathology, and 5) survival. See Table 22 (Sponsor's Table) for study design.

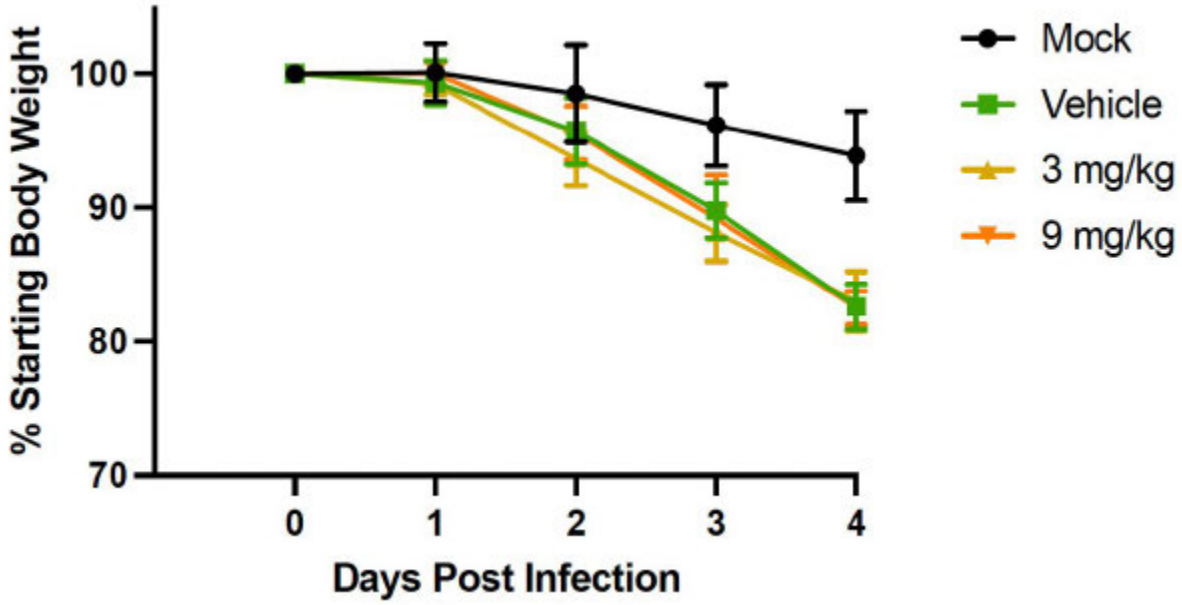
**Table 22. Study Design for In Vivo Assessment of VERU-111 in SARS-CoV-2-Infected Aged Mouse ARDS Model (Sponsor's Table)**

| Group | Treatment | Virus | Mice | Endpoint Day 2 | Endpoint Day 5 |
|---|---|---|---|---|---|
| 1 | Negative control (diluent, infected) | $10^3$ MA10 | 10 | 5 | 5 |
| 2 | Mock control (diluent, uninfected) | - | 10 | 0 | 10 |
| 3 | VERU-111, 3 mg/kg | $10^3$ MA10 | 10 | 5 | 5 |
| 4 | VERU-111, 9 mg/kg | $10^3$ MA10 | 10 | 5 | 5 |

Source: Sponsor's table from Report No. ARDS-MM
Abbreviations: ARDS, acute respiratory distress syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

**Results:** As shown in Figure 22 (Sponsor's Figure), SARS-CoV-2 infected mice treated with VERU-111 at both 3 mg/kg or 9 mg/kg had the same bodyweight lost post viral infection as the vehicle control group.

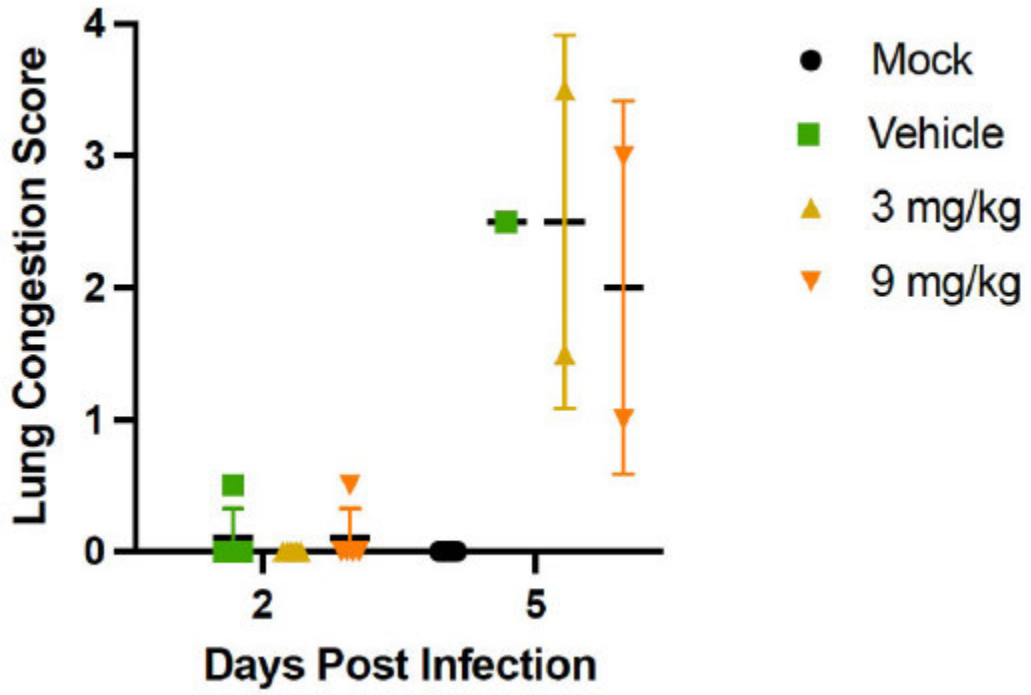
**Figure 22. Weight Loss Post-Viral Infection**




Source: Sponsor's figure from Report No. ARDS-MM

As shown in Figure 23 (Sponsor's Figure), at Day 5 post infection with SARS-CoV-2, the mean lung congestion score in live mice that had been treated with VERU-111 at 9 mg/kg was slightly decreased compared to live mice that had been treated with VERU-111 at 3 mg/kg or the vehicle. The study report notes, that since more mice died in the vehicle control group than in the VERU-111 treated groups, it is unclear what the lung congestion score comparison would be if the sickest animals who died were included.

**Figure 23. Congestion Score of Lung at Terminal Endpoints Post Infection**




Source: Sponsor's figure from Report No. ARDS-MM

Lung specimens were evaluated by histopathology and were graded for vasculitis/endotheliitis, type II pneumocyte hyperplasia, bronchiolar degeneration/necrosis, bronchiolar hyperplasia, bronchointerstitial pneumonia, and global pneumonia severity score by a board-certified veterinary pathologist (Table 23). The lungs of mice that died during the study were not submitted to histopathology examinations. As shown in Table 24 (Sponsor's Table), there was a dose-dependent reduction in bronchointerstitial inflammation (Day 2) and in global pneumonia severity score (Day 2 and Day 5) in SARS-CoV-2 infected mice that had been treated with VERU-111 compared to the vehicle control group, which suggested a reduction in pulmonary inflammation.

**Table 23. Pathology Observations in SARS-CoV-2 Infected Aged Mice**

| Removal Reason(s): ALL<br>Summary: Incidence | Female | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 | Group 7 | Group 8 |
| Number of Animals: | 5 | 5 | 5 | 1 | 5 | 2 | 5 | 2 |
| **LUNGS** | | | | | | | | |
| Examined | 5 | 5 | 5 | 1 | 5 | 2 | 5 | 2 |
| Normal | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| bronchiole; Hyperplasia | 0 | 0 | 4 | 1 | 4 | 2 | 5 | 2 |
| .... minimal | 0 | 0 | 4 | 0 | 4 | 0 | 5 | 0 |
| .... mild | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 2 |
| bronchiole; Hyperplasia; unable to score | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| pneumocyte type ii; Hyperplasia | 0 | 0 | 3 | 1 | 4 | 2 | 3 | 2 |
| .... minimal | 0 | 0 | 3 | 0 | 4 | 1 | 3 | 0 |
| .... mild | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 2 |
| blood vessel; Inflammation | 1 | 2 | 5 | 1 | 5 | 2 | 5 | 2 |
| .... minimal | 1 | 2 | 0 | 1 | 0 | 2 | 0 | 2 |
| .... mild | 0 | 0 | 5 | 0 | 5 | 0 | 5 | 0 |
| bronchointerstitial; Inflammation | 0 | 0 | 5 | 1 | 5 | 2 | 5 | 2 |
| .... minimal | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| .... mild | 0 | 0 | 2 | 0 | 2 | 0 | 4 | 0 |
| .... moderate | 0 | 0 | 3 | 1 | 2 | 2 | 1 | 2 |
| Pneumonia | 0 | 0 | 5 | 1 | 5 | 2 | 5 | 2 |
| .... mild | 0 | 0 | 1 | 0 | 3 | 0 | 3 | 0 |
| .... moderate | 0 | 0 | 3 | 0 | 2 | 1 | 2 | 2 |
| .... marked | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 0 |
| bronchiole; Necrosis | 0 | 0 | 4 | 1 | 5 | 2 | 5 | 2 |
| .... mild | 0 | 0 | 2 | 1 | 3 | 2 | 2 | 1 |
| .... moderate | 0 | 0 | 2 | 0 | 2 | 0 | 3 | 1 |
| bronchiole; Necrosis; unable to score | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

Source: Sponsor's table from Report No. ARDS-MM

**Table 24. Observational Assessments of Histopathologic Analysis of Lungs From Mice With ARDS**

- Bronchointerstitial inflammation (2 days) – animals with moderate inflammation
  - Vehicle 3/5 (60%)
  - 3 mg sabizabulin 2/5 (40%)
  - 9 mg sabizabulin 1/5 (20%) – 67% reduction
- Global pneumonia severity score (2 days) – animals with moderate or marked pneumonia
  - Vehicle 4/5 (80%)
  - 3 mg sabizabulin 2/5 (40%)
  - 9 mg sabizabulin 2/5 (40%) – 50% reduction
- Global pneumonia severity score (5 days) – animals with moderate or marked pneumonia
  - Vehicle 1/1 (100%)
  - 3 mg sabizabulin 1/2 (50%)
  - 9 mg sabizabulin 0/2 (0%) – 100% reduction

Source: Sponsor's table from Report No. ARDS-MM

As shown in Table 25 (Sponsor's Table), as early as Day 2, the number of treatment failures (death or moderate to marked pneumonia) was less in SARS-CoV-2 infected mice that had been treated with VERU-111 (4/10 for combined 3 mg/kg and 9 mg/kg) compared to the vehicle control group (4/5). By Day 5, the number of treatment failures was also less in SARS-CoV-2 infected mice that had been treated with VERU-111 (7/10 for combined 3 mg/kg and 9 mg/kg) compared to the vehicle control group (5/5).

**Table 25. Number of Clinical Treatment Failures Defined as Death or Respiratory Distress (Moderate or Marked Pneumonia)**

| Treatment Failures | Day 2 | Day 5 |
|---|---|---|
| Vehicle | 4/5 (80%) | 5/5 (100%) |
| 3 mg/kg | 2/5 (40%) | 4/5 (80%) |
| 9 mg/kg | 2/5 (40%) | 3/5 (60%) |
| All treated | 4/10 (40%) | 7/10 (70%) |

Source: Sponsor's table from Report No. ARDS-MM

On Day 5 post infection, SARS-CoV-2 infected mice that had been treated with VERU-111 at either 3 mg/kg or 9 mg/kg had a 40% combined survival (4/10) vs. 20% survival (1/5) for the vehicle control group.

**Conclusion(s):** In an aged mouse model of acute respiratory distress syndrome, BALB/c mice infected with mouse-adapted SARS-CoV-2 and simultaneously administered once daily oral gavage doses of VERU-111 (3 mg/kg or 9 mg/kg) displayed a decrease in deaths and global pneumonia severity score. Of note, the number of mice on Day 5 was low compared to Day 2, which limited the confidence in the results (i.e., mice that died during the study were not submitted to histopathology examinations of the lungs). The decreases in bronchointerstitial

inflammation and/or lung congestion were less convincing. There were no comparable studies with colchicine to allow for a comparison between VERU-111 and colchicine.

## 11.2 Summary of Data Reviewed for Nonclinical Virology-Related Studies

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 critical cell functions and not direct-acting antiviral activity. The reader is referred to the Clinical Virology review for more details.

# 12 Chemistry, Manufacturing, Controls, and Product Quality information

The reader is referred to the following reviews in DARRTS:

- Biopharmaceutics review filed 10/28/2022 under EUA 000113.
- Chemistry, Manufacturing, Controls, and Product Quality reviews filed 11/02/2022 and 11/07/2022 under EUA 000113.

# 13 Office of Scientific Integrity Clinical Trial Site Inspections

The reader is referred to the OSI consult review document filed in DARRTS under EUA 000113 on 10/11/2022. Clinical trial site inspections of multiple sites as well as the contract research organization were undertaken for this EUA review. No actions were indicated based on the basis of these inspections.

# 14 Recommendations From Treatment Guidelines and Other Sources

At the time of this review, the COVID-19 Treatment Guidelines Panel recommends remdesivir, dexamethasone, and either baricitinib or tocilizumab in the population of patients hospitalized with COVID-19 who require oxygen, which is similar to the subject population enrolled in trials of VERU-111. The strength of the evidence for using each of these therapeutics varies depending on the method of oxygen delivery that the patient is requiring to maintain oxygen saturations and other factors. See the National Institutes of Health (NIH) COVID-19 Treatment Guidelines (NIH 2021) for further details.

# 15 Advisory Committee Summary

A summary of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, on November 9, 2022, is provided below. The reader is referred to the transcript of the PADAC meeting for full details of the committee discussions.

The committee discussed the request for Emergency Use Authorization 113, for sabizabulin oral capsule, a tubulin polymerization inhibitor, submitted by Veru Inc., for the treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk of acute respiratory distress syndrome. A focus of the discussion included the treatment effect size in the context of the high placebo mortality rate, the limited size of the safety database, and identifying the proposed population.

The PADAC included Sponsor and FDA presentations, clarifying questions from the PADAC, as well as the Open Public Hearing, followed by discussion and voting questions.

***Questions to the Committee:***

1. **DISCUSSION:** Discuss the strength of the all-cause mortality data, specifically considering the uncertainties raised by the Agency in Study 902, including the high observed placebo mortality rate, potential for unblinding, differences in standard of care before and during the trial, differences in timing of enrollment, potential differences in goals of care decision-making, and defining the studied population.

Overall, the Committee acknowledged that Study 902 met its primary endpoint of all-cause mortality at Day 60 and that the results were clinically significant. However, the Committee also agreed that the validity and strength of the data in Study 902 are questionable and insufficient to determine efficacy of VERU-111 due to the uncertainties raised by the Agency. Several Committee members expressed their concern with the small study sample size, the precision of efficacy estimates, and that unblinding in the study due to dissimilarities in drug powder appearance may have influenced outcomes and the validity of the results. Additionally, differences in standard of care before and during the trial, as well as differences in timing of enrollment, were noted to influence the interpretability and applicability of the data by some members. Some members expressed concern regarding the high placebo mortality in the World Health Organization Ordinal Scale for Improvement (WHO) 4 group. Another member noted that the observed high placebo mortality rate may have been less concerning overall for study conduct given the fast-evolving nature of the COVID-19 pandemic, but that it may have influenced the mortality estimates in this particular subject pool due to the small sample size and 2:1 randomization schema. One member noted that even small baseline differences in such a small placebo control group could exert a large impact on the mortality estimate. One member noted that having data on goals of care and other aspects of standard of care (e.g., ventilation strategies) would make a difference in understanding the mortality; another member noted that potential differences in goals of care decision-making may exist widely and will be variable across clinical trials studying this disease.

2. **DISCUSSION:** Discuss your level of concern regarding the limited size of the safety database for this new molecular entity.

The majority of the Committee members expressed concern regarding the limited size of the safety database given that VERU-111 is a new molecular entity. Multiple members expressed concerns regarding the uncertainty of the safety profile provided, but also noted that these safety concerns may be mitigated by the potential mortality benefit and the proposed context of use in hospitalized patients. Members highlighted that the small safety database may not have captured rare adverse events. One member added that the lack of clarity regarding VERU-111's mechanism of action made it unclear which safety signals should be monitored.

3. **VOTE:** Do the known and potential benefits of VERU-111 when used for the treatment of adult patients hospitalized with COVID-19 at high risk of ARDS outweigh the known and potential risks of VERU-111?
    a. If yes, discuss the appropriate patient population in which VERU-111 should be authorized.
    b. If no, discuss what additional data would be necessary to assess the benefits vs. the risks of treatment.

**Vote Result**: **Yes: 5 No: 8 Abstain: 0**

The majority of the Committee members voted "No", indicating that the known and potential benefits of VERU-111 when used for the treatment of adult patients hospitalized with COVID-19 at high risk of ARDS do not outweigh the known and potential risks of VERU-111. Members expressed concerns that the data from the small study sample size lack robustness and the study design raises more questions and uncertainties. Additionally, members agreed that the uncertainty in the proposed patient population for use and the unclear mechanism of action of this drug in COVID-19 make it difficult to determine the appropriate patient population in which VERU-111 should be authorized and the appropriate timing of administration. Members recommended that the Applicant conduct additional studies which include patients with a wider variety of demographics, and some members suggested that the Sponsor focus on a more narrowly-defined population of COVID-19 patients, to better determine which patients could benefit. In addition, members commented that an emergency use authorization may hinder assessment of the risk-benefit profile in the long term. Some members stated that it would be reasonable to request that a larger clinical trial be conducted to better assess VERU-111's risk-benefit profile given the high prevalence of hospitalized patients with COVID-19 at high risk of ARDS. Some members commented that the appropriate patient population in which VERU-111 should be authorized might be patients who are hospitalized with a score of a 5 or 6 on the World Health Organization (WHO) Ordinal Scale for Clinical Improvement who failed maximum standard of care therapy.

Committee members who voted "Yes" agreed the data presented were sufficient to meet EUA criteria. Some of these members expressed their shared concerns that Study 902's small sample size and study design limitations made it difficult to assess efficacy and safety of VERU-111. One member that voted yes noted that they agreed with all the uncertainties advocated by those voting "No" as well. However, since there are patients that could potentially benefit from this drug, members suggested that the EUA could be granted to give these patients facing the high mortality rate of ARDS more options, while larger clinical trials are conducted concurrently.

4. **DISCUSSION:** If authorized, the Agency believes that additional data are necessary to understand the benefit-risk assessment as a condition of authorization. Please discuss the proposed design aspects of a study to provide this additional data.

Overall, the Committee members agreed with the Agency that additional data are necessary to understand the benefit-risk assessment as a condition of authorization, should sabizabulin be authorized for emergency use. Several members agreed that understanding the mechanism of action is important to better understand the benefit-risk assessment as a condition of authorization. A couple of members recommended measuring biomarkers for host-immune response and biomarkers for VERU-111's hypothesized antiviral mechanism of action. Members stated that correlating findings from biomarkers with a meaningful clinical endpoint would help determine which patient population would benefit from this drug. Another member recommended enrolling patients at earlier stages of COVID-19 to address the issue related to timing of administering VERU-111, while others suggested narrowing the patient population to subjects with WHO 5 or 6 severity for future study. Members noted that enrollment criteria and data collection that addressed the timing of enrollment, goals of care data collection, and elements of standard of care therapy would help reduce the uncertainties in the trial results. Some members also recommended that subsequent studies should further stratify patients who are hospitalized based on diagnosis at time of hospitalization. These members highlighted that comparing those patients who are hospitalized due to COVID-19 versus those hospitalized primarily due to other conditions that are further complicated by coincident COVID-19 is important for evaluating efficacy. See the transcript for details of the Committee's discussion.

# 16 Benefit-Risk Assessment and Recommendations

The efficacy and safety data for the Sponsor's Emergency Use Authorization request rely primarily on Study 902, a 2:1 randomized, double blind, placebo controlled, efficacy and safety trial of VERU-111 in hospitalized subjects with COVID-19 on supplemental oxygen, that ultimately randomized 204 subjects with WHO 5 and 6 COVID-19 severity and a subset of WHO 4 severity, and was stopped early after an interim efficacy analysis showed a statistically significant difference in ACM between study arms.

**Safety**

In summarizing the safety review, the most important observation to consider is that the COVID-19-specific safety database for this new molecular entity only included 149 subjects exposed to VERU-111 between Studies 901 and 902. This total COVID-19-specific exposure is considerably smaller than current standard of care drugs available, approved, or authorized for COVID-19 such as dexamethasone, remdesivir, baricitinib, and tocilizumab, while the more recent authorization of anakinra included exposure to anakinra in 405 subjects with COVID-19 and additional exposure in other non-COVID-19 indications. The lack of a robust safety database contributes to the uncertainty in the potential safety of the product, and limits the review team's ability to draw conclusions on rare events or serious adverse events. With these limitations, the available data suggest imbalances in common adverse events including urinary tract infections, gastrointestinal adverse events (including diarrhea and nausea/vomiting that are familiar from the safety profile of colchicine), as well as anemia, dermatologic events, and a small imbalance in venous thromboembolism events. The overall impact of these potential safety signals on benefit-risk is dependent primarily on the level of confidence for the potential efficacy signal for all-cause mortality.

**Efficacy**

For the primary endpoint of all-cause mortality at Day 60, at interim, 76.5% of subjects treated in the VERU-111 arm and 53.8% of the subjects in the placebo arm remained alive. The odds ratio

for odds of staying alive was 3.2 in favor of treatment and the risk difference indicated a 23.1% change in the risk of mortality. Among all 204 randomized subjects, 78.4% of subjects treated in the Veru arm and 58.6% of the subjects in the placebo arm remained alive at Day 60. The odds ratio for the odds of staying alive was 2.8 in favor of treatment and the analysis indicated a 19% greater chance of remaining alive in the treatment group. The primary analysis conclusion remained robust to missing data assumptions. Sensitivity analyses including the addition of covariates to control for baseline imbalances had minimal impact on the primary analysis results, and subgroup analyses results were consistent with the primary analysis. These post-hoc analyses were simplistic explorations using available data and may not have correctly captured the relationship between all imbalanced factors and the outcome, and further exploration of the effect of interaction of imbalanced factors was not possible due to the limitations of the sample size. As such, these exploratory analyses cannot completely eliminate the potential impact of random baseline imbalances across treatment groups on the study findings.

Additional secondary and exploratory endpoint data suggested that the proportion of subjects alive odds of being alive at Day 29 was higher in the VERU-111 arm, with an odds ratio of 2.15, 95% CI: 1.02, 4.56 and a risk difference of 11.9% favoring treatment; this difference was lower at Day 29 and earlier timepoints than at Day 60. A positive trend for efficacy was seen in secondary endpoints of “alive and free of respiratory failure at day 29”, “days in ICU”, “days in hospital”, “days on mechanical ventilation”, and “clinical improvement on WHO scale”. However, it is important to note that the calculation of each of the secondary endpoints were influenced by the mortality results, since each secondary endpoint contains a component of mortality or provides a numerical penalty for mortality events. Thus, while supportive, these results were influenced by results in mortality, and so the interpretation of mortality endpoints influences the interpretation of these endpoints as well.

When considering the observed efficacy differences, the Division identified multiple uncertainties that potentially limited interpretation of the mortality data.

**Placebo Mortality**

The comparatively high placebo mortality rate observed in Study 902, especially at US and North American sites as well as in the randomized subset of subjects with baseline WHO 4 severity, raises uncertainty in the interpretation of the observed all-cause mortality results. Prior and concurrent studies conducted in populations with similar baseline severity have reported lower Day 60 mortality rates for the placebo arm. Given placebo mortality data from contemporary trials to Study 902 – as well as earlier trials conducted when treatment options were more limited and in the presence of variants associated with a higher mortality rate – the mortality rate observed in Study 902 appears to be higher than what would be expected in the study population.

**Potential Unblinding**

The potential unblinding events from opening study drug capsules may have led to performance bias in Study 902. The potential influence of performance bias contributes to uncertainty in other aspects of the trial conduct (e.g., standard of care therapies, goals of care), as well as potentially endangering study validity. Several features of Study 902 may have increased its vulnerability to performance bias. Many of the frequent and clinically important medical interventions required for the care of subjects with severe and critical COVID-19 require medical decision-making about the benefit-risk of additional interventions in the context of the provider’s perception of the subject’s overall prognosis, which may have been influenced by knowledge of

treatment assignment. In addition, treatment expectations and communication (including goals of care) may have been influenced by the fact that the only data available to investigators regarding the efficacy of VERU-111 touted a significant mortality benefit from the small, proof-of-concept-focused Study 902. Goals of care decision-making is a frequent occurrence in critically ill patients, and potential unblinding and prior available efficacy data may have led to subconscious influence on goals of care decision-making as a form of performance bias. Study 902 did not collect formal datapoints on goals of care decision-making, however evidence from the study narratives suggest goals of care decision-making that would influence study endpoints did occur, including subjects whose goals of care did not include intubation and mechanical ventilation. These considerations once again are heightened by the fact that this was a small trial with a 2:1 randomization ratio and potential unblinding events, where only a few death events in the placebo arm that are not directly attributable to treatment assignment might have had an exaggerated effect on the mortality results. Finally, the urgency of these pharmacological and non-pharmacological interventions may have been influenced by the overall care patterns of the pandemic.

**Standard of Care Therapies**

The use of local standard of care for COVID-19 at international study sites introduces uncertainty in the interpretation of the mortality data for US healthcare systems, because in some cases the SOC appeared to differ substantially from accepted elements of US SOC for COVID-19. The rates of SOC therapy use (e.g., remdesivir, immunomodulators) and durations of SOC therapies such as corticosteroids suggest that standard of care in Study 902 may not be representative of US SOC practices. In addition, there were small, but clinically relevant imbalances in Study 902 in baseline SOC medications for COVID-19 and in the proportion of subjects in the ICU at baseline. Data collection on non-pharmacologic elements of SOC at baseline, before randomization, and after randomization in Study 902 was limited, and the lack of these datapoints limits the exploration of the potential influence of performance bias on post-randomization care in the setting of potential unblinding events. These uncertainties in SOC limit the review team's ability to assess the full scope of their potential influence on the efficacy results.

**Mechanism of Action and Colchicine Data**

The mechanism of action of VERU-111 in COVID-19 is uncertain, but the proposed anti-inflammatory mechanism relies on data from colchicine. The Sponsor has presented no compelling nonclinical or clinical evidence of their claim of an additional anti-viral mechanism of action. Further complicating this uncertainty, data from colchicine – which also disrupts microtubules through a similar mechanism of action – has not shown evidence of effectiveness in the treatment of COVID-19 in larger, double-blind, randomized, controlled trials.

**Timing of Enrollment and SOC Therapies**

The timing of enrollment in subjects' COVID-19 clinical course in Study 902 also raises uncertainties in the interpretation of the efficacy results. Without an upper limit on how long subjects could have been hospitalized or received COVID-19 care, subjects were likely at different stages of disease and recovery prior to randomization. COVID-19 severity and trajectory data prior to randomization were limited, limiting the review team's ability to more thoroughly assess the effects of this issue on the efficacy estimates. However, the limited available data suggest that at least some subjects were already on a clinical trajectory of improvement prior to randomization in study 902, including two subjects who were previously

intubated during their COVID-19 hospitalization and extubated prior to randomization. While the scope of this uncertainty is unclear, these examples complicate the interpretation of the efficacy results in this small study.

**Clinical Population**

Finally, there are additional potential uncertainties related to the clinical relevance of – and the data collection for – the designated population described as "high risk for ARDS". It is unclear whether the proposed grouping of comorbidities is clinically meaningful or clinically useful to designate a distinct group of patients in clinical care. The term has no defined regulatory or clinical meaning, and it is not clear whether the Sponsor's criteria would accurately identify the group of subjects who are at high risk of ARDS, those who are not at high risk of ARDS, or even those who would benefit from VERU-111. In addition, no data were collected on some of the chosen parameters, heightening the uncertainty on which parameters – if any – would best guide physician decision-making in the setting of an authorization. Finally, consideration of authorization in only a specific, more clearly defined, severity subset (e.g., WHO 5 and 6 severity) is further limited by the considerably smaller size of such subsets in addition to the uncertainties noted above.

**Summary**

When taken separately, no single uncertainty noted here would directly undermine the efficacy results from Study 902. Many of these issues might not influence the overall interpretation in a very large trial, but each leads to considerable uncertainty in this small trial with a 2:1 randomization ratio, small baseline imbalances, limited data collection, and concerns for potential unblinding events. In addition, many of these uncertainties are unclear in scope based on available study data, which limits the review team's ability to assess their potential effects on the efficacy results through additional sensitivity analyses. However, when taken together with the small sample size and two-to-one randomization ratio of Study 902, these multiple uncertainties create significant limitations in the interpretation of the efficacy and safety results. These issues limit the review team's ability to fully evaluate the potential risks and potential benefits of VERU-111 for the treatment of hospitalized patients with COVID-19 at high risk of ARDS without additional data.

In summary, the Division acknowledges that COVID-19 is a serious or life-threatening disease or condition caused by the agent specified in the declaration of emergency. However, given the significant uncertainties summarized above and the input and discussion from the PADAC, the Division concludes that – based on the totality of the scientific evidence available to FDA – the review team is not able to make a determination that the known and potential benefits outweigh the known and potential risks of the product when used to treat the serious or life-threatening disease or condition. The review team is therefore unable to make the determination that it is reasonable to believe that this product may be effective in treating the serious or life-threatening disease or condition. Based on these determinations, the Division recommends that the Director decline to authorize VERU-111 for the treatment of hospitalized subjects with COVID-19 at high risk of ARDS.

Despite this recommendation not to authorize based on the currently available data, at the time of this review the Division is actively providing feedback on a protocol for an additional randomized, double-blind, placebo-controlled trial submitted by the Sponsor to provide additional evidence of the efficacy and safety of VERU-111 in COVID-19. Considerations for the design of additional trials were discussed by the Pulmonary-Allergy Drugs Advisory Committee (see Section 15), and the review team's summary of elements of trial design for a future trial of

VERU-111 is detailed below (see Section 17). Given the unmet need for safe and effective COVID-19 therapies noted above, additional data from a well-designed trial that addresses the uncertainties noted in the clinical development program to date may have the potential to address the limitations noted in development to date and allow for reconsideration of authorization.

# 17 Considerations for Additional Trials

Given the Division's recommendation not to authorize VERU-111, additional trials are warranted to characterize the safety and efficacy of VERU-111 for the treatment of hospitalized patients with COVID-19. Such trials would allow for further characterization of the safety profile of VERU-111, address uncertainties identified in the interpretation of the efficacy results of Study 902, and provide 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 ability of the trial to provide additional clinically interpretable efficacy and safety data in hospitalized subjects with COVID-19 relies on revising key design elements from Study 902.

Randomization in a 1:1 ratio would improve the precision of treatment effect estimates compared to 2:1 randomization at a fixed sample size. Stratifying allocation by site and adjusting for site in the analysis could improve the interpretability of efficacy data by reducing the variance in the outcome resulting from site differences. In addition, depending on the target population chosen by the Sponsor, stratifying recruitment to ensure that there is adequate representation of each severity grade would improve the reliability of the inferences about the treatment effects within severity levels.

Adequate blinding and use of a matched placebo is of paramount importance to any future trial of VERU-111 to ensure trial validity. A fully matched placebo would eliminate unblinding concerns and also eliminate the resultant concerns related to the potential effects of performance bias on the efficacy results through its effects on pharmacologic standard of care treatments, non-pharmacologic standard of care treatments, and goals of care decision-making.

The review team and Advisory Committee members noted that the targeted COVID-19 population in Study 902 was unclear in terms of whether the proposed definition accurately identified a population of clinical relevance, whether there was adequate representation of each element of the defined population in the trial, and whether efficacy would be maintained across comorbidities identified as part of the definition. Collecting data on each element of the defined "high risk of ARDS" comorbidities in all subjects would begin to address this issue. Stratifying recruitment by baseline severity would also address one aspect of this uncertainty. In addition, a larger sample size would also provide more robust characterization of the defined group. Alternatively, expansion of the targeted population to a more identifiable population such as "hospitalized subjects with COVID-19 requiring supplemental oxygen by simple nasal cannula, simple mask, high flow nasal cannula, noninvasive positive pressure ventilation, or invasive mechanical ventilation to maintain oxygen saturations" (i.e., the entirety of patients with WHO 4, 5, or 6 severity, rather than the current approach that only includes a subset of WHO 4) might also eliminate this concern in conjunction with stratification of recruitment by severity.

Given its expected context of use, limiting the timing of enrollment to subjects who are randomized at a similar, early stage of their hospitalized COVID-19 disease course would improve the interpretability of the efficacy and safety results. This goal would be accomplished by imposing an upper limit on the days of hospitalization prior to enrollment; while an Advisory

Committee member suggested a limit of two days' time, a limit of up to five days would likely also be acceptable and lead to increased interpretability. Notably, this approach has been used by other trials of drugs to treat COVID-19.

The Sponsor has consistently focused on an all-cause mortality primary endpoint during their COVID-19 drug development, and all-cause mortality remains the most clinically relevant outcome in COVID-19. Efficiency could be improved for this additional trial when using a mortality outcome by pre-specifying appropriate interim analyses should a strong efficacy signal be observed. Alternatively, the primary endpoint of "alive and free of respiratory failure" at a relevant study date (e.g., Day 60, or possibly Day 29 or 45) could potentially improve statistical power while still providing clinically meaningful data to support a determination of "may be effective" for an EUA or even possibly substantial evidence of effectiveness for an eventual approval.

While acknowledging that standard of care may vary across US sites and international sites, providing some protocol-mandated guidance on standard of care would likely also improve the interpretability of the efficacy data. Recommendations regarding the indications, choice of, and durations of pharmacologic standard of care therapies with references to accepted treatment guidelines (e.g., NIH COVID-19 Treatment Guidelines) would likely accomplish this. Adherence to internationally recognized recommendations regarding non-pharmacologic measures accepted to influence mortality or other clinically relevant outcomes (e.g., low-tidal volume ventilation for ARDS, proning for severe ARDS, conservative fluid strategy for ARDS) should also be mandated by the protocol. Data capture on each of these points (e.g., use of remdesivir, dexamethasone, immunomodulators such as baricitinib, presence of ARDS, use of low tidal volume ventilation for ARDS, etc.) would be valuable for sensitivity analysis, should this prove necessary for interpretation. Similarly, data on subjects' goals of care decision-making at the time of randomization would allow for an understanding of their possible effect on trial outcomes in conjunction with data capture of changes in goals of care during the trial (e.g., data capture of a change to "do not intubate" or any other withdrawal or withholding of life-sustaining therapy).

Given that the placebo mortality in Study 902 (and especially in the WHO 4 group and US sites) was high in comparison to some comparable, contemporary COVID-19 trials, the size of a future trial is still an area of uncertainty. Based on these concerns and the other uncertainties noted above, power calculations with assumptions of a more conservative effect size and somewhat lower placebo mortality would be prudent. Additionally, the Division previously proposed that a safety database of ~500 subjects receiving VERU-111 for the proposed indication would be an expectation for Emergency Use Authorization, and this should be considered for future trial design as well. Based on Advisory Committee feedback, strong consideration should be given to appropriate timeframes for interim analyses so that – should a strong efficacy signal again be observed – the trial could be stopped in an efficient timeframe.

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. The Division has considered the feasibility and utility of multiple trial designs in conjunction with the Sponsor and general agreement has been reached on the following trial design elements specifically:

- A randomized, double-blind, fully matched placebo-controlled superiority design of VERU-111 + standard-of-care versus placebo+standard of care among a population of subjects hospitalized with COVID-19.

Additional guidance will be provided in response to a recent protocol elements submission by the Sponsor.

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# 19 Appendices

## 19.1 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 26). 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 26. 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<br>(Study 101)<br><br>Nonrandomized, Open-label, multiple ascending dose study<br><br>Study ongoing | VERU-111 4.5 to 45 mg daily for up to four 7- to 21-day cycles PO<br><br>VERU-111 4.5 to 45 mg daily for up to four 7- to 21-day cycles PO + SOC secondary androgen-blocking agent<br><br>Up to four 21-day cycles | 33<br><br>6 | Adult male with histo- or cytologically proven metastatic castration-resistant small cell prostate cancer<br><br>Prior treatment with ≥1 novel androgen receptor blocking therapy<br><br>ECOG performance status ≤2<br><br>No clinically relevant anemia, creatinine elevation, hepatic dysfunction, neutropenia, thrombocytopenia | Primary<br>Safety: Incidence of grade 3 to 5 toxicities<br><br>Efficacy: Radiographic progression-free survival<br><br>Secondary<br>PSA Progression-free survival<br><br>Progression-free survival<br><br>$PSA_{50}$ Response rate<br><br>Objective response rate |
| V3011102<br>(VERACITY)<br><br>Randomized, open-label, active control, duration<br><br>Study ongoing | VERU-111 32 mg daily PO<br><br>VERU-111 26 mg daily PO<br><br>Androgen receptor targeting agent (Abiraterone or enzalutamide)<br><br>Until evidence of progression | 82<br><br>82<br><br>82 | Adult male with histo- or cytologically proven metastatic castration-resistant adenocarcinoma of the prostate (excluding small cell carcinoma)<br><br>Prior treatment with ≥1 novel androgen receptor blocking therapy<br><br>ECOG performance status ≤2<br><br>No clinically relevant anemia, creatinine elevation, hepatic dysfunction, neutropenia, thrombocytopenia | Primary<br>Radiographic progression-free survival<br><br>Secondary<br>Overall survival<br>Objective response rate<br>Duration of objective response<br>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

## 19.2 Trial Design and Efficacy Review, V0211901 (Study 901)

### 19.2.1 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:

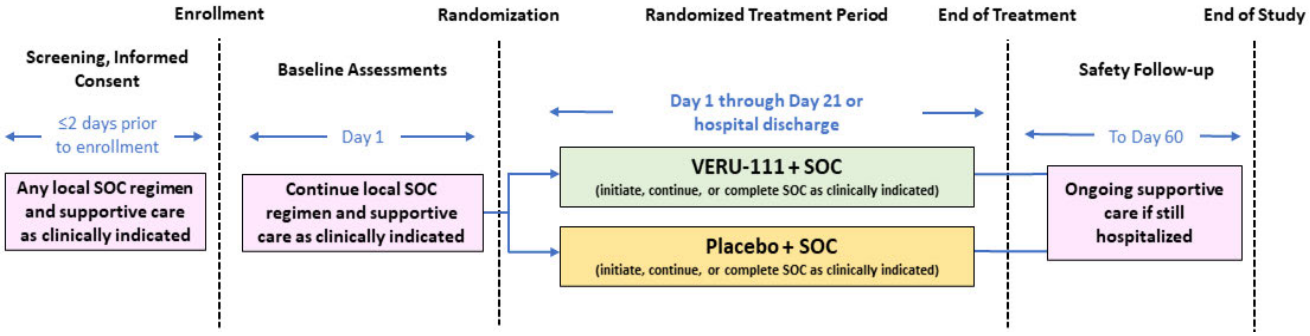
- To assess the safety and tolerability of VERU-111

### 19.2.2 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 24, below.

**Figure 24. Trial Schematic, Study 901**




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

**Trial Duration and Clinical Visits**

As shown in Figure 24, 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.

### 19.2.3 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

### 19.2.4 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.

### 19.2.5 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

### 19.2.6 Ethics

The ethical statements for Study 901 included in the protocol are substantively similar to those included for Study 902. See Section 7.1.9 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.

### 19.2.7 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

### 19.2.8 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 27). 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 27. Schedule of Safety Assessments, Study 901**

| 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

### 19.2.9 Study 901 Results in Detail

Key efficacy analyses for Study 901 are presented in Table 28, below.

**Table 28. Key Efficacy Analyses, ITT Set, Trial V0211901**

| Analyses | 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) | - |

| Analyses | VERU-111 18 mg N=19 | Placebo N=20 |
|---|---|---|
| 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; SE, standard error

# 19.3 Nonclinical Toxicology Studies

## Introduction

The nonclinical development program for VERU-111 consisted of primary pharmacology (in vitro and in vivo), GLP-compliant safety pharmacology (in vitro human-ether-a-go-go-related gene [hERG] assay, central nervous system (CNS) evaluation in rats, and cardiovascular and respiratory evaluation in dogs), pharmacokinetics (PK; single-dose intravenous or oral gavage in rats, single-dose or repeat-dose intravenous or oral gavage in dogs under fed/fasted conditions, repeat-dose oral capsule in dogs, radiolabeled oral excretion and tissue distribution in rats, and radiolabeled mass balance and metabolite identification in dogs), GLP-compliant repeat-dose toxicity (28-day oral in rats, 28-day oral in dogs, and 91-day oral in rats), GLP-compliant genotoxicity (in vitro reverse mutation assay and in vitro micronucleus assay), GLP-compliant phototoxicity (in vitro neutral red uptake phototoxicity assay), and information from the literature (related to mechanism of action). There are no carcinogenicity, reproductive and developmental toxicology, or local tolerance studies with VERU-111.

## Safety Pharmacology

The safety pharmacology of VERU-111 was evaluated both in vitro and in vivo. The in vitro safety pharmacology study with VERU-111 included a GLP-compliant hERG assay. The in vivo safety pharmacology studies with VERU-111 included a GLP-compliant CNS safety pharmacology study in rats and a GLP-compliant cardiovascular and respiratory safety pharmacology in dogs. The safety pharmacology studies with VERU-111 were previously reviewed under IND 149282 and/or IND 140406 and key study findings are described below.

### Title: Evaluation of the Effects of VERU-111 on Cloned hERG Channels Expressed in Human Embryonic Kidney (HEK293) Cells (Study No. 2649-009)

In the in vitro hERG assay, hERG potassium channels were stably expressed in HEK293 cells and cells were then superfused with vehicle or VERU-111 (actual concentrations of 1.2, 3.6, or 12.7mcM). The effects on hERG-related potassium current were assessed using whole-cell patch clamp electrophysiology methods. VERU-111 showed a dose-dependent inhibition of hERG-mediated potassium currents in HEK293 cells ranging from about 13% to 28% inhibition from 3.6mcM to 27mcM VERU-111. Based on the concentration response data for VERU-111, $IC_{20}$ values were calculated as 7.27mcM (based on actual concentrations) and 9.23mcM (based on nominal concentrations).

**Title: Neurobehavioral Evaluation of Orally Administered VERU-111 in Rats (Study No. 2649-010)**

In the in vivo CNS safety pharmacology study, male CD® [Crl:CD®(SD)] rats (n=8/group) were treated once daily via oral gavage with single doses of vehicle or VERU-111 (3, 10, or 30 mg/kg). Assessment of neurobehavioral effects and general toxicity were based on mortality, functional observational battery (FOB) evaluations (conducted at predose on Day -1 and at approximately 2 and 24 hours postdose), and clinical observations. In the 30 mg/kg group, there was one death within 24 hours after treatment with VERU-111. Of note, the cause of death could not be determined but was attributed to VERU-111 based on deaths at 30 mg/kg/day VERU-111 in the 28-day repeat-dose oral toxicity study in dogs. There were no deaths in the 3 or 10 mg/kg dose groups. There were several FOB findings noted, primarily at 2 hours after treatment with VERU-111, which included an increase in palpebral closure at ≥3 mg/kg, a decrease in rearing at ≥10 mg/kg, a decrease in body temperature at ≥10 mg/kg, and a decrease in arousal at 30 mg/kg. Nearly all the findings resolved within 24 hours after dosing with VERU-111.

**Title: Cardiovascular and Respiratory Evaluation of Orally Administered VERU-111 in the Beagle Dog (Study No. 2649-011)**

In the in vivo cardiovascular and respiratory safety pharmacology study, male Beagle dogs (n=4) were treated (according to a Latin square design with a 7-day washout between treatments) with single oral doses via gelatin capsules of vehicle or VERU-111 (2, 4, or 8 mg/kg). Body temperature, blood pressure, heart rate, ECG, and respiratory function were continuously monitored via telemetry for at least 2 hours prior to dosing and for at least 24 hours postdose. There were no deaths during the study. Vomitus was noticed between 4 and 24 hours after the 8 mg/kg dose. There were no treatment-related effects on cardiovascular parameters (blood pressure, heart rate, or ECG parameters [QRS duration and the RR, PR, QT and QTc intervals]) or respiratory parameters (respiratory rate, tidal volume, and minute volume) at up to 8 mg/kg VERU-111.

**Pharmacokinetics/ADME/Toxicokinetics**

The PK of VERU-111 was assessed in three non-GLP-compliant in vivo studies as follows: 1) single-dose intravenous or oral gavage administration in rats; 2) single-dose or repeat-dose intravenous or oral gavage administration in dogs under fasted/fed conditions; and 3) repeat-dose oral capsule administration in dogs. Further, Li et al. evaluated the distribution, metabolism, and excretion profile of VERU-111 in ICR mice, Sprague-Dawley (SD) rats, and Beagle dogs (Li et al. 2012). These PK studies and the Li et al. reference were previously reviewed under IND 149282 and key study findings are described below.

Of note, a toxicokinetic (TK) assessment of VERU-111 was included in the GLP-compliant repeat-dose oral toxicity studies (28-day in rats and dogs and 91-day in rats). The TK data for the 28-day toxicity studies in rats and dogs are described below with the description of the 28-day toxicity studies.

**Title: Determination of the Pharmacokinetics of a Single Test Article Following Intravenous or Oral Administration to Rats (Study No. 2649-002)**

The PK of a single intravenous dose of VERU-111 (2 mg/kg) and single oral gavage doses of VERU-111 (1, 2, 15, and 30 mg/kg) was assessed in rats (n=3/sex/group). After single oral

administration of VERU-111, exposure (mean $C_{max}$ and AUC) increased in dose-dependent manner across doses. Systemic exposure after oral administration was less than after intravenous administration (oral bioavailability =17% to 47%).

**Title: Determination of the Pharmacokinetics of a Single Test Article Following Oral or Intravenous Administration to Dogs Under Fasted/Fed Conditions (Study No. 2649-003)**

The PK of an oral gavage dose of VERU-111 (5 mg/kg) was assessed under fasted and fed conditions in Beagle dogs (n=6/sex/group). Additionally, the PK of an intravenous dose of VERU-111 (5/1 mg/kg) and oral doses of VERU-111 (5 and 10 mg/kg) were assessed in Beagle dogs (n=6/sex/group). After oral gavage administration of 5 mg/kg VERU-111, systemic exposure ($AUC_{0-24h}$) increased under fasted conditions (2.3-fold on Day 1 and 1.5-fold on Day 7) compared to fed conditions. In general, systemic exposure to repeat administration of VERU-111 did not consistently increase in dose-proportional manner. Systemic exposure after oral administration was less than after intravenous administration (mean oral bioavailability on Day 7=35%).

**Title: Pharmacokinetic Study of VERU-111 Following Oral Administration to Dogs (Study No. 2649-006)**

The PK after oral capsule administration of VERU-111 (5 and 10 mg/kg) on Days 1, 3, and 7 was assessed in male Beagle dogs (n=3/group) on Day 1 (single-dose) and Day 7 (repeat-dose). Systemic exposure ($AUC_{0-24h}$) increased in a dose-proportional manner and did not appear to change after repeat administration.

**Distribution, Metabolism, and Excretion Profile of VERU-111 in ICR Mice, Sprague-Dawley (SD) Rats, and Beagle Dogs. (Based on Published Studies From Li et al. 2012)**

Li et al. evaluated the PK parameters after intravenous and oral administration of VERU-111 (identified as Compound-II in the publication) in ICR mice, SD rats, and Beagle dogs (Li et al. 2012). The key study findings are described below:

Distribution (nude mice):

- Only the distribution of VERU-111 into the brain was evaluated in this study.
- VERU-111 was present in the brains of mice after single oral administration at 20 mg/kg (brain/plasma concentration ratios =5% at 1 hour and 9% at 4 hours). (Of note, the 28-day toxicity studies in rats and dogs did not show any treatment-related brain findings).

Metabolism (in vitro):

- The interaction of VERU-111 with five different CYP450 enzymes (i.e., CYP2D6, CYP2C9, CYP1A2, CYP2C19 and CYP3A4) was evaluated.
- VERU-111 showed high $IC_{50}$ values (in the mcM range) for different CYP450 enzymes.
- The authors concluded that CYP-mediated drug-drug-interactions are unlikely.
- The authors stated that in vitro metabolism of VERU-111 in liver microsomes (from dog, rat, mouse, and human) showed abundant metabolite (two) formation only in dog microsomes (data not shown).

Excretion:

- Higher clearance of VERU-111 in dogs was observed compared to rodents, with no clear mechanistic explanation. (Of note, this may be the explanation for lower VERU-111 exposures in 28-day repeat-dose study in dogs.)

The Sponsor has also indicated that they are currently conducting a non-GLP PK, excretion, and tissue distribution study of [14C]-VERU-111 following oral administration in male rats (Study No. 2649-031) and a non-GLP PK, mass balance, and metabolite identification study of [14C]-VERU-111 following oral administration in male dogs (Study No. 2649-032). The Sponsor indicates these studies are ongoing and that the final study reports will be submitted to the EUA as soon as available. Of note, the final study reports were not submitted during this EUA review.

### 19.3.1 Toxicology Findings

**General Toxicology: Repeat-Dose Toxicity**

The repeat-dose toxicity of VERU-111 was evaluated in GLP-compliant 28-day and 91-day oral toxicity studies in rats and a GLP-compliant 28-day oral toxicity study in dogs. Key study findings for the 28-day oral toxicity studies with VERU-111 in rats and dogs are described below. The 91-day oral toxicity study with VERU-111 in rats is not described below as it is not needed to support this EUA submission where clinical dosing is limited to 21 days.

**Title: A 28-Day Oral Gavage Toxicity Study in Rats (Study No. 2649-012)**

In the 28-day oral toxicity and TK study in rats (about 6 weeks of age), male and female rats (n=10/sex/group) were treated once daily via oral gavage with vehicle (0.5% [w/v] methylcellulose [4000 cps] in deionized water) or VERU-111 (0.3, 1, 3, 10, or 30/20 mg/kg/day) for 28 days. Corresponding satellite groups (0, 0.3, 1, 3, 10, or 20 mg/kg/day VERU-111 for 28 days) were included for TK evaluations (n=3/sex/group for vehicle control group and n=6/sex/group for VERU-111 treated groups). The recovery of animals after a treatment-free period was not evaluated in the study. The 0.3 and 1 mg/kg/day groups were added to the study at a later date.

Due to mortality/morbidity, males in the 10 and 30/20 mg/kg/day groups were only dosed from Days 1 to 4 and females in the 10 and 20 mg/kg/day groups were only dosed from Days 1 through 3. Toxicity was noted in the 30 mg/kg/day group following the first dose; hence the dose was reduced to 20 mg/kg/day. By Day 4 or Day 5, all animals in groups ≥10 mg/kg/day were found dead or sacrificed moribund. The Sponsor attributed the cause of death/unscheduled euthanasia in seven animals to intestinal findings. The cause of death for the remaining deaths/unscheduled euthanasia was undetermined but significant postmortem changes to the intestinal tract were noted by histopathology evaluation, which indicated that stomach and/or intestinal findings (ulcers, degeneration, and/or necrosis) could be the underlying cause of death. See Table 29. Animals in the 0.3, 1, and 3 mg/kg/day groups completed 28 days of dosing.

**Table 29. Unscheduled Euthanasia and/or Deaths in 28-Day Toxicology Study With VERU-111 in Rats, Study No. 2649-012**

| Animal No | Sex | Dose Level (mg/kg) | Fate/ Animal disposition | Fate Day | Cause of death/ Euthanasia |
|---|---|---|---|---|---|
| 3001 | M | 10 | FD | 4 | Undetermined |
| 3002 | M | 10 | EE | 4 | Cecum; Mucosal necrosis/degeneration |
| 3007 | M | 10 | FD | 4 | Undetermined |
| 3008 | M | 10 | EE | 4 | Duodenum; Mucosal necrosis/degeneration |
| 3010 | M | 10 | FD | 5 | Undetermined |
| 4003 | M | 30/20 | FD | 4 | Undetermined |
| 4004 | M | 30/20 | FD | 4 | Undetermined |
| 4008 | M | 30/20 | FD | 4 | Undetermined |
| 4110 | M | 30/20 | FD | 5 | Undetermined |
| 3501 | F | 10 | EE | 4 | Cecum; Mucosal necrosis/degeneration |
| 3507 | F | 10 | FD | 4 | Cecum; Mucosal necrosis/degeneration |
| 3508 | F | 10 | EE | 4 | Rectum; Mucosal necrosis/degeneration |
| 4603 | F | 30/20 | FD | 5 | Cecum; Mucosal necrosis/degeneration |
| 4506 | F | 30/20 | FD | 4 | Undetermined |
| 4507 | F | 30/20 | EE | 4 | Cecum; Mucosal necrosis/degeneration |
| EE: Euthanized in extremis; FD: Found dead | | | | | |

Source: Table prepared by the Reviewer
Abbreviations: F, female; M, male; VERU-111, sabizabulin

Several animals treated with ≥10 mg/kg/day had decreased activity, soft feces, hunched posture, thin appearance, sparse or wet hair, and/or red material around nose/eyes. The most frequent clinical observations in these animals were noted on Days 2 and 5.

Decreases in bodyweight, with corresponding decreases in food consumption, were noted at doses ≥10 mg/kg/day. Animals in the 3 mg/kg/day group exhibited lower bodyweight gain over the 4-week treatment period compared to the vehicle control group. Males in the 3 mg/kg/day group consumed 23% less food compared to vehicle control animals. See Table 30 (bodyweight changes).

**Table 30. Bodyweight Changes in 28-Day Toxicology Study With VERU-111 in Rats, Study No. 2649-012**

| | Males | | | | | | Females | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | VERU-111 (mg/kg/day) | | | | | | VERU-111 (mg/kg/day) | | | | | |
| **BW** | **0** | **0.3** | **1** | **3** | **10** | **30/20** | **0** | **0.3** | **1** | **3** | **10** | **30/20** |
| BW, Day -1 (g) | 350.3 | 204.1 | 203.6 | 347.7 | 346.4 | 333.7 | 228.1 | 169.6 | 164.1 | 228 | 225.4 | 221.5 |
| BW, Day 28 (g) | 489.6 | 432.5 | 417.1 | 445.5 | - | - | 279.1 | 252.8 | 245.5 | 271.2 | - | - |
| Δ | 139.3 | 228.4 | 213.5 | 97.8 | - | - | 51 | 83.2 | 81.4 | 43.2 | - | - |
| BW, % Day -1 | 39.8 | 111.9 | 104.9 | 28.1 | - | - | 22.4 | 49.1 | 49.6 | 18.9 | - | - |
| BW, % Control | 100.0 | 281.4 | 263.7 | 70.7 | - | - | 100.0 | 219.4 | 221.9 | 84.7 | - | - |

Source: Table prepared by the Reviewer
Abbreviations: BW, body weight; Δ, change; VERU-111, sabizabulin

The 0.3 and 1 mg/kg/day groups were added to the study at a later date.

Moderate to marked decreases in absolute reticulocyte count and mild to moderate decreases in platelet counts were noted in both sexes at ≥10 mg/kg/day that reflected decreased hematopoiesis and corresponded to decreased hematopoietic cellularity of the bone marrow. Mild to moderate decreases in lymphocyte counts in males at ≥10 mg/kg/day and females at

10 mg/kg/day, and moderate decreases in eosinophil counts were noted in both sexes at ≥10 mg/kg/day. Decreased lymphocyte counts corresponded to decreased lymphocytes in multiple lymphoid tissues (likely secondary to intestinal degeneration/necrosis). Moderate prolongations (about 15%) in activated partial thromboplastin time (APTT) were noted among individual animals of both sexes at doses ≥10 mg/kg/day. Findings indicative of an inflammatory response, such as increased neutrophils (30/20 mg/kg/day only) and fibrinogen (≥10 mg/kg/day), were also noted. Increases in alanine aminotransferase (ALT; 1.8- to 5.4-fold) and aspartate aminotransferase (AST; 1.7- to 5.7-fold) were reported in animals treated with doses ≥10 mg/kg/day. Minimal to moderate increases in alkaline phosphatase (ALP; 1.2- to 4.2-fold) were also observed at all doses. These observations also correlated with minimal to moderate karyocytomegaly and minimal to mild single-cell necrosis and vacuolation in the liver.

Organ weight changes were noted in the spleen (50% decrease in the 10 mg/kg/day group and 30% decrease in the 30 mg/kg/day group), thymus (70% decrease in the 10 mg/kg/day group and 50% decrease in the 30 mg/kg/day group), adrenal gland (about 3-fold increase in absolute weight and about 1.8-fold increase in % brain weight in ≥10 mg/kg/day groups), and heart (about 25% to 30% decrease in absolute and % brain weight at ≥10 mg/kg/day). These organ weight changes due to VERU-111 treatment were not dose-dependent.

Test article related histopathology changes were observed in animals treated with VERU-111 at doses ≥3 mg/kg/day in several target organs including the gastrointestinal (GI) tract, heart, liver, lymphatic system, male reproductive system, and adrenal glands as follows (See Table 31):

- GI: minimal to marked findings of squamous cell hyperplasia (≥3 mg/kg/day), erosion/ulceration (≥3 mg/kg/day), villus atrophy (≥3 mg/kg/day), and/or single cell necrosis (≥10 mg/kg/day) of the epithelial surface in the non-glandular region of the stomach and degenerative and regenerative findings in the mucosa of the duodenum, jejunum, ileum, cecum, colon and/or rectum (generally at ≥10 mg/kg/day)
- Heart: minimal to moderate myofiber degeneration/necrosis and/or hemorrhage (≥10 mg/kg/day)
- Liver: minimal to moderate karyocytomegaly (≥10 mg/kg/day), minimal to mild single cell necrosis (≥10 mg/kg/day), and/or vacuolation (≥3 mg/kg/day) (generally correlated with increased ALP, ALT, and AST)
- Bone marrow: mild to severe findings of decreased cellularity in the hematopoietic cells of bone marrow (≥3 mg/kg/day) that correlated with decreased reticulocyte and platelet counts
- Lymphatic system: minimal to marked multi-organ lymphoid depletion (thymus, spleen, lymph nodes, and/or GALT) (≥3 mg/kg/day) (generally correlated with decreased spleen and thymus weight, decreased lymphocytes)
- Male reproductive system: moderate to severe tubular degeneration/necrosis and/or minimal to moderate dilation of seminiferous tubules of the testis resulting in moderate to marked decreased sperm and/or increased germ cell debris in epididymis (≥10 mg/kg/day)
- Adrenal glands: minimal to moderate diffuse cortical hypertrophy and minimal vacuolation (≥3 mg/kg/day)

**Table 31. Histopathology Findings in 28-Day Toxicology Study With VERU-111 in Rats, Study No. 2649-012**

| | Males | | | | | | Females | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | VERU-111 (mg/kg/day) | | | | | | VERU-111 (mg/kg/day) | | | | | |
| **Organ/Tissue** | **0** | **0.3** | **1** | **3** | **10** | **30/20** | **0** | **0.3** | **1** | **3** | **10** | **30/20** |
| **Stomach, nonglandular, n** | 10 | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Erosion/ulcer | | | | 5 | | 1 | | | | | 2 | |
| Minimal | | | | | | | | | | | 2 | |
| Mild | | | | 2 | | | | | | | | |
| Moderate | | | | 3 | | 1 | | | | | | |
| Hyperplasia, squamous cell | | | | 9 | 2 | | 1 | | | 3 | | |
| Minimal | | | | 1 | 1 | | 1 | | | 1 | | |
| Mild | | | | 2 | 1 | | | | | 1 | | |
| Moderate | | | | 4 | | | | | | 1 | | |
| Marked | | | | 2 | | | | | | | | |
| Necrosis, single cell | | | | | 5 | 8 | | | | | 3 | 5 |
| Minimal | | | | | 2 | 4 | | | | | 1 | 1 |
| Mild | | | | | 3 | 3 | | | | | 2 | 4 |
| Moderate | | | | | | 1 | | | | | | |
| **Stomach, glandular, n** | 10 | 10 | 10 | 10 | 7 | 9 | 10 | 10 | 10 | 10 | 10 | 9 |
| Degeneration/necrosis, mucosal | | | | | 1 | | | | | | 2 | 2 |
| Minimal | | | | | 1 | | | | | | | |
| Mild | | | | | | | | | | | 1 | 1 |
| Moderate | | | | | | | | | | | 1 | 1 |
| Degeneration/regeneration, mucosal | | | | | 2 | 4 | | | | | 1 | 1 |
| Mild | | | | | 2 | 3 | | | | | 1 | 1 |
| Moderate | | | | | | 1 | | | | | | |
| Necrosis, single cell | | | | | 2 | 1 | | | | | 1 | 2 |
| Minimal | | | | | 2 | 1 | | | | | 1 | 2 |
| **Small intestine, duodenum, n** | 10 | 10 | 10 | 10 | 7 | 6 | 10 | 10 | 10 | 10 | 10 | 8 |
| Atrophy, villus | | | | 1 | 2 | | | | | | 3 | 1 |
| Moderate | | | | 1 | 2 | | | | | | | 1 |
| Marked | | | | | | | | | | | 3 | |
| Degeneration/necrosis, mucosal | | | | | 4 | 3 | | | | | 6 | 2 |
| Minimal | | | | | | | | | | | 1 | |
| Mild | | | | | 2 | | | | | | 4 | 1 |
| Marked | | | | | 2 | 3 | | | | | 1 | 1 |
| Degeneration/regeneration, mucosal | | | | | 3 | 3 | | | | | 4 | 5 |
| Minimal | | | | | | | | | | | 2 | 4 |
| Mild | | | | | | 1 | | | | | 1 | 1 |
| Moderate | | | | | 3 | 2 | | | | | 1 | |
| **Small intestine, ileum, n** | 10 | 10 | 10 | 10 | 7 | 6 | 10 | 10 | 10 | 10 | 10 | 8 |
| Atrophy, villus | | | | 1 | 2 | | | | | | 3 | 1 |
| Moderate | | | | 1 | 2 | | | | | | | 1 |
| Marked | | | | | | | | | | | 3 | |
| Degeneration/necrosis, mucosal | | | | | 2 | | | | | | 3 | 1 |
| Mild | | | | | 2 | | | | | | 3 | 1 |

| | Males | | | | | | Females | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | VERU-111 (mg/kg/day) | | | | | | VERU-111 (mg/kg/day) | | | | | |
| **Organ/Tissue** | **0** | **0.3** | **1** | **3** | **10** | **30/20** | **0** | **0.3** | **1** | **3** | **10** | **30/20** |
| Degeneration/regeneration, mucosal | | | | | 5 | 6 | | | | | 7 | 5 |
| Minimal | | | | | | | | | | | 1 | 4 |
| Mild | | | | | | 2 | | | | | 3 | |
| Moderate | | | | | 4 | 3 | | | | | 3 | |
| Marked | | | | | 1 | 1 | | | | | | 1 |
| **Small intestine, jejunum, n** | 10 | 10 | 10 | 10 | 7 | 6 | 10 | 10 | 10 | 10 | 10 | 9 |
| Atrophy, villus | | | | 1 | 2 | | | | | | 3 | 2 |
| Moderate | | | | 1 | 2 | | | | | | | 2 |
| Marked | | | | | | | | | | | 3 | |
| Degeneration/necrosis, mucosal | | | | | 2 | | | | | | 3 | 2 |
| Mild | | | | | 2 | | | | | | 3 | 2 |
| Degeneration/regeneration | | | | | | | | | | | 1 | |
| Moderate | | | | | | | | | | | 1 | |
| Degeneration/regeneration, mucosal | | | | | 5 | 6 | | | | | 6 | 6 |
| Minimal | | | | | | | | | | | 1 | 5 |
| Mild | | | | | | 2 | | | | | 3 | |
| Moderate | | | | | 3 | 1 | | | | | 1 | |
| Marked | | | | | 2 | 3 | | | | | 1 | 1 |
| **Large intestine, colon, n** | 10 | 10 | 10 | 10 | 7 | 6 | 10 | 10 | 10 | 10 | 10 | 10 |
| Degeneration/necrosis, mucosal | | | | 1 | 3 | 1 | | | | | 4 | 2 |
| Minimal | | | | | 2 | 1 | | | | | 1 | |
| Mild | | | | 1 | 1 | | | | | | | 1 |
| Moderate | | | | | | | | | | | 3 | 1 |
| Degeneration/regeneration, mucosal | | | | | 3 | 4 | | | | | | 1 |
| Mild | | | | | 2 | 2 | | | | | | |
| Moderate | | | | | 1 | 2 | | | | | | 1 |
| **Large intestine, rectum, n** | 10 | 10 | 10 | 10 | 8 | 7 | 10 | 10 | 10 | 10 | 10 | 10 |
| Degeneration/necrosis, mucosal | | | | 1 | | | | | | | 3 | 1 |
| Mild | | | | 1 | | | | | | | | 1 |
| Marked | | | | | | | | | | | 3 | |
| Degeneration/regeneration, mucosal | | | | | 5 | 4 | | | | | | 1 |
| Minimal | | | | | 2 | 2 | | | | | | |
| Moderate | | | | | 3 | 1 | | | | | | 1 |
| Marked | | | | | | 1 | | | | | | |
| **Large intestine, cecum, n** | 10 | 10 | 10 | 10 | 7 | 6 | 10 | 10 | 10 | 10 | 10 | 9 |
| Atrophy, mucosal | | | | 1 | | | | | | | | |
| Marked | | | | 1 | | | | | | | | |
| Degeneration/necrosis, mucosal | | | | | 2 | | | | | | 3 | 2 |
| Mild | | | | | 1 | | | | | | 1 | |
| Moderate | | | | | 1 | | | | | | | 1 |
| Marked | | | | | | | | | | | 2 | 1 |

| | Males | | | | | | Females | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | VERU-111 (mg/kg/day) | | | | | | VERU-111 (mg/kg/day) | | | | | |
| **Organ/Tissue** | **0** | **0.3** | **1** | **3** | **10** | **30/20** | **0** | **0.3** | **1** | **3** | **10** | **30/20** |
| Degeneration/regeneration, mucosal | | | | | 5 | 4 | | | | | 2 | 1 |
| Minimal | | | | | 1 | 1 | | | | | | |
| Mild | | | | | 1 | 2 | | | | | 1 | |
| Moderate | | | | | 3 | 1 | | | | | 1 | |
| Marked | | | | | | | | | | | | 1 |
| **Heart, n** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Degeneration/necrosis, myofiber | | | | | 10 | 10 | | | | | 5 | 9 |
| Minimal | | | | | 4 | 4 | | | | | | 4 |
| Mild | | | | | 3 | 1 | | | | | 2 | 3 |
| Moderate | | | | | 3 | 5 | | | | | 3 | 2 |
| Hemorrhage | | | | | 1 | | | | | | 2 | |
| Minimal | | | | | 1 | | | | | | | |
| Mild | | | | | | | | | | | 2 | |
| **Liver, n** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Karyocytomegaly | | | | | 9 | 7 | | | | | 6 | 5 |
| Minimal | | | | | 4 | 3 | | | | | 3 | 1 |
| Mild | | | | | 2 | | | | | | | |
| Moderate | | | | | 3 | 4 | | | | | 3 | 4 |
| Necrosis, single cell | | | | | 5 | 9 | | | | | 2 | 2 |
| Minimal | | | | | 4 | 7 | | | | | 1 | 1 |
| Mild | | | | | 1 | 2 | | | | | 1 | 1 |
| Vacuolation, periportal | | | | 2 | 3 | 1 | | | 1 | 8 | 3 | 1 |
| Minimal | | | | 2 | 2 | 1 | | | 1 | 6 | 2 | 1 |
| Mild | | | | | 1 | | | | | 2 | 1 | |
| **Bone marrow, femur, n** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Cellularity, decreased, hematopoietic | | | | 3 | 10 | 10 | | | | | 10 | 10 |
| Mild | | | | 2 | | | | | | | | |
| Moderate | | | | 1 | | | | | | | | 1 |
| Marked | | | | | 1 | | | | | | | 5 |
| Severe | | | | | 9 | 10 | | | | | 10 | 4 |
| **Bone marrow, sternum, n** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Cellularity, decreased, hematopoietic | | | | 1 | 10 | 10 | | | | | 10 | 10 |
| Moderate | | | | 1 | | | | | | | | 2 |
| Marked | | | | | 1 | 10 | | | | | 7 | 5 |
| Severe | | | | | 9 | | | | | | 3 | 3 |
| **Thymus, n** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Apoptosis | | | | | | 1 | | | | | | 3 |
| Minimal | | | | | | | | | | | | 1 |
| Mild | | | | | | 1 | | | | | | 2 |
| Depletion, lymphoid, cortex | | | | 2 | 10 | 9 | | | | | 10 | 8 |
| Minimal | | | | | | | | | | | | 2 |
| Mild | | | | | | 1 | | | | | | 3 |
| Moderate | | | | 1 | 1 | 2 | | | | | 6 | |
| Marked | | | | 1 | 9 | 6 | | | | | 4 | 3 |

| | Males | | | | | | Females | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | VERU-111 (mg/kg/day) | | | | | | VERU-111 (mg/kg/day) | | | | | |
| **Organ/Tissue** | **0** | **0.3** | **1** | **3** | **10** | **30/20** | **0** | **0.3** | **1** | **3** | **10** | **30/20** |
| Hemorrhage | | 1 | 2 | | 3 | 5 | | | 1 | | 1 | 2 |
| Minimal | | 1 | 2 | | | 1 | | | 1 | | 1 | |
| Mild | | | | | 1 | | | | | | | 1 |
| Moderate | | | | | 1 | 2 | | | | | | |
| Marked | | | | | 1 | 1 | | | | | | 1 |
| Severe | | | | | | 1 | | | | | | |
| **Spleen, n** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Apoptosis | | | | | | 1 | | | | | | |
| Moderate | | | | | | 1 | | | | | | |
| Depletion, lymphoid, generalized | | | | 1 | 9 | 6 | | | | | 3 | 3 |
| Minimal | | | | | 4 | | | | | | | |
| Mild | | | | | 2 | 5 | | | | | | 1 |
| Moderate | | | | 1 | 3 | 1 | | | | | 2 | 2 |
| Marked | | | | | | | | | | | 1 | |
| Depletion, red pulp | | | | | 5 | 1 | | | | | 3 | 2 |
| Mild | | | | | 1 | | | | | | | |
| Moderate | | | | | 4 | 1 | | | | | 3 | 2 |
| **Lymph node, mandibular, n** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Depletion, lymphoid, generalized | | | | 1 | 9 | 8 | | | | | 5 | 5 |
| Minimal | | | | | 1 | | | | | | 1 | 1 |
| Mild | | | | | 6 | 8 | | | | | 2 | 3 |
| Moderate | | | | 1 | 2 | | | | | | | 1 |
| Marked | | | | | | | | | | | 2 | |
| **Lymph node, mesenteric, n** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Depletion, lymphoid, generalized | | | | 2 | 6 | 9 | | | | | 8 | 9 |
| Minimal | | | | 1 | 4 | | | | | | 1 | |
| Mild | | | | 1 | 2 | 9 | | | | | 6 | 8 |
| Moderate | | | | | | | | | | | 1 | 1 |
| **Gut-associated lymphoid tissue, n** | 10 | 10 | 10 | 10 | 8 | 8 | 10 | 10 | 10 | 10 | 10 | 9 |
| Decreased lymphocytes, generalized | | | | 1 | 7 | 6 | | | | | 5 | 4 |
| Minimal | | | | | 3 | 2 | | | | | 1 | 1 |
| Mild | | | | | 4 | 2 | | | | | 1 | 1 |
| Moderate | | | | 1 | | 2 | | | | | 1 | 2 |
| Marked | | | | | | | | | | | 2 | |
| **Testis, n** | 10 | 10 | 10 | 10 | 10 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |
| Degeneration/necrosis, tubular | | | | | 10 | 10 | | | | | | |
| Moderate | | | | | 3 | 3 | | | | | | |
| Marked | | | | | 7 | 6 | | | | | | |
| Severe | | | | | | 1 | | | | | | |
| Dilation, seminiferous tubules, bilateral | | | | | 8 | 9 | | | | | | |
| Minimal | | | | | | 3 | | | | | | |
| Mild | | | | | 5 | 4 | | | | | | |
| Moderate | | | | | 3 | 2 | | | | | | |

| | Males | | | | | | Females | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | VERU-111 (mg/kg/day) | | | | | | VERU-111 (mg/kg/day) | | | | | |
| **Organ/Tissue** | **0** | **0.3** | **1** | **3** | **10** | **30/20** | **0** | **0.3** | **1** | **3** | **10** | **30/20** |
| **Epididymis, n** | 10 | 10 | 10 | 10 | 10 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |
| Germ cell debris, increased, unilateral | | | | | | 1 | | | | | | |
| Moderate | | | | | | 1 | | | | | | |
| Oligospermia/germ cell debris, bilateral | | | | | 5 | 5 | | | | | | |
| Moderate | | | | | 1 | 2 | | | | | | |
| Marked | | | | | 4 | 3 | | | | | | |
| Oligospermia/germ cell debris, unilateral | | | | | 5 | 5 | | | | | | |
| Moderate | | | | | 2 | 4 | | | | | | |
| Marked | | | | | 3 | 1 | | | | | | |
| **Gland, adrenal, n** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Hypertrophy, diffuse, cortical | | | | 3 | 6 | 4 | 2 | | | 2 | 9 | 9 |
| Minimal | | | | 3 | 3 | 4 | | | | 2 | 5 | 4 |
| Mild | | | | | 3 | | 2 | | | | 4 | 4 |
| Moderate | | | | | | | | | | | | 1 |
| Vacuolation | | | | | | 1 | | | | | | |
| Minimal | | | | | | 1 | | | | | | |

Source: Table prepared by the Reviewer
Abbreviations: n, number of animals; VERU-111, sabizabulin

There were no observed sex-related differences in $C_{max}$ and $AUC_{0\text{-}24h}$. There were more than dose-proportional increases in $C_{max}$ and $AUC_{0\text{-}24h}$ values following oral gavage of VERU-111 for 28 days. Systemic exposure to VERU-111 did not consistently change following repeated administration of VERU-111. See Table 32.

**Table 32. Toxicokinetic Parameters in 28-Day Toxicology Study With VERU-111 in Rats, Study No. 2649-012**

| Study Day | Dose (mg/kg) | Sex | $C_{max}$ (ng/mL) | $AUC_{0-24h}$ (ng*hr/ml) | Accumulation Ratio ($AUC_{dayX/Day1}$) | Fold ▲ in AUC vs. LD |
|---|---|---|---|---|---|---|
| 1 | 0.3 | M | 8.42 | 51.1 | | |
| | | F | 18.9 | 72.7 | | |
| | | Combined | 13.7 | 62 | | 1.0 |
| | 1 | M | 29.4 | 171 | | |
| | | F | 62.9 | 253 | | |
| | | Combined | 46.2 | 212 | | 3.4 |
| | 3 | M | 226 | 1150 | | |
| | | F | 185 | 1400 | | |
| | | Combined | 205 | 1275 | | 20 |
| | 10 | M | 500 | 3260 | | |
| | | F | 885 | 4490 | | |
| | | Combined | 693 | 3875 | | 62 |
| | 30/20 | M | 1070 | 5760 | | |
| | | F | 1290 | 8630 | | |
| | | Combined | 1180 | 7195 | | 116 |
| 28 | 0.3 | M | 14.3 | 111 | | |
| | | F | 18.3 | 104 | | |
| | | Combined | 16.3 | 107.5 | 1.8 | 1 |
| | 1 | M | 20.9 | 265 | | |
| | | F | 35.4 | 275 | | |
| | | Combined | 28.2 | 270 | 1.3 | 2.5 |
| | 3 | M | 77.6 | 1170 | | |
| | | F | 83.9 | 1030 | | |
| | | Combined | 81 | 1100 | 0.9 | 10 |

Source: Table prepared by the Reviewer
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum serum concentration; F, female; LD, low dose M, male; VERU-111, sabizabulin

The observed findings appeared to be fairly characteristic of tubulin inhibitors (e.g., toxicity to rapidly dividing cells in the bone marrow and GI tract, lymphoid depletion in several organs, etc.). The no observed adverse effect level (NOAEL) was determined to be 3 mg/kg/day based on mortality and adverse histopathology findings at higher doses (≥10 mg/kg/day). Only animals in the ≤3 mg/kg/day groups completed 28 days of treatment.

At 3 mg/kg/day, the average combined $C_{max}$ =81 ng/mL and $AUC_{0-24h}$ =1100 ng*hr/mL.

**Title: VERU-111: A 28-Day Oral Capsule Toxicity Study in Dogs (Study No. 2649-013)**

In the 28-day oral toxicity and TK study in dogs (age 5.5 to 6 months of age), male and female dogs (n=3/sex/group) were treated once daily via oral gelatin capsule with vehicle (Torpac gelatin capsules) or VERU-111 (2, 4, or 8 mg/kg/day) for 28 days. TK evaluations were performed in the main study animals. The recovery of animals after a treatment-free period was not evaluated in the study.

There were no unscheduled deaths during the study.

Clinical signs at doses ≥4 mg/kg/day included inappetence, vomiting/emesis, and/or thin appearance, and watery and/or mucoid feces (8 mg/kg/day only).

Adverse decreases in absolute bodyweight (≥10%) were evident in females in the 4 mg/kg/day group and males and females in the 8 mg/kg/day groups. Dose-dependent decreases in bodyweight gains were noted in male and female animals. See Table 33. Bodyweight changes corresponded with decreased food consumption. Lower food consumption was observed in the 2 mg/kg (10% to 23%) and 4 mg/kg (13% to 17%) groups. The animals in the 8 mg/kg/day group consumed significantly lower food compared to the vehicle control group throughout the study. Of note, there were no histopathology findings in the GI tract.

**Table 33. Bodyweight Changes in 28-Day Toxicology Study With VERU-111 in Beagle Dogs, Study No. 2649-013**

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **VERU-111 PO** | 0 mg/kg | 2 mg/kg | 4 mg/kg | 8 mg/kg | 0 mg/kg | 2 mg/kg | 4 mg/kg | 8 mg/kg |
| **Day -1** | | | | | | | | |
| *n* | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Body weight (kg) | 7.8 | 7.9 | 8.2 | 8.0 | 5.5 | 5.5 | 5.3 | 5.3 |
| **Week 4** | | | | | | | | |
| *n* | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Body weight (kg) | 9.0 | 8.9 | 8.5 | 7.3 | 6.1 | 5.8 | 5.4 | 5.0 |
| % control | 100 % | 98 % | 94 % | **81 %** | 100 % | 96 % | **89 %** | **83 %** |
| Δ day -1 (kg) | 1.2 | 1.0 | 0.4 | -0.7 | 0.6 | 0.4 | 0.1 | -0.3 |
| BW Gain (% D-1) | 15.6% | 12.0% | 4.5% | -8.4% | 10.3% | 6.4% | 2.5% | -5.6% |
| BW Gain (% control) | 100 % | 78.1 % | **30.1 %** | **-54.8 %** | 100 % | 61.8 % | **23.5 %** | **-52.9 %** |

Source: Table prepared by the Reviewer
Abbreviations: BW, body weight; VERU-111, sabizabulin

Adverse increases (≥10%) in PR, QT, and QTc (males only) intervals were noted at Week 4 in the 8 mg/kg/day groups. See Table 34 (PR intervals), Table 35 (QT intervals), and Table 36 (QTc intervals).

**Table 34. PR Interval Changes in 28-Day Toxicology Study With VERU-111 in Beagle Dogs, Study No. 2649-013**

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **VERU-111 (mg/kg) Oral** | 1<br>0 mg/kg | 2<br>2 mg/kg | 3<br>4 mg/kg | 4<br>8 mg/kg | 1<br>0 mg/kg | 2<br>2 mg/kg | 3<br>4 mg/kg | 4<br>8 mg/kg |
| **Pretest** | | | | | | | | |
| *n* | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| PR (msec) | 89.9 | 83.5 | 59.5 | 87.9 | 78.7 | 92.6 | 83.1 | 93.8 |
| **Day 1*** | | | | | | | | |
| *n* | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| PR (msec) | 94.7 | 89.2 | 92.9 | 92.5 | 80.5 | 93.0 | 82.2 | 93.1 |
| **Week 4*** | | | | | | | | |
| *n* | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| PR (msec) | 87.4 | 85.7 | 93.7 | **105.9** | 80.5 | 91.0 | 82.5 | **106.7** |
| % Control | 100% | 98% | 107% | **121%** | 100% | 113% | 103% | **133%** |
| % D1 | 92% | 96% | 101% | **114%** | 100% | 98% | 100% | **115%** |
| * The observation reported in the table are post-dose on respective observation days | | | | | | | | |

Source: Table prepared by the Reviewer
Abbreviations: VERU-111, sabizabulin

**Table 35. QT Interval Changes in 28-Day Toxicology Study With VERU-111 in Beagle Dogs, Study No. 2649-013**

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **VERU-111 (mg/kg) Oral** | 1<br>0 mg/kg | 2<br>2 mg/kg | 3<br>4 mg/kg | 4<br>8 mg/kg | 1<br>0 mg/kg | 2<br>2 mg/kg | 3<br>4 mg/kg | 4<br>8 mg/kg |
| **Pretest** | | | | | | | | |
| *n* | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| QT (msec) | 182.0 | 819.0 | 191.7 | 196.7 | 184.6 | 198.2 | 195.2 | 197.1 |
| **Day 1*** | | | | | | | | |
| *n* | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| QT (msec) | 183.8 | 187.7 | 198.7 | 203.8 | 191.2 | 204.7 | 205.7 | 206.7 |
| **Week 4*** | | | | | | | | |
| *n* | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| QT (msec) | 190.5 | 196.7 | 200.8 | **244.5** | 189.0 | 202.9 | 199.1 | **226.7** |
| % Control | 100% | 103% | 105% | **128%** | 100% | 107% | 105% | **120%** |
| % D1 | 104% | 105% | 101% | **120%** | 99% | 99% | 97% | **110%** |

* The observation reported in the table are post-dose on respective observation days

Source: Table prepared by the Reviewer
Abbreviations: VERU-111, sabizabulin

**Table 36. QTc Interval (Vandewater) Changes in 28-Day Toxicology Study With VERU-111 in Beagle Dogs, Study No. 2649-013**

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **VERU-111 (mg/kg) Oral** | 1<br>0 mg/kg | 2<br>2 mg/kg | 3<br>4 mg/kg | 4<br>8 mg/kg | 1<br>0 mg/kg | 2<br>2 mg/kg | 3<br>4 mg/kg | 4<br>8 mg/kg |
| **Pretest** | | | | | | | | |
| *n* | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| QTc (msec) | 225.8 | 224.0 | 230.1 | 231.6 | 223.8 | 239.0 | 233.8 | 234.1 |
| **Day 1*** | | | | | | | | |
| *n* | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| QTc (msec) | 231.3 | 232.0 | 236.7 | 230.6 | 230.3 | 236.0 | 241.0 | 240.7 |
| **Week 4*** | | | | | | | | |
| *n* | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| QTc (msec) | 229.1 | 227.5 | 235.8 | **256.1** | 231.1 | 237.5 | 230.5 | **247.9** |
| % Control | 100% | 99% | 103% | **112%** | 100% | 103% | 100% | **107%** |
| % D1 | 99% | 98% | 100% | **111%** | 100% | 101% | 96% | **103%** |

* The observation reported in the table are post-dose on respective observation days

Source: Table prepared by the Reviewer
Abbreviations: VERU-111, sabizabulin

Organ weight changes were noted in the thymus (decrease in absolute and % brain weights in the 8 mg/kg/day group (>50% for males and >35% for females), adrenal gland (decrease in absolute and % brain weights in the 8 mg/kg/day group (>15% in males and females), and epididymides and prostate (decrease in absolute and % brain weights). Changes in the epididymides and prostate were attributed to immature organ development in the peripubertal dogs. See Table 37.

**Table 37. Organ Weight Changes in 28-Day Toxicology With VERU-111 in Beagle Dogs, Study No. 2649-013**

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **VERU-111 (mg/kg)** | 0 | 2 | 4 | 8 | 0 | 2 | 4 | 8 |
| **Adrenal Gland (#examined)** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Absolute Weight (g) | 1.24 | 1.28 | 1.35 | 1.00 | 1.24 | 0.98 | 0.95 | 1.10 |
| % Control | 100% | 103% | 109% | 80% | 100% | 79% | 76% | 89% |
| % Body Weight | 0.014 | 0.015 | 0.017 | 0.014 | 0.021 | 0.017 | 0.018 | 0.022 |
| % Control | 100% | 107% | 116% | 97% | 100% | 83% | 88% | 107% |
| % Brain Weight | 0.017 | 0.017 | 0.017 | 0.014 | 0.020 | 0.015 | 0.013 | 0.016 |
| % Control | 100% | 101% | 102% | 79% | 100% | 75% | 67% | 84% |
| **Epididymides (#examined)** | 3 | 3 | 3 | 3 | NE | NE | NE | NE |
| Absolute Weight (g) | **2.08** | **1.74** | **1.67** | **1.59** | | | | |
| % Control | 100% | 84% | 80% | 77% | | | | |
| % Body Weight | 0.024 | 0.021 | 0.021 | 0.022 | | | | |
| % Control | 100% | 87% | 85% | 91% | | | | |

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **VERU-111 (mg/kg)** | 0 | 2 | 4 | 8 | 0 | 2 | 4 | 8 |
| % Brain Weight | 0.029 | 0.023 | 0.0216 | 0.0215 | | | | |
| % Control | 100% | 82% | 75% | 75% | | | | |
| **Prostate (#examined)** | 3 | 3 | 3 | 3 | NE | NE | NE | NE |
| Absolute Weight (g) | **3.83** | **1.45** | **1.42** | **1.18** | | | | |
| % Control | 100% | 38% | 37% | 31% | | | | |
| % Body Weight | 0.044 | 0.017 | 0.018 | 0.016 | | | | |
| % Control | 100% | 39% | 39% | 36% | | | | |
| % Brain Weight | 0.053 | 0.020 | 0.018 | 0.016 | | | | |
| % Control | 100% | 37% | 35% | 30% | | | | |
| **Thymus (#examined)** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Absolute Weight (g) | **11.05** | **12.54** | **7.47** | **5.34** | 7.72 | 6.48 | 5.18 | 5.46 |
| % Control | 100% | 114% | 68% | 48% | 100% | 84% | 67% | 71% |
| % Body Weight | 0.128 | 0.148 | 0.093 | 0.075 | 0.128 | 0.114 | 0.101 | 0.112 |
| % Control | 100% | 116% | 73% | 59% | 100% | 90% | 79% | 88% |
| % Brain Weight | 0.152 | 0.169 | 0.097 | 0.072 | 0.123 | 0.098 | 0.073 | 0.082 |
| % Control | 100% | 111% | 64% | 48% | 100% | 80% | 59% | 67% |

Source: Table prepared by the Reviewer
Abbreviations: NE, not examined; VERU-111, sabizabulin

At 8 mg/kg/day, depletion of hematopoietic cells in the sternal bone marrow (3/3 males and 3/3 females) and depletion of lymphocytes in the thymus (1/3 males and 1/3 females) were noted. See Table 38.

**Table 38. Histopathology Findings in 28-Day Toxicology Study With VERU-111 in Beagle Dogs, Study No. 2649-013**

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **VERU-1411 (mg/kg) PO** | 0 | LD 2 | MD 4 | HD 8 | 0 | LD 2 | MD 4 | HD 8 |
| # of animals | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Bone, Sternum (# examined)** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Decreased hematopoietic cellularity | | | | | | | | |
| Minimal | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| **Total** | **0** | **0** | **0** | **3** | **0** | **0** | **0** | **3** |
| **Thymus (# examined)** | **3** | **3** | **3** | **3** | **3** | **3** | **3** | **3** |
| Depletion of cortical lymphoid cells | | | | | | | | |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Total** | **0** | **0** | **0** | **1** | **0** | **0** | **0** | **1** |

Source: Table prepared by the Reviewer
Abbreviations: HD, high dose; LD, low dose; MD, mid dose; PO, by mouth; VERU-111, sabizabulin

There were no observed sex-related differences in $C_{max}$ and $AUC_{0\text{-}12h}$. There were approximately dose-proportional increases in $C_{max}$ and $AUC_{0\text{-}12h}$ values. Systemic exposure to VERU-111 did not consistently change following repeated administration of VERU-111. See Table 39.

**Table 39. Toxicokinetic Parameters in 28-Day Toxicology Study With VERU-111 in Beagle Dogs, Study No. 2649-013**

| Study Day | Dose (mg/kg) | Sex | $C_{max}$ (ng/ml) | $AUC_{0-12h}$ (ng*hr/ml) | Accumulation Ratio ($AUC_{dayX/Day1}$) | Fold ▲ in AUC vs. LD |
|---|---|---|---|---|---|---|
| 1 | 2 | M | 16.2 | 46.7 | | |
| | | F | 23.9 | 39.3 | | |
| | | Combined | 20 | 43 | | 1 |
| | 4 | M | 49 | 99 | | |
| | | F | 33 | 92 | | |
| | | Combined | 41 | 95 | | 2.2 |
| | 8 | M | 56 | 186 | | |
| | | F | 40 | 155 | | |
| | | Combined | 48 | 171 | | 4 |
| 28 | 2 | M | 13.2 | 39.9 | | |
| | | F | 11.7 | 34.9 | | |
| | | Combined | 12.5 | 37.5 | 1.8 | 1 |
| | 4 | M | 28 | 84.4 | | |
| | | F | 18 | 63.3 | | |
| | | Combined | 23 | 74 | 1.3 | 2 |
| | 8 | M | 25.5 | 120 | | |
| | | F | 42 | 168 | | |
| | | Combined | 34 | 144 | 0.9 | 3.9 |

Source: Table prepared by the Reviewer
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum serum concentration; F, female; LD, low dose; M, male; VERU-111, sabizabulin

The observed findings were generally characteristic of tubulin inhibitors (e.g., clinical signs of vomiting/emesis, depletion of hematopoietic cells in the sternal bone marrow, and lymphoid depletion in the thymus). The NOAEL was identified as 4 mg/kg/day based on the adverse bodyweight loss, lengthening of the PR, QT, and QTc intervals, and histopathology findings in animals in the 8 mg/kg/day group. At 4 mg/kg/day, average combined $C_{max}$ =23 ng/mL and $AUC_{0-12h}$ =74 ng*hr/mL ($AUC_{0-24h}$ =148 ng*hr/mL). The findings at the high dose of 8 mg/kg/day might be considered monitorable.

**General Comments on Safety Margins of VERU-111 Based on Pivotal 28-Day Repeat-Dose Toxicity Studies in Rats and Dogs**

As described above, the NOAELs in the 28-day oral toxicity studies with VERU-111 in rats and dogs were determined to be 3 mg/kg/day and 4 mg/kg/day, respectively.

In the 28-day toxicity study with VERU-111 in rats, the NOAEL of 3 mg/kg/day resulted in an average combined $C_{max}$ =81 ng/mL and $AUC_{0-24h}$ =1100 ng*hr/mL. Of note, the 3 mg/kg/day dose corresponds to a human equivalent dose (HED) of 29 mg/day for a 60 kg human.

In the 28-day toxicity study with VERU-111 in dogs, the NOAEL of 4 mg/kg/day resulted in an average combined $C_{max}$ =23 ng/mL and $AUC_{0-12h}$ =74 ng*hr/mL ($AUC_{0-24h}$ =148 ng*hr/mL). Of note, the 4 mg/kg/day dose corresponds to a HED of 133 mg/day for a 60 kg human. The findings at 8 mg/kg/day could be considered monitorable in the clinical setting and resulted in an average combined $C_{max}$ =34 ng/mL and $AUC_{0-12h}$ =144 ng*hr/mL ($AUC_{0-24h}$ =288 ng*hr/mL). Of note, the 8 mg/kg/day dose corresponds to a HED of 266 mg/day for a 60 kg human.

The clinical safety margins for the proposed clinical dose of VERU-111 (i.e., 9 mg sabizabulin for 21 days) compared to the NOAELs from the pivotal 28-day toxicity studies in rats and dogs are 2.4x and 0.32x, respectively (on a plasma drug exposure [AUC] basis) and 20x and 27x, respectively (on a mg/kg basis). The findings in the dog study at 8 mg/kg/day could be considered monitorable in the clinical setting, resulting in clinical safety margins of 0.63x (on an exposure basis) and 53x (on a mg/kg basis). Safety margins were calculated on a mg/kg basis to account for the local toxicity observed in the GI tract after oral dosing to rats and dogs. See Table 40.

Of note, based on the significant differences in the exposures between rats and dogs, and more severe toxicities including death in rats, the rat was identified as the most sensitive animal species.

**Table 40. Safety Margins Based on NOAEL From Pivotal Toxicology Studies**

| | Nonclinical | | | Clinical Safety Margins | |
|---|---|---|---|---|---|
| **Species/ Duration** | **NOAEL** | **HED** | **$AUC_{0-24h}$** | **MRHD Based on mg/kg (9 mg = 0.15 mg/kg*)** | **MRHD Based on Dose Exposure (9 mg = 0.15 mg/kg*)[1]** |
| Rat/28-day | 3 mg/kg/day | 29 mg =0.48 mg/kg* | 1100 ng·hr/mL | 20x | 2.4x |
| Dog/28-day | 4 mg/kg/day | 133 mg =2.22 mg/kg* | 148 ng·hr/mL | 27x | 0.32x |
| Dog/28-day | 8 mg/kg/day | 266 mg =4.44 mg/kg* | 288 ng·hr/mL | 53x | 0.63x |

Source: Table prepared by the Reviewer
(*) Calculation based on a 60 kg adult
[1] According to the Sponsor, the multiple dose pharmacokinetics of sabizabulin have been assessed at 9 mg/day in hospitalized COVID-19 patients ($C_{max}$ =57.5 ng/mL and $AUC_{0-24h}$ =455.4 ng*hr/mL).
Abbreviation: AUC, area under the concentration-time curve; HED, human equivalent dose; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level

## Genetic Toxicity

The genetic toxicity of VERU-111 HCL was evaluated in a GLP-compliant in vitro reverse mutation assay (Ames assay) and a GLP-compliant in vitro assay in mammalian cell (in vitro micronucleus assay in TK6 cells). The genetic toxicity studies with VERU-111 HCL were previously reviewed under IND 149282 and key study findings are described below. VERU-111 has not been evaluated in an in vivo clastogenicity assay in rodents.

The in vitro genetic toxicology studies with VERU-111 are considered sufficient to support EUA for VERU-111 as a treatment for SARSCoV-2 infection in patients at high risk for ARDS, but an in vivo micronucleus study should be available with an NDA to complete the standard battery of genetic toxicology studies per the ICH S2(R1) Guidance. This was conveyed to the Sponsor at the time of the Type B pre-EUA meeting.

**Title: Bacterial Reverse Mutation Assay (Study No. AG19KX.502ICH.BTL)**

In the in vitro Ames assay, VERU-111 HCL at concentrations up to 5000 mcg/plate did not cause any changes of revertant colony counts with any of the tester strains in either the absence or presence of metabolic S9 activation. Under the conditions tested, VERU-111 HCL was negative for mutagenic potential in the in vitro Ames assay.

**Title: In Vitro Mammalian Cell Micronucleus Assay in TK6 Cells (Study No. AG19KX.361CRESTICH.BTL)**

In the in vitro micronucleus assay in TK6 cells, statistically significant and dose-dependent increases in micronuclei induction were seen with VERU-111 HCL in the non-activated 4-hour treatment group (at 0.0653, 0.102, and 0.16 mcg/mL VERU-111 HCL), S9-activated 4-hour treatment group (at 4.1, 6.4, and 8 mcg/mL VERU-111 HCL), and non-activated 27-hour treatment group (at 0.00485, 0.00788, and 0.0109 mcg/mL VERU-111 HCL). Based on subsequent CREST staining, the frequency of kinetochore positive micronuclei for 4 hours with S9 activation (at 4.1, 6.4, and 8 mcg/mL VERU-111 HCL) and for 27 hours without S9 activation (at 0.00485, 0.00788, and 0.0109 mcg/mL VERU-111 HCL) was ≥70%, indicating VERU-111 HCL-induced micronuclei via a primarily aneugenic mechanism of action. Under the conditions tested, VERU-111 HCL was positive for the induction of micronuclei in the non-activated and S9-activated test systems in the in vitro micronucleus assay using TK6 cells. Subsequent CREST analysis indicated that VERU-111 HCL induced micronuclei predominantly by an aneugenic mechanism of action.

**General Comments on Genetic Toxicity of VERU-111**

Based on pharmacology studies, VERU-111 appears to act as a tubulin inhibitor. Microtubule inhibitors can stabilize or destabilize microtubules, thereby suppressing microtubule dynamics required for proper mitotic function, effectively blocking cell cycle progression, and resulting in apoptosis. As a tubulin inhibitor, VERU-111 could potentially adversely impact rapidly dividing cells in organs and tissues such as the GI tract, bone marrow, and male reproductive organs (of note, such effects were noted in the 28-day toxicity study with VERU-111 in rats). Also, as determined by the in vitro micronucleus assay, there is a plausible risk for aneugenicity with VERU-111, which would be expected to be a threshold-based toxicity.

The findings of aneugenicity in the in vitro micronucleus assay in TK6 cells should be conveyed in EUA Fact Sheet if approved.

**Reproductive and Developmental Toxicology**

There are no reproductive and developmental toxicology studies with VERU-111 (either conducted by the Sponsor or identified from the literature). At the time of the Type B pre-EUA meeting, it was conveyed to the Sponsor that since reproductive and developmental toxicology studies have not been conducted with VERU-111, a written assessment of the potential for possible effects of VERU-111 on reproduction/development should be provided to support an EUA. The Sponsor did not provide a formal written assessment in the EUA submission but mentioned the following in the toxicology written summary:

- Per the Sponsor, VERU-111 has a similar mechanism of action as colchicine (i.e., microtubule destabilizing agent).
  - Colchicine has been shown to be teratogenic in mice, rats, and hamsters and impact spermatogenesis in male rats (Allard et al. 1993; Ferm 1964; Handel 1979; Ingalls et al. 1968; Petit and Isaacson 1976; Russell et al. 1981).
- VERU-111 was shown to induce micronuclei predominantly by an aneugenic mechanism of action based on an in vitro micronucleus assay in TK6 cells (genetic toxicology study).
- Per the Sponsor, given VERU-111's similar mechanism of action as colchicine as a microtubule destabilizing agent, and its potential to induce micronuclei via an aneugenic

mechanism of action based on the in vitro micronucleus assay, it is highly likely that the use of VERU-111 in a pregnant woman will result in impairment in the growth of the developing fetus and may result in birth defects in and/or death of the developing fetus.

The Sponsor has agreed to provide a warning statement in the EUA Fact Sheet that use of sabizabulin in a pregnant woman is likely to be harmful to the developing fetus. As such, sabizabulin is not recommended for use in pregnancy.

**Special Toxicology Studies**

VERU-111 was evaluated for phototoxicity in a GLP-compliant in vitro neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts. The in vitro phototoxicity study with VERU-111 was previously reviewed under IND 149282 and key study findings are described below.

**Title: Neutral Red Uptake Phototoxicity Assay of VERU-111 in BALB/c 3T3 Mouse Fibroblasts (Study No. 20144101)**

VERU-111 (0.562 to 31.6 mcg/mL in the definitive study) was evaluated for phototoxicity in the in vitro neutral red uptake phototoxicity assay using BALB/c 3T3 mouse fibroblasts. Under the study conditions, VERU-111 was found to be phototoxic in this in vitro assay. The $IC_{50}$ for VERU-111-mediated phototoxicity in the presence of UVR exposure was estimated at 0.237 mcg/mL.

The Sponsor has agreed to provide a warning statement in the EUA Fact Sheet that patients should avoid or minimize exposure to sunlight (including sunlamps), use a sunblock (SPF 50 or higher), and wear clothing that protects against sun exposure and that patients should avoid concomitant medications known to cause photosensitivity.

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/s/

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BANU A KARIMI SHAH
02/23/2023 06:43:19 PM

JULIE G BEITZ
02/24/2023 07:48:07 AM