MIAMI HEADQUARTERS
2916 N. Miami Avenue
Suite 1000
Miami, Florida 33127
305.509.6897 Phone
www.verupharma.com

Center for Drug Evaluation and Research

Pulmonary-Allergy Drugs Advisory Committee (PADAC) Meeting Briefing Document

Sabizabulin

Treatment of SARS-CoV-2 Infection in Hospitalized Patients With Moderate to Severe COVID-19 Infection Who Are at High Risk for Acute Respiratory Distress Syndrome (ARDS)

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Veru Inc.
Miami, Florida, U.S.A.

ADVISORY COMMITTEE BRIEFING MATERIALS:
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LIST OF ABBREVIATIONS

AE	Adverse event
ARDS	Acute respiratory distress syndrome
$AUC_{0\text{-}12hr}$	Area under the plasma concentration-time curve from 0 to 12 hours
$AUC_{0\text{-}24hr}$	Area under the plasma concentration-time curve from 0 to 24 hours
AUC_{Tlast}	Area under the plasma concentration-time curve from 0 hour to the time of the final quantifiable sample
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
COVID-19	Coronavirus disease of 2019
ECG	Electrocardiogram
EUA	Emergency use authorization
FC	Formulated capsule
HED	Human equivalent dose
HEK293	Human embryonic kidney cell line
HER2	human epidermal growth factor receptor 2
hERG	Human ether-a-go-go related gene
IC_{20}	20% inhibitory concentration
IC_{50}	50% inhibitory concentration
ICU	Intensive care unit
ITT	Intent-to-treat
MDR	multidrug resistance
NIV	Non-invasive ventilation
NOAEL	No Observed Adverse Effect Level
OR	Odds ratio
OUS	Outside the United States
P-gp	permeability glycoprotein
PIC	Powder in capsule
PK	Pharmacokinetic(s)
PT	Preferred term
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	System organ class
STD_{10}	severely toxic dose in 10% (or more) of the test subjects

$T_{1/2}$	half life
TEAE	Treatment emergent adverse event
US	United States
VERU-111	Sabizabulin
WHO	World Health Organization

1. EXECUTIVE SUMMARY

This document reviews the evidence supporting the Emergency Use Authorization (EUA) of sabizabulin (also referred to as VERU-111) for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in hospitalized patients with moderate to severe COVID-19 infection who are at high risk for acute respiratory distress syndrome (ARDS). Sabizabulin is intended for oral dosing at 9 mg daily for up to 21 days or until the patient is discharged from the hospital, whichever comes first.

The ongoing SARS-CoV-2 global pandemic/endemic is currently causing a significant burden of illness, hospitalization, and death with over 624,063,972 cases and 6,552,441 deaths due to COVID-19 worldwide and counting (Worldometers.info; accessed 04 October 2022). In the United States (US), COVID-19 continues to have a dramatic effect on morbidity and mortality. To date, there have been over 96.2 million COVID-19 cases, 5.26 million hospitalizations, and 1.05 million deaths (CDC, 2022). As of 04 October 2022, the 7-day averages were 42,828 for new COVID cases, 3,471 for new COVID-19 related hospital admissions, and 322 for new deaths (CDC, 2022). As of 02 October 2022 there are currently a total of 25,185 COVID-19 patients hospitalized in the US and a total of 2,797 COVID-19 patients in the Intensive Care Unit (ICU) (Ritchie et al., 2022). It is also recognized that COVID-19 surges can create stress on hospital capacity and result in excess deaths in all types of critical care patient populations, not just those with COVID-19 (French et al., 2022). ARDS remains a frequent serious complication of severe COVID-19 infection (Tzotzos et al., 2020; Wu et al., 2020; Aranda et al., 2021). It has been reported that up to 33% of hospitalized patients with COVID-19 have ARDS and 75% to 92% of patients admitted to the intensive care unit (ICU) with COVID-19 have ARDS (Chand et al., 2020; Patel et al., 2020; Tzotzos et al., 2020). The mortality rate of COVID-19 associated ARDS is 45% and among patients who died from COVID-19 there is a 90% incidence of ARDS (Tzotzos et al., 2020). As the COVID-19 pandemic/endemic continues, there is a need to remain vigilant and focused on preparedness for the next wave of infections. As President Biden stated in a 60 Minutes interview on 18 September 2022, “We still have a problem with COVID,” it is clear that this disease will be a problem for the foreseeable future, and there is a need for additional therapies, especially for those patients with moderate-to-severe COVID-19 infection.

Though antiviral and anti-inflammatory/immunomodulator drugs have been FDA-approved or authorized for emergency use in hospitalized COVID-19 patients at high risk of ARDS, these treatments only demonstrate at best a modest effect on reduction in mortality (0% to 5.7% absolute reduction in death compared to standard of care) [Veklury® (remdesivir) (Gilead Sciences, Inc., 2022); dexamethasone; Olumiant (baricitinib) (Eli Lilly and Co., 2022c); Actemra (tocilizumab) (Genentech, Inc., 2021)]. Per National Institutes of Health treatment guidelines for COVID-19, it is recognized that for hospitalized patients on low to moderate oxygen therapy, the corticosteroid dexamethasone is the only anti-inflammatory agent regularly administered (NIH, 2022). There are additional COVID-19 treatments that have been authorized for emergency use in the US for treatment of patients with mild to moderate COVID-19 who are not hospitalized but may be at risk of progression to severe COVID-19, however these products are not authorized or approved for use in hospitalized patients with severe disease that require oxygen support [Paxlovid (nirmatrelvir tablets/ritonavir tablets) (Pfizer Inc., 2022), Lagevrio™ (molnupiravir capsules) (Merck Sharp & Dohme LLC, 2022)]. Additionally, antibody

treatments, such as bamlanivimab/etesevimab (Eli Lilly and Co., 2022a) and bebtelovimab (Eli Lilly and Co., 2022b) are also authorized for emergency use in the US for non-hospitalized mild-to-moderate COVID-19 patients who may be at risk for hospitalization or death, but these treatments are virus strain-specific and have limited use as new virus variants emerge. Regardless of the relative benefits of each of these options, it is clear that physicians and patients need additional treatment options to prevent death during this rapidly and constantly evolving COVID-19 pandemic/endemic.

Sabizabulin is an orally available, small molecule bis-indole novel microtubule disruptor that targets, binds, and crosslinks both the α and β tubulin subunits to inhibit polymerization and to induce depolymerization of tubulin subunits that compose microtubules. Microtubules are crucial intracellular structures that are used for cell signaling, intracellular trafficking, and cell division.

Due to this pharmacologic effect to inhibit cell division by selectively disrupting highly active microtubule dynamics, the Sponsor (Veru Inc.) first began investigating the safety and efficacy of sabizabulin in 2018 for the treatment of advanced prostate cancer, a disease that is defined by uncontrolled, rapid cell division. Ongoing investigation shows the promise of sabizabulin as a drug candidate for the treatment of prostate cancer as chronic daily dosing has improved radiographic progression-free survival and was well-tolerated. With the outset of the COVID-19 pandemic in March 2020, the Sponsor recognized that sabizabulin, based on its mechanism of action to inhibit highly active microtubule dynamics, could have the potential to be both an antiviral as well as an anti-inflammatory agent to treat COVID-19 infections. Microtubules are critical for both trafficking of viruses and viral replication within infected host cells (independent of virus type or strain), as well as for triggering the innate immune system by viruses and the subsequent release of cytokines.

Because of the strong scientific rationale that sabizabulin could be a potential novel therapy for COVID-19 infection, the Sponsor met with the Food and Drug Administration (FDA) in April 2020 and designed a proof-of-concept Phase 2 pilot study to evaluate sabizabulin versus placebo in hospitalized moderate to severe COVID-19 patients receiving standard of care treatment who were at high risk for ARDS and death. From this meeting, a dose of 9 mg sabizabulin formulated capsule was selected based the approximate 3.2-fold safety margin to the no adverse effect level (NOAEL) observed from 28-day sabizabulin toxicology studies using a human equivalent dose calculation; this dose is also significantly lower than the maximum tolerated dose (MTD) of sabizabulin determined in prostate cancer patients (approximately 29% of the MTD). In February 2021, the completed Phase 2 study demonstrated that sabizabulin treatment resulted in clinically meaningful reductions in mortality, days in the intensive care unit (ICU), and days on mechanical ventilation in hospitalized patients with moderate to severe COVID-19 (delta) infections.

A confirmatory multicenter, placebo controlled, global Phase 3 study to evaluate the efficacy and safety of sabizabulin in hospitalized moderate to severe COVID-19 patients who were at high risk for ARDS was subsequently designed in consultation with the FDA including the determination of the sample size based on 92.8% power which was calculated using the treatment effect observed in the Phase 2 study. Standard of care treatment was allowed for both groups. In April 2022, the confirmatory Phase 3 clinical trial was halted by the Independent Data Monitoring Committee due to clear evidence of effectiveness based on a planned interim

analysis of the first 150 patients randomized. In the interim analysis, treatment with sabizabulin 9 mg once daily resulted in a clinically meaningful and statistically significant 55.2% relative reduction in deaths (p=0.0042) at Day 60; findings from this interim analysis were subsequently peer-reviewed and published in the New England Journal of Medicine Evidence (Barnette et al., 2022). Similarly, results from the complete dataset of 204 patients in this Phase 3 clinical study showed that sabizabulin treatment compared to placebo demonstrated a 51.6% relative reduction in mortality at Day 60 (p=0.0046). All secondary key endpoints were also shown to be clinically and statistically significant, including the result that viral load by Day 9 decreased by 42.9% in the sabizabulin treatment group, whereas in the placebo group viral load increased by 412%, consistent with the antiviral mechanism of sabizabulin.

Moreover, numerous sensitivity analyses have been conducted that confirm the robustness of these findings. Overall, there is clear clinical benefit with a strong treatment effect demonstrated in the primary endpoint analyses from the Phase 2 and Phase 3 COVID-19 studies, and all sensitivity analyses conducted to examine subgroups in the pivotal Phase 3 study also favor sabizabulin over the placebo control.

The safety database for the sabizabulin clinical development program consists of acute use data from Phase 2 and Phase 3 studies in hospitalized COVID-19 patients (149 patients at 9 mg daily for ≤ 21 days) and chronic use data from ongoing Phase 1b/2 and Phase 3 studies in prostate cancer (117 patients treated at up to 32 mg daily for up to 3 years), for a total of 266 patients in the safety database. In the Phase 2 and Phase 3 COVID-19 studies, sabizabulin was well tolerated with significantly fewer serious adverse events and life-threatening adverse events reported for sabizabulin compared to placebo groups. As death is both a primary endpoint in the COVID-19 studies as well as an adverse event, it is not surprising that fewer COVID-19 related deaths were seen in the treatment group. The reported safety profiles from the safety database suggest that sabizabulin treatment is well tolerated and is associated with few adverse events when used as proposed for COVID-19 treatment.

The nonclinical program for sabizabulin consists of studies in pharmacology (including mechanism of action studies: antiviral, anti-inflammatory, and *in vivo* ARDS mouse model), pharmacokinetics, toxicology, toxicokinetics, genotoxicity, and phototoxicity. Sabizabulin is well tolerated in these nonclinical models with a safety margin of approximately 3.2-fold when comparing the no adverse effect level to the clinical COVID-19 dose using a human equivalent dose calculation.

The totality of evidence for sabizabulin demonstrates clear clinical benefit with a strongly favorable benefit: risk profile, which supports its use under an EUA as likely effective and safe. Sabizabulin can address a significant unmet medical need for safe and effective oral therapeutics to treat hospitalized patients with moderate to severe COVID-19. Importantly, the mechanism of action of sabizabulin (targeting the microtubule trafficking network used by the virus to infect cells) is independent of coronavirus variant, so when new variants of COVID-19 should develop that could be even more virulent causing greater numbers of severe cases, the availability of sabizabulin would be critical in the treatment armamentarium in moderate to severe hospitalized COVID-19 patients at high risk for ARDS and death.

The Sponsor acknowledges the unique nature of an Emergency Use Authorization and consistent with this procedure is committed to comprehensive monitoring of the safe use of the product

following authorization as well as the generation of data to support its ultimate full approval. Likewise, comprehensive physician and patient education regarding appropriate use will complement the product at introduction.

The Sponsor notes that the FDA has stated that a focus of the discussion at this advisory committee meeting will include "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." To facilitate the discussion, the Sponsor provides its perspective on these points directly in the subsections below and provides additional information supporting these positions throughout this briefing document.

1.1. FDA Discussion Point 1: "The treatment effect size in the context of the high placebo mortality rate"

A comprehensive analysis was made of all similar COVID-19 efficacy contemporary studies to determine whether the placebo mortality rate seen in the pivotal Phase 3 study of sabizabulin differed in any way such that it could alter the interpretation of the findings of the study. This analysis demonstrates that the mortality rates observed in the placebo group (Day 29 = 29.4%) of the Phase 3 COVID-19 sabizabulin Full Study population are in-line and consistent with other contemporary COVID-19 clinical trials based on the proportion of severe patients enrolled.

The primary endpoint of Phase 3 COVID-19 study (mortality up to Day 60) was met in the Interim Analysis population in which a statistically significant (p=0.0042) 55.2% relative reduction (25% absolute reduction) in deaths was observed with sabizabulin treatment compared to placebo. The Day 29 placebo mortality in the Interim Analysis population was 35.2% compared to mortality rate of 16% in the sabizabulin group (54.5% relative reduction in deaths).

In the Full Study (overall) population of 204 randomized subjects, the mortality up to Day 60 also had a statistically significant (p=0.0046) 51.6% relative reduction (20.5% absolute reduction) in deaths in the sabizabulin treatment compared to placebo group. The Day 29 mortality rate in Full Study population was 29.4% in the placebo group compared 15.4% in the sabizabulin group (47.6% relative reduction).

In collaboration with and at the direction of the United States Food and Drug Administration (FDA), the Phase 3 COVID-19 study purposefully enrolled patients starting in May of 2021 who had the highest risk for death and who had already shown evidence of disease progression. Additionally, both delta and omicron coronavirus variants were represented in the enrolled patient population (based upon the dates of study enrollment). Specifically, to assure the highest risk population was enrolled, the key inclusion criteria were:

- Patients were required to have an oxygen saturation level of ≤94% on room air (prior to oxygen support)
- Patients requiring supplemental oxygen (WHO 4 on the WHO Ordinal Scale for Clinical Improvement) were required to have at least one high risk comorbidity (as defined by and received from the FDA)
- Patients requiring non-invasive ventilation (NIV) or high-flow oxygen (WHO 5 on the WHO Ordinal Scale for Clinical Improvement) could be enrolled with or without a high-risk comorbidity

- Patients requiring mechanical ventilation with intubation (WHO 6 on the WHO Ordinal Scale for Clinical Improvement) could be enrolled with or without a high-risk comorbidity

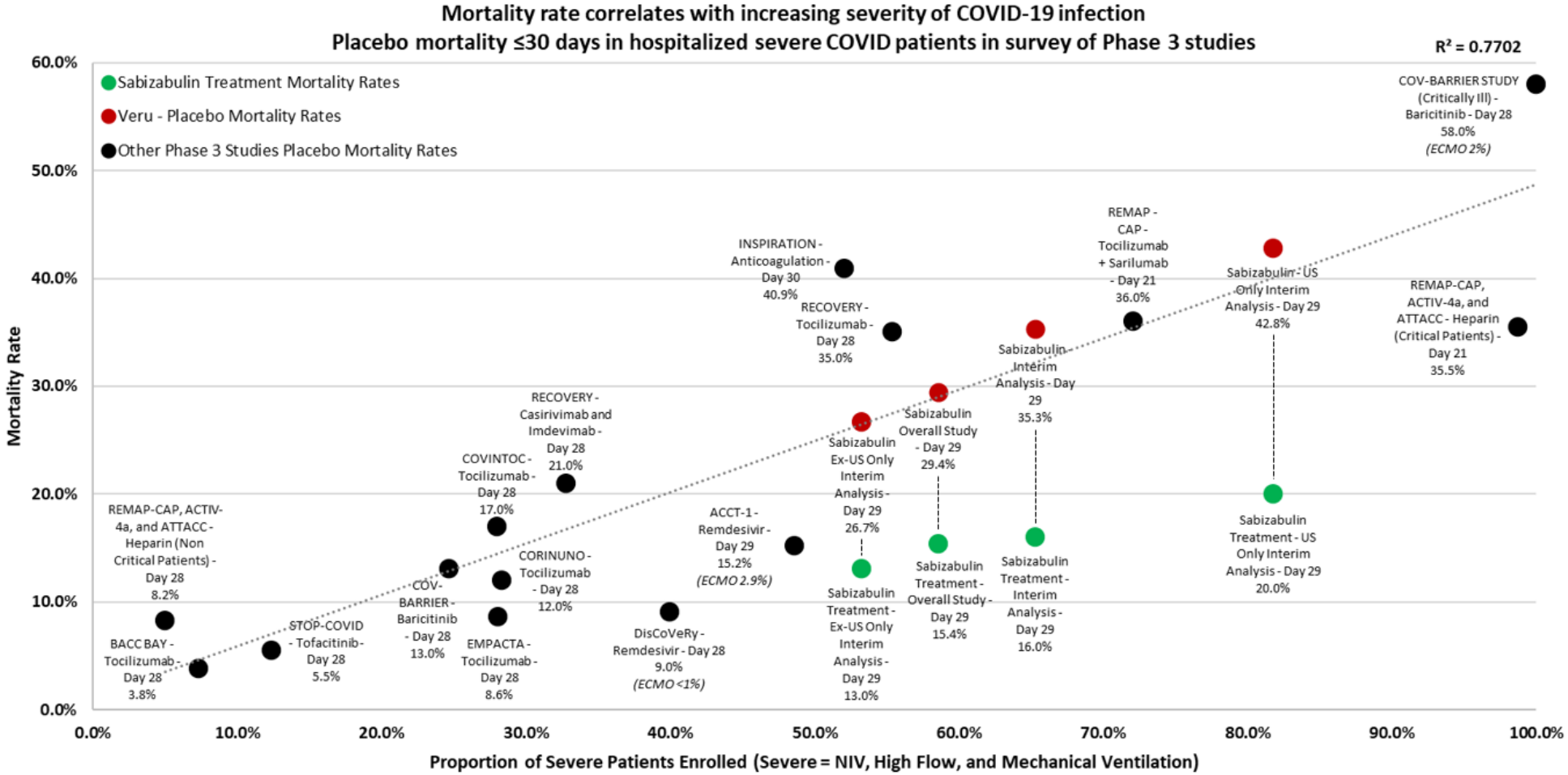
To determine whether the placebo mortality rate in the Phase 3 sabizabulin COVID-19 study is higher than contemporaneous COVID-19 studies, Veru conducted a comparative analysis of the mortality rates observed in the placebo (standard of care) groups across COVID-19 studies in the context of the proportion of patients with severe COVID-19 infections enrolled (see Section 3.3.3.2.6.2).

The results from this analysis strongly demonstrate that the placebo mortality rate at Day 29 in the Phase 3 COVID-19 sabizabulin study align with other contemporary studies conducted in similar patient populations. These data are visualized by plotting the mortality rate observed at or around Day 29 in the control group (placebo plus standard of care) in each of the studies by the proportion of patients in each study with severe disease (defined as WHO 5 or 6; Figure 1). The regression line in this graph is calculated based on all studies that were contemporaneous to Veru's Phase 3 COVID-19 sabizabulin study (black dots) but did not include the Phase 3 COVID-19 sabizabulin study (red and green dots). The R^2 of 0.7702 demonstrated a high level of correlation between mortality rate and severity of COVID-19 infection in patients at baseline. When the Day 29 mortality rates for the Interim Analysis population, US-only Interim Analysis population, outside the US (OUS)-only Interim Analysis population, and the Full Study population from the Phase 3 COVID-19 sabizabulin study were plotted on the graph (red dots), the placebo mortality rates in these various populations from the Phase 3 COVID-19 sabizabulin study fit within the mortality rates reported from in these contemporaneous studies.

The graphical representation below also illustrates the mortality benefit (effect size) of sabizabulin treatment (green dots) compared to placebo (red dots).

The effectiveness of sabizabulin, including the effect size, is demonstrated in the primary endpoint analysis and is supported by every subgroup analysis conducted as well as the secondary efficacy endpoints in this high-risk patient population regardless of the mortality rate observed in the corresponding placebo groups. Further, the safety profile of sabizabulin demonstrates the efficacy of the drug in the reduction of adverse events and serious adverse events commonly associated with COVID-19 infection progression.

Figure 1: Comparison of Phase 3 COVID-19 Studies with Respect to Mortality up to Day 30 as a Function of Proportion of Patients with Severe Disease



Red and Green Dots: Phase 3 COVID-19 sabizabulin study V3011902 data; Black Dots: other studies.
Trend line is calculated based on data from other studies only (does not include Phase 3 COVID-19 sabizabulin study V3011902 data points).
Source: see Table 30 for study references.

1.2. FDA Discussion Point 2: "The limited size of the safety database"

While the sample size for efficacy appears to be limited, both sample size estimation power calculations and final trial results confirm that the patient database for sabizabulin is sufficient to support both efficacy and safety determinations in line with EUA requirements. Additional safety evaluations of sabizabulin are also expected to be ongoing concurrent with product availability under an EUA.

Overall, the sabizabulin safety database consists of 266 patients:

- 149 patients with moderate-to-severe COVID-19 infection who are at high risk for ARDS (acute use setting; 9 mg administered daily for up to 21 days or until hospital discharge, whichever comes first), and
- 117 patients with advanced prostate cancer (chronic use setting; 32 mg daily dose for up to 3 years; patients are still being enrolled in a Phase 3 study in which safety monitoring is ongoing).
  - It should be noted that since the latest data cut-off in these prostate cancer studies (28 April 2022), an additional 15 patients have been enrolled to receive sabizabulin in the Sponsor's Phase 3 prostate cancer study and two patients remain in follow-up in the Sponsor's Phase 1b/2 study (these two patients have remained on chronic daily dosing of sabizabulin 32 mg for approximately 3 years). No new safety signals have been identified from either of these ongoing studies.

The total size of the safety database of 266 patients for sabizabulin should be deemed adequate to support its use under an EUA for the following reasons:

- Safety data from clinical studies indicate that sabizabulin is well tolerated at the COVID-19 dose (9 mg daily for up to 21 days or until hospital discharge, whichever comes first).
- Safety data from prostate cancer patients receiving a higher dose (32 mg) of sabizabulin in a chronic daily dosing setting show that sabizabulin is well tolerated, and these data are relevant to the use of sabizabulin in COVID-19 treatment because both patient cohorts are of similar age and both have comorbidities.
- The safety risk associated with providing sabizabulin under an EUA is minimized due to its indicated short term and carefully controlled use, as the target patients for which sabizabulin is to be used are hospitalized and under direct care (constant safety monitoring).
- Additional safety data will be collected in patients that receive sabizabulin under an EUA through usual FDA-stipulated spontaneous reporting channels to support its ultimate full approval.

Thus, sufficient safety data are and will be available to support the authorization of sabizabulin for emergency use and to support the safe intended use. As the benefits of sabizabulin are expected to far outweigh any safety risks and additional safety data will be collected, the benefit:

risk balance can continue to be monitored while the product is available to patients with the greatest need under an EUA.

1.3. FDA Discussion Point 3: "Identifying the Proposed Population"

The proposed indication statement and proposed population are appropriate based on the inclusion/exclusion criteria used for the Phase 3 COVID-19 sabizabulin clinical study which purposefully enrolled patients at high risk for ARDS and allowed current standard of care treatments to be administered along with the study drug. The proposed EUA Fact Sheet for sabizabulin that has been submitted to FDA for review is provided in Appendix A for ease of reference. As detailed in the Fact Sheet, the specific proposed wording is:

"The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product sabizabulin for the treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk for ARDS."

Patients at high risk for ARDS are defined as patients who:

- Are on supplemental oxygen with at least one known comorbidity that has been identified as a risk factor for ARDS, including asthma, chronic lung disease, diabetes, hypertension, severe obesity (BMI ≥40), 65 years of age or older, primarily reside in a nursing home or long-term care facility, or immunocompromised; or
- Are on non-invasive ventilation or high-flow oxygen; or
- Are intubated and placed on mechanical ventilation; and
- Have an oxygen saturation (SpO_2) level ≤94% on room air prior to receiving oxygen support.

2. BACKGROUND

2.1. Ongoing Medical Need

In the US and around the world, the COVID-19 pandemic/endemic continues to have a dramatic effect on morbidity and mortality with over 624,063,972 cases and 6,552,441 deaths worldwide and counting (Worldometers.info; accessed 04 October 2022). Even now, around 300-500 patients in the US are dying of COVID-19 each day (Worldometers.info; accessed 04 October 2022), but with another likely surge projected for this fall and winter, deaths will again rise even higher. Importantly, acute respiratory distress syndrome (ARDS) remains a frequent complication of severe COVID-19 infection (Tzotzos et al., 2020; Wu et al., 2020; Aranda et al., 2021). Up to 33% of hospitalized patients with COVID-19 have ARDS and 75% to 92% of patients admitted to the intensive care unit (ICU) with COVID-19 have ARDS (Chand et al., 2020; Patel et al., 2020; Tzotzos et al., 2020). The mortality rate of COVID-19 associated ARDS is 45% and there is a 90% incidence of ARDS among patients who died from COVID-19 (Tzotzos et al., 2020).

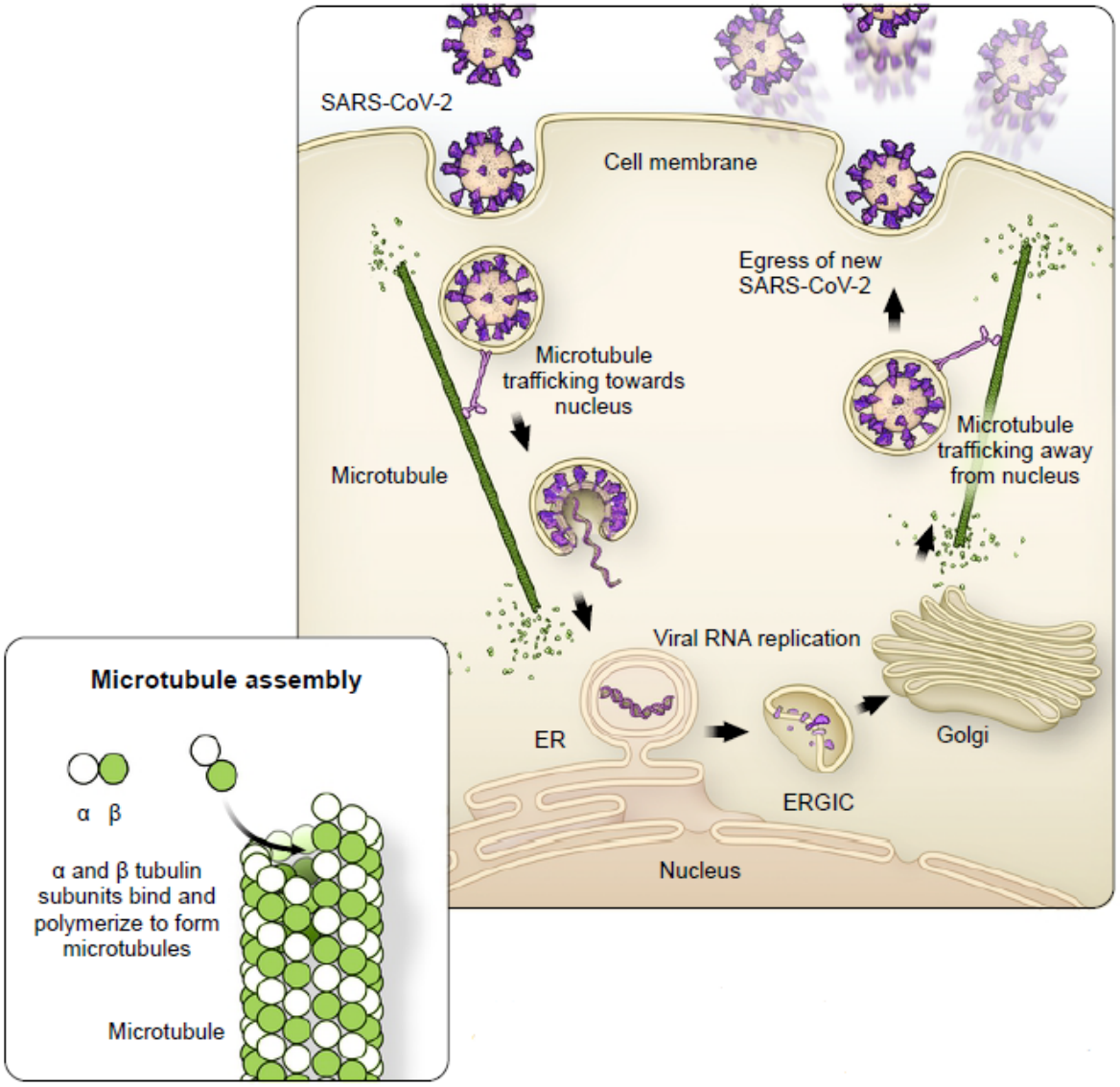
While the United States has reduced restrictions and is "opening up," the daily death rate continues to be unacceptable and of serious concern. COVID-19 mutant variants have the potential to become more virulent and evade vaccinated host immunity resulting in a higher mortality rate. There is no question that the management of the pandemic/endemic requires additional safe and effective treatment options for managing the death and disability caused by COVID-19 infections. Sabizabulin offers great promise as an addition to the armamentarium, as the clinical evidence of effectiveness of the drug is strong and the mechanism of action targets microtubules in host cells rather than the virus itself, which makes sabizabulin antiviral activity independent of virus variant. Thus, sabizabulin can be of benefit to patients as SARS-CoV-2 continues to mutate and evolve and the disease continues to transition from a pandemic to an endemic state.

2.2. Description of SARS-CoV-2 and the role of microtubules in host cells

SARS-CoV-2 is an enveloped, non-segmented, positive-sense, single stranded RNA virus with club-like spikes that project from its surface. It belongs to the *betacoronavirus* category which includes SARS-CoV and MERS-CoV. These highly contagious viruses have been responsible for epidemics with variable severity with both respiratory and extra-respiratory clinical manifestations, highly contagious, and mortality rates between 10-35% (Cascella et al., 2020).

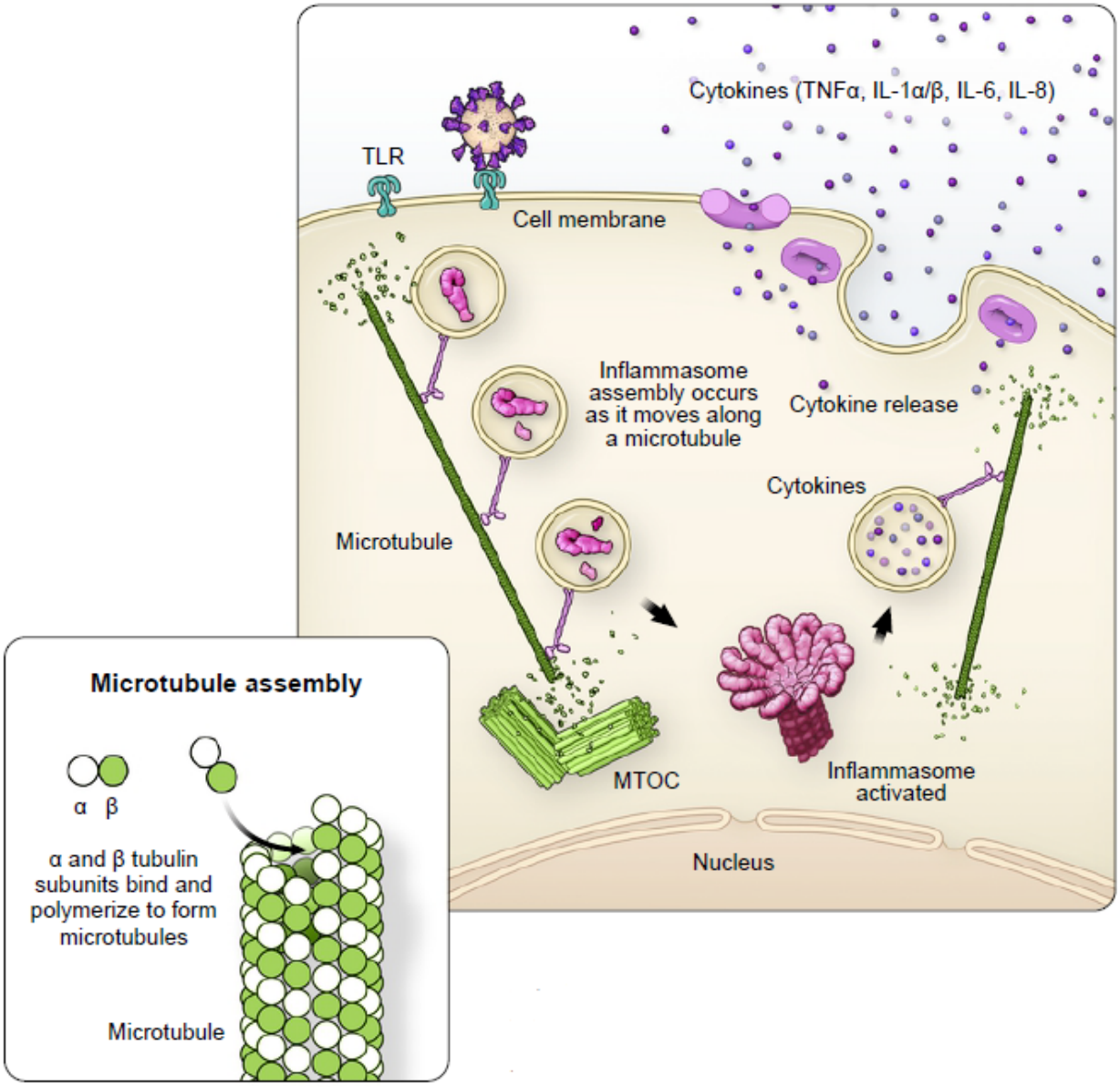
As shown in Figure 2, the stages of the COVID-19 viral life cycle associated with microtubules include: virus-cell surface interactions, virus entry and internalization; virus intracellular transport to the perinuclear region for replication of RNA in double membrane vesicles in ER, viral assembly in the intermediate space between ER and Golgi called Endoplasmic Reticulum-Golgi Intermediate Compartment (ERGIC), packaging of virions in Golgi, and then outbound trafficking to egress infectious viral particles out of the cell to spread the virus (Naghavi and Walsh, 2017; Simpson and Yamauchi, 2020; Wen et al., 2020; V'kovski et al., 2021). Microtubules are formed by the polymerization of alpha and beta tubulin subunits. Tubulin interacts with a highly conserved sequence of amino acids on the cytoplasmic domain of *alphacoronavirus* and *betacoronavirus* SARS-CoV spike S proteins (Rüdiger et al., 2016). Rudiger et al. (2016) reported that disruption of microtubule trafficking impairs the egress of these poorly assembled virions and less infectious viruses. Microtubule-based transportation is a critical aspect of virus life cycle (Döhner et al., 2005; Naghavi and Walsh, 2017; Scherer et al., 2022).

Figure 2: COVID-19 Viral Life Cycle Associated with Microtubules



Additionally, as illustrated in Figure 3, by binding to Toll Like Receptors (TLRs) or E protein viroporin, SARS-CoV-2 triggers the activation of inflammasomes (especially NLRP3 inflammasome) which is an integral part of the innate immune system to attack unknown offending pathogens such as viruses (Nieto-Torres et al., 2015; Freeman and Swartz, 2020; Marchetti et al., 2021). The inflammasome is a multimeric protein complex that is spatially separated within the cell and whose protein components are brought together, when triggered, by microtubules (Malik and Kanneganti, 2017; Demidowich et al., 2020; Magupalli et al., 2020; Wu and McGoogan, 2020). Inflammasomes activate IL-1β and IL-18 proinflammatory cascades that lead to the cytokine storm responsible for the hyperimmune response that leads to ARDS, multiple organ failure, sepsis, and death (Lacy and Stow, 2011; Triantafilou and Triantafilou, 2014; Nieto-Torres et al., 2015; Demidowich et al., 2020; Ye et al., 2020). Thus, the mechanism of action of sabizabulin is both anti-viral and anti-inflammatory.

Figure 3: Immune Response Triggered by SARS-CoV-2 Infection



2.3. Description of Product

Sabizabulin is an oral small molecule bisindole that targets, binds to, and crosslinks the alpha and beta tubulin subunits of microtubules of cells to inhibit formation and cause depolymerization of microtubules undergoing high activity (Chen et al., 2012; Li et al., 2012; Wang et al., 2019). Microtubules are especially active during cancer cell division and in periods of high intracellular trafficking of critical growth receptors, macromolecules, and virus infection as well as in triggering the innate immune response and release of inflammatory proteins responsible for the exaggerated inflammatory immune response.

Veru first began investigating the safety and efficacy of sabizabulin in 2018 for the treatment of advanced prostate cancer, a disease that is defined by uncontrolled and rapid cell division.

Ongoing studies confirm the potential utility of chronic daily dosing of sabizabulin to increases radiographic progression-free survival in prostate cancer patients while also being well-tolerated.

Beginning in March 2020, as COVID-19 emerged as a major threat to public health and the World Health Organization declared the COVID-19 outbreak a pandemic, the worldwide scientific community quickly mobilized to combat this lethal pathogen. It was at this time that the Sponsor recognized that sabizabulin may be an antiviral and anti-inflammatory agent that can be used to treat COVID-19 infection because of its action on microtubules which govern the trafficking of macromolecules and viruses within host cells (independent of virus type or strain) as well as suppresses the innate immune system and release of cytokines (Malik and Kanneganti, 2017; Demidowich et al., 2020; Magupalli et al., 2020). Targeting host factors, like microtubules, disrupts viral life cycle (regardless of viral variant) to inhibit production of infectious virions (Wen et al., 2020; Norris and Ovádi, 2021; Oliva et al., 2022). In general, microtubule stabilizing and depolymerizing activity has been shown *in vitro* to have broad antiviral activity, and microtubule depolymerizing activity shows better efficacy than microtubule stabilizing activity (Oliva et al., 2022). *In vitro* and *in vivo* nonclinical research studies conducted by Veru have confirmed that sabizabulin inhibits SARS-CoV-2 infectious viral production, suppresses the production and release of cytokines (cytokine storm), and improves survival and reduces inflammation in a mouse ARDS model.

Based on the mechanism of action of sabizabulin, as well as its preclinical and clinical experience, sabizabulin may have a two-pronged benefit in the treatment of SARS-CoV-2 virus infection and the debilitating and sometimes lethal respiratory effects of the virus caused by inflammatory mediators.

1. As an antiviral, sabizabulin may suppress viral load by targeting and disrupting microtubules critical for viral microtubule trafficking, viral replication, viral assembly, and new virion egress and spread.
2. As an anti-inflammatory agent, sabizabulin may reduce virally induced severe hyperinflammation caused by the cytokine storm leading to septic shock, acute respiratory distress syndrome, multiple organ failure, and death.

2.4. Need for Additional Therapies

While there are a number of treatment options that have been developed and either authorized or approved to date, there remains a large medical need for additional options, including those with mechanistic differences from those that are already available. For instance, there are currently no microtubule depolymerization inhibitors under development for the treatment of COVID-19 infections.

The principal treatment for patients with severe COVID-19 infection is dexamethasone, supportive care, and oxygen therapy. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock (NIH, 2022).

Currently there are two FDA-approved drugs to treat hospitalized patients with COVID-19, and several other therapies that are authorized for emergency use in hospitalized or non-hospitalized patients with COVID-19. None of these agents work by a similar mechanism of action (dual

antiviral and anti-inflammatory activities) as sabizabulin, and none have demonstrated a reduction in mortality of patients as large as that observed in clinical studies to date for sabizabulin.

The two FDA-approved drugs for COVID-19 treatment of hospitalized patients are the following:

- Veklury® (remdesivir) is FDA-approved antiviral agent as an intravenous (IV) infusion for the treatment of 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 (Gilead Sciences, Inc., 2022). In hospitalized patients, Veklury failed to demonstrate any benefit in overall mortality (Beigel et al., 2020).
- Olumiant (baricitinib) is FDA-approved anti-inflammatory agent as an oral tablet for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (Eli Lilly and Co., 2022c). Baricitinib is a Janus kinase (JAK) inhibitor, a class of drugs that block extracellular signals from multiple cytokines that are involved in inflammatory diseases and thought to contribute to inflammation and worsening of COVID-19. Olumiant showed a 5.7% absolute reduction (33.5% relative reduction) in mortality by Day 60 compared to standard of care (Marconi et al., 2021; Ely et al., 2022). It is important to note that baricitinib treatment has significant side effects.

Though antiviral and anti-inflammatory/immunomodulator drugs have been FDA-approved or authorized for emergency use in hospitalized COVID-19 patients at high risk of ARDS (remdesivir, baricitinib, and tocilizumab), these treatments only demonstrate at best a modest effect on reduction in mortality (0% to 5.7% absolute reduction in death compared to standard of care) [Veklury® (remdesivir) (Gilead Sciences, Inc., 2022); dexamethasone, Olumiant (baricitinib) (Eli Lilly and Co., 2022c); Actemra (tocilizumab) (Genentech, Inc., 2021)]. By comparison, the observed efficacy of sabizabulin from Phase 2 and Phase 3 studies (combined 20.1% absolute reduction and 53.6% relative reduction in mortality compared to placebo + standard of care at Day 60) far exceeds any observed mortality benefit for either of these currently approved alternative therapies. Regardless of the relative differences between these agents, additional treatment options are needed to meet public health needs as the COVID-19 pandemic/endemic continues to evolve.

There are additional COVID-19 treatments that have been authorized for emergency use in the US for treatment of patients with mild to moderate COVID-19 who are not hospitalized but may be at risk of progression to severe COVID-19, however these products are not authorized or approved for use in hospitalized patients with severe disease that require oxygen support [Paxlovid (nirmatreivir tablets/ritonavir tablets) (Pfizer Inc., 2022), Lagevrio™ (molnupiravir capsules) (Merck Sharp & Dohme LLC, 2022)]. Additionally, antibody treatments, such as bamlanvimab/estesevimab (Eli Lilly and Co., 2022a) and bebtelovimab (Eli Lilly and Co., 2022b) are also authorized for emergency use in the US for non-hospitalized mild-to-moderate COVID-19 patients who may be at risk for hospitalization or death, but these treatments are virus

strain-specific and have limited use as new virus variants emerge. Additional treatment options are also in various stages of development.

Overall, currently available and anticipated COVID-19 therapies are not expected to adequately address the ongoing demand for safe and effective therapies to treat moderate-to-severe COVID-19 in hospitalized patients who are at high risk of ARDS and death.

2.5. Proposed Authorized Use Under EUA

The Sponsor has submitted a Request for Emergency Use Authorization (EUA) for sabizabulin for once daily oral treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk for ARDS.

3. CLINICAL DEVELOPMENT PROGRAM

The overall clinical development program for sabizabulin (VERU-111) capsule consists of a Phase 2 and a Phase 3 study in COVID-19 patients, as well as ongoing Phase 1b/2 and Phase 3 studies in prostate cancer patients. A summary of all sabizabulin studies providing efficacy and/or safety information to support an EUA for sabizabulin for the treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk for ARDS is provided in Table 1.

It should be noted that based on FDA advice, a dose of 9 mg sabizabulin formulated capsule was selected for use in COVID-19 patients based on the approximate 3.2-fold safety margin to the no adverse effect level (NOAEL) observed from 28-day sabizabulin toxicology studies using a human equivalent dose calculation.

Table 1: Listing of Sabizabulin Clinical Studies

Type of Study	Study Number (status)	Primary Objective(s) of the Study	Subject Population	Study Design and Type of Control	Test Article; Regimen; Route	Number of Subjects (ITT Set)	Treatment Duration
Efficacy and Safety	V0211901 (completed)	Demonstrate the efficacy of sabizabulin in the treatment of SARS-CoV-2 infection by assessing its effect on the proportion of subjects that were alive without respiratory failure at Day 29	Subjects with documented COVID-19 infection (by standard diagnostic method) and at high risk for the development of ARDS.	Randomized, Placebo-Controlled	Sabizabulin 18 mg (powder in capsule); Daily; Oral or via nasogastric tube	Placebo: 20 Sabizabulin: 19	Up to 21 days or hospital discharge, whichever comes first
Efficacy and Safety	V3011902 (completed)	To demonstrate the efficacy of sabizabulin in the treatment of SARS-CoV-2 infection by assessing its effect on the proportion of subjects that die on study (up to Day 60)	Subjects with documented COVID-19 infection (confirmed by PCR test) and at high risk for the development of ARDS.	Randomized, Placebo-Controlled	Sabizabulin 9 mg (formulated capsule); Daily; Oral or via nasogastric tube	Placebo: 70 Sabizabulin: 134	Up to 21 days or hospital discharge, whichever comes first
Safety	V1011101 (study ongoing)	Phase 1b - To assess the safety/tolerability of sabizabulin and to determine the maximum tolerated dose of sabizabulin in patients with metastatic, castration resistant prostate	Men with metastatic castration resistant prostate cancer with prior treatment with at least one novel androgen receptor	Phase 1b: 3+3 design to determine maximum tolerated dose and recommended Phase 2 dose	<u>Phase 1b</u> Sabizabulin 4.5 mg to 81 mg (powder in capsule); Daily; Oral	Sabizabulin: 80	Daily (chronic)

Type of Study	Study Number (status)	Primary Objective(s) of the Study	Subject Population	Study Design and Type of Control	Test Article; Regimen; Route	Number of Subjects (ITT Set)	Treatment Duration
		cancer (mCRPC) who have failed a novel androgen blocking agent therapy. Phase 2 - To estimate the median radiographic progression-free survival (rPFS)	targeting therapy such as abiraterone acetate or enzalutamide	Phase 2: Open-label safety and efficacy	<u>Phase 2</u> Sabizabulin 63 mg (powder in capsule)/32 mg (formulated capsule); Daily; Oral		
Safety	V3011102 (study ongoing, recruiting)	To demonstrate the efficacy of sabizabulin in the treatment of metastatic castration resistant prostate cancer in patients who have failed prior treatment with at least one androgen receptor targeting agent as measured by radiographic progression-free survival (blinded independent central read)	Men with metastatic castration-resistant prostate cancer in patients who have failed prior treatment with at least one androgen receptor targeting agent	Phase 3: Open-label, randomized, active-controlled, safety and efficacy	Sabizabulin 32 mg (formulated capsule); Daily; Oral	245 planned, 37 subjects receiving sabizabulin as of 28 April 2022 (52 subjects receiving sabizabulin as of 01 October 2022)	Daily (chronic)

CSR: clinical study report; ITT: intent-to-treat

3.1. Overview of Biopharmaceutics

There have been two formulations of sabizabulin (VERU-111) capsule: a powder in a capsule (PIC) and a formulated capsule (FC). The PIC product was used in Phase 2 clinical development and the FC product was used in the Phase 3 COVID-19 sabizabulin study and is also being used in the ongoing Phase 3 clinical study in prostate cancer. As discussed in the Overview of Clinical Pharmacology below (Section 3.2), the FC formulation of sabizabulin is about twice as bioavailable as the PIC formulation.

To support dosing of sabizabulin using a nasogastric (NG) tube, Veru conducted a preliminary *in vitro* study to assess the in-use dosing stability, recovery, and compatibility of sabizabulin capsules, 9 mg when administered via NG tube. In this study, sabizabulin capsule contents were dispersed in 20 mL water (pH 6.0-8.0) and the dispersion was tested for stability, and for recovery and compatibility with three different NG tube materials: silicone (Fr 8), polyvinylchloride (PVC; Fr 8), and polyurethane (Fr 12). In the recovery tests, the 20 mL drug product dispersion was flushed through the NG tube using 40 mL of water; this flushing step was also performed in the compatibility test after the dispersion was held in the NG tube for 10 minutes. Results from this study demonstrate that:

- The drug product dispersed/dissolved in water at room temperature is stable for at least 8 hours prior to dosing through the NG tube.
- At least 90% recovery of drug product was observed when sabizabulin capsules, 9 mg drug product was dispersed in 20 mL of water, administered through an NG tube (PVC, polyurethane, or silicone), and flushed with an additional 40 mL of water.
- The 20 mL dispersion/solution of drug product in water was stable for 10 minutes at room temperature while in contact with NG tube material (PVC, polyurethane, or silicone) producing no drug substance degradation.

3.2. Overview of Clinical Pharmacology

The clinical pharmacology of sabizabulin has been assessed in three clinical trials:

- A PK sub-study under protocol V1011101 (comparative bioavailability of PIC and FC formulations, food effect),
- A PK sub-study under protocol V0211901 (PK parameters of 18 mg PIC), and
- A PK assessment of trough plasma levels in patients participating in protocol V3011902 (trough PK levels of 9 mg FC).

Overall, these studies conclude that:

- The $T_{1/2}$ of sabizabulin is approximately 5 hours and steady state is reached within 5 days of daily dosing;
- Administration of sabizabulin with a standard FDA-defined high fat meal (approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively) has minimal effect on the extent of bioavailability (AUC_{0-24h}) of the

sabizabulin PIC product and minimal effect on the AUC or C_{max} of the sabizabulin FC product;

- The PK parameters of sabizabulin 18 mg PIC are slightly higher than directly proportional to 63 mg PIC dose;
- The FC formulation of sabizabulin 9 mg was about twice as bioavailable as the PIC formulation of sabizabulin 18 mg; and
- Trough plasma concentration of sabizabulin from the 18 mg PIC formulation appears similar to that of the 9 mg FC formulation.

3.3. Overview of Efficacy

Evidence of effectiveness is derived from a Phase 2 study (Study V0211901) and a Phase 3 study (Study V3011902) investigating the safety and efficacy of sabizabulin (VERU-111) for the treatment of hospitalized patients with moderate to severe COVID-19 infection who are at high risk for ARDS. It is important to note that Study V3011902 was stopped early by an Independent Data Monitoring Committee due to clear clinical benefit and no safety concerns identified. Further, results from the Full Study population of 204 patients from this study demonstrated that sabizabulin treatment resulted in a 51.6% relative reduction in deaths compared to the placebo group (p=0.0046). These results in the Full Study population confirm the Interim Analysis conclusions of clinically meaningful and statistically significant efficacy profile and a favorable safety profile which led to the Phase 3 clinical study stopping early.

3.3.1. Design

3.3.1.1. Study V0211901

Study V0211901 was entitled *"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)."* This study was a multicenter, randomized, double-blind, placebo-controlled clinical study to determine efficacy and safety of 18 mg PIC sabizabulin for the treatment of hospitalized moderate to severe COVID-19 adult patients who are at high risk for ARDS. A placebo control was chosen to establish equipoise in this small study, and patients were randomized to sabizabulin treatment or placebo in a 1:1 manner.

The study was conducted entirely in the United States between 18 June 2020 and 09 December 2020.

Key inclusion criteria for this study were the following:

- ≥18 years of age with documented evidence of COVID-19 infection (by standard diagnostic method).
- High risk for developing ARDS due to a known comorbidity for being at risk such as:
  - Asthma (moderate to severe),
  - Chronic Lung Disease, Diabetes,

  - Chronic Kidney Disease being treated with dialysis,
  - Severe Obesity (BMI ≥40),
  - 65 years of age or older,
  - primarily reside in a nursing home or long-term care facility, or immunocompromised.
- Peripheral capillary oxygen saturation (SpO2) ≤ 94% on room air at screening.

Key exclusion criteria were the following:

- Pregnant or breastfeeding.
- Required ventilation + additional organ support – pressors, renal replacement therapy (RRT), ECMO (WHO Ordinal Scale for Clinical Improvement – Score of 7) and subjects who required ventilation with a WHO Ordinal Scale for Clinical Improvement – Score of 6 for >5 days at screening.
- Moderate to severe renal impairment.
- Hepatic impairment.

Standard of care treatments available for hospitalized patients with COVID-19 under Emergency Use Authorization by the US FDA were allowed in the study.

Subjects received either 18 mg PIC of sabizabulin or matching placebo, orally or via nasogastric tube, daily for up to 21 days or until the subject was discharged from the hospital, whichever came first.

3.3.1.2. Study V3011902

Study V3011902 was entitled *"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)."* This was a multicenter, multinational, randomized, double-blind, placebo-controlled clinical study to determine efficacy and safety of 9 mg FC sabizabulin for the treatment of hospitalized moderate to severe COVID-19 adult patients who are at high risk for ARDS. Subjects were randomized in a 2:1 fashion to the sabizabulin and placebo groups, respectively.

The study was conducted in the United States, Argentina, Bulgaria, Brazil, Colombia, and Mexico between 19 May 2021 and 03 June 2022.

Key inclusion criteria for this study were the following:

- ≥18 years of age and documented SARS-CoV-2 infection by polymerase chain reaction test.
- Patients with:
  - WHO Ordinal Scale for Clinical Improvement score of 4 at high risk for ARDS who had at least 1 of the known comorbidities for being at high risk, such as:
    - asthma [moderate to severe],

        - chronic lung disease,
        - diabetes,
        - hypertension,
        - severe obesity [body mass index ≥40],
        - 65 years of age or older,
        - primarily resided in a nursing home or long-term care facility,
        - or immunocompromised
    - WHO Ordinal Scale for Clinical Improvement score of 5 or 6 regardless of presence of comorbidities.
- Peripheral capillary oxygen saturation (SpO2) ≤94% on room air at Screening.

Key exclusion criteria were the following:

- Pregnant or breastfeeding
- Required ventilation plus additional organ support - pressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO) (WHO Ordinal Scale for Clinical Improvement – Score of 7). Note: short-term as-needed use of pressors was allowed.
- Moderate to severe renal impairment.
- Hepatic impairment.

Standard of care (SOC) for the treatment of SARS-CoV-2 infection (COVID-19) in hospitalized adult patients was allowed in the study. SOC varied by region and was accounted for in the case record forms.

Randomization was stratified by baseline WHO Ordinal Scale for Clinical Improvement score of 4 (supplemental oxygen), 5 (NIV or high-flow oxygen) and 6 (mechanical ventilation) such that subjects with a WHO Ordinal Scale of 4, 5 and 6 at baseline were approximately equally distributed between the treatment groups. The WHO Ordinal Scale for Clinical Improvement is a scale that is commonly used to measure clinical improvement among clinical trial participants including studies in COVID-19.

The study required that each subject in the study receive a 9 mg daily oral (or via nasogastric tube) dose of sabizabulin or placebo for up to 21 days (Day 21) or until the patient was discharged from the hospital (whichever came first) with efficacy and safety follow up continuing to Day 60 of the study.

Selected clinical sites for this confirmatory Phase 3 COVID-19 sabizabulin study were inspected by FDA in August 2022 and were found to be compliant with current Good Clinical Practices (GCP) guidelines.

3.3.2. Endpoints for Efficacy Evaluation

The endpoints for efficacy evaluation in Study V0211901 and Study V3011902 are presented side-by-side in the table below:

It is important to note that the primary efficacy endpoints for these studies were objective and not subject to interpretation or bias:

- In Study V0211901 the primary efficacy endpoint was the proportion of subjects alive and free of respiratory failure at Day 29.
- In Study V3011902 the primary efficacy endpoint was the proportion of subjects that die on study (up to Day 60).

Table 2: Efficacy Endpoints: Studies V0211901 and V3011902

Type	Study V0211901	Study V3011902
Primary	***Proportion of subjects that were alive without respiratory failure at Day 29***	***Proportion of subjects that die on study (up to Day 60)***
Secondary	1. WHO Ordinal Scale for Clinical Improvement (8-point ordinal scale) 2. Proportion of subjects that were Grade 5, 6, 7, or 8 on the WHO Ordinal Scale for Clinical Improvement at Day 15 3. Proportion of subjects that were Grade 5, 6, 7, or 8 on the WHO Ordinal Scale for Clinical Improvement at Day 22 4. Proportion of subjects that were Grade 5, 6, 7, or 8 on the WHO Ordinal Scale for Clinical Improvement at Day 29 5. Change in mean WHO Ordinal Scale for Clinical Improvement at Day 15 6. Change in mean WHO Ordinal Scale for Clinical Improvement at Day 22 7. Change in mean WHO Ordinal Scale for Clinical Improvement at Day 29 8. Proportion of subjects with normalization of fever and oxygen saturation through Day 15, Day 22, and Day 29 9. Days on mechanical ventilation 10. Percentage of subjects discharged from hospital by Day 15 (and Day 22) 11. All-cause mortality at Day 15, Day 22, Day 29, and Day 60 12. Proportion of subjects alive and free of respiratory failure at Day 15 and Day 22 13. Proportion of subjects alive and discharged from the intensive care unit (ICU) at Day 15, Day 22, and Day 29 14. Proportion of subjects alive and discharged from hospital at Day 15, Day 22, and Day 29 15. Days in ICU 16. Days in hospital 17. Proportion of subjects on mechanical ventilation at Day 15, Day 22, and Day 29	1. The proportion of subjects that are alive without respiratory failure at Day 15, Day 22, and Day 29. Day 29 is the key secondary endpoint. Respiratory failure is defined as endotracheal intubation and mechanical ventilation, extracorporeal membrane oxygenation, high-flow nasal cannula oxygen delivery, noninvasive positive pressure ventilation, clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision making is driven solely by resource limitation. 2. Days in ICU 3. WHO Ordinal Scale for Clinical Improvement change from baseline to Day 15, Day 22, and Day 29 4. Days on mechanical ventilation 5. Days in hospital 6. Proportion of subjects that die on study at Day 15, Day 22, and Day 29. 7. Change from baseline in viral load (baseline to Day 9)

3.3.3. Efficacy Results

3.3.3.1. Study V0211901

In this Phase 2 study 39 subjects were randomized in a 1:1 fashion and received 18 mg PIC of sabizabulin (19 subjects) or matching placebo (20 subjects), orally or through nasogastric tube, daily for up to 21 days or until the subject was discharged from the hospital, whichever came first. Overall, 33 subjects (84.6%) completed the study, with 6 subjects discontinuing prematurely. The mean (SD) treatment exposure was comparable in both the treatment groups: 9.0 (6.64) days in the sabizabulin group and 11.2 (6.74) days in the placebo group.

The effective dose of sabizabulin (18 mg PIC) appeared to minimize the frequency and severity of COVID-19 virus infection and the lethal respiratory adverse effects of the virus compared to placebo. Although V0211901 was a proof-of-concept study, sabizabulin was shown to have a clinical beneficial effect in hospitalized adult patients with COVID-19 who were at high risk for ARDS. Data from Study V0211901 were used as hypothesis-generating for the design of the Phase 3 protocol V3011902.

3.3.3.1.1. Efficacy by Primary Variable

In Study V0211901, the primary efficacy endpoint was the proportion of subjects alive and free of respiratory failure at Day 29.

A higher proportion of subjects were alive without respiratory failure at all the time points in the sabizabulin group as compared to the placebo group. Responders were subjects who were discharged from the hospital or had Grade 3 or 4 on the WHO Ordinal Scale for Clinical Improvement at the visit. At Day 29, a higher proportion of subjects were alive without respiratory failure in the sabizabulin group (89.5%) as compared to the placebo group (70%) (Table 3).

Logistic regression for the proportion of subjects alive and free of respiratory failure by visit (Table 4) showed that at Day 29, the odds ratio between the sabizabulin 18 mg PIC vs Placebo groups was 2.58 (95% CI: 0.37, 18.07; p value = 0.3394).

Table 3: Study V0211901: Primary Efficacy Endpoint – Proportion of Subjects Alive and Free of Respiratory Failure by Visit (ITT Population)

Visit	Responder Status	Sabizabulin (N=19) n (%)	Placebo (N=20) n (%)
Day 15	Responder[a]	16 (84.2)	13 (65.0)
	Non-Responder[b]	3 (15.8)	7 (35.0)
Day 22	Responder[a]	16 (84.2)	14 (70.0)
	Non-Responder[b]	3 (15.8)	6 (30.0)
Day 29	Responder[a]	17 (89.5)	14 (70.0)
	Non-Responder[b]	2 (10.5)	6 (30.0)

[a] Responders were subjects who had been discharged from the hospital or had Grade 0-4 on the WHO Ordinal Scale for Clinical Improvement at the visit.
[b] Non-responders were subjects who died before the visit or had Grade 5-8 on the WHO Ordinal Scale for Clinical Improvement on the day of the visit.
Abbreviations: N = number of subjects in the randomized set; n = number of subjects in the specific category; WHO = World Health Organization

Table 4: Study V0211901: Primary Efficacy Endpoint – Logistic Regression for the Proportion of Subjects Alive and Free of Respiratory Failure at Day 29 (ITT Population)

Effect	Degrees of Freedom	Chi-Square	p-value
Treatment	1	0.91	0.3394
Study Site	4	2.03	0.7302
Remdesivir Use	1	0.25	0.6152
Dexamethasone Use	1	0.01	0.9235
Baseline WHO Scale	1	4.23	0.0396
Treatment	**Odds**	**95% CI**	**p-value**
Sabizabulin 18 mg PIC	6.75	(1.05, 43.57)	0.0448
Placebo	2.61	(0.49, 13.92)	0.2601
Treatment Comparison	**Odds Ratio**	**95% CI**	**p-value**
Sabizabulin 18 mg PIC vs. Placebo	2.58	(0.37, 18.07)	0.3394

Responders were subjects who had been discharged from the hospital or had Grade 0-4 on the WHO Ordinal Scale for Clinical Improvement at the visit.
Non-responders were subjects who died before the visit or had Grade 5-8 on the WHO Ordinal Scale for Clinical Improvement on the day of the visit.
Abbreviations: CI = confidence interval; ITT = Intent-to-Treat; WHO = World Health Organization

3.3.3.1.2. Efficacy by Secondary Variables

The key secondary endpoint outcomes for this study were the following:

- An 82% relative reduction (25% absolute reduction) in mortality at Day 60 was observed in the sabizabulin treated group (1/19 patients, 5.3%) compared to the placebo group (6/20, 30%).

- A 73% relative reduction in days in the ICU was observed in the sabizabulin treated group (2.6±5.8 days) compared to placebo group (9.6±12.4).
- A 78% relative reduction in days on mechanical ventilation was observed in the sabizabulin treated group (1.2±6.1 days) compared to placebo group (5.1±11.2 days).

3.3.3.2. Study V3011902

Study V3011902 was a Phase 3 pivotal efficacy and safety study of hospitalized adult patients with moderate to severe COVID-19 who were at high risk for ARDS. The primary endpoint for the study was the proportion of patients that died up to day 60. Approximately 210 patients were planned for enrollment with randomization of patients to sabizabulin and matching placebo in a 2:1 fashion. At a planned interim analysis for the first 150 patients randomized into the study (Interim Analysis Intent-to-Treat [IA ITT] population) an Independent Data Monitoring Committee unanimously voted to stop the study early for evidence of clear clinical benefit and noted that no safety concerns were observed in the study. In the IA ITT population, there were 150 patients (98 patients received sabizabulin 9 mg capsule and 52 patients received Placebo). In the Full Study population there were 204 patients (134 patients received sabizabulin 9 mg capsule and 70 received Placebo).

At the end of the Phase 3 study there were 6 patients for whom mortality status at Day 60 was unknown (4 patients in the VERU-111 group and 2 patients in the Placebo group). For each of these 6 cases the clinical study sites made multiple attempts to reach the patient at Day 60 (phone calls to the patient and emergency contacts, registered mail) but these attempts were unsuccessful. In addition, attempts were made to confirm the patients' mortality status through available medical records, public records, and review of local obituaries, etc. Ultimately, the sites were not able to determine whether these patients were alive or deceased at Day 60 and therefore this data is confirmed to be missing.

3.3.3.2.1. Efficacy by Primary Variable

Treatment with sabizabulin resulted in a clinically meaningful and statistically significant reduction in mortality compared to placebo. A summary of the primary endpoint is provided for the Interim Analysis (IA) ITT population in Table 5, and for the overall ITT population in Table 6.

Table 5: Study V3011902: Proportion of Subjects That Died Prior To Day 60 (IA ITT Population)

Efficacy Parameter	Sabizabulin	Placebo	% Relative Reduction	% Absolute Reduction
Proportion of patients that died by day 60 – IA ITT population	19/94 (20.2%)	23/51 (45.1%)	55.2%	24.9%
	Odds Ratio	**95% CI**	**p-value**	
Sabizabulin vs. Placebo	3.23	(1.45, 7.22)	0.0042	

Model effects are displaying median of the p-values for imputed analyses. Odds Ratio and associated 95% Confidence Interval (CI) is presented for the probability of survival at Day 60. An odds ratio > 1 indicates benefit in sabizabulin group. Multiple imputation used for missing vital status at Day 60. Imputation model included treatment, region, sex, remdesivir use, dexamethasone use and WHO strata, and additionally subject's discharge status and early treatment discontinuation status.
Abbreviations: CI = confidence interval; ITT = Intent-to-Treat

Table 6: Study V3011902: Proportion of Subjects That Died Prior to Day 60 (ITT Population)

Efficacy Parameter	Sabizabulin	Placebo	% Relative Reduction	% Absolute Reduction
Proportion of patients that died by day 60 – ITT population	25/130 (19.2%)	27/68 (39.7%)	51.6%	20.5%
	Odds Ratio	**95% CI**	**p-value**	
Sabizabulin vs. Placebo	2.77	(1.37, 5.60)	0.0046	

Model effects are displaying median of the p-values for imputed analyses. Odds Ratio and associated 95% Confidence Interval (CI) is presented for the probability of survival at Day 60. An odds ratio > 1 indicates benefit in sabizabulin group. Multiple imputation used for missing vital status at Day 60. Imputation model included treatment, region, sex, remdesivir use, dexamethasone use and WHO strata, and additionally subject's discharge status and early treatment discontinuation status.
Abbreviations: CI = confidence interval; ITT = Intent-to-Treat

Kaplan-Meier Analysis (ITT Population)

The probability of dying, based on Kaplan-Meier estimates, was numerically lower for sabizabulin 9 mg versus placebo at each assessed time point (Table 7). Treatment comparisons using log-rank and Wilcoxon χ^2 tests (sabizabulin versus placebo) were statistically significant in favor of sabizabulin:

- Log-rank χ^2: 9.639, $P = 0.0019$
- Wilcoxon χ^2: 9.307, $P = 0.0023$

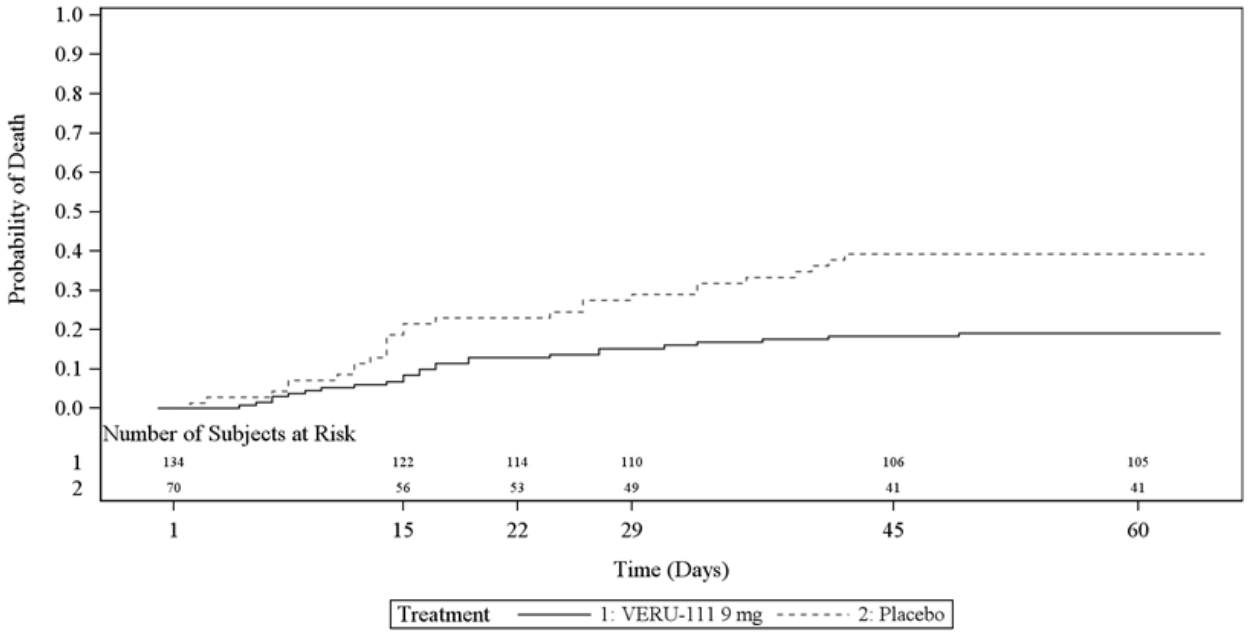
Table 7: Study V3011902: Kaplan-Meier Estimates for Overall Mortality (ITT Population)

	Sabizabulin 9 mg (N=134)	Placebo (N=70)	Absolute Risk Reduction (Placebo versus Sabizabulin 9 mg) Estimate (95% CI)
Number (%) of patients who died	25 (18.7)	27 (38.6)	-
Number (%) of patients censored	109 (81.3)	43 (61.4)	-
Kaplan-Meier Estimates			
25th percentile (95% CI)	NA (37.0, NA)	26.0 (14.0, 40.0)	-
Median (95% CI)	NA (NA, NA)	NA (41.0, NA)	-
75th percentile (95% CI)	NA (NA, NA)	NA (NA, NA)	-
Probability of dying by Day 15 (95% CI)	8.4 (4.7, 14.6)	21.6 (13.6, 33.2)	13.2 (2.4, 24.0)
Probability of dying by Day 22 (95% CI)	13.0 (8.3, 20.0)	23.0 (14.8, 34.8)	10.0 (-1.4, 21.5)
Probability of dying by Day 29 (95% CI)	15.3 (10.1, 22.7)	28.9 (19.7, 41.2)	13.7 (1.3, 26.0)
Probability of dying by Day 45 (95% CI)	18.3 (12.7, 26.1)	39.3 (28.9, 51.9)	21.0 (7.6, 34.3)
Probability of dying by Day 60 (95% CI)	19.1 (13.3, 27.0)	39.3 (28.9, 51.9)	20.2 (6.8, 33.6)

Abbreviations: CI = confidence interval; ITT = Intent-to-Treat; NA = not applicable.

There was clear separation between the sabizabulin 9 mg and placebo Kaplan-Meier curves for time to death (Figure 4).

Figure 4: Study V3011902: Time to Death (ITT Population)



Overall, the following conclusions are made for the primary analysis:

- The percentage of patients in the ITT Set (all randomized subjects) who had died up to Day 60 was lower in the sabizabulin 9 mg group compared with placebo (19.2% and 39.7%, respectively).
  - A similar result was noted in the Safety Set (18.0% and 38.8%, respectively) and the modified Intent to Treat (mITT) Set (18.1% and 38.8%, respectively). The Safety Set consisted of all randomized subjects who received at least one dose of study medication and the mITT Set consisted of all randomized subjects who completed the efficacy portion of the trial and who did not have any major protocol violations.
- The odds ratio (OR) for survival at Day 60 in the ITT Set was statistically significant in favor of sabizabulin (OR: 2.77 [95% CI: 1.37, 5.60], $P = 0.0046$).
  - A similar result was noted in the Safety Set (2.92 [95% CI: 1.43, 5.96], $P = 0.0033$) and the mITT Set (OR: 2.88 [95% CI: 1.41, 5.88], $P = 0.0037$)
  - When logistic regression analysis was repeated using an identity link function, the OR for mortality was statistically significant in favor of sabizabulin (0.19 [95% CI: 0.06, 0.31], $P = 0.0029$).
- The Kaplan-Meier curves for overall mortality in the ITT Set showed clear separation between the sabizabulin 9 mg and placebo groups.
- In a Cox proportional hazards model, the hazard ratio for overall mortality in the ITT Set was statistically significant in favor of sabizabulin (hazard ratio: 0.43 [95% CI: 0.25, 0.75], $P = 0.0029$).
- A sensitivity analysis using the tipping-point approach was also conducted to assess the robustness of the primary analysis approach and found that the results were consistently in favor of sabizabulin versus placebo. The tipping-point analysis considered the full range of possible response rates in the six patients with missing data in the primary analysis. Multiple imputation was used for each pair of response rates under consideration. Both the imputation model and the analysis model incorporated the covariates used in the primary analysis. The tipping point analysis was done by systematically changing the assumed response rates from 0 to 100% in a stepwise manner. The imputation was performed independently within the 2 treatment groups so that, in the most extreme case, the imputed response rate was 0% (all missing patients dead) in the sabizabulin arm and 100% (all missing patients alive) in the placebo arm. In the extreme case, the p-value remained statically significant at p=0.0086.

3.3.3.2.2. Efficacy of Primary Variable – Prespecified Subgroup Analyses

3.3.3.2.2.1. Standard of Care

In Study V3011902, patients were permitted to receive COVID-19 standard of care treatments including dexamethasone and remdesivir. Analyses were conducted to determine if there were

differences in the mortality in patients who did or did not receive standard of care treatments. The following tables describe the number of subjects by arm (including deaths on-study) for:

- Subjects that initiated treatment with remdesivir prior to Day 1 of the study (Table 8)
- Subjects that initiated treatment with dexamethasone prior to Day 1 of the study (Table 9)
- Subjects that received COVID-19 vaccine (Table 10)
- Subjects that received a US authorized COVID-19 vaccine (Table 11)

Table 8: Study V3011902: Subjects Who Initiated Remdesivir Prior To or On Day 1 of the Study

	Sabizabulin	Placebo	Absolute Change (percentage points)	Relative Change (%)	p-value
NO	92	51			
Deaths (%)	16 (17.4%)	17 (33.3%)	-15.9	-47.7%	
YES	38	17			
Deaths (%)	9 (23.7%)	10 (58.8%)	-35.1	-59.7%	0.0283

NOTE: The mortality presented in this table is up to Day 60.

Table 9: Study V3011902: Subjects Who Initiated Dexamethasone Treatment Prior To or On Day 1 of the Study

	Sabizabulin	Placebo	Absolute Change (percentage points)	Relative Change (%)	p-value
NO	26	15			
Deaths (%)	1 (3.8%)	5 (33.3%)	-29.5	-88.6%	
YES	104	53			
Deaths (%)	24 (23.1%)	22 (41.5%)	-18.4	-44.3%	0.0367

NOTE: The mortality presented in this table is up to Day 60.

Table 10: Study V3011902: Subjects Who Were Vaccinated (1, 2, or 3 shots)

	Sabizabulin	Placebo	Absolute Change (percentage points)	Relative Change (%)
NO	83	41		
Deaths (%)	15 (18.1%)	18 (43.9%)	-25.8	-58.8%
YES	47	27		
Deaths (%)	10 (21.3%)	9 (33.3%)	-12.0	-36.0%

NOTE: The mortality presented in this table is up to Day 60.

Table 11: Study V3011902: Subjects Who Were Vaccinated with a US Authorized Vaccine

	Sabizabulin	Placebo	Absolute Change (percentage points)	Relative Change (%)
NO	118	61		
Deaths (%)	22 (18.6%)	23 (37.7%)	-19.1	-50.7%
YES	12	7		
Deaths (%)	3 (25.0%)	4 (57.1%)	-32.1	-56.2%

NOTE: The mortality presented in this table is up to Day 60.

Conclusions

1. Sabizabulin shows a statistically significant and clinically meaningful reduction in mortality (-59.7% relative reduction) in patients who initiated remdesivir treatment prior to initiation of study drug. There is also a clinically meaningful reduction in mortality (-47.7% relative reduction) in patients who did not initiate treatment with remdesivir prior to initiation of study drug. Based on these data, Veru proposes that sabizabulin may be administered with or without prior initiation of remdesivir treatment. Sabizabulin may be first line therapy in this patient population.
2. Sabizabulin shows a statistically significant and clinically meaningful reduction (-44.6% relative reduction) in mortality in patients who initiated dexamethasone treatment prior to initiation of study drug. There is also a clinically meaningful reduction in mortality (-88.6% relative reduction) in patients who did not initiate treatment with dexamethasone prior to initiation of study drug. Based on these data, the Sponsor proposes that sabizabulin may be administered with or without prior initiation of dexamethasone treatment. Sabizabulin may be first line therapy or part of first line therapy (coadministration with corticosteroid therapy) in this patient population.
3. A clinically meaningful reduction in mortality was observed in vaccinated patients (any vaccine), unvaccinated patients, vaccinated patients (US authorized vaccine), and patients that were not vaccinated with a US authorized vaccine.

3.3.3.2.2.2. WHO Ordinal Scale Score at Baseline

In Study V3011902 randomization was stratified by WHO Ordinal Scale at randomization. It is noted that some patients showed disease progression after randomization and prior to first dose. The data presented here represent the WHO score on Day 1 (not randomization). Analyses were conducted to determine the mortality in patients with WHO 4 (supplemental oxygen/passive oxygen), WHO 5 (NIV or high-flow oxygen), and WHO 6 (mechanical ventilation). The following table describes the number of subjects by arm (including deaths on-study) for subjects by WHO Ordinal Score at baseline (Day 1).

Table 12: Study V3011902: Subjects by WHO Status on Day 1 of the Study

	Sabizabulin	Placebo	Absolute Change (percentage points)	Relative Change (%)	p-value
WHO 4	58	29			
Deaths (%)	3 (5.2%)	8 (27.6%)	-22.4	-81.2%	0.0090
WHO 5	60	31			
Deaths (%)	20 (33.3%)	15 (48.4%)	-15.1	-31.2%	0.3206
WHO 6	12	8			
Deaths (%)	2 (16.7%)	4 (50.0%)	-33.3	-66.7%	0.2100

NOTE: The mortality presented in this table is up to Day 60.

Conclusions:

1. Sabizabulin shows a clinically meaningful reduction in mortality in each of the WHO Ordinal Scores at baseline. As discussed elsewhere in this document, the Sponsor notes that the patient population enrolled in this study represented patients that have significant progression of COVID infection and/or have a high risk for further progression. At the request of FDA, the inclusion/exclusion criteria for Study V3011902 were specifically chosen to enroll the patients who were in the highest risk population.

3.3.3.2.2.3. By Country/Region

Study V3011902 was conducted in the United States, Brazil, Bulgaria, Mexico, Argentina, and Colombia. The following table describes the number of subjects by arm (including deaths on-study) for subjects by country and by region:

Table 13: Study V3011902: Subjects by Country

	Sabizabulin	Placebo	Absolute Change (percentage points)	Relative Change (%)
United States	42	23		
Deaths (%)	12 (28.6%)	13 (56.5%)	-27.9	-49.4%
Brazil	52	26		
Deaths (%)	10 (19.2%)	10 (38.5%)	-19.3	-50.1%
Bulgaria	31	17		
Deaths (%)	1 (3.2%)	3 (17.6%)	-14.4	-81.8%
Argentina	2	1		
Deaths (%)	0 (0.0%)	0 (0.0%)	NA	NA
Mexico	2	1		
Deaths (%)	2 (100.0%)	1 (100.0%)	NA	NA
Colombia	1	0		
Deaths (%)	0 (0.0%)	0 (0.0%)	NA	NA

NOTE: The mortality presented in this table is up to Day 60.

Table 14: Study V3011902: Subjects by US vs. OUS

	Sabizabulin	Placebo	Absolute Change (percentage points)	Relative Change (%)
United States	42	23		
Deaths (%)	12 (28.6%)	13 (56.5%)	-27.9	-49.4%
OUS	88	45		
Deaths (%)	13 (14.8%)	14 (31.1%)	-16.3	-52.4%

NOTE: The mortality presented in this table is up to Day 60.

Conclusions

1. In countries in which a sufficient number of patients were enrolled (US, Brazil, and Bulgaria) to evaluate treatment comparison, sabizabulin shows a clinically meaningful reduction in mortality in each of these countries.
2. The overall mortality in the placebo group in the US (56.5%) is higher than the OUS population (31.1%). This is most likely related to the difference in the severity of patients at baseline between the US (81.7% of the patients were WHO 5 or 6) and OUS (44.4% of the patients were WHO 5 or 6). Regardless of region, the reduction in mortality in the sabizabulin group is marked compared to the placebo group.

3.3.3.2.3. Efficacy of Primary Variable – Sensitivity Analyses to Test for Robustness of Data

3.3.3.2.3.1. Subgroup Analyses

The following tables show the absolute and relative reduction in risk of mortality by Day 60 compared to placebo by subgroup for the Full Study population (all 204 subjects enrolled). Specifically,

- Table 15 examines various subgroups in the study based on demographic, baseline characteristics, and dominant COVID-19 variant (considering 3 plausible cut-offs for the delta-omicron variant dominance switch: 15 December 2021, 15 January 2022, and 15 February 2022). Based on the mechanism of action of sabizabulin (disruption and depolymerization of microtubules of the host cells) **it is expected that the effects of sabizabulin are both virus-independent and variant-independent.**
- Table 16 examines various subgroups in the study based on comorbidities that are known to increase risk of ARDS; and
- Table 17 examines various subgroups in the study who received prior vaccination or certain types of COVID-19 standard of care treatments.

These sensitivity analyses show that there is a reduction in mortality by Day 60 in all subgroups receiving sabizabulin compared to placebo. These results further support the robustness of the overall primary endpoint analysis as similar mortality reductions with sabizabulin treatment are observed in all subgroups concerning demographics, baseline characteristics, SARS-CoV-2 variant, comorbidities, vaccination status, and COVID-19 standard of care. In the "backward logistic regression" analysis where the effect of multiple variables and combination of variables was assessed, the effectiveness of sabizabulin in reduction in mortality is maintained (p=0.0050; see Section 3.3.3.2.3.2).

Table 15: Study V3011902: Absolute and Relative Reduction in Risk of Mortality by Day 60 Compared to Placebo in Subgroups Based on Demographics, Baseline Characteristics, and SARS-CoV-2 Variant

Subgroup	Sabizabulin	Placebo	Absolute difference	Relative difference
Males	15/88 (17.0%)	19/43 (44.2%)	-27.1%	-61.4%
Females	10/42 (23.8%)	8/25 (32.0%)	-8.2%	-25.6%
Age <60 years	4/44 (9.1%)	7/20 (35.0%)	-25.9%	-74.0%
Age ≥60 years	21/86 (24.4%)	20/48 (41.7%)	-17.2%	-41.4%
WHO 4	3/58 (5.2%)	8/29 (27.6%)	-22.4%	-81.2%
WHO 5	20/60 (33.3%)	15/31 (48.4%)	-15.1%	-31.2%
WHO 6	2/12 (16.7%)	4/8 (50.0%)	-33.3%	-66.6%
US	12/42 (28.6%)	13/23 (56.5%)	-27.9%	-49.4%

Subgroup	Sabizabulin	Placebo	Absolute difference	Relative difference
OUS	13/88 (14.8%)	14/45 (31.1%)	-16.3%	-52.4%
Delta Variant (randomized prior to 12/15/2021)	13/48 (27.1%)	12/26 (46.2%)	-19.1%	-41.3%
Omicron Variant (randomized on or after 12/15/2021)	12/82 (14.6%)	15/42 (35.7%)	-21.1%	-59.1%
Omicron Variant (randomized on or after 1/15/2022)	7/61 (11.5%)	9/32 (28.1%)	-16.6%	-59.1%
Omicron Variant (randomized on or after 2/15/2022)	2/17 (11.8%)	3/12 (25.0%)	-13.2%	-52.8%

Table 16: Study V3011902: Absolute and Relative Reduction in Risk of Mortality by Day 60 Compared to Placebo in Subgroups Based on Comorbidities Known to Increase Risk of ARDS

Subgroup	Sabizabulin	Placebo	Absolute difference	Relative difference
Hypertension	20/84 (23.8%)	17/45 (37.8%)	-14.0%	-37.0%
Pneumonia	16/76 (21.1%)	15/44 (34.1%)	-13.0%	-38.1%
Diabetes	12/45 (26.7%)	12/28 (42.9%)	-16.2%	-37.8%
≥65 years of age	16/65 (24.6%)	16/40 (40.0%)	-15.4%	-38.5%
Severe Respiratory Issues*	4/36 (11.1%)	6/13 (46.2%)	-35.1%	-76.0%
Severe Obesity (BMI ≥40)	3/23 (13.0%)	3/6 (50.0%)	-37.0%	-74.0%
Hypertension +3 other comorbidities	9/40 (22.5%)	6/16 (37.5%)	-15.0%	-40.0%
Pneumonia +3 other comorbidities	8/31 (25.8%)	5/15 (33.3%)	-7.5%	-22.5%
≥65yoa + 3 other comorbidities	5/28 (17.9%)	5/13 (38.5%)	-20.6%	-53.5%
≥4 comorbidities	10/43 (23.2%)	6/18 (33.3%)	-10.1%	-30.2%
≥3 comorbidities	16/73 (21.9%)	14/41 (34.1%)	-12.2%	-35.8%
≥2 comorbidities	25/106 (23.6%)	23/58 (39.7%)	-16.1%	-40.5%

Severe respiratory issues = Asthma, Bronchiectasis, Bronchitis chronic, Chronic obstructive pulmonary disease, Interstitial lung disease, Pulmonary fibrosis, and/or Pulmonary sarcoidosis

Table 17: Study V3011902: Absolute and Relative Reduction in Risk of Mortality by Day 60 Compared to Placebo in Subgroups Based on Vaccination Status and COVID-19 Standard of Care Treatments

Subgroup	Sabizabulin	Placebo	Absolute difference	Relative difference
Vaccinated	10/47 (21.3%)	9/27 (33.3%)	-12.1%	-36.2%
Unvaccinated	15/83 (18.1%)	18/41 (43.9%)	-25.8%	-58.8%
Remdesivir YES	9/38 (23.7%)	10/17 (58.8%)	-35.1%	-59.7%
Remdesivir Treatment co-administered on study (from Day 1 of the study)	5/27 (18.5%)	4/8 (50.0%)	-31.5%	-63.0%
Remdesivir NO	16/92 (17.4%)	17/51 (33.3%)	-15.9%	-47.8%
Dexamethasone YES	24/104 (23.1%)	22/53 (41.5%)	-18.4%	-44.4%
Dexamethasone Treatment co-administered on study (from Day 1 of the study)	20/103 (19.4%)	19/49 (38.8%)	-19.4%	-49.9%
Dexamethasone NO	1/26 (3.8%)	5/16 (31.3%)	-27.4%	-87.7%
Any Systemic Corticosteroid	25/127 (19.7%)	25/65 (38.5%)	-18.8%	-48.8%
Tocilizumab YES	4/8 (50.0%)	6/7 (85.7%)	-35.7%	-41.7%
Tocilizumab NO	21/122 (17.2%)	21/61 (34.4%)	-17.2%	-50.0%
JAK inhibitor YES	1/9 (11.1%)	3/8 (37.5%)	-26.4%	-70.4%
JAK inhibitor NO	24/121 (19.8%)	24/60 (40.0%)	-20.2%	-50.4%

3.3.3.2.3.2. Backward Logistic Regression

To assess the effect (and combination of effects) of various factors in the study on the primary endpoint of the study (mortality by Day 60), a backward logistic regression with stepwise procedure was conducted. The following factors were included in this analysis:

- treatment,
- region,
- sex,
- remdesivir use at baseline,
- dexamethasone use at baseline,
- WHO scale score at randomization,
- selected respiratory issues (Asthma, Bronchiectasis, Bronchitis chronic, Chronic obstructive pulmonary disease, Interstitial lung disease, Pulmonary fibrosis, Pulmonary sarcoidosis),

- asthma,
- history of heart failure,
- diabetes,
- severe obesity (BMI ≥40 kg/m^2),
- age ≥65 years, and
- ≥3 of selected respiratory issues/history of heart failure/diabetes/BMI ≥40/age ≥65.

The results of this stepwise logistic regression are provided in Table 18 and show that when these factors are taken into account, they have very little effect on the overall statistical conclusion of the primary endpoint. Sabizabulin has a highly statistically significant effect on reducing mortality by Day 60 compared to placebo in this analysis (p = 0.0050; odds ratio: 2.93 [95% confidence interval: 1.38, 6.22]). Therefore, it is concluded that any small potential imbalances in these study factors do not appear to have a singular or combined effect on the observed benefit of sabizabulin in the primary study endpoint, reduction in death by Day 60.

Table 18: Study V3011902: Backward Logistic Regression for Proportion of Subjects Alive by Day 60 (ITT Set)

Effect	Degrees of Freedom	Chi-Square	p-value
Treatment	NA	NA	0.0042
Region (North America / South America / Europe)	NA	NA	0.0050
Sex (Male / Female)	NA	NA	0.0636
Remdesivir use (No / Yes)	NA	NA	0.3647
Dexamethasone use (No / Yes)	NA	NA	0.0571
WHO Scale strata for randomization (4, 5, 6)	NA	NA	0.0423
Diabetes	NA	NA	0.1059
Age >=65 years	NA	NA	0.0010
>=3 of 'Selected Respiratory Issues', 'History of Heart Failure', 'Diabetes', 'BMI>=40', 'Age>=65'	NA	NA	0.3613
Treatment	**Odds**	**95% CI**	**p-value**
Sabizabulin 9 mg	6.40	(2.70, 15.20)	<0.0001
Placebo	2.18	(0.89, 5.36)	0.0883
Treatment Comparison	**Odds Ratio**	**95% CI**	**p-value**
Sabizabulin 9 mg vs. Placebo	2.93	(1.38, 6.22)	0.0050

Responders are subjects who are alive at the time point.
Non-responders are subjects who died before the time point.
Missing vital status was handled using multiple imputation methods. Imputation model included treatment, region, sex, remdesivir use at baseline, dexamethasone use at baseline and WHO strata, and additionally subject's discharge status and early treatment discontinuation status.
Analysis model was selected using stepwise logistic regression on the observed data using entry criteria 0.4 and stay criteria 0.5.
Terms included in the stepwise procedure were: treatment, region, sex, remdesivir use at baseline, dexamethasone use at baseline, WHO strata, selected respiratory issues, asthma, history of heart failure, diabetes, severe obesity (BMI >=40 kg/m2), age >=65 years and >=3 of (selected respiratory issues, history of heart failure, diabetes, BMI>=40, age>=65).
Model effects are displaying median of the p-values for the imputed analyses.
An odds ratio > 1 indicates benefit in the Sabizabulin group.

3.3.3.2.4. Efficacy by Secondary Variables

Analyses of secondary endpoints in the Phase 3 COVID-19 sabizabulin study were consistently in favor of sabizabulin versus placebo, including:

- The proportion of patients dead or with respiratory failure at Days 15, 22, 29 and 60 (Table 19) [non-responders in the analysis 'alive without respiratory failure'; this endpoint is analogous to the Phase 2 primary endpoint]
- Days in the ICU (Table 20)
- Days on mechanical ventilation (Table 21)
- Days in the hospital (Table 22)
- Viral load (Table 23)

Table 19: Study V3011902: Proportion of Patients Dead or with Respiratory Failure [Non-Responders in the Alive Without Respiratory Failure Analysis] (ITT population)

	Sabizabulin	Placebo	Absolute change	% Relative change	p-value
Day 15	37/131 (28.2%)	29/69 (42.0%)	-13.8	-32.9%	0.0863
Day 22	35/131 (26.7%)	30/69 (43.5%)	-16.8	-38.6%	0.0269
Day 29	34/130 (26.2%)	30/68 (44.1%)	-17.9	-40.6%	0.0186
Day 60	26/130 (20.0%)	27/68 (39.7%)	-19.7	-49.6%	0.0066

Conclusions (Proportion of Patients Dead or with Respiratory Failure):

1. The proportion of patients that died or had respiratory failure (non-responders in the analysis for 'alive without respiratory failure'; this endpoint is analogous to the Phase 2 primary endpoint) at each time point assessed showed a clinical benefit in the sabizabulin group compared to placebo. At the primary analysis day for this secondary endpoint, Day 29, there was a statistically significant (p=0.0186) reduction in treatment failures in the sabizabulin group compared to placebo.
2. Observationally, the proportion of treatment failures in the sabizabulin group reduces at each subsequent time point from Day 15 to Day 29 while in the placebo group, the proportion of treatment failures increases over this time frame.
3. The statistically significant (p=0.0066) benefit in the proportion of patients that were dead or with respiratory failure in the sabizabulin group compared to placebo is maintained to Day 60.

Table 20: Study V3011902: Days in ICU (ITT population)

	n	Mean	SD	Median
Sabizabulin	134	16.0	23.50	2.0
Placebo	70	26.3	28.11	9.0
Treatment comparison	**LS mean**	**SE**	**95% CI**	**p-value**
	-9.9	3.44	-16.7, -3.1	0.0045

NOTE: in this analysis, the days in the ICU in patients that died on study is set at the worst possible outcome (60 days)

Conclusions (Days in ICU):

3. Treatment with sabizabulin resulted in a statistically significant (p=0.0045) reduction in days in ICU by the protocol defined and FDA required analysis.
4. Not presented in the table, without the imputation of worst possible outcome (60 days) for the patients that died on study, there is a 1.9 day reduction in days in the ICU in the sabizabulin group (mean of 7.4 days) vs. the placebo group (mean of 9.3 days), representing a 20.4% relative reduction in actual days in the ICU in the sabizabulin group compared to placebo. This finding shows that sabizabulin treatment will reduce the burden on hospital and critical care staff in a surge of infections.

Table 21: Study V3011902: Days on Mechanical Ventilation (ITT population)

	n	Mean	SD	Median
Sabizabulin	134	13.7	23.57	0.0
Placebo	70	24.6	29.00	0.0
Treatment comparison	**LS mean**	**SE**	**95% CI**	**p-value**
	-10.4	3.56	-17.5, -3.4	0.0038

NOTE: in this analysis, the days on mechanical ventilation in patients that died on study is set at the worst possible outcome (60 days).

Conclusions (Days on Mechanical Ventilation):

1. Treatment with sabizabulin resulted in a statistically significant (p=0.0038) reduction in days on mechanical ventilation by the protocol defined and FDA required analysis.
2. Not presented in the table, without the imputation of worst possible outcome (60 days) for the patients that died on study, there is a 1.6 day reduction in days on mechanical ventilation in the sabizabulin group (mean of 4.4 days) vs. the placebo group (mean of 6.0 days), representing a 26.7% relative reduction in actual days on mechanical ventilation in the sabizabulin group compared to placebo. This finding shows that

sabizabulin treatment will reduce the burden on hospital and critical care staff in a surge of infections.

Table 22: Study V3011902: Days in the Hospital (ITT population)

	n	**Mean**	**SD**	**Median**
Sabizabulin	134	24.0	21.78	13.0
Placebo	70	31.0	24.61	16.5
Treatment comparison	**LS mean**	**SE**	**95% CI**	**p-value**
	-6.3	3.13	-12.4, -0.1	0.0463

NOTE: in this analysis, the days on mechanical ventilation in patients that died on study is set at the worst possible outcome (60 days)

Conclusions (Days in Hospital):

1. Treatment with sabizabulin resulted in a statistically significant (p=0.0463) reduction in days in the hospital by the protocol defined and FDA required analysis.
2. Not presented in the table, without the imputation of worst possible outcome (60 days) for the patients that died on study, there is a 0.8 day increase in days in the hospital in the sabizabulin group (mean of 16.2 days) vs. the placebo group (mean of 15.4 days). As defined, in this analysis, the patients that died are assigned the actual days they were in the hospital. One possible explanation for this result is that sabizabulin treatment may cause a prolonged hospital stay in patients that would have otherwise died in the placebo group. This analysis shows that even with a 51.6% relative reduction in mortality, the actual average days in the hospital with no imputation for deaths is no different between the treatment groups.

Table 23: Study V3011902: Viral load (ITT population)

	n	**Mean**	**SD**	**Median**	**% Relative Change from Baseline**
Sabizabulin					
Baseline	119	3222891.6	18760830.02	9380.0	--
Change from BL to Last on-Study	101	-1383566.0	30515153.10	-4422.0	-42.9%
Change from BL to Day 9 only	68	-811345.0	36345622.22	-6956.0	-25.2%
Placebo					
Baseline	64	2368764.6	12831731.51	3320.0	--
Change from BL to Last on-Study	52	9761507.2	83144880.94	-834.5	+412%
Change from BL to Day 9 only	37	17500303.3	98692922.60	-1527.0	+739%

Conclusions (Viral Load):

1. The comparison of the effect on viral load by treatment group did not reach statistical significance due to the high variability in the measurement. This is not unexpected with the current technique and assays used to assess viral load.
2. Mean viral load from baseline to last on-study assessment showed a 42.9% relative reduction in the sabizabulin group compared to a 412% increase in the placebo group. In the Day 9 only assessment, the mean viral load decreased by 25.2% in the sabizabulin group and increased by 739% in the placebo group.
3. To minimize the effect of variability, a comparison of the median value at baseline and at Day 9 and last on-study assessment was conducted which shows a beneficial effect of sabizabulin. Specifically, there is a 47.1% reduction in median viral load in the sabizabulin group in the last on-study assessment compared to a 25.1% reduction in the placebo group. This represents an 87.6% relative reduction in the sabizabulin group compared to placebo. In the Day 9 only assessment, there is a 74.2% reduction in median viral load in the sabizabulin group compared to a 46.0% reduction in the median viral load in the placebo group. This represents a 61.3% relative reduction in median viral load in the sabizabulin group compared to placebo.
4. The observed reduction in viral load with sabizabulin treatment is expected based on the antiviral mechanism of action of sabizabulin (see Nonclinical Pharmacology, Section 4.2)

3.3.3.2.5. Efficacy by Secondary Variables – Sensitivity Analyses to Test for Robustness of Data

A sensitivity analysis was conducted on the key secondary endpoints (regarding the total time of hospitalization, total time in the ICU, and total time on mechanical ventilation) to describe hospital-free survival days, ICU-free days, and mechanical ventilation-free days for each individual patient up to 60 days of follow-up. In this analysis, a patient contributed observations until day 60 or the time of censoring, whichever occurred first. 'Days' in this analysis were counted as alive and 'not in the hospital,' 'not in the ICU,' or 'not on mechanical ventilation' (three separate analyses). The method used for this analysis is generalized from the procedure reported in McCaw et al. (2020), in which one can obtain the estimated mean of the hospitalization-free survival days, the mean of ICU-free survival days, and the mean of mechanical ventilation-free survival days for each treatment group (McCaw et al., 2020). One can then use the difference or ratio of the means from the two study arms to quantify the treatment effect. The results of these analyses are presented in the following tables:

- Hospital-Free Days (Alive and Not In The Hospital) [Table 24]
- ICU-Free Days (Alive and Not In The ICU) [Table 25]
- Mechanical Ventilation-Free Days (Alive and Not On Mechanical Ventilation) [Table 26]

It is concluded from these sensitivity analyses that there are statistically significant and clinically meaningful increases in the sabizabulin group compared to placebo for mean days alive and out of the hospital, mean days alive and not in the ICU, and mean days alive and not on mechanical

ventilation. This analysis further confirms the benefit of sabizabulin in hospitalized patients with moderate to severe COVID-19 at high risk for ARDS.

Table 24: Study V3011902: Hospital-Free Days (Alive and Not In The Hospital)

	Mean Days	SE	Lower 95% CI	Upper 95% CI	
Placebo	28.0	2.88	22.4	33.6	
Sabizabulin	36.1	1.81	32.6	39.7	
Contrast Analysis	**Estimate**	**SE**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Absolute difference (sabizabulin – placebo)	8.11	3.44	1.45	14.80	0.017
Ratio (sabizabulin/placebo)	1.29	0.147	1.03	1.61	0.026

CI: confidence interval; SE: standard error.

Table 25: Study V3011902: ICU-Free Days (Alive and Not In The ICU)

	Mean Days	SE	Lower 95% CI	Upper 95% CI	
Placebo	34.2	3.14	28.0	40.3	
Sabizabulin	44.2	1.88	40.5	47.9	
Contrast Analysis	**Estimate**	**SE**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Absolute difference (sabizabulin – placebo)	10.0	3.66	2.88	17.20	0.00597
Ratio (sabizabulin/placebo)	1.29	0.131	1.06	1.58	0.01080

CI: confidence interval; SE: standard error.

Table 26: Study V3011902: Mechanical Ventilation-Free Days (Alive and Not On Mechanical Ventilation)

	Mean Days	SE	Lower 95% CI	Upper 95% CI	
Placebo	37.5	3.06	31.5	43.5	
Sabizabulin	46.8	1.80	43.2	50.3	
Contrast Analysis	**Estimate**	**SE**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Absolute difference (sabizabulin – placebo)	9.29	3.55	2.33	16.30	0.00888
Ratio (sabizabulin/placebo)	1.25	0.113	1.05	1.49	0.01420

CI: confidence interval; SE: standard error.

3.3.3.2.6. Additional Efficacy Analyses (Based on Requests and Comments by FDA During the EUA Review Process)

3.3.3.2.6.1. Mortality by Day 60 Considering Standard of Care Treatments

In Study V3011902, patients were permitted to receive COVID-19 standard of care treatments including corticosteroids and remdesivir. Additional analyses were conducted to determine the mortality in patients who did or did not receive various standard of care treatments. The following tables describe the number of subjects by arm (including deaths on-study) for:

- Subjects receiving corticosteroids or remdesivir ≥7 days prior to randomization (Table 27);
- Subjects receiving corticosteroids during admission (after Day 3 on the study) (Table 28); and
- Subjects receiving remdesivir during admission (after Day 3 on the study) (Table 29).

Considering these data, the following conclusions are made:

1. No difference was observed in patients who were admitted to the hospital and received standard of care for ≥7 days prior to randomization (54.5% relative reduction in mortality) versus the patients that were in the hospital for <7 days prior to randomization or did not receive corticosteroid or remdesivir ≥7 days prior to randomization (51.1% relative reduction in mortality). Therefore, it is reasonable to conclude that sabizabulin treatment should not be limited by the number of days in the hospital prior to initiation of therapy.
2. No difference was observed in patients receiving remdesivir during the study (55.9% relative reduction in mortality) vs. patients that did not receive remdesivir during the study (50.3% relative reduction in mortality). Therefore, it is reasonable to conclude that sabizabulin may be administered with or without remdesivir coadministration.
3. The effectiveness of sabizabulin in mortality benefit appears to be predominantly in patients that received concomitant corticosteroid therapy on or after Day 3 of the study (63.9% relative reduction in mortality in combination with corticosteroid therapy verses corticosteroid alone [placebo]). Therefore, it is reasonable to conclude that sabizabulin can be co-administered with a corticosteroid.
4. The effectiveness of sabizabulin in mortality benefit is observed in all subgroups of patients regardless of standard of care treatment or when the standard of care treatment was started during the study. This observation further supports the robustness of the finding that sabizabulin has a meaningful benefit in reducing mortality in this patient population.

Table 27: Study V3011902: Subjects Receiving Corticosteroids or Remdesivir ≥7 days Prior to Randomization

	Sabizabulin	Placebo	Absolute Change (percentage points)	Relative Change (%)
NO	112	60		
Deaths (%)	21 (18.8%)	23 (38.3%)	-19.6	-51.1%
YES	22	10		
Deaths (%)	4 (18.2%)	4 (40.0%)	-21.8	-54.5%

NOTE: The mortality presented in this table is up to Day 60. The 6 subjects (4 in sabizabulin and 2 in placebo) for whom vital status is unknown on Day 60 are considered as alive.

Table 28: Study V3011902: Subjects Receiving Corticosteroids During Admission (Co-administration On or After Day 3 of the Study)

	Sabizabulin	Placebo	Absolute Change (percentage points)	Relative Change (%)
NO	45	25		
Deaths (%)	10 (22.20%)	6 (24.0%)	-1.8	-7.4%
YES	89	45		
Deaths (%)	15 (16.9%)	21 (46.7%)	-29.8	-63.9%

NOTE: The mortality presented in this table is up to Day 60. The 6 subjects (4 in sabizabulin and 2 in placebo) for whom vital status is unknown on Day 60 are considered as alive.

Table 29: Study V3011902: Subjects Receiving Remdesivir During Admission (Co-administration On or After Day 3 of the Study)

	Sabizabulin	Placebo	Absolute Change (percentage points)	Relative Change (%)
NO	117	61		
Deaths (%)	20 (17.1%)	21 (34.4%)	-17.3	-50.3%
YES	17	9		
Deaths (%)	5 (29.4%)	6 (66.7%)	-37.3	-55.9%

NOTE: The mortality presented in this table is up to Day 60. The 6 subjects (4 in sabizabulin and 2 in placebo) for whom vital status is unknown on Day 60 are considered as alive.

3.3.3.2.6.2. Comparison of Mortality Rates Observed in Phase 3 COVID-19 Sabizabulin Study (V3011902) With Contemporaneous COVID-19 Studies

There have been numerous other contemporary COVID-19 clinical trials with comparable baseline severities (primarily WHO 4, 5 and 6 ordinal severity) conducted in a similar timeframe to the Phase 3 COVID-19 sabizabulin study (V3011902) and which reported the placebo group

(standard of care) mortality rates separately by disease severity. It is noted that because clinical studies are conducted under widely varying conditions including different SARS-CoV-2 variants, adverse reaction rates (including deaths) observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice. Despite these limitations, the Sponsor has conducted a comparative analysis of the mortality rates observed in the placebo (standard of care) group in these contemporaneous COVID-19 studies compared to the Phase 3 COVID-19 sabizabulin study V3011902 (full analysis, interim analysis, and US vs. OUS; see Table 30).

In collaboration with and at the direction of the US FDA, the Phase 3 COVID-19 sabizabulin study purposefully enrolled patients who were at the highest risk for death and patients that had already shown evidence of disease progression. Specifically, the key inclusion criteria to assure the highest risk population was enrolled were:

- Patients were required to have an oxygen saturation level of ≤94% on room air (prior to oxygen support)
- Patients requiring supplemental oxygen (WHO 4) were required to have at least one high risk comorbidity (defined by and received from the FDA)
- Patients requiring high-flow oxygen, non-invasive ventilation (NIV) or high-flow oxygen (WHO 5) with or without a high-risk comorbidity
- Patients requiring mechanical ventilation (WHO 6) with or without high-risk comorbidity.

The patient populations at the greatest risk that drive the higher mortality rates are those who had an ambient air oxygen saturation level of ≤94% and who required NIV or high-flow oxygen or mechanical ventilation. The Phase 3 clinical studies referenced in the NIH COVID-19 treatment clinical guidelines were surveyed for mortality rates for patients in the placebo groups who required NIV or high-flow oxygen or mechanical ventilation at baseline and also had data for these risk categories individually reported. To visualize mortality rates across studies, the Sponsor has plotted the mortality rate observed in the control group (placebo plus standard of care) in each of the studies in Table 30 by the proportion of patients in each study with severe disease (defined as WHO 5 or 6; see Executive Summary, Figure 1). The regression line in Figure 1 is calculated based on all of the contemporary COVID-19 studies (black dots) but did not include the Phase 3 COVID-19 sabizabulin study (V3011902; red and green dots). The R^2 of this line is 0.7702. This analysis shows that the overall mortality rate (%) of the standard of care (placebo) group of COVID-19 patients correlates to the proportion (%) of patients enrolled in the studies with severe disease at baseline (WHO 5 or 6). Additionally, when the Interim Analysis population, US-only Interim Analysis population, OUS-only Interim Analysis population, and the Full Study population from Phase 3 COVID-19 sabizabulin study (V3011902) are plotted on the graph (red dots), the placebo mortality rates in these various populations from the sabizabulin study fit within the mortality rates observed in these contemporaneous studies. This graphical representation also illustrates the mortality benefit of sabizabulin treatment (green dots) compared to placebo (red dots).

Based on the analysis presented above, the mortality rates in the placebo group in the Phase 3 COVID-19 sabizabulin study (V3011902) (Interim Analysis population, US-only Interim Analysis population, OUS-only Interim Analysis population, and the Full Study population) are consistent and expected based on the proportion of severe patients enrolled. Furthermore, one would expect the death rate in the placebo group at Day 60, the primary endpoint in the sabizabulin Phase 3 COVID-19 sabizabulin study (V3011902), to also be even higher than the death rates from studies that reported only up to Day 30.

Table 30: Phase 3 COVID-19 Studies Included in the Mortality Comparison Analysis

Trial	Citation	Reference
Veru Overall Study	Data on File at Veru	Data on file
Veru Interim Analysis	Barnette, et al., Oral Sabizabulin for High-Risk, Hospitalized Adults with Covid-19: Interim Analysis, The New England Journal of Medicine Evidence, July 2022, https://doi.org/10.1056/EVIDoa2200145	(Barnette et al., 2022)
REMAP - CAP	The REMAP-CAP Investigators, Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19, The New England Journal of Medicine, April 2021, N Engl J Med 2021; 384:1491-1502, DOI: 10.1056/NEJMoa2100433	(Gordon et al., 2021)
RECOVERY Trial	RECOVERY Collaborative Group, Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial, The Lancet, May 2021, VOLUME 397, ISSUE 10285, P1637-1645, https://doi.org/10.1016/S0140-6736(21)00676-0	(Abani et al., 2021)
EMPACTA	Salama, et al., Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia, The New England Journal of Medicine, January 2021, N Engl J Med 2021; 384:20-30 DOI: 10.1056/NEJMoa2030340	(Salama et al., 2021)
COVINTOC	Soin, et al., Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial, The Lancet, March 2021, VOLUME 9, ISSUE 5, P511-521, https://doi.org/10.1016/S2213-2600(21)00081-3	(Soin et al., 2021)
CORIMUNO	Hermine, et al., Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia A Randomized Clinical Trial, JAMA Network, October 2020, JAMA Intern Med. 2021;181(1):32-40. doi:10.1001/jamainternmed.2020.6820	(Hermine et al., 2021)
BACC BAY	Stone, et al., Efficacy of Tocilizumab in Patients Hospitalized with Covid-19, The New England Journal of Medicine, December 2020, N Engl J Med 2020; 383:2333-2344 DOI: 10.1056/NEJMoa2028836	(Stone et al., 2020)
COV-BARRIER (Primary)	Marconi, et al., Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial, The Lancet, December 2021, VOLUME 9, ISSUE 12, P1407-1418, https://doi.org/10.1016/S2213-2600(21)00331-3	(Marconi et al., 2021)

Trial	Citation	Reference
STOP-COVID	Guimarães, et al., Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia, The New England Journal of Medicine, July 2021, N Engl J Med 2021; 385:406-415 DOI: 10.1056/NEJMoa2101643	(Guimarães et al., 2021)
RECOVERY	RECOVERY Collaborative Group, Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial, The Lancet, February 2022, VOLUME 399, ISSUE 10325, P665-676, DOI:https://doi.org/10.1016/S0140-6736(22)00163-5	(Abani et al., 2022)
ACCT-1	Beigel, et al., Remdesivir for the Treatment of Covid-19 — Final Report, The New England Journal of Medicine, November 2020, N Engl J Med 2020; 383:1813-1826 DOI: 10.1056/NEJMoa2007764	(Beigel et al., 2020)
REMAP-CAP, ACTIV-4a, and ATTACC	The REMAP-CAP, ACTIV-4a, and ATTACC Investigators, Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19, The New England Journal of Medicine, August 2021, N Engl J Med 2021; 385:777-789 DOI: 10.1056/NEJMoa2103417	(Goligher et al., 2021)
REMAP-CAP, ACTIV-4a, and ATTACC	The ATTACC, ACTIV-4a, and REMAP-CAP Investigators, Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19, The New England Journal of Medicine, August 2021, N Engl J Med 2021; 385:790-802 DOI: 10.1056/NEJMoa2105911	(Lawler et al., 2021)
DisCoVeRy	Ader, et al., Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial, The Lancet, September 2021, VOLUME 22, ISSUE 2, P209-221, DOI:https://doi.org/10.1016/S1473-3099(21)00485-0	(Ader et al., 2022)
INSPIRATION	INSPIRATION Investigators, Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit The INSPIRATION Randomized Clinical Trial, JAMA Network, March 2021, JAMA. 2021;325(16):1620-1630. doi:10.1001/jama.2021.4152	(Sadeghipour et al., 2021)
COV-BARRIER STUDY (Critically Ill)	Ely, et al., Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial, The Lancet, February 2022, VOLUME 10, ISSUE 4, P327-336, DOI:https://doi.org/10.1016/S2213-2600(22)00006-6	(Ely et al., 2022)

3.3.3.2.6.3. Mortality or Drug Dosing by Nasogastric Tube by Day 60 In Patients Who Started Treatment Orally

Efficacy analyses were also conducted to examine the mortality or dosing through nasogastric tube of patients who started treatment orally. In this analysis, based on Kaplan-Meier estimates, the probability of dying or receiving study drug dosing through a nasogastric tube was numerically lower for sabizabulin 9 mg versus placebo at each assessed time point (Table 31). Treatment comparisons using log-rank and Wilcoxon χ^2 tests (sabizabulin versus placebo) were statistically significant in favor of sabizabulin:

- Log-rank χ^2: 5.602, P = 0.0208
- Wilcoxon χ^2: 5.183, P = 0.0258

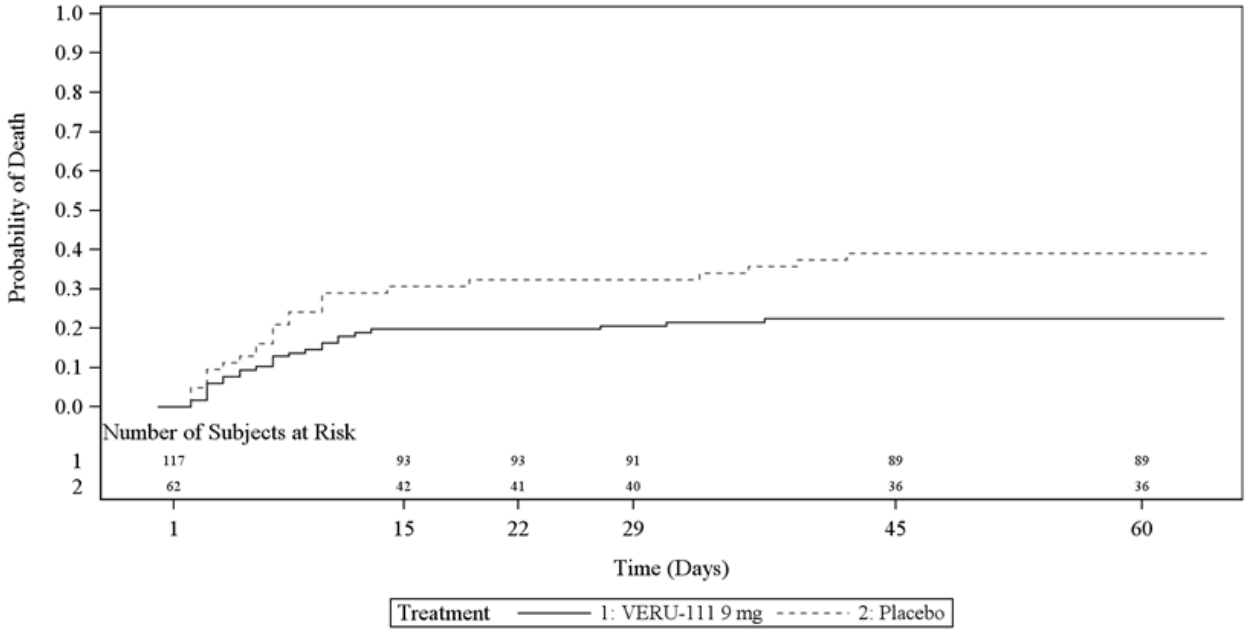
Table 31: Study V3011902: Kaplan-Meier Estimates for Overall Mortality or Dosing Through Nasogastric Tube (Patients who Started Treatment Orally in the Intent-to-Treat Set)

	Sabizabulin 9 mg (N=117)	Placebo (N=62)	Absolute Risk Reduction (Placebo versus Sabizabulin 9 mg) Estimate (95% CI)
Number (%) of patients who died	26 (22.2)	24 (38.7)	-
Number (%) of patients censored	91 (77.8)	38 (61.3)	-
Kaplan-Meier Estimates			
25th percentile (95% CI)	NA (11.0, NA)	10.0 (6.0, 36.0)	-
Median (95% CI)	NA (NA, NA)	NA (39.0, NA)	-
75th percentile (95% CI)	NA (NA, NA)	NA (NA, NA)	-
Probability of dying by Day 15 (95% CI)	19.8 (13.6, 28.3)	30.7 (20.8, 43.8)	10.9 (-2.7, 24.5)
Probability of dying by Day 22 (95% CI)	19.8 (13.6, 28.3)	32.3 (22.2, 45.5)	12.5 (-1.2, 26.3)
Probability of dying by Day 29 (95% CI)	20.6 (14.3, 29.2)	32.3 (22.2, 45.5)	11.7 (-2.1, 25.5)
Probability of dying by Day 45 (95% CI)	22.4 (15.8, 31.1)	39.1 (28.2, 52.5)	16.7 (2.3, 31.1)
Probability of dying by Day 60 (95% CI)	22.4 (15.8, 31.1)	39.1 (28.2, 52.5)	16.7 (2.3, 31.1)

Abbreviations: CI = confidence interval; NA = not applicable.

There was also clear separation between the sabizabulin 9 mg and placebo Kaplan-Meier curves for time to death or dosing through nasogastric tube (Figure 5).

Figure 5: Study V3011902: Time to Death or Dosing Through Nasogastric Tube (Patients who Started Treatment Orally in the Intent-to-Treat Set)



3.3.4. Efficacy Conclusions

Overall, data from Phase 2 (Study V0211901) and Phase 3 (Study V3011902) clinical studies demonstrate the efficacy of sabizabulin in hospitalized adult patients with moderate to severe COVID-19 infection who were at high risk for ARDS.

Data from Phase 2 (Study V0211901) demonstrate the following:

- Sabizabulin shows clinically meaningful outcomes in this proof-of-concept Phase 2 study.
- Results for the primary efficacy endpoint (proportion of subjects alive without respiratory failure) support that sabizabulin is efficacious for the treatment of COVID-19 in patients at high risk for ARDS at Day 15, Day 22, and Day 29.
- All the parameters measured in the study (including proportion of patients alive without respiratory failure, mortality status up to Day 60, days in ICU, and days on mechanical ventilation) showed clinically meaningful outcomes with sabizabulin compared to placebo and there were no parameters that did not indicate benefit with sabizabulin treatment compared to placebo (although some parameters did not reach statistical significance in this small study).

Data from Phase 3 (Study V3011902) demonstrate the following:

- Interim Analysis data from Study V3011902 (First 150 patients enrolled) show that treatment with sabizabulin 9 mg once daily resulted in a clinically meaningful and statistically significant 55.2% relative reduction in deaths (p=0.0042) at Day 60; findings from this interim analysis were subsequently peer-reviewed and published in

the New England Journal of Medicine Evidence (Barnette et al., 2022). Based on the interim analysis, the study was stopped by the Independent Data Monitoring Committee due to clear evidence of efficacy.

- Data from the complete dataset in the V3011902 study (ITT population; 204 patients) show clinically meaningful and statistically significant reductions in mortality compared to placebo at Day 60 (primary endpoint), Day 29, and Day 15. Specifically, treatment with sabizabulin resulted in a clinically relevant and statistically significant 51.6% relative reduction (20.5% absolute reduction) in mortality up to Day 60 compared to placebo (p=0.0046).
- Prespecified subgroup analyses relating to standard of care treatment indicate that sabizabulin treatment is effective when administered both as first-line therapy or as part of first-line therapy (co-administered with corticosteroid therapy) in hospitalized patients requiring oxygen support, and that sabizabulin treatment results in a clinically meaningful reduction in mortality in patients regardless of prior initiation of remdesivir treatment.
- Clinically meaningful reductions in mortality were also observed in patients regardless of vaccination status or vaccination type.
- Other prespecified subgroup analyses show that sabizabulin treatment results in a clinically meaningful reduction in mortality in each of the WHO Ordinal Scores at baseline (WHO 4, WHO 5, and WHO 6), and also in all of the countries in which a sufficient number of patients were enrolled (US, Brazil, and Bulgaria).
- It is noted that the overall mortality in the placebo group in the US (56.5%) is higher than the OUS population (31.1%), which is most likely related to the difference in the proportion of patients with severe COVID-19 infection at baseline between the US (81.7% of the patients were WHO 5 or 6) and OUS (44.4% of the patients were WHO 5 or 6). Regardless of region, the reduction in mortality in the sabizabulin group is marked compared to the placebo group.
- Sensitivity analyses were conducted to test for robustness of the study data and found that mortality reductions with sabizabulin treatment are observed in all subgroups concerning demographics, baseline characteristics, SARS-CoV-2 variant, comorbidities, vaccination status, and COVID-19 standard of care.
- A backward logistic regression was also performed on the primary efficacy endpoint data, taking into account multiple covariates including treatment, region, sex, remdesivir use at baseline, dexamethasone use at baseline, WHO strata, selected respiratory issues, asthma, history of heart failure, diabetes, severe obesity, age ≥65 years, and ≥3 of the following: selected respiratory issues, history of heart failure, diabetes, severe obesity, age≥65. The results from this analysis showed that treatment with sabizabulin continued to show a highly statistically significant effect on reducing mortality by Day 60 compared to placebo (p=0.0050). It is concluded from this analysis that any small potential imbalances in these study factors do not appear to have a singular or combined effect on the observed benefit of sabizabulin in the primary study endpoint, reduction in death by Day 60.

- Analysis of secondary endpoints in Study V3011902 further support the efficacy of sabizabulin and show that:
  - Compared to placebo, sabizabulin treatment resulted in a 40.6% relative reduction in mortality or respiratory failure at Day 29 (p=0.0186), and a 49.6% relative reduction at Day 60 (p=0.0066).
  - A 39.2% relative reduction in days in the ICU (p=0.0045), and a 44.3% relative reduction in days on mechanical ventilation (p=0.0038) were observed in the sabizabulin group compared to placebo by the protocol defined and FDA required analysis.
  - Sabizabulin treatment also resulted in a statistically significant (p=0.0463) reduction in days in the hospital by the protocol defined and FDA required analysis.
  - Secondary endpoint analysis of mean viral load from baseline to last on-study assessment showed a 42.9% relative reduction in the sabizabulin treated group compared to a 412% increase in the placebo group.
  - Sensitivity analyses to test for robustness of data in the secondary endpoints showed statistically significant and clinically meaningful increases in the sabizabulin group compared to placebo for mean days alive and out of the hospital, mean days alive and not in the ICU, and mean days alive and not on mechanical ventilation. This analysis further confirms the benefit of sabizabulin in hospitalized patients with moderate to severe COVID-19 at high risk for ARDS.
- Additional efficacy analyses for Study V3011902 requested by FDA during the EUA review process further indicate that:
  - Sabizabulin treatment is effective when co-administered with a corticosteroid therapy, and that the efficacy of sabizabulin compared to placebo is unaffected by the number of days patients are hospitalized prior to receiving sabizabulin, or by treatment with remdesivir.
  - It is noted that when comparing the placebo mortality rate observed in Study V3011902 to placebo (standard of care) groups in contemporaneous COVID-19 studies, the mortality rates in the placebo group for the interim and full analyses of Study V3011902 (as well as OUS and US-only subgroups) are consistent and as expected based on the proportion of severe COVID-19 patients enrolled in the study.
  - Sabizabulin treatment shows a statistically significant reduction in ‘mortality or progression to dosing through nasogastric tube’ by Day 60 compared to placebo.

Overall, when the data from the Phase 2 and Phase 3 COVID-19 sabizabulin studies are combined, the Day 60 mortality rate for patients treated with sabizabulin was 17.4% (26/149) compared to 37.5% (33/88) in placebo patients representing a 20.1% absolute reduction and

53.6% relative reduction in mortality at Day 60 in the sabizabulin treated patients compared to placebo.

These data have informed the proposed draft Fact Sheet for sabizabulin (Appendix A), including the proposed population and the presentation of clinical efficacy results.

3.4. Overview of Safety

3.4.1. Safety

Sabizabulin has been investigated in two double-blind, placebo-controlled clinical trials in moderate to severe COVID-19 patients who were at high risk for ARDS (Phase 2 Study V0211901 and Phase 3 Study V3011902). In these studies, sabizabulin was administered to hospitalized patients once per day orally or via nasogastric tube for up to 21 days or hospital discharge (whichever came first) at a dose of 18 mg (powder in capsule [PIC] formulation, Phase 2 study), or 9 mg (formulated capsule [FC] formulation, Phase 3 study).

Sabizabulin is also currently being developed for the treatment of advanced prostate cancer (Phase 1b/2 and Phase 3 studies are ongoing). Patients with advanced prostate cancer in the Phase 1b/2 study have received daily administration of sabizabulin of up to 81 mg (PIC formulation, Study V1011101) and in the Phase 3 study patients are receiving daily administration of daily sabizabulin 32 mg (FC formulation; Study V3011102). Safety information for these higher doses of sabizabulin in the prostate cancer population supports a maximum tolerated dose of 63 mg PIC (32 mg FC). As these prostate cancer studies are ongoing, Veru provides interim safety data from Study V1011101 and Study V3011102 to support an EUA for sabizabulin (data cut-off 28 April 2022).

The clinical safety database, which is comprised of the Phase 2 and Phase 3 studies in COVID-19 patients and the available data from ongoing Phase 1b/2 and Phase 3 studies in advanced prostate cancer patients, is sufficient to support an EUA for sabizabulin for the treatment of SARS-CoV-2 infection in hospitalized adult patients with moderate to severe COVID-19 infection who are at high risk for ARDS.

3.4.2. Extent of Exposure

Overall, sabizabulin has been administered to 266 patients in two categories:

- Patients with moderate-to-severe COVID-19 infection who are at high risk for ARDS (total patients exposed: 149), and
- Patients with advanced prostate cancer (all male; total patients exposed: 117 as of 28 April 2022, the latest safety data cut-off for these ongoing clinical trials. Since the data cut-off, an additional 15 patients have been enrolled in the Sponsor's Phase 3 prostate cancer study and two patients remain in follow-up in the Sponsor's Phase 1b/2 study. No new safety signals have been identified from either of these ongoing studies).

To facilitate review, safety information in the following sections is grouped by COVID-19 studies (V0211901 and V3011902) and Prostate Cancer studies.

3.4.2.1. Study V0211901

A total of 39 subjects received at least 1 dose of study drug (19 subjects in the 18 mg PIC sabizabulin group and 20 subjects in the placebo group). The mean (SD) treatment exposure was comparable in both the treatment groups: 9.0 days (6.64) in the sabizabulin group and 11.2 days (6.74) in the placebo group.

3.4.2.2. Study V3011902

In Study V3011902 a total of 199 subjects received at least 1 dose of study drug (130 subjects in the 9 mg sabizabulin treated group and 69 subjects in the placebo group). The mean (SD) treatment exposure was comparable in both the treatment groups: 11.4 days (6.56) in the sabizabulin group and 11.6 days (6.01) in the placebo group.

3.4.2.3. Prostate Cancer Studies

In Study V1011101 (ongoing, enrollment complete), a total of 80 patients received at least 1 dose of sabizabulin (dose range: 4.5 to 81 mg PIC formulation). The Phase 1b/2 study is currently in the follow-up phase with 2 patients active on study (1 patient in Phase 1b at a dose of 63 mg PIC/32 mg FC who has continued on the study for ~3 years, and 1 patient in Phase 2 at the 63 mg PIC/32 mg FC dose who has continued on the study for ~1.5 years). Overall, in Phase 1b the average duration on therapy is currently 61.6 days, and in Phase 2 the average duration on therapy is currently 46.3 days (based on the most recent data cut-off of 28 April 2022).

In Study V3011102 (enrollment ongoing), a total of 37 patients have received 32 mg sabizabulin FC formulation. The Phase 3 study is ongoing, and in the 37 patients who have received sabizabulin at 32 mg FC, the mean duration on therapy is currently 63 days (based on the most recent data cut-off of 28 April 2022).

3.4.3. Treatment-Emergent Adverse Events

3.4.3.1. Study V0211901

In Study V0211901, 24 subjects (61.5%) reported a total of 72 TEAEs. TEAEs were reported by 12 subjects (63.2%) who received sabizabulin and 12 subjects (60.0%) who received placebo. Overall, the most commonly (≥20%) reported SOC categories for TEAEs were gastrointestinal disorders (23.1%) and investigations (20.5%).

In the sabizabulin group, the most commonly (≥2 subjects) reported TEAEs by preferred term (PT) were constipation and aspartate aminotransferase increased (3 subjects each) and alanine aminotransferase increased (2 subjects). All other TEAEs were singular events, and none of these events were deemed to be related to study drug.

In the placebo group, the most commonly (≥2 subjects) reported TEAEs by PT were respiratory failure (4 subjects), pneumothorax and septic shock (3 subjects each), and acute kidney injury, alanine aminotransferase increased, constipation, and pneumomediastinum (2 subjects each). All other TEAEs were singular events, and none of these events were deemed to be related to study drug.

In Study V0211901, 1 subject in the sabizabulin group discontinued due to an AE. This subject, who received two doses of sabizabulin, developed a Grade 4 event of cardiac arrest and was discontinued on the same day. The subject had SpO_2 of 84 at baseline, was non-compliant with study procedures, and refused forced O_2. The subject's O_2 level continued to drop and dropped to 55 at the time of cardiac arrest. The subject did not recover from the event and did not complete the study.

3.4.3.2. Study V3011902

Overall, 136 subjects (68.3%) reported a total of 663 TEAEs (Table 33). TEAEs were reported by 82 subjects (63.1%) who received sabizabulin and 54 subjects (78.3%) who received placebo.

Overall, the most commonly (≥20% in either treatment group) reported System Organ Class (SOC) categories for TEAEs were:

- cardiac disorder (12.3% sabizabulin vs. 30.4% placebo),
- infections and infestations (30.0% sabizabulin vs. 40.6% placebo),
- metabolism and nutrition disorders (16.2% sabizabulin vs. 26.1% placebo),
- respiratory, thoracic, and mediastinal disorders (25.4% sabizabulin vs. 46.4% placebo), and
- vascular disorders (13.8% sabizabulin vs. 24.6% placebo).

Additionally, a review of the System Organ Classes that had a higher incidence of events in the sabizabulin group compared to placebo was conducted. These categories are listed in Table 32 below.

Table 32: Study V3011902: System Organ Class Categories in Which a Higher Proportion of Patients Reported TEAEs in the Sabizabulin Group Compared to Placebo

System Organ Class	Sabizabulin (N=130)	Placebo (N=69)
Blood and lymphatic system disorders	12 (9.2)	4 (5.8)
Gastrointestinal disorders	21 (16.2)	6 (8.7)
Skin and subcutaneous tissue disorders	10 (7.7)	2 (2.9)

In the sabizabulin group, the most commonly (≥5% subjects) reported TEAEs by PT were:

- anemia (5.4% sabizabulin vs. 4.3% placebo),
- constipation (6.9% sabizabulin vs. 8.7% placebo),
- pneumonia (6.2% sabizabulin vs. 13.0% placebo),
- urinary tract infection (6.2% sabizabulin vs. 1.4% placebo),
- acute kidney injury (8.5% sabizabulin vs. 11.6% placebo),

- acute respiratory failure (5.4% sabizabulin vs. 4.3% placebo), and
- respiratory failure (10.0% sabizabulin vs. 20.3% placebo).

Considering the TEAEs and SOCs reported in Study V3011902, the following observations and conclusions are made:

1. The benefit: risk ratio of sabizabulin is clinically relevant based on the reduction in deaths (51.6% reduction in sabizabulin group) and reduction in life threatening TEAEs in the sabizabulin group compared to placebo such as: septic shock (79.2% reduction), pneumonia (52.3% reduction), pneumothorax (92.1% reduction), and respiratory failure (50.7% reduction).
2. The proportion of patients in the sabizabulin group that report any TEAE (19.4% fewer) and any serious TEAE (37.1% fewer) was lower than in the placebo group.
3. The efficacy of sabizabulin in the treatment of COVID-19 is further demonstrated in the reduction in some TEAEs often associated with the progression of COVID-19 infection (septic shock, acute kidney injury, hypoxia, pneumothorax, respiratory failure, and hypotension).
4. The SOCs and TEAEs that are observed at a higher rate in the sabizabulin group compared to the placebo group (SOCs: Blood and lymphatic system disorders, Gastrointestinal disorders, Skin and subcutaneous tissue disorders; TEAEs: anemia, diarrhea, vomiting, urinary tract infections, various skin disorders such as allergic dermatitis, intertrigo, rash, and decubitus ulcer) can be managed with therapy in hospitalized patients being treated with sabizabulin and are not (or are not immediately) life threatening.
5. The SOCs in which the incidence of TEAEs are at least 20% lower in the sabizabulin group compared to the placebo group are:
    a. Cardiac Disorders (-59.5%),
    b. Infections and infestations (-26.1%),
    c. Metabolism and nutrition disorders (-37.9%),
    d. Musculoskeletal and connective tissue disorders (-47.2%),
    e. Nervous system disorders (-40.8%),
    f. Psychiatric disorders (-20.7%),
    g. Renal and urinary disorders (-38.8%),
    h. Respiratory, thoracic, and mediastinal disorders (-45.3%),
    i. Vascular disorders (-43.9%).

Table 33: Study V3011902: Treatment-Emergent Adverse Events Occurring in ≥5% of Patients in Any Treatment Group (Safety Set)

System Organ Class Preferred Term	Sabizabulin 9 mg (N=130)	Placebo (N=69)	Overall (N = 199)
		n (%)	
Subjects with any TEAE	82 (63.1)	54 (78.3)	136 (68.3)
Blood and lymphatic system disorders	12 (9.2)	4 (5.8)	16 (8.0)
Anemia	7 (5.4)	3 (4.3)	10 (5.0)
Cardiac disorders	16 (12.3)	21 (30.4)	37 (18.6)
Atrial fibrillation	6 (4.6)	5 (7.2)	11 (5.5)
Bradycardia	6 (4.6)	5 (7.2)	11 (5.5)
Gastrointestinal disorders	21 (16.2)	6 (8.7)	27 (13.6)
Constipation	9 (6.9)	6 (8.7)	15 (7.5)
General disorders and administration site conditions	9 (6.9)	4 (5.8)	13 (6.5)
Infections and infestations	39 (30.0)	28 (40.6)	67 (33.7)
Pneumonia	8 (6.2)	9 (13.0)	17 (8.5)
Septic shock	2 (1.5)	5 (7.2)	7 (3.5)
Urinary tract infection	8 (6.2)	1 (1.4)	9 (4.5)
Investigations	20 (15.4)	10 (14.5)	30 (15.1)
Metabolism and nutrition disorders	21 (16.2)	18 (26.1)	39 (19.6)
Hyperkalemia	6 (4.6)	6 (8.7)	12 (6.0)
Hypernatremia	6 (4.6)	4 (5.8)	10 (5.0)
Hypokalemia	6 (4.6)	5 (7.2)	11 (5.5)
Hypophosphatemia	2 (1.5)	4 (5.8)	6 (3.0)
Musculoskeletal and connective tissue disorders	5 (3.8)	5 (7.2)	10 (5.0)
Nervous system disorders	10 (7.7)	9 (13.0)	19 (9.5)
Psychiatric disorders	12 (9.2)	8 (11.6)	20 (10.1)
Anxiety	4 (3.1)	4 (5.8)	8 (4.0)
Delirium	5 (3.8)	4 (5.8)	9 (4.5)
Renal and urinary disorders	15 (11.5)	13 (18.8)	28 (14.1)
Acute kidney injury	11 (8.5)	8 (11.6)	19 (9.5)
Respiratory, thoracic and mediastinal disorders	33 (25.4)	32 (46.4)	65 (32.7)
Acute respiratory failure	7 (5.4)	3 (4.3)	10 (5.0)
Hypoxia	3 (2.3)	4 (5.8)	7 (3.5)

System Organ Class Preferred Term	Sabizabulin 9 mg (N=130)	Placebo (N=69)	Overall (N = 199)
		n (%)	
Pneumothorax	1 (0.8)	7 (10.1)	8 (4.0)
Pulmonary embolism	4 (3.1)	3 (4.3)	7 (3.5)
Respiratory failure	13 (10.0)	14 (20.3)	27 (13.6)
Skin and subcutaneous tissue disorders	10 (7.7)	2 (2.9)	12 (6.0)
Vascular disorders	18 (13.8)	17 (24.6)	35 (17.6)
Hypotension	5 (3.8)	8 (11.6)	13 (6.5)

AEs are coded using MedDRA version 24.0.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

3.4.3.3. COVID-19 Studies: Phase 2 and Phase 3 Combined Analysis of TEAEs

The most common TEAEs (≥2%) in the sabizabulin treated group in the Phase 2 and Phase 3 clinical studies combined are presented in Table 34. Overall, the display of TEAEs in this combined safety population is similar to that observed in the Phase 3 Study V3011902, which is expected as the Phase 3 study was much larger than the Phase 2 study.

Table 34: Studies V0211901 and V3011902 Combined Analysis: TEAEs Occurring in ≥2% of Subjects Receiving Sabizabulin by PT

Adverse Reaction	Sabizabulin 9 mg (N=149)	Placebo (N=89)
Anemia	4.7%	4.5%
Atrial Fibrillation	4.0%	6.7%
Bradycardia	4.0%	5.6%
Tachycardia	2.0%	1.1%
Constipation	8.1%	9.0%
Diarrhea	3.4%	1.1%
Dyspepsia	2.0%	0
Vomiting	2.0%	0
Pyrexia	3.4%	0
COVID-19	3.4%	4.5%
Infection	2.0%	0
Pneumonia	5.4%	10.1%
Pulmonary sepsis	2.0%	1.1%
Sepsis	4.7%	4.5%
Septic shock	2.0%	9.0%
Urinary Tract Infection	5.4%	1.1%
Alanine aminotransferase increased	4.0%	4.5%
Aspartate aminotransferase increased	2.7%	2.2%
Fibrin D dimer increased	2.7%	2.2%
Gamma-glutamyltransferase increased	2.7%	2.2%

Serum ferritin increased	2.0%	2.2%
Transaminases increased	4.0%	2.2%
Hyperkalemia	4.0%	6.7%
Hypernatremia	4.0%	4.5%
Hypokalemia	4.7%	5.6%
Hypertension	2.0%	1.1%
Anxiety	2.7%	4.5%
Delirium	3.4%	4.5%
Acute Kidney Injury	7.4%	11.2%
Haematuria	2.0%	2.2%
Acute Respiratory Failure	4.7%	3.4%
Hypoxia	2.0%	4.5%
Pulmonary Embolism	2.7%	3.4%
Respiratory failure	8.7%	20.2%
Decubitis ulcer	2.7%	0
Deep Vein Thrombosis	2.0%	1.1%
Hypotension	3.4%	10.1%

3.4.3.4. Prostate Cancer Studies

In study V1011101, the most commonly reported (>20%) TEAEs by subjects who have received 63 mg PIC sabizabulin are:

- Diarrhea (64.8%),
- Fatigue (40.7%),
- Nausea (38.9%),
- Decreased appetite (38.9%),
- Weight decreased (27.8%),
- ALT increased (22.2%),
- Back pain (22.2%), and
- Constipation (20.4%).

In study V3011102, the most commonly reported (>20%) TEAEs by subjects who have received 32 mg FC sabizabulin are:

- Diarrhea (18.9%), NOTE: the change in formulation from PIC to FC was expected to decrease the incidence of gastrointestinal disorders due to increased bioavailability and decreased dose with the FC.
- Nausea (18.9%),
- Fatigue (13.5%),
- Decreased appetite (16.2%),

- Back pain (13.5%),
- Constipation (10.8%),
- Arthralgia (10.8%), and
- Uncoded (10.8%)

3.4.4. Adverse Drug Reactions

3.4.4.1. Study V0211901

In Study V0211901 there were no treatment-related adverse events.

3.4.4.2. Study V3011902

There were 21 (10.6%) subjects that reported a treatment related TEAE: 13 (10.0%) subjects in the sabizabulin group and 8 (11.6%) of the subjects in the placebo group. Gastrointestinal disorders (6 patients, 4.6%) and Investigations (5 patients, 3.8%) were the most common SOCs for treatment-related TEAEs in the sabizabulin group, compared to Investigations (4 patients, 5.8%) and Respiratory, thoracic, and mediastinal disorders (3 patients, 4.3%) in the placebo group.

The only treatment-related TEAE reported by ≥2% of subjects in the sabizabulin treated group was ‘Transaminases increased’ (3 patients, 2.3%). By comparison, in the placebo group, there were 2 treatment-related TEAEs reported by ≥2% of subjects: ‘Hepatic enzyme increased’ (2 patients, 2.9%), and ‘Respiratory failure’ (2 patients, 2.9%).

3.4.4.3. Prostate Cancer Studies

In Study V1011101, when considering patients from the Phase 1b and 2 studies together who received at least one dose of 63 mg PIC sabizabulin (54 total patients), the most common system organ class for related TEAEs was Gastrointestinal disorders (38 patients, 70.4%). The most common (≥20%) treatment-related TEAEs were:

- Diarrhea (59.3%),
- Nausea (33.3%),
- Decreased appetite (29.6%),
- Fatigue (27.8%), and
- ALT increased (22.2%).

In Study V3011102, related TEAEs have occurred in 51.4% of patients in the sabizabulin group, and 43.8% of patients in the active control group. The most common system organ class for related TEAEs in the sabizabulin group is Gastrointestinal disorders (10 patients, 27%;). The most common system organ classes for related TEAEs in the Control group are General disorders and administration site conditions and Nervous system disorders (3 patients, 18.8% for each of these SOCs).

The most common (≥10%) treatment-related TEAEs in the sabizabulin group are:

- Diarrhea (7 patients, 18.9%),
- Nausea (7 patients, 18.9%),
- Decreased appetite (6 patients, 16.2%), and
- Fatigue (4 patients, 10.8%).

The most common (≥10%) treatment-related TEAEs in the Control group are:

- Fatigue (4 patients, 18.8%), and
- Dizziness (2 patients, 12.5%).

3.4.5. Deaths and Other Serious Adverse Events

3.4.5.1. Study V0211901

3.4.5.1.1. Deaths

Overall, 7 subjects died during the study (1 subject who received sabizabulin and 6 subjects who received placebo). One subject who received sabizabulin reported Grade 5 toxicity (fatal) TEAE of septic shock. Six subjects who received placebo reported Grade 5 toxicity (fatal) TEAEs of septic shock (2 subjects), respiratory failure (2 subjects), COVID-19 (1 subject), and death of unknown cause (1 subject; this subject's death occurred >7 days after treatment end and therefore was not considered treatment emergent).

3.4.5.1.2. Serious TEAEs

A total of 8 (20.5%) subjects (3 subjects who received sabizabulin and 5 subjects who received placebo) had serious TEAEs.

3.4.5.1.3. TEAEs Leading to Study Drug Discontinuation

Overall, 1 subject in the study discontinued due to an AE. This subject, who received sabizabulin, developed a Grade 4 event of cardiac arrest and was discontinued on the same day. The subject had SpO_2 of 84 at baseline, was non-compliant with study procedures, and refused forced O_2. The subject's O_2 level continued to drop and dropped to 55 at the time of cardiac arrest. The subject did not recover from the event and did not complete the study.

3.4.5.2. Study V3011902

3.4.5.2.1. Deaths

In patients who received at least one dose of study drug (safety set), there were 23 deaths (17.7%) in the sabizabulin 9 mg FC group, and 25 deaths (36.2%) in the placebo group. The most common fatal TEAEs, by SOC, were infections and infestations (10 [7.7%] patients in the sabizabulin 9 mg group and 7 [10.1%] patients in the placebo group) and respiratory, thoracic, and mediastinal disorders (8 [6.2%] patients in the sabizabulin 9 mg group and 10 [14.5%] patients in the placebo group).

The most common fatal TEAE, by PT, was respiratory failure in both groups (5 [3.8%] patients in the sabizabulin 9 mg group and 4 [5.8%] patients in the placebo group). The next most common fatal TEAEs reported in patients who received sabizabulin were COVID-19 (3 [2.3%] patients; 2 [2.9%] patients in the placebo group), acute respiratory failure (2 [1.5%] patients; 3 [4.3%] patients who received placebo), and severe acute respiratory syndrome (2 [1.5%] patients; no patients in the placebo group). In patients who received placebo, the next most common fatal TEAE, by PT, was pneumonia (3 [4.3%] patients; 1 [0.8%] patient in the sabizabulin 9 mg group).

Table 35: Study V3011902: Fatal Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)

	Sabizabulin 9 mg (N=130)	Placebo (N=69)	Overall (N = 199)
		n (%)	
Number of deaths	23 (17.7)	25 (36.2)	48 (24.1)
Cardiac disorders	1 (0.8)	4 (5.8)	5 (2.5)
Bradycardia	0	1 (1.4)	1 (0.5)
Cardiac arrest	0	1 (1.4)	1 (0.5)
Cardio-respiratory arrest	1 (0.8)	1 (1.4)	2 (1.0)
Cardiovascular insufficiency	0	1 (1.4)	1 (0.5)
General disorders and administration site conditions	1 (0.8)	2 (2.9)	3 (1.5)
Death	1 (0.8)	0	1 (0.5)
Multiple organ dysfunction syndrome	0	2 (2.9)	2 (1.0)
Infections and infestations	10 (7.7)	7 (10.1)	17 (8.5)
Burkholderia cepacia complex infection	1 (0.8)	0	1 (0.5)
COVID-19	3 (2.3)	2 (2.9)	5 (2.5)
Device related infection	1 (0.8)	0	1 (0.5)
Pneumonia	1 (0.8)	3 (4.3)	4 (2.0)
Sepsis	1 (0.8)	0	1 (0.5)
Septic shock	1 (0.8)	2 (2.9)	3 (1.5)
Severe acute respiratory syndrome	2 (1.5)	0	2 (1.0)
Nervous system disorders	1 (0.8)	1 (1.4)	2 (1.0)
Cerebrovascular accident	0	1 (1.4)	1 (0.5)
Coma	1 (0.8)	0	1 (0.5)
Renal and urinary disorders	1 (0.8)	0	1 (0.5)
Renal failure	1 (0.8)	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders	8 (6.2)	10 (14.5)	18 (9.0)
Acute respiratory failure	2 (1.5)	3 (4.3)	5 (2.5)

	Sabizabulin 9 mg (N=130)	Placebo (N=69)	Overall (N = 199)
		n (%)	
Hypoxia	1 (0.8)	2 (2.9)	3 (1.5)
Pulmonary embolism	0	1 (1.4)	1 (0.5)
Respiratory failure	5 (3.8)	4 (5.8)	9 (4.5)
Vascular disorders	1 (0.8)	1 (1.4)	2 (1.0)
Hypovolemic shock	0	1 (1.4)	1 (0.5)
Shock	1 (0.8)	0	1 (0.5)

AEs are coded using MedDRA version 24.0.
Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

3.4.5.2.2. Serious TEAEs

Overall, 70 subjects (35.2%) reported serious TEAEs. Serious TEAEs were reported by 38 subjects (29.2%) who received sabizabulin and 32 subjects (46.4%) who received placebo. The most common serious TEAEs, by SOC, were respiratory, thoracic, and mediastinal disorders (23 [17.7%] patients in the sabizabulin 9 mg group and 23 [33.3%] patients in the placebo group) and infections and infestations (20 [15.4%] patients in the sabizabulin 9 mg group and 15 [21.7%] patients in the placebo group).

The most common serious TEAEs, by PT, were respiratory failure (13 [10.0%] patients), acute kidney injury (6 [4.6%] patients) and acute respiratory failure (5 [3.8%] patients) in the sabizabulin 9 mg group, and respiratory failure (14 [20.3%] patients), acute kidney injury (6 [8.7%] patients), and pneumothorax (6 [8.7%] patients) in the placebo group.

Table 36: Study V3011902: Serious Treatment-Emergent Adverse Events Occurring in ≥5% of Patients in Any Treatment Group, by System Organ Class and Preferred Term (Safety Set)

	Sabizabulin 9 mg (N=130)	Placebo (N=69)	Overall (N = 199)
		n (%)	
Any TEAE	38 (29.2)	32 (46.4)	70 (35.2)
Cardiac disorders	3 (2.3)	7 (10.1)	10 (5.0)
Atrial fibrillation	0	1 (1.4)	1 (0.5)
Bradycardia	1 (0.8)	1 (1.4)	2 (1.0)
Cardiac arrest	0	3 (4.3)	3 (1.5)
Cardio-respiratory arrest	2 (1.5)	1 (1.4)	3 (1.5)
Cardiovascular insufficiency	0	1 (1.4)	1 (0.5)
Pulmonary valve incompetence	0	1 (1.4)	1 (0.5)
Infections and infestations	20 (15.4)	15 (21.7)	35 (17.6)

	Sabizabulin 9 mg (N=130)	Placebo (N=69)	Overall (N = 199)
		n (%)	
Acinetobacter infection	1 (0.8)	0	1 (0.5)
Burkholderia cepacia complex infection	1 (0.8)	0	1 (0.5)
COVID-19	4 (3.1)	3 (4.3)	7 (3.5)
COVID-19 pneumonia	0	1 (1.4)	1 (0.5)
Clostridium difficile colitis	1 (0.8)	0	1 (0.5)
Device related infection	1 (0.8)	0	1 (0.5)
Endocarditis staphylococcal	1 (0.8)	0	1 (0.5)
Enterococcal sepsis	1 (0.8)	0	1 (0.5)
Infection	1 (0.8)	0	1 (0.5)
Pneumonia	4 (3.1)	4 (5.8)	8 (4.0)
Pneumonia Acinetobacter	1 (0.8)	0	1 (0.5)
Pneumonia bacterial	0	2 (2.9)	2 (1.0)
Pulmonary sepsis	2 (1.5)	1 (1.4)	3 (1.5)
Sepsis	4 (3.1)	2 (2.9)	6 (3.0)
Septic shock	2 (1.5)	5 (7.2)	7 (3.5)
Severe acute respiratory syndrome	2 (1.5)	0	2 (1.0)
Urinary tract infection	2 (1.5)	0	2 (1.0)
Urinary tract infection bacterial	2 (1.5)	0	2 (1.0)
Urosepsis	1 (0.8)	0	1 (0.5)
Renal and urinary disorders	7 (5.4)	8 (11.6)	15 (7.5)
Acute kidney injury	6 (4.6)	6 (8.7)	12 (6.0)
Renal failure	1 (0.8)	0	1 (0.5)
Renal impairment	0	1 (1.4)	1 (0.5)
Tubulointerstitial nephritis	0	1 (1.4)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	23 (17.7)	23 (33.3)	46 (23.1)
Acute respiratory failure	5 (3.8)	3 (4.3)	8 (4.0)
Dyspnea	1 (0.8)	1 (1.4)	2 (1.0)
Hypoxia	2 (1.5)	3 (4.3)	5 (2.5)
Laryngeal stenosis	1 (0.8)	0	1 (0.5)
Organizing pneumonia	0	1 (1.4)	1 (0.5)
Pneumomediastinum	0	1 (1.4)	1 (0.5)
Pneumothorax	1 (0.8)	6 (8.7)	7 (3.5)
Pulmonary embolism	3 (2.3)	3 (4.3)	6 (3.0)

	Sabizabulin 9 mg (N=130)	Placebo (N=69)	Overall (N = 199)
		n (%)	
Pulmonary hemorrhage	0	1 (1.4)	1 (0.5)
Respiration abnormal	0	1 (1.4)	1 (0.5)
Respiratory acidosis	0	1 (1.4)	1 (0.5)
Respiratory failure	13 (10.0)	14 (20.3)	27 (13.6)

AEs are coded using MedDRA version 24.0.
Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

3.4.5.2.3. TEAEs Leading to Study Drug Discontinuation

TEAEs leading to study drug discontinuation were reported in 9 (4.5%) patients overall, including 6 (4.6%) patients in the sabizabulin 9 mg group and 3 (4.3%) patients in the placebo group.

The most commonly reported TEAEs leading to study drug discontinuation, by SOC, were investigations (2 [1.5%] patients in the sabizabulin 9 mg group and 2 [2.9%] patients in the placebo group).

As shown below in Table 37, all TEAEs leading to study drug discontinuation, by PT, were each reported in 1 patient.

Overall, TEAEs leading to discontinuation were equal between the treatment groups (4.6% in the sabizabulin group vs. 4.3% in the placebo group). The preferred terms for the AEs that led to discontinuation in the sabizabulin group do not represent TEAEs that are observed at a higher rate in the sabizabulin group (COVID-19 [n=1], endocarditis staphylococcal [n=1], alanine aminotransferase increased [n=1], liver function test increased [n=1], acute kidney injury [n=1], respiratory failure [n=1]), with the exception of dysphagia (n=1) which was not observed in any patients in the placebo group.

Table 37: Study V3011902: Treatment-Emergent Adverse Events Leading to Treatment Discontinuation (Drug Withdrawn), by System Organ Class and Preferred Term (Safety Set)

	Sabizabulin 9 mg (N=130)	Placebo (N=69)	Overall (N = 199)
	n (%)		
Any TEAE resulting in study drug discontinuation	6 (4.6)	3 (4.3)	9 (4.5)
Gastrointestinal disorders	1 (0.8)	0	1 (0.5)
Dysphagia	1 (0.8)	0	1 (0.5)
Infections and infestations	1 (0.8)	0	1 (0.5)
COVID-19	1 (0.8)	0	1 (0.5)
Endocarditis staphylococcal	1 (0.8)	0	1 (0.5)
Investigations	2 (1.5)	2 (2.9)	4 (2.0)
Alanine aminotransferase increased	1 (0.8)	0	1 (0.5)
Hepatic enzyme increased	0	1 (1.4)	1 (0.5)
Liver function test abnormal	0	1 (1.4)	1 (0.5)
Liver function test increased	1 (0.8)	0	1 (0.5)
Renal and urinary disorders	1 (0.8)	0	1 (0.5)
Acute kidney injury	1 (0.8)	0	1 (0.5)
Respiratory, thoracic, and mediastinal disorders	1 (0.8)	1 (1.4)	2 (1.0)
Dyspnea	0	1 (1.4)	1 (0.5)
Respiratory failure	1 (0.8)	0	1 (0.5)

AEs are coded using MedDRA version 24.0.
Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

3.4.5.3. COVID-19 Studies: Phase 2 and Phase 3 Combined Analysis of Serious TEAEs

Serious TEAEs occurred in (27.5%) of the subjects receiving sabizabulin and (41.6%) receiving placebo in the Phase 2 and Phase 3 clinical studies combined; most serious TEAEs were COVID-19 related. The most common serious TEAEs in the sabizabulin group observed in the Phase 2 and Phase 3 clinical trials combined are presented in Table 38. In the sabizabulin group, the most commonly (≥5% subjects) reported serious TEAE by PT was respiratory failure (8.7% sabizabulin vs. 18.0% placebo).

Table 38: Studies V0211901 and V3011902 Combined Analysis: Serious TEAEs Reported by ≥2% of Patients Treated with Sabizabulin by PT

Serious Adverse Reaction	Sabizabulin 9 mg (N=149)	Placebo (N=89)
COVID-19	2.7%	4.5%
Pneumonia	2.7%	4.5%
Sepsis	2.7%	2.2%
Septic shock	2.0%	7.9%
Acute Kidney Injury	4.0%	7.9%
Acute Respiratory Failure	3.4%	4.5%
Pulmonary embolism	2.0%	3.4%
Respiratory Failure	8.7%	18.0%

Overall, the display of serious TEAEs in this combined population is similar to that observed in the Phase 3 Study V3011902, which is expected as the Phase 3 study was much larger than the Phase 2 study.

3.4.5.4. Prostate Cancer Studies

In Study V1011101, 4 patients had a TEAE with outcome of death in the study, one of which received 81 mg sabizabulin and had a treatment-related TEAE with outcome of death (patient (b) (6), Phase 1b). When considering patients from the Phase 1b and 2 studies together who received at least one dose of 63 mg PIC sabizabulin (54 total patients), the most common system organ class for related TEAEs was Gastrointestinal disorders (8 patients, 14.8%). The only serious TEAE that has occurred in 3 patients or more in patients who received 63 mg PIC sabizabulin was diarrhea (3 patients, 5.6%). This study remains ongoing at this time.

In Study V3011102 (an open-label efficacy and safety study), 2 patients have died during the study (one in the sabizabulin group and one in the Control group) and both deaths were deemed unrelated to study drug. A total of 8 subjects (15.1%) have reported 21 serious TEAEs in the ongoing study: 6 patients (16.2%, 18 TEAEs) in the sabizabulin treatment group and 2 patients (12.5%, 3 TEAEs) in the Control group. The only serious TEAEs that have been reported in ≥2 subjects are COVID-19 (2 patients, 5.4%, sabizabulin group) and Uncoded (2 patients, 5.4%, sabizabulin group). No serious TEAEs have been reported by ≥2 patients in the open-label, control group so far in the study. This study remains ongoing at the time of submission.

3.4.6. Laboratory Evaluations, Vital Signs, and Other Safety Evaluations

3.4.6.1. Study V0211901

There were no clinically meaningful findings in the clinical laboratory assessments (chemistry, hematology, and urinalysis), vital signs, physical examination, and chest X-ray findings.

3.4.6.2. Study V3011902

In Study V3011902 there have been no laboratory abnormalities that were severe TEAEs, SAEs, or led to death. There were no clinically meaningful findings in laboratory assessments, vital

signs, physical examinations, or other safety evaluations that could be directly related to the study drug.

The following TEAEs occurred in ≥2% in the sabizabulin treated group and a higher incidence than observed in the placebo group: alanine aminotransferase increase (3.1% in sabizabulin group vs. 2.9% in the placebo group), fibrin D-dimer increased (3.1% in sabizabulin group vs. 2.9% in placebo group), gamma-glutamyltransferase increased (2.3% sabizabulin group vs. 1.4% placebo group), serum ferritin increased (2.3% sabizabulin group vs. 2.9% placebo group), and transaminases increased (4.6% sabizabulin group vs. 2.9% placebo group). Veru considers these observations to be not clinically meaningful. Two patients in the sabizabulin group and two patients in the placebo group discontinued treatment due to a TEAE for liver function test abnormality.

3.4.6.3. Prostate Cancer Studies

In Study V1011101:

- Among 80 subjects only one clinically meaningful change from baseline in hematology results has been noted: Subject (b) (6) male, 77 years, Black, Hemoglobin 76 g/L on Day 71 (-26 g/L from baseline). It is noted that this subject had a subsequent follow-up on day 83 (end of study), and the hemoglobin level was noted as low but not clinically significant.
- Clinically significant changes from baseline in clinical chemistry values have been noted in 4 patients. Two patients have had clinically significant changes in sodium levels (one high, one low), one patient has had high creatinine levels, and one patient has had high ALT/AST levels.
- No clinically meaningful changes in mean values from baseline were identified for urinalysis parameters

In Study V3011102:

- No clinically meaningful changes have been identified for hematology or clinical chemistry parameters.
- The potential hepatotoxicity of sabizabulin was monitored in Study V3011102 by examining ALT, AST, ALP and total bilirubin levels of patients over time. No patients in the study show signs of drug-induced liver injury.

3.4.7. Potential Effects on ECG and QTc Interval

3.4.7.1. Study V0211901

No clinically significant ECG findings were observed for any of the subjects in either treatment group.

3.4.7.2. Study V3011902

Overall, there were no clinically meaningful ECG findings in this study. Shifts in ECG results from normal at baseline to abnormal clinically-significant post-baseline were reported in 3 (3.0%) patients in the sabizabulin 9 mg group and 1 (2.1%) patient in the placebo group.

3.4.7.3. Prostate Cancer Studies

No information on potential effects on ECG and QTc interval from prostate cancer studies is available at this time.

3.4.8. Safety Conclusions

The totality of evidence supports that sabizabulin is safe and generally well-tolerated in hospitalized moderate to severe COVID-19 patients at high risk for ARDS as well as in Prostate Cancer patients.

Specifically, the following conclusions are made from COVID-19 Study V0211901:

- Overall, no treatment related treatment-emergent adverse events (TEAEs) or other significant TEAEs were reported during the study.
- There were no treatment-related serious TEAEs and all serious TEAEs were unrelated to study drug.
- A similar number of subjects (12 subjects each) had TEAEs who received sabizabulin and placebo. No events were considered to be related to study drug.
- Most of the TEAEs were reported by single subjects in both treatment groups.
- The majority of TEAEs were of Grade 1, reported by a total of 13 (33.3%) subjects. Overall, 7 subjects died during the study (1 subject who received sabizabulin and 6 subjects who received placebo).
- Eight subjects had serious TEAEs (3 subjects who received sabizabulin and 5 subjects who received placebo), which were considered by the investigator to be not related or unlikely related to the study drug.
- There were no other significant TEAEs during the study.
- There were no clinically meaningful findings in the clinical laboratory assessments (chemistry, hematology, and urinalysis), vital signs, physical examination, ECGs, or chest X-ray findings.

In COVID-19 Study V3011902, the overall conclusions of the safety of sabizabulin in hospitalized patients with moderate to severe COVID-19 infection who are at high risk for ARDS are:

1. The benefit: risk ratio of sabizabulin is clinically relevant based on the reduction in deaths (51.6% reduction in sabizabulin group) and reduction in life threatening TEAEs in the sabizabulin group compared to placebo such as: septic shock (79.2% reduction), pneumonia (52.3% reduction), pneumothorax (92.1% reduction), respiratory failure (50.7% reduction), and acute kidney injury (26.7% reduction), which demonstrates a

meaningful representation of pharmacologic benefit and the efficacy of sabizabulin in the treatment of moderate to severe COVID-19 infection.

2. Sabizabulin was well tolerated compared to placebo in this study.
   - The proportion of subjects experiencing any TEAE was lower in the sabizabulin treated group (63.1%) than in the placebo group (78.3%).
   - The most common TEAEs reported in the sabizabulin treated group were:

     anemia (5.4% sabizabulin vs. 4.3% placebo),
     constipation (6.9% sabizabulin vs. 8.7% placebo),
     pneumonia (6.2% sabizabulin vs. 13.0% placebo),
     urinary tract infection (6.2% sabizabulin vs. 1.4% placebo),
     acute kidney injury (8.5% sabizabulin vs. 11.6% placebo),
     acute respiratory failure (5.4% sabizabulin vs. 4.3% placebo), and
     respiratory failure (10.0% sabizabulin vs. 20.3% placebo).

     All the most common TEAEs reported in the sabizabulin treated group occurred at a higher rate in the placebo group except for urinary tract infection and acute respiratory failure. While the incidence of acute respiratory failure is slightly higher than in the sabizabulin treated group compared to placebo, the incidence of respiratory failure is 103% higher in the placebo group compared to the sabizabulin group. Therefore, it is concluded that this is an anomaly in the preferred terms in the study. There is no mechanism of action or rationale for why there is an imbalance in urinary tract infection in the sabizabulin treated group.
   - The SOCs and TEAEs that are observed at a higher rate in the sabizabulin group compared to the placebo group,

     SOCs: Blood and lymphatic system disorders, Gastrointestinal disorders, Skin and subcutaneous tissue disorders;
     TEAEs: anemia, diarrhea, vomiting, urinary tract infections, various skin disorders such as allergic dermatitis, intertrigo, rash, and decubitus ulcer

     can be managed with therapy in hospitalized patients being treated with sabizabulin and are not (or are not immediately) life threatening.
   - The SOCs in which the incidence of TEAEs are at least 20% lower in the sabizabulin group compared to the placebo group are:

     Cardiac Disorders (-59.5%),
     Infections and infestations (-26.1%),
     Metabolism and nutrition disorders (-37.9%),
     Musculoskeletal and connective tissue disorders (-47.2%),
     Nervous system disorders (-40.8%),
     Psychiatric disorders (-20.7%),
     Renal and urinary disorders (-38.8%),

Respiratory, thoracic, and mediastinal disorders (-45.3%),
Vascular disorders (-43.9%).

- The proportion of subjects experiencing a serious TEAE was lower in the sabizabulin treated group (29.2%) compared to the placebo group (46.4%). The most common serious TEAEs in the sabizabulin treated group were:

  respiratory failure (10.0% sabizabulin vs. 20.3% placebo),
  acute kidney injury (4.6% sabizabulin vs. 8.7% placebo), and
  acute respiratory failure (3.8% sabizabulin vs. 4.3% placebo)

  All of these serious TEAEs were experienced by a higher proportion of subjects in the placebo group than in the sabizabulin treated group.

- Overall, TEAEs leading to discontinuation were equal between the treatment groups (4.6% in the sabizabulin group vs. 4.3% in the placebo group). The preferred terms for the AEs that led to discontinuation in the sabizabulin group do not represent TEAEs that are observed at a higher rate in the sabizabulin group (COVID-19 [n=1], endocarditis staphylococcal [n=1], alanine aminotransferase increased [n=1], liver function test increased [n=1], acute kidney injury [n=1], respiratory failure [n=1]), with the exception of dysphagia (n=1) which was not observed in any patients in the placebo group.

3. Overall, 48 subjects died during the study who were treated with at least one dose of study drug: 23 (17.7%) in the sabizabulin group and 25 (36.2%) in the placebo group.
4. There were no clinically meaningful findings in the clinical laboratory assessments (chemistry, hematology, and urinalysis) or in assessments of vital signs, physical examination, ECGs, or chest X-ray.

In studies of sabizabulin in advanced prostate cancer in which higher doses of sabizabulin (up to 81 mg) were investigated, the maximum tolerated dose (MTD) was determined to be 63 mg PIC/32 mg FC. Overall, sabizabulin at the MTD has been well-tolerated, with the most common TEAEs being reported under gastrointestinal disorders (such as diarrhea, fatigue, and nausea) and investigations (such as liver enzyme increases). It is important to note that although the TEAE ‘diarrhea’ is common in both prostate cancer studies, the available data from these studies indicate that the overall percentage of ‘diarrhea’ decreased by approximately 70% in the Phase 3 Prostate Cancer Study compared to the Phase 1b/2 Prostate Cancer Study. This may be due to the change in formulation of sabizabulin used in Phase 3 (32 mg FC) compared to the Phase 1b/2 (63 mg PIC) which allowed for a decrease in sabizabulin dose of about 50%. It is important to note that in the Phase 2 and Phase 3 COVID-19 sabizabulin studies ‘diarrhea’ was not a clinically significant reported safety finding for the 9 mg sabizabulin dose.

4. NONCLINICAL DEVELOPMENT PROGRAM

4.1. Overview of the Nonclinical Testing Strategy

Nonclinical studies assessing the safety of sabizabulin have been conducted to support the clinical development of sabizabulin for the treatment of SARS-CoV-2 as well as for the treatment of metastatic castration-resistant prostate cancer. The doses of sabizabulin that have been studied for the prostate cancer indication (up to 81 mg, PIC formulation) are higher than that studied for the treatment of SARS-CoV-2 (up to 18 mg PIC; 9 mg FC) and support a maximum tolerated dose of 63 mg PIC (32 mg FC). Under the prostate cancer program, sabizabulin has been evaluated through a nonclinical study program designed in accordance with the Agency's Guidance for Industry: S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (March 2010).

The nonclinical program for sabizabulin consists of pharmacology, pharmacokinetics, toxicology, toxicokinetics, genotoxicity, and phototoxicity studies and information from the published literature. An overview of the nonclinical program for sabizabulin is provided below (Table 39).

Table 39: Sabizabulin Nonclinical Program

Study Type / Duration	Route	Dose	Species	GLP
Primary Pharmacodynamics				
In vitro tubulin binding and polymerization assays	In vitro	sabizabulin HCl	In vitro	No
In vitro cytopathic assay	In vitro	sabizabulin HCl	Vero E6 cells	No
In vitro viral titer assay	In vitro	sabizabulin HCl	Vero E6 cells	No
In vitro LPS shock cytokine assay	In vitro	sabizabulin HCl	Isolated mouse spleen cells	No
In vivo ARDS Mouse Model	Oral gavage	3 mg/kg and 9 mg/kg sabizabulin HCl	BALB/c mice infected with mouse-adapted SARS-CoV-2	No
Safety Pharmacology				
In vitro hERG/Single dose	In vitro	0, 1.5, 4.5, 15 μM sabizabulin hydrocholoride	HEK293 cells	Yes
CNS/Single dose	Oral gavage	0, 3, 10, 30 mg/kg sabizabulin hydrocholoride diluted in 0.5% (w/v) methylcellulose in diH2O	CD® (Crl:CD® [SD]) rats	Yes
Cardiovascular/ Pulmonary/ Single dose	Oral capsule	0, 2, 4, 8 mg/kg sabizabulin HCl powder in gelatin capsule formulation	Beagle dogs	Yes

Table 39: Sabizabulin Nonclinical Program

Study Type / Duration	Route	Dose	Species	GLP
Pharmacokinetics				
Single dose	IV or oral gavage	2 mg/kg (IV); 1, 2, 15, 30 mg/kg (PO) sabizabulin HCl	CD® (Crl:CD® [SD]) rats	Yes
Repeat Dose/Days 1, 3, and 7; Food Effect	IV or oral gavage	IV: 5/1 mg/kg; PO: 5 mg/kg fasted, 5 mg/kg fed, 10 mg/kg fed, 5 mg/kg fed Sabizabulin HCl	Beagle dogs	Yes
Repeat Dose/Days 1, 3, and 7	Oral capsule	5 mg/kg and 10 mg/kg Sabizabulin HCl powder in gelatin capsule formulation	Beagle dogs	Yes
A PK Excretion, and Tissue Distribution Study in Rats *(Ongoing)*	Oral gavage	3 mg/kg/day [^{14}C]-sabizabulin HCl	CD® (Crl:CD® [SD]) rats	No
A PK, Mass Balance and Metabolite Identification Study in Dogs *(Ongoing)*	Oral gavage	4 mg/kg/day [^{14}C]-sabizabulin HCl	Beagle Dogs	No
Repeated-dose toxicity with toxicokinetic analysis				
Rat/Up to 28 days	Oral gavage	0, 0.3, 1, 3, 10, and 30/20 mg/kg/day Sabizabulin hydrocholoride diluted in 0.5% (w/v) methylcellulose in diH2O	CD® (Crl:CD® [SD]) rats	Yes
Rat/91 days	Oral gavage	0, 0.3, 1, and 3 mg/kg/day Sabizabulin hydrochloride diluted in 0.5% (w/v) methylcellulose in diH2O	CD® (Crl:CD® [SD]) rats	Yes
Dog/28 days	Oral capsule	0, 2, 4, and 8 mg/kg/day Sabizabulin HCl powder in gelatin capsule formulation	Beagle dogs	Yes

Table 39: Sabizabulin Nonclinical Program

Study Type / Duration	Route	Dose	Species	GLP
Genotoxicity				
In vitro reverse mutation assay	In vitro	Sabizabulin HCl	*S. typhimurium* TA98, TA100, TA1535, TA1537; *E. coli* WP2 *uvr*A	Yes
In vitro micronucleus assay	In vitro	Sabizabulin HCl	TK6 cells	Yes
Carcinogenicity	–	–	–	–
Reproductive and developmental toxicity	–	–	–	–
Local Tolerance	–	–	–	–
Other Studies				
Phototoxicity	In vitro	Sabizabulin HCl	BALB/c 3T3 Mouse Fibroblasts	Yes

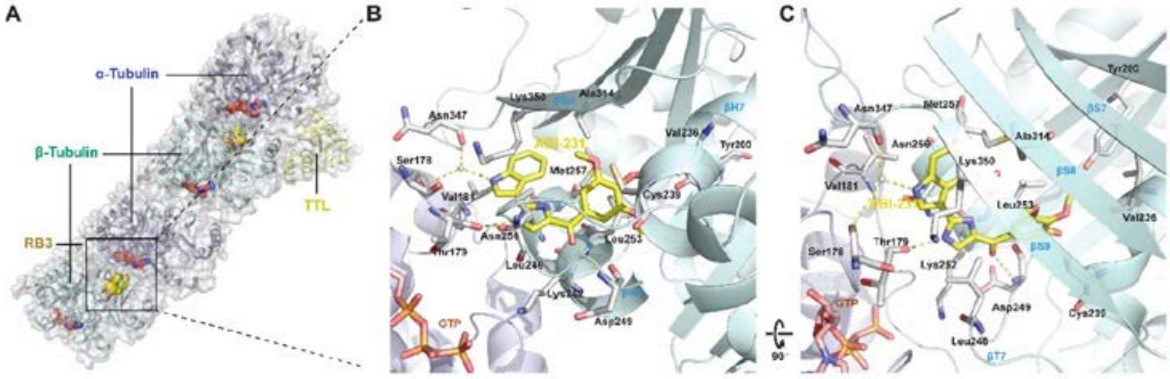
CNS = central nervous system; GLP = Good Laboratory Practice; IV = intravenous; NA = not applicable; PO = oral.

4.2. Nonclinical Pharmacology

4.2.1. Mechanism of Action

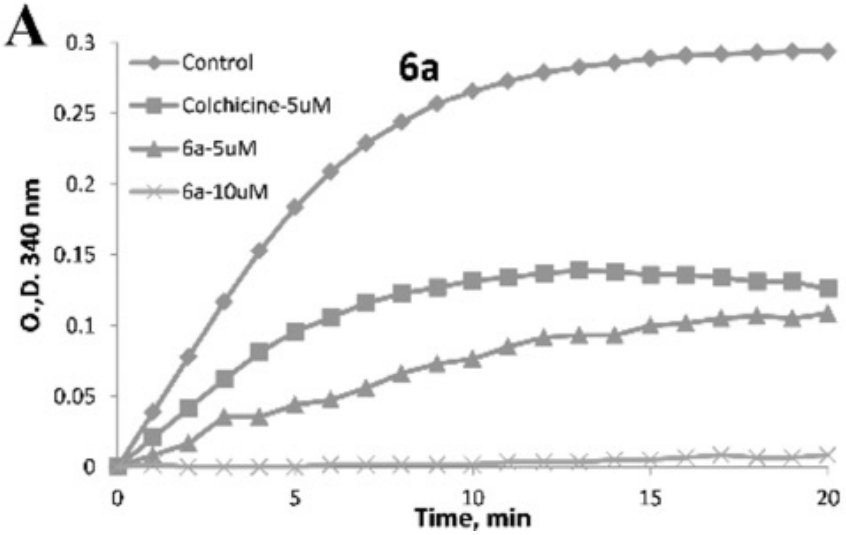
Sabizabulin is an oral novel microtubule disruptor that targets, binds, and crosslinks both the α and β tubulin subunits to inhibit polymerization and to induce depolymerization of microtubules in cells at low nanomolar concentrations (Chen et al., 2012; Li et al., 2012; Wang et al., 2019) [see Figure 6 and Figure 7]. Sabizabulin binds within the pocket of β tubulin (hydrogen bonds with β-Asp249 and β-Asn347) and reaches across the interface between β tubulin and α tubulin to form 2 more hydrogen bonds with α tubulin (hydrogen bond with α-Thr179 and "water bridge" hydrogen bond with α-Thr179) [see Figure 6]. Thus, sabizabulin tightly crosslinks α and β tubulin subunits (Wang et al., 2019).

Figure 6: Complex Structure of Sabizabulin (yellow) within Tubulin Protein



Source: (Wang et al., 2019)

Figure 7: Sabizabulin (Compound 6a) Inhibits 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: (Chen et al., 2012)

Sabizabulin is more effective than colchicine in inhibiting tubulin polymerization (Chen et al., 2012) and more effective than colchicine in suppressing cancer growth *in vitro* and *in vivo* (Kashyap et al., 2020; Mahmud et al., 2020). Sabizabulin also decreases the transcription of βI, βIII, and βIV-tubulin isoforms (Li et al., 2012). Sabizabulin is not a substrate for MDRs including P-gp and CYP3A4. *In vivo*, sabizabulin disrupts the cytoskeleton by inhibiting formation and causing depolymerization of microtubules that are undergoing high activity (Chen et al., 2012; Li et al., 2012; Wang et al., 2019). Microtubules are very active especially during cancer cell division and in periods of high intracellular trafficking of critical growth receptors, macromolecules, and virus infection as well as in triggering the innate immune response and release of inflammatory proteins responsible for inflammation. This central mechanism of action contributes to both the antiviral and anti-inflammatory activities. Sabizabulin treatment of various cancer cells (triple negative breast cancer, lung, and pancreatic cancers) cause the microtubule intracellular networks to be disrupted from spindle shape and organized to globular and disorganized (Deng et al., 2020; Kashyap et al., 2020; Mahmud et al., 2020).

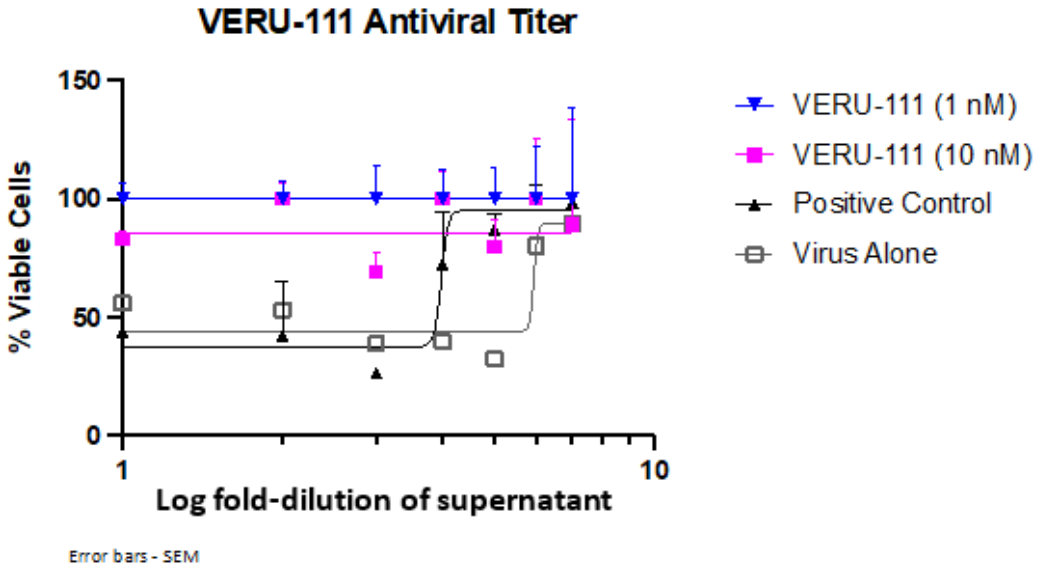
Based on sabizabulin's mechanistic similarities to other microtubular depolymerizing agents (Oliva et al., 2022), as well as its preclinical and clinical experience, sabizabulin could have a two-pronged approach to the treatment of SARS-CoV-2 virus infection:

- As an antiviral, sabizabulin has efficacy against SARS CoV-2 by targeting and disrupting microtubules for critical for viral microtubule trafficking, viral replication, viral assembly and new virion egress during its life cycle.
- As an anti-inflammatory agent, sabizabulin may reduce virally induced severe hyperinflammation because of the cytokine storm leading to septic shock, acute respiratory distress syndrome, multiple organ failure, and death.

4.2.2. In vitro antiviral titer assay

An antiviral titer assay was performed to determine whether sabizabulin was able inhibit the production of infectious SARS-CoV-2 virus particles. In order to produce infectious virus particles, Vero E6 cells need to complete the SARS-CoV-2 replication life cycle: viral entry, viral trafficking, viral replication, viral packaging and new viral particles egress into the tissue culture media. Two doses of sabizabulin (1 nM and 10 nM) were chosen to incubate with Vero E6 cells + SARS-CoV-2 virus for 48 hours, then the quantity of infectious SARS-CoV-2 virus particles (titer) was measured by collecting the supernatants and then diluting aliquots (10^{-1}-10^{-7}) to measure tissue culture infectious dose 50% ($TCID_{50}$) for cytopathic effect (CPE) in newly plated Vero E6 cells. To control for the direct effects of sabizabulin on cell viability, 1 nM and 10 nM sabizabulin were each incubated with Vero E6 cells as controls to determine baseline viable cell numbers with drug alone. The results of the antiviral titer assay showed that the positive control, calpain inhibitor IV, had a $TCID_{50}$ of 10,000-fold-dilution versus 1,000,000-fold dilution for virus alone. In contrast, both the 1 nM and 10 nM sabizabulin treated cells were 80-100% viable and no $TCID_{50}$ was reached, indicating that there a significant reduction in infectious SARS-CoV-2 virus particles in the supernatant with sabizabulin treatment (see Figure 8). Based on this *in vitro* antiviral titer assay, sabizabulin has potent antiviral activity at blood concentrations of sabizabulin that are achieved in patients with 9 mg daily dosing.

Figure 8: $TCID_{50}$ Infectious Viral Assay



Supernatants from untreated and drug treated virus infected Vero E6 cells and controls were diluted from 10^{-1} to 10^{-7} and incubated with fresh Vero E6 cells to determine cytopathic effect. Cell viability was measured by a luminescence assay (CellTiter-Glo) and $TCID_{50}$ was calculated.
VERU-111 = sabizabulin.

4.2.3. In vitro cytokine assays

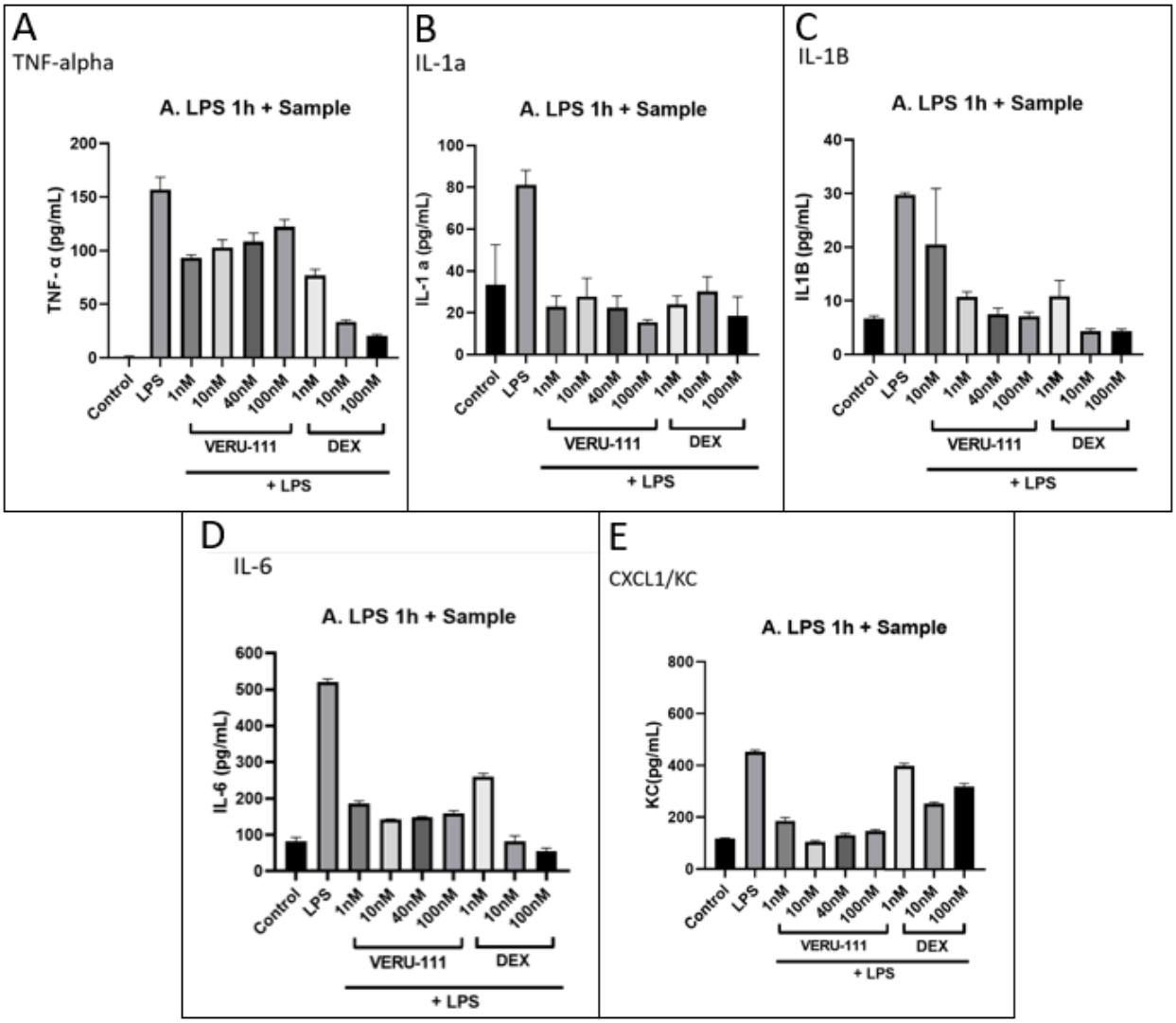
The anti-inflammatory activity of sabizabulin was assessed in an *in vitro* mouse model of septic shock (University of Tennessee Health Science Center). This study assessed the effects of sabizabulin on cytokine production by stimulating isolated mouse spleen cells with lipopolysaccharide (LPS), an endotoxin that causes shock. At a concentration that represents the blood levels observed in clinically dosed patients, sabizabulin (40 nM) significantly reduced the production of key cytokines known to be involved with COVID-19 cytokine storm: TNFα (-31%) (p=0.006), IL-1α (-123%) (p=0.0005), IL-1β (-97%) (p=0.0003), IL-6 (-85%) (p<0.00008), and IL-8 homologue [CXCL1/KC] (-96%) (p<0.0000007). This reduction was similar to, or greater than (depending on the specific cytokine), that observed with dexamethasone (10 nM), a steroid and a known inhibitor of cytokine production during inflammation (see Table 40 and Figure 9). Thus, sabizabulin demonstrated significant anti-inflammatory activity in a mouse septic shock model at blood concentrations of sabizabulin that are achieved in patients with 9 mg daily dosing.

Table 40: Effect of Sabizabulin on LPS-Induced Cytokine Release in Isolated Mouse Spleen Cells: Fold Change in Comparison to LPS Alone

	TNF-α	IL-1β	IL-1α	IL-6	KC/IL-8
Sabizabulin (40 nM)	-31%	-97%	-123%	-85%	-96%
Dexamethasone (10 nM)	-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

Figure 9: Anti-inflammatory Activity of Sabizabulin (VERU-111) in a Mouse Septic Shock Model



VERU-111 (sabizabulin) (1-100nM) and dexamethasone (1-100nM) reduced LPS-stimulated cytokines in isolated mouse spleen cells treated with LPS:
A. VERU-111 treatment (1-100nM) and dexamethasone (1-10nM) reduced LPS-stimulated production of TNF-α. Dexamethasone (1-10nM) was better.
B. VERU-111 treatment (1-100nM) had a dose dependent reduction and dexamethasone had a reduction in LPS-stimulated production of IL-1α. VERU-111 and dexamethasone had similar suppression to control levels.
C. VERU-111 treatment (1-100nM) had a dose dependent reduction and dexamethasone had a reduction in LPS-stimulated production of IL-1β. VERU-111 and dexamethasone had similar suppression to control levels.
D. VERU-111 (1-100nM) had a reduction and dexamethasone (1-10nM) had a dose dependent reduction in LPS-stimulated IL-6 production.
E. VERU-111 (1-100nM) and dexamethasone (1-10nM) had a reduction in LPS-stimulated CXC1/KC (mouse homologue of IL-8) production; however, VERU-111 reduced cytokine levels to control levels and had markedly greater reduction of CXC1/KC than dexamethasone.

4.2.4. *In vivo* ARDS mouse model

In an NIH ARDS mouse model, BALB/c mice infected with mouse-adapted SARS-CoV-2, administered sabizabulin via oral gavage once daily (3 mg/kg and 9 mg/kg) for 5 days. Comprehensive pathology reports observed that there was a dose dependent reduction in bronchointerstitial inflammation (2 days) and in global pneumonia severity score both at 2 days and 5 days in sabizabulin treated mice compared to virus vehicle group (see Table 41). If clinical benefit is defined based on the reduction of treatment failures, where treatment failure is death or moderate or marked pneumonia, then sabizabulin treatment resulted in an 40% absolute reduction of treatment failures as early as Day 2 (4 of 5 mice [80%] in the virus vehicle group versus 4 of 10 mice [40%] in the combined sabizabulin treated groups) By Day 5, sabizabulin treatment had a 30% absolute reduction in treatment failures (5 of 5 mice [100%] in the virus vehicle group versus 7 of 10 mice [70%] in the combined sabizabulin treated groups). Sabizabulin treatment also reduced mortality in mice infected with SARS-CoV-2 with a 40% survival rate in 3 mg/kg and 9 mg/kg sabizabulin treated groups combined, versus a 20% survival rate in the virus vehicle infected group (see Table 42).

Table 41: Observational Assessments of Histopathologic Analysis of Lungs from Mice with ARDS

Treatment	# Animals Affected (%)
Bronchointerstitial Inflammation (2 days)- Animals with moderate inflammation	
Vehicle	3/5 (60)
3 mg/kg Sabizabulin	2/5 (40)
9 mg/kg Sabizabulin	1/5 (20)[a]
Global Pneumonia Severity Score (2 days)- Animals with moderate or marked pneumonia	
Vehicle	4/5 (80)
3 mg/kg Sabizabulin	2/5 (40)
9 mg/kg Sabizabulin	2/5 (40)[b]
Global Pneumonia Severity Score (5 days)- Animals with moderate or marked pneumonia	
Vehicle	1/1 (100)
3 mg/kg Sabizabulin	1/2 (50)
9 mg/kg Sabizabulin	0/2 (0)[c]

[a]67% reduction
[b]50% reduction
[c] 100% reduction

Table 42: Number of Clinical Treatment Failures Defined as Death or Respiratory Distress (moderate or marked pneumonia) For Each Study Group

Group	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%)

4.2.5. Nonclinical Safety Pharmacology

The effects of sabizabulin on the central nervous system, cardiovascular system, and respiratory system have been evaluated in an *in vitro* hERG study, as well as studies in rats and dogs. Sabizabulin at concentrations of 3.6 µM to 12.7 µM (nominal concentrations of 4.5 to 15 µM) produced a concentration-dependent increase in inhibition of hERG-mediated potassium currents ranging from approximately 13% to 28% (IC_{20} was 7.67 µM, nominal IC_{20} value was 9.23 µM), although no effects on were observed in the cardiovascular safety pharmacology study in dogs, with no adverse findings observed up to and including the 8 mg/kg dose of sabizabulin. Oral administration of sabizabulin (up to 10 mg/kg) was not associated with any adverse effects on neurobehavioral function in rats; the 30 mg/kg dose produced death in a single rat within 24 hours of dose administration although a cause of death could not be determined from the necropsy. No deaths were observed at doses of 3 mg/kg and 10 mg/kg.

Oral administration of sabizabulin (up to 8 mg/kg) was not associated with any adverse effects on cardiovascular or respiratory function in dogs. Sabizabulin, administered orally at doses of 2, 4, and 8 mg/kg to dogs, did not produce mortality or effects on blood pressure, heart rate, or the evaluated electrocardiogram or respiratory parameters.

4.3. Pharmacokinetics

The pharmacokinetics (PK) of sabizabulin has been assessed in 8 Sponsor-conducted studies, as summarized below. Additionally, *in vitro* metabolism testing and brain penetration of sabizabulin were reported in a publication (Li et al., 2012).

4.3.1. Absorption and Plasma Level

Following a single oral administration of 1, 2, 15, and 30 mg/kg doses of sabizabulin in rats, mean C_{max} and $AUC_{0\text{-}24hr}$ values increased with increasing dose in an approximately dose proportional manner across the dose range. In rats, systemic exposure ($AUC_{0\text{-}24hr}$) to sabizabulin following oral administration of sabizabulin was less than following a 2 mg/kg IV bolus administration of sabizabulin.

Following daily oral gavage administration of sabizabulin for up to 90 days in rats, C_{max} and $AUC_{0\text{-}24hr}$ values for sabizabulin increased with increasing dose. On Day 1, a 1:3.3:10-fold

increase in dose resulted in an approximate 1:3.2:11.2-fold increase in C_{max} values and an approximate 1:4.5:16.0-fold increase in AUC_{0-24hr} values. On Day 28, a 1:3.3:10-fold increase in dose resulted in an approximate 1:1.7:4.8-fold increase in C_{max} values and an approximate 1:2.5:10.2-fold increase in AUC_{0-24hr} values. On Day 90, a 1:3.3:10-fold increase in dose resulted in an approximate 1:3.5:12.5-fold increase in C_{max} values and an approximate 1:4.6:12.2-fold increase in AUC_{0-24hr} values.

Following oral gavage administration of 5 mg/kg sabizabulin on Days 1, 3, and 7 in beagle dogs, systemic exposure (AUC_{0-24hr} and C_{max}) was more variable and generally greater for fasted animals when compared to fed animals. Following oral gavage administration of 5 and 10 mg/kg sabizabulin on Days 1, 3, and 7 in dogs, C_{max} values for sabizabulin did not appear to change with increasing dose on Days 1 and 7, while AUC_{0-24hr} values for sabizabulin did not appear to change with increasing dose on Day 1 and generally increased with increasing dose on Day 7. Systemic exposure to sabizabulin did not consistently change following repeated administration of sabizabulin. Oral bioavailability (F) was approximately 5.54% and 3.66% at 5 and 10 mg/kg, respectively, on Day 1 and was approximately 37.8% and 33.8% at 5 and 10 mg/kg, respectively on Day 7.

Following oral (capsule) administration of 5 mg/kg and 10 mg/kg doses of sabizabulin on Days 1, 3, and 7 in dogs, mean sabizabulin C_{max} and AUC_{0-24hr} values generally appeared to increase with increasing dose in an approximately dose proportional manner. Similarly, following oral administration of 2, 4, and 8 mg/kg doses of sabizabulin in dogs, following daily oral capsule administration of sabizabulin, C_{max} and AUC_{0-12hr} values generally appeared to increase with increasing dose. In both studies, systemic exposure to sabizabulin did not appear to change following repeated administration of sabizabulin.

In rat and dog studies, sabizabulin $T_{1/2}$ was observed to be approximately 1-5 hours.

4.3.2. Distribution

The results of tissue distribution in Sprague-Dawley and Long-Evans (LE) rats after oral administration of [^{14}C]-sabizabulin in male LE rats suggests that [^{14}C]-sabizabulin related radioactivity had low exposure in the CNS but high in kidney, liver, and uveal tract, and in gastrointestinal contents. The results from LE rats suggest that [^{14}C]-sabizabulin related radioactivity may bind to melanin. Dosimetry evaluation recommended a maximum dose to human subjects of $\leq$ 4.48 mCi.

The brain penetration of sabizabulin has been studied in nude mice (Li et al., 2012). Sabizabulin achieved significant brain/plasma concentration ratios at both 1 (5.4 ± 1.9%) and 4 hours (8.9 ± 1.7%) after a single dose administration of 20 mg/kg. There was no evidence of drug accumulation in the brain.

4.3.3. Metabolism

The metabolism of sabizabulin in vivo is being assessed in 2 studies in rats and dogs, respectively. Preliminary results identified 8 metabolites overall from sixteen observed metabolites in dogs. Only metabolite M3 was found in the plasma along with unchanged sabizabulin. Four metabolites were identified in the urine and eight in the feces. Metabolite M3 and unchanged sabizabulin were the predominant metabolites in the urine, feces, and plasma.

In dogs, the major metabolite of sabizabulin, M3, is the result of the mono-oxidation. Double oxidation, sulfation, and oxidation with dimerization were also observed.

Preliminary results show that sabizabulin is extensively metabolized in the rat. Principal routes of metabolism are oxidation, O-demethylation at all three possible sites, and glucuronidation.

Sabizabulin was tested in CYP enzyme inhibition assays for CYP2D6, CYP2C9, CYP1A2, CYP2C19 and CYP3A4. Sabizabulin exhibited metabolic stability with high IC_{50} values suggesting that CYP mediated drug-drug interactions are not likely.

4.3.4. Excretion

After a single oral dose to male beagle dogs, [^{14}C]-sabizabulin had a mean total recovery of 84.5% ± 6.88% with a mean fecal recovery of 60.7% ± 12.0%, a mean urine recovery of 15.6% ± 5.66%, a mean cage rinse recovery of 5.42% ± 0.423%, and a mean cage wipe recovery of 2.83% ± 2.52%.

In SD rats, after a single oral dose of [^{14}C]-sabizabulin in rats, the mean total recovery was 93.3% with a mean fecal recovery 86.1%. In bile duct canulated (BDC) rats the mean total recovery was 94.9% with a mean bile recovery of 57.9%, a mean fecal recovery of 30.1%, suggesting biliary excretion appeared to be the primary route of elimination for total [^{14}C]-sabizabulin related radioactivity. The sum of urinary excretion and biliary excretion in BDC rats indicates that the oral absorption of [^{14}C]-sabizabulin was ≥64.1%.

A study in the published literature demonstrated that the clearance of sabizabulin is high in the dog, and two abundant metabolites (a hydroxylated metabolite and an unknown metabolite with +34 m/z than the parent) were observed in the dog and in dog liver microsomes that were not observed with mouse, rat, or human liver microsomes (Li et al., 2012).

4.4. Toxicology

4.4.1. Repeat-Dose Toxicity

4.4.1.1. 28-day Toxicity Study in Rats

In a 28-day repeat-dose toxicity study in rats, due to toxicity following the first dose at 30 mg/kg/day, the dose was reduced to 20 mg/kg/day. Dosing for animals at 10 and 30/20 mg/kg/day was discontinued following the fourth dose on Day 4, animals at 0.3, 1, and 3 mg/kg/day completed 28 days of dosing.

Based on the data from this 28-day study in rats, the severely toxic dose in 10% (or more) of the animals (STD_{10}) was 10 mg/kg/day corresponding to a 96 mg human equivalent dose in a 60 kg human. No severely toxic events were observed in the 3 mg/kg/day dose group which is a human equivalent dose of 28.8 mg in a 60 kg human.

4.4.1.2. 91-day Toxicity Study in Rats

In a 91-day repeat-dose toxicity study in rats, there was no sabizabulin-related mortality, and test article-related clinical observations were limited to salivation noted in 4 males and 1 female at 3 mg/kg/day. Minimal effects on body weight (5%) increase and liver enzymes (ALT and AST

increases) were noted in male rats at 3 mg/kg/day, however the change in liver enzymes lacked a microscopic correlate. In the microscopic evaluations, there was mild to marked squamous cell hyperplasia in males and minimal squamous cell hyperplasia in a single female at 3 mg/kg/day. These findings were interpreted as non-adverse given a lack of clinical correlation and occurring in isolation, without other related gross or microscopic findings. Overall, in this study, following daily administration of sabizabulin to rats via oral gavage for at least 91 days the No-Observed-Adverse-Effect Level (NOAEL) was determined to be 3 mg/kg/day (human equivalent dose [HED] of 29 mg/day).

4.4.1.3. 28-day Toxicity Study in Dogs

In the 28-day repeat dose study in dogs, treatment with sabizabulin (oral capsules) did not impact animal survival. There were no sabizabulin related effects noted in ophthalmoscopic evaluations, in the evaluations of the hematology, coagulation, and urinalysis clinical pathology parameters, or in the macroscopic observations. Based on the results of this study, the NOAEL for sabizabulin administered to beagle dogs for 28 days was 4 mg/kg/day based on the adverse body weight losses and a lengthening of the PR, QT, and QTc intervals in animals administered 8 mg/kg/day. The exposure of an 8 mg/kg dose of sabizabulin corresponds to a HED of 267 mg in a 60 kg human and the NOAEL dose of 4 mg corresponds to a 133 mg dose of sabizabulin in a 60 kg human.

4.4.2. Genotoxicity

Sabizabulin has been shown to be non-mutagenic in bacterial reverse mutation assay (AMES test).

Sabizabulin has also been shown to induce micronuclei in the non-activated and S-9 activated test systems in the *in vitro* mammalian micronucleus test using TK6 cells. Sabizabulin does not appear to be clastogenic, but it does induce aneuploidy which is consistent with its known pharmacologic action to disrupt microtubules during cellular division without structural damage to DNA.

4.4.3. Carcinogenicity

Carcinogenicity studies have not been conducted with sabizabulin. However, with the potential for sabizabulin to produce aneuploidy (cells with an unequal number of chromosomes), an increased risk of malignancy is possible with sabizabulin.

4.4.4. Reproductive Toxicity

Although reproductive and developmental toxicology studies have not been conducted with sabizabulin, as noted above *in vitro* mutagenicity studies demonstrated sabizabulin induced micronuclei predominantly by an aneugenic mechanism of action. Colchicine, a microtubule depolymerization agent, which is used chronically, has been demonstrated to be teratogenic in mice, rats and hamsters and impact spermatogenesis in male rats (FERM, 1964; Ingalls et al., 1968; Petit and Isaacson, 1976; Handel, 1979; Russell et al., 1981; Allard et al., 1993). Given this, based on the mechanism of action of sabizabulin as a microtubule depolymerization agent, it is highly likely that the use of sabizabulin in a pregnant individual will result in impairment in

the growth of the developing fetus and may result in birth defects and/or death of the developing fetus; thus, sabizabulin is not recommended for use in pregnant women.

4.4.5. Local Tolerance and Other Studies

Sabizabulin demonstrated phototoxic potential, with a photo-irritancy factor (PIF) of approximately 121 to 148 (criterion for phototoxic is PIF > 5) and mean photo effect (MPE) of 0.661 to 0.741 (criterion for phototoxic is MPE > 0.15).

Based on these results, patients will be instructed to avoid or minimize exposure to sunlight (including sunlamps), to use sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure until sabizabulin is eliminated from the body. Patients are advised to avoid concomitant medications known to cause photosensitivity.

4.5. Nonclinical Conclusions

The nonclinical studies on sabizabulin can be summarized by the following conclusion statements:

- Sabizabulin inhibits tubulin polymerization more potently than colchicine. Sabizabulin reduces SARS-CoV-2 infectious viral titers. An ARDS mouse model (BALB/c mice infected with mouse-adapted SARS-CoV-2) treated with sabizabulin demonstrated a reduction in deaths, bronchointerstitial inflammation and global pneumonia severity score. As inhibition of microtubule polymerization and inducing depolymerization of microtubules have been shown to suppress leucocyte mediated inflammatory activities (Slobodnick et al., 2018), sabizabulin treatment reduced the production of key cytokines known to be involved with COVID 19 cytokine storm (TNFα, IL-1, IL-1β, IL-6, and IL-8 homologue) in LPS-stimulated isolated murine spleen cells. These nonclinical studies demonstrate that sabizabulin has both antiviral and anti-inflammatory activities through disruption of very active microtubule dynamics at blood concentrations of sabizabulin that are achieved in patients with 9 mg daily dosing.
- The pharmacokinetics of sabizabulin in the animal models tested (dogs and rats) appear to show good oral bioavailability, increasing exposure with increasing doses, and in animals in which the $T_{1/2}$ is evaluable, a $T_{1/2}$ of approximately 1-5 hours.
- The 28-day dog and 91-day rat toxicokinetic studies, demonstrated that the achieved steady state levels obtained from daily dosing at the NOAEL should be sufficient to result in a human efficacious dose without limiting toxicity. The NOAEL in the rat was 3 mg/kg/day and the NOAEL in the dog was 4 mg/kg/day, which correspond to HEDs of 29 mg/day and 133.3 mg/day for a 60 kg human, providing a wide safety margin (3.2-fold and 14-fold, respectively). The human equivalent doses corresponding to the rat and dog NOAELs are well above the proposed dose of 9 mg sabizabulin and support the safety of 9 mg sabizabulin once daily for up to 21 days or hospital discharge, whichever comes first. Therefore, a dose of 9 mg sabizabulin formulated capsule was selected for use in COVID-19 patients based on the NOAEL observed from 28-day sabizabulin toxicology studies.

- Oral administration of sabizabulin was not associated with any adverse effects on neurobehavioral function in rats (up to 10 mg/kg) or any adverse effects on cardiovascular function in dogs (up to 8 mg/kg).
- Sabizabulin has been shown to be non-mutagenic in bacterial reverse mutation assay and has also been shown to induce micronuclei. Sabizabulin does not appear to be clastogenic, but it does induce aneuploidy from pharmacologic action to disrupt cellular division without structural damage to DNA.
- Although nonclinical reproductive and developmental studies have not been conducted with sabizabulin, given the mechanism of action (microtubule depolymerization agent) it is likely that use of sabizabulin in a pregnant individual will result in impairment in the growth of the developing fetus and may result in birth defects and/or death of the developing fetus; thus, the use of sabizabulin is not recommend during pregnancy. Female patients of childbearing potential should use effective contraception while receiving sabizabulin and at least 7 days after last dose of sabizabulin. A female partner of a male patient of childbearing potential should use effective contraception while receiving sabizabulin and at least 90 days after last dose of sabizabulin.
- Carcinogenicity studies have not been conducted with sabizabulin, but because sabizabulin has the potential to produce aneuploidy (cells with an unequal number of chromosomes), an increased risk of malignancy is possible.
- Sabizabulin has been shown to be positive for phototoxic potential. Patients will be instructed to avoid or minimize exposure to sunlight, to use a sunblock, to wear clothing that protects against sun exposure, and to avoid concomitant medications known to cause photosensitivity until sabizabulin is eliminated from the body.

These nonclinical data have informed the descriptions of the risks and use conditions for sabizabulin in the proposed draft Fact Sheet (Appendix A) to ensure safe use.

5. BENEFIT-RISK ASSESSMENT

In the United States there are 300-500 patients dying of COVID-19 each day (Worldometers.info accessed 04 October 2022, and NY Times COVID-19 Tracker accessed 05 October 2022). With new variants emerging and waning population immunity, another COVID-19 infection surge is projected for this fall and winter and death rates will rise even higher. The ongoing SARS-CoV-2 global pandemic/endemic continues to cause a significant burden of illness, hospitalization, and death, especially in patients who are at high risk for ARDS. Sabizabulin has demonstrated a clearly favorable benefit: risk ratio which strongly supports its use under an EUA in hospitalized patients with moderate to severe COVID-19 infection who are at high risk for ARDS, one of the groups at highest risk for dying and who have a critical need for additional effective and safe treatments.

Overall, the efficacy and safety results from Phase 2 and Phase 3 COVID-19 sabizabulin studies in this hospitalized COVID-19 patient population show that sabizabulin administered at 9 mg daily for up to 21 days significantly reduced deaths, days on mechanical ventilation, and days in the ICU and hospital, and was well-tolerated.

1. As for efficacy, the following clinical benefits of sabizabulin were observed:
    - In the Phase 2 Study V0211901, sabizabulin treatment reduced the mortality at Day 60 (82% relative reduction), days in ICU (73% relative reduction), and days on mechanical ventilation (78% relative reduction) compared to placebo. Sabizabulin was well-tolerated and no safety risks were identified for this dose.
    - In the confirmatory multicenter, randomized, placebo-controlled Phase 3 clinical study V3011902, sabizabulin 9 mg treatment showed a clinically meaningful and statistically significant reduction in deaths at Day 15, Day 29, and Day 60 (the primary endpoint). The relative reduction in mortality observed in the Interim Analysis (55.2%) and Full Study (51.6%) populations with sabizabulin treatment compared to placebo demonstrated clear clinical benefit.
        - All sensitivity analyses (subgroup analyses and stepwise logistic regression, a method to evaluate the contribution of multiple comorbidities at the same time) support the robustness of the primary endpoint findings. As for the COVID-19 variant, a subgroup of special interest, the relative reduction in deaths (effect size) with sabizabulin treatment was maintained whether the patient population had delta or omicron COVID-19 variants and had different placebo mortality rates.
        - All of the key secondary endpoints and sensitivity analyses also demonstrated that sabizabulin treatment had a clear benefit. Sabizabulin showed a clinically meaningful and statistically significant reduction in days in the ICU, days on mechanical ventilation, and days in the hospital compared to placebo.
        - The inclusion/exclusion criteria in this study selected for hospitalized patients that had moderate to severe COVID-19 infection and who demonstrated progression to more severe COVID-19 infection. The mortality rate observed in the placebo group + standard of care in the Full Phase 3 COVID-19 sabizabulin study for

these hospitalized patients at Day 29 (29.4%) was in line with other reported contemporary COVID-19 studies with a similar proportion of severe patients enrolled. The effectiveness (effect size) of sabizabulin treatment is demonstrated in the primary endpoint analysis and is supported by every subgroup analysis conducted as well as the secondary efficacy endpoints in this high-risk patient population regardless of the mortality rate observed in the corresponding placebo groups and underscores the critical need for additional safe and effective treatments that can prevent deaths for these COVID-19 patients.

- The safety profile of sabizabulin also supported the efficacy of sabizabulin as there was a reduction in adverse events and serious adverse events often associated with COVID-19 infection progression.
- The mortality benefit of sabizabulin treatment compared to placebo is overwhelmingly significant and is also meaningful from an emotional, pharmacoeconomic, societal, and economic perspectives.

2. The current safety database supports the well tolerated safety profile for sabizabulin evaluated in COVID-19 and prostate cancer clinical development programs with a total of 266 patients:
    - In the Phase 3 COVID-19 sabizabulin study V3011902, acute daily dosing of sabizabulin 9 mg for up to 21 days was well tolerated, and the safety profile appeared to be better than that observed in the placebo group with a lower proportion of subjects experiencing any TEAE or any serious TEAE in the sabizabulin group compared to placebo. The efficacy of sabizabulin in the treatment of moderate to severe COVID-19 is further demonstrated in the reduction in some TEAEs often associated with the progression of COVID-19 infection (septic shock, acute kidney injury, hypoxia, pneumothorax, respiratory failure, and hypotension).
    - In the Phase 1b/2 and Phase 3 prostate cancer clinical development programs, sabizabulin was also well-tolerated in prostate cancer patients. Prostate cancer patients are a relevant population as they were of similar age and had similar comorbidities as the Phase 2 and Phase 3 COVID-19 patients. Sabizabulin is well-tolerated in prostate cancer patients who receive chronic daily dosing (32 mg) of approximately 3.5 times the intended 9 mg dose for COVID-19 patients (in some patients for up to 3 years), which further supports the low safety risk of sabizabulin at a lower dose in the acute treatment setting for hospitalized moderate to severe COVID-19 patients at high risk for ARDS and death.

During development of sabizabulin, Veru has taken measures to mitigate risk and optimize benefit. The clinical development program for sabizabulin was designed in collaboration with FDA to investigate the safety and efficacy of sabizabulin in treating hospitalized moderate to severe COVID-19 patients who were at high risk for ARDS and death. As advised by the Agency, blinded, placebo-controlled studies were conducted in Phase 2 and Phase 3 such that the clinical benefit of sabizabulin, a reduction in patient deaths up to Day 60, could be assessed objectively using mortality as the most important primary endpoint, thereby minimizing the risk of false positive results.

As sabizabulin is a new chemical entity, investigations are planned to further characterize the nonclinical aspects of the product prior to submitting an NDA. The Sponsor is committed to collecting additional safety information as safety will also be monitored under the EUA.

In order to further ensure safe use, sabizabulin should not be used in the following groups:

- Patients less than 18 years of age (sabizabulin has not been studied in these patients)
- Non-hospitalized patients (sabizabulin has not been studied in these patients)
- Patients who are not on oxygen supplementation (sabizabulin has not been studied in these patients)
- Pregnant women (based on non-clinical mutagenicity tests conducted with sabizabulin, there is a very high likelihood that use of sabizabulin in a pregnant woman will be toxic to the developing fetus)

In the final analysis, sabizabulin has been shown to be effective and safe in the treatment of hospitalized moderate to severe COVID-19 patients who were at high risk for ARDS and death. Sabizabulin meets critical eligibility criteria of likely effective and safe for its availability under an EUA as Phase 2 and Phase 3 clinical studies show a combined reduction in mortality of over 50% with sabizabulin treatment compared to placebo, all sensitivity analyses on the data show robustness in sabizabulin efficacy, secondary endpoints show robust clinical benefit, and sabizabulin has been well-tolerated in both acute and chronic dosing settings at doses higher than the intended 9 mg dosage strength for COVID-19.

The intended population, hospitalized moderate to severe COVID-19 patients who are at high risk for ARDS, remains underserved in the US with the need for effective drugs that significantly reduce mortality and morbidity from COVID-19 infection. With a current daily mortality rate of 300-500 deaths per day, COVID-19 remains a medical emergency and it appears that COVID-19 will remain an emergency for the foreseeable future. Sabizabulin's mechanism of action is that it targets the host cell microtubules so its activity is independent of virus variant making it potentially a unique COVID-19 therapeutic agent. As infections from the current omicron variant increase, and when new variants of COVID-19 develop that may be even more virulent and evade vaccinated host immunity resulting in a higher mortality rate, the Sponsor proposes that sabizabulin will be critical in the treatment armamentarium in moderate to severe hospitalized COVID-19 patients who are at high risk for ARDS and death. Sabizabulin has demonstrated a clearly favorable benefit: risk ratio with a mortality benefit that strongly supports the use of sabizabulin under an EUA in hospitalized adult patients with moderate to severe COVID-19 infection who are at high risk for ARDS, one of the groups at highest risk for dying and remains a serious unmet medical need for which additional safe and effective treatments are essential.

Based on the safety and efficacy data for sabizabulin and to ensure the safe use of sabizabulin under an EUA, the Sponsor has developed a draft Fact Sheet for healthcare providers and for patients and caregivers for the product (Appendix A) which has been submitted to FDA for review. The Sponsor acknowledges the unique nature of an Emergency Use Authorization, and consistent with this procedure, is committed to comprehensive monitoring of the safe use of the product following authorization as well as the generation of data to support its ultimate full approval.

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APPENDIX A. PROPOSED SABIZABULIN FACT SHEET FOR HEALTHCARE PROVIDERS AND FOR PATIENTS AND CAREGIVERS

The following is the proposed EUA Fact Sheet for sabizabulin for healthcare providers as well as the sabizabulin Fact Sheet for patients and caregivers that have been submitted to FDA for review.

FACT SHEET FOR HEALTHCARE PROVIDERS:
EMERGENCY USE AUTHORIZATION FOR SABIZABULIN

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use sabizabulin under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for sabizabulin.

SABIZABULIN capsules, for oral use
Original EUA Authorized Date: YYYY

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF SABIZABULIN UNDER EMERGENCY USE AUTHORIZATION

Refer to FULL FACTSHEET for details.

EUA FOR SABIZABULIN

The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of the unapproved sabizabulin, a microtubule depolymerization agent that reduces mortality, days in the ICU, days on mechanical ventilation, and increases the proportion of patients alive without respiratory failure in hospitalized adults with moderate to severe COVID-19 infection at high risk for acute respiratory distress syndrome (ARDS). Sabizabulin is not FDA-approved for any indication including for the treatment of COVID-19. Prior to initiating treatment with sabizabulin, carefully consider the known and potential risks and benefits. (1)

LIMITATIONS OF AUTHORIZED USE (1)

- Sabizabulin is not authorized
  - For use in patients less than 18 years of age
  - For use in non-hospitalized patients
  - For use in patients that are not on oxygen supplementation
  - For use in pregnant women
  - For prevention of COVID-19

Sabizabulin may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed and authorized under state law to prescribe drugs in the therapeutic class to which sabizabulin belongs (i.e., microtubule depolymerization agent).

Sabizabulin is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of sabizabulin under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See the box in the beginning of the Full Fact Sheet for details on the requirements for administration of sabizabulin under emergency use authorization.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

DOSAGE AND ADMINISTRATION

9 mg (one capsule) taken orally daily with or without food. Sabizabulin capsule contents may be administered via nasogastric tube. (2.1)

DOSAGE FORMS AND STRENGTHS

Capsules: 9 mg (3)

CONTRAINDICATIONS

No contraindications have been identified based on the limited available data on the emergency use of sabizabulin authorized under this EUA. (4)

WARNINGS AND PRECAUTIONS

Serious and unexpected adverse events may occur that have not been previously reported with sabizabulin use. (5)

- Embryo-Fetal Toxicity: Use of sabizabulin in a pregnant woman is likely to be toxic to the developing fetus. (5.1)
- Phototoxicity: Patients should avoid or minimize exposure to sunlight and avoid medications known to cause photosensitivity. (5.2)
- Concomitant Medications: Sabizabulin should not be used with retroviral/antiretroviral medications (except remdesivir), experimental medications (except convalescent plasma), or colchicine. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥5%) occurring at a higher rate in the sabizabulin 9mg dose than placebo include anemia, urinary tract infection, and acute respiratory failure.
At doses higher than 9 mg, sabizabulin has been associated with diarrhea, nausea, vomiting, fatigue, and increased liver transaminases. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to sabizabulin (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Veru Inc., at Veru@medcomminc.com or call Veru Inc. at 1-833-828-9283.

DRUG INTERACTIONS

No drug interactions have been identified based on the limited available clinical data on the emergency use of sabizabulin authorized in this EUA. (7)

USE IN SPECIFIC POPULATIONS

Renal Impairment: Use of sabizabulin in patients with a creatinine clearance <60 mL/min is not recommended. (8.6)
Hepatic Impairment: Use of sabizabulin in patients with ALT and/or AST levels >3 times the upper limit of normal and patients with total bilirubin greater than the upper limit of normal is not recommended. (8.7)

See FACT SHEET FOR PATIENTS AND CAREGIVERS

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***Sections or subsections omitted from the EUA are not listed.**

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF SABIZABULIN UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of sabizabulin, the following steps are required. Use of sabizabulin under this EUA is limited to the following (all requirements must be met):

5. Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk for Acute Respiratory Distress Syndrome (ARDS*) [see Emergency Use Authorization (1)]*.
6. As the prescribing healthcare provider, review the information within the "Fact Sheet for Patients and Caregivers" with your patient and/or caregiver prior to the patient receiving sabizabulin. Healthcare providers must provide the patient/caregiver with an electronic or hard copy of the "Fact Sheet for Patients and Caregivers" prior to the patient receiving sabizabulin and must document that the patient/caregiver has been given an electronic or hard copy of the "Fact Sheet for Patients and Caregivers".
7. The prescribing healthcare providers must inform the patient/caregiver that:
    a. Sabizabulin is an unapproved drug that is authorized for use under this Emergency Use Authorization.
    b. There are no adequate, approved, available products for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk for Acute Respiratory Distress Syndrome (ARDS).
    c. Other therapeutics are currently authorized for the same use as sabizabulin. For additional information on all products authorized for treatment of hospitalized patients with COVID-19 at high risk for ARDS, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization
    d. There are benefits and risks of taking sabizabulin as outlined in the "Fact Sheet for Patients and Caregivers."
    e. Veru has established a pregnancy surveillance program.
    f. Pregnant females should not be administered sabizabulin.
    g. Females of childbearing potential should not be administered sabizabulin
    h. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months (90 days) after the last dose.
8. The prescribing healthcare provider must assess whether a female of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)]*.
9. Based on findings from studies of cells, sabizabulin may cause fetal harm when administered to pregnant individuals. Sabizabulin should not be used during pregnancy,

as outlined in the "Fact Sheet for Patients and Caregivers" *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)]*.

10. If the decision is made to use sabizabulin during pregnancy, this would be considered off-label use and is not recommended. However, the prescriber must document that the known and potential benefits and the potential risks of sabizabulin use during pregnancy, including birth defects and spontaneous abortion as outlined in the "Fact Sheet for Patients and Caregivers," were discussed with the patient.
11. The prescribing healthcare provider must document that a pregnant individual was made aware of Veru's pregnancy surveillance program by calling 1-833-828-9283 or by emailing Veru@medcomminc.com.
    a. If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing healthcare provider to disclose patient specific information to Veru, the prescribing healthcare provider must provide the patient's name and contact information to Veru.

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events potentially related to sabizabulin within 7 calendar days from the healthcare provider's awareness of the event [see Adverse Reactions (6.4)]. For information on clinical studies of sabizabulin and other therapies for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk for Acute Respiratory Distress Syndrome (ARDS), see www.clinicaltrials.gov.

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product sabizabulin for treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk for ARDS:

- 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.

LIMITATIONS OF AUTHORIZED USE

- Sabizabulin is not authorized for use in patients who are less than 18 years of age *[see Dosage and Administration (2.1), Use in Specific Populations (8.4)]*.
- Sabizabulin is not authorized for initiation of treatment in patients who are not hospitalized or are hospitalized for reasons other than COVID-19. Benefit of treatment with sabizabulin has not been studied in subjects when treatment was

initiated prior to hospitalization due to COVID-19 *[see Dosage and Administration (2.1)]*.

- Sabizabulin is not authorized for use for longer than 21 consecutive days.
- Sabizabulin is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Sabizabulin may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which sabizabulin belongs (i.e., microtubule depolymerization agents).

Sabizabulin is not approved for any use, including for use for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk for Acute Respiratory Distress Syndrome (ARDS).

Prior to initiating treatment with sabizabulin, carefully consider the known and potential risks and benefits *[see Warnings and Precautions (5.1, 5.2), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13)]*.

Sabizabulin is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of sabizabulin under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration)

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that:
  - The product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
  - The known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the

product, taking into consideration the material threat posed by the biological agent(s);

- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition

Information Regarding Approved Available Alternatives for the EUA Authorized Use

Olumiant (baricitinib) is FDA-approved as an oral tablet for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Although Olumiant is an approved alternative treatment of COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing who are hospitalized and require respiratory support, FDA does not consider Olumiant to be an adequate alternative to sabizabulin for this authorized use. Baricitinib is a Janus kinase (JAK) inhibitor, a class of drugs that block extracellular signals from multiple cytokines that are involved in inflammatory diseases and thought to contribute to inflammation and worsening of COVID-19.

Veklury® (remdesivir) is FDA-approved as an intravenous (IV) infusion for the treatment of 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. Although Veklury is an approved alternative treatment of COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing who are hospitalized, FDA does not consider Veklury to be an adequate alternative to sabizabulin for this authorized use. Veklury is a nucleoside ribonucleic acid polymerase inhibitor that has demonstrated antiviral activity against SARS-CoV-2.

Sabizabulin is an orally available microtubule depolymerization agent which acts to disrupt and suppress the SARS-CoV-2 viral life cycle (e.g. cell surface interaction, intracellular transport, and infectious viral particle release) and also to suppress inflammation (cytokine storm) triggered by COVID-19. This is distinct from Olumiant which acts solely to block extracellular inflammatory signals, and from Veklury which acts solely to inhibit viral replication.

For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of Sabizabulin in Adult Patients

The dose in adult patients is one 9 mg capsule taken orally once daily with or without food *[see Clinical Pharmacology (12.3)]*. Sabizabulin should be administered to patients in the hospital that are 18 years of age or older, require oxygen supplementation, with one or more pre-defined risk for factors for disease progression: Asthma (moderate to severe), Chronic Lung Disease, Diabetes, Hypertension, Severe Obesity (BMI ≥40), 65 years of age or older, primarily reside in a nursing home or long-term care facility, immunocompromised, or require non-invasive

ventilation or high-flow oxygen or intubation and mechanical ventilation. Dosing may continue for 21 days or until the patient is discharged from the hospital.

Sabizabulin is not authorized for use for longer than 21 consecutive days because the efficacy and safety of sabizabulin dosing longer than 21 days has not been established in this population.

If the patient misses a dose of sabizabulin within 12 hours of the time it is usually taken, the patient should not take the dose of sabizabulin on that day and should return to the normal dosing schedule the following day. The number of doses of sabizabulin should not exceed 21 doses.

Sabizabulin may be administered via nasogastric (NG) tube (French size 8 or larger). For NG tube administration:

- While wearing gloves, open the capsule and empty the entire contents of the capsule into a clean container with 20 mL of distilled water. Do not transfer the capsule shell into the container.
- Gently swirl the mixture in the container until all of the powder is uniformly dispersed in the liquid.
- After the capsule's contents have dispersed, draw up the mixture into a catheter tip syringe. Apply steady pressure to dispense the contents of the syringe into the NG tube.
- Rinse the container with an additional 40 mL of distilled water, then draw up the volume into the syringe and use it to flush the NG tube.

2.2 Dosage Adjustments in Specific Populations

No dosage adjustment is recommended in the geriatric population *[see Use in Specific Populations (8.5)]*.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 9 mg, white, size 3 HPMC+ capsules imprinted with V09 in black ink.

4 CONTRAINDICATIONS

Sabizabulin is not contraindicated in any population. Please see LIMITATIONS OF USE.

5 WARNINGS AND PRECAUTIONS

Serious and unexpected adverse events may occur that have not been previously reported with sabizabulin use.

5.1 Embryo-Fetal Toxicity

Based on non-clinical mutagenicity tests conducted with sabizabulin, there is a very high likelihood that use of sabizabulin in a pregnant woman will be toxic to the developing fetus. *[see Contraindications (4) and Patient Counseling Information (17.1)]*.

5.2 Phototoxicity

Sabizabulin showed phototoxic potential in an *in vitro* assay *[see Animal Toxicology and/or Pharmacology (13.2)]*. Until sabizabulin is eliminated from the body, 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. Additionally, patients should avoid concomitant medications known to cause photosensitivity.

5.3 Concomitant Medications

Sabizabulin has not been used concomitantly with retroviral/antiretroviral medications (except remdesivir), experimental medications (except convalescent plasma), or colchicine. Therefore, concomitant use of sabizabulin with these medications is not recommended.

In clinical trials in hospitalized COVID-19 patients, concomitant use of sabizabulin with standard of care, including remdesivir, tocilizumab, tofacitinib, baracitinib, dexamethasone, and other corticosteroids was allowed.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

The following adverse reactions have been observed in the clinical studies of SABIZABULIN that supported the EUA. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Additional adverse events associated with SABIZABULIN may become apparent with more widespread use.

Overall, approximately 283 subjects have been exposed to sabizabulin from doses of 2.25 to 40.5 mg per day in clinical trials. At doses higher than 9 mg per day in males with advanced prostate cancer, the most common adverse events were diarrhea, nausea, vomiting, fatigue, and increased liver transaminases. The safety assessment of sabizabulin is primarily based on the analysis of 149 hospitalized subjects with COVID-19 at high risk for ARDS treated with 9 mg SABIZABULIN in two double-blind placebo-controlled studies *[see Clinical Studies (14)]*. This included one randomized, double-blind, multicenter, placebo-controlled Phase 2 trial and one randomized, double-blind, multicenter, placebo-controlled Phase 3 trial.

The Phase 2 study was a randomized, placebo-controlled multicenter study conducted in the US to assess the efficacy and safety of 9 mg SABIZABULIN (daily for up to 21 days) in treatment of SARS-CoV-2 infection in hospitalized subjects with moderate to severe COVID-19 infection who were at high risk for ARDS. The safety analysis was based on 19 patients in the SABIZABULIN arm and 20 patients in the placebo arm. Discontinuation of study treatment due to an adverse reaction occurred in 1 patient who received sabizabulin and no subjects receiving placebo.

The Phase 3 study was a randomized, double-blind placebo-controlled multicenter study to assess the efficacy and safety of 9 mg SABIZABULIN (daily for up to 21 days) in treatment of SARS-CoV-2 infection in hospitalized subjects with moderate to severe COVID-19 infection

who were at high risk for ARDS. Discontinuation of study treatment due to an adverse reaction occurred in 4.6% of subjects receiving sabizabulin and 4.3% of subjects receiving placebo.

The most common adverse reactions (≥2%) in the sabizabulin treated group in the Phase 2 and Phase 3 clinical studies combined are presented in Table 1.

Table 1: Adverse Reactions Occurring in ≥2% of Subjects Receiving Sabizabulin

Adverse Reaction	**Placebo (N=89)**	**Sabizabulin 9 mg (N=149)**
Anemia	4.5%	4.7%
Atrial Fibrillation	6.7%	4.0%
Bradycardia	5.6%	4.0%
Tachycardia	1.1%	2.0%
Constipation	9.0%	8.1%
Diarrhea	1.1%	3.4%
Dyspepsia	0	2.0%
Vomiting	0	2.0%
Pyrexia	0	3.4%
COVID-19	4.5%	3.4%
Infection	0	2.0%
Pneumonia	10.1%	5.4%
Pulmonary sepsis	1.1%	2.0%
Sepsis	4.5%	4.7%
Septic shock	9.0%	2.0%
Urinary Tract Infection	1.1%	5.4%
Alanine aminotransferase increased	4.5%	4.0%
Aspartate aminotransferase increased	2.2%	2.7%
Fibrin D dimer increased	2.2%	2.7%
Gamma-glutamyltransferase increased	2.2%	2.7%
Serum ferritin increased	2.2%	2.0%
Transaminases increased	2.2%	4.0%
Hyperkalemia	6.7%	4.0%
Hypernatremia	4.5%	4.0%
Hypokalemia	5.6%	4.7%
Hypertension	1.1%	2.0%
Anxiety	4.5%	2.7%
Delirum	4.5%	3.4%
Acute Kidney Injury	11.2%	7.4%
Haematuria	2.2%	2.0%
Acute Respiratory Failure	3.4%	4.7%
Hypoxia	4.5%	2.0%
Pulmonary Embolism	3.4%	2.7%
Respiratory failure	20.2%	8.7%
Decubitis ulcer	0	2.7%

Deep Vein Thrombosis	1.1%	2.0%
Hypotension	10.1%	3.4%

Serious adverse reactions occurred in (27.5%) of the subjects receiving sabizabulin and (41.6%) receiving placebo in the Phase 2 and Phase 3 clinical studies combined; most serious adverse reactions were COVID-19 related. The most common serious adverse reactions in the sabizabulin group observed in the Phase 2 and Phase 3 clinical trials combined are presented in Table 2.

Table 2: Serious Adverse Reactions Reported by ≥2% of Patients Treated with Sabizabulin

Serious Adverse Reaction	**Placebo (N=89)**	**Sabizabulin 9 mg (N=149)**
COVID-19	4.5%	2.7%
Pneumonia	4.5%	2.7%
Sepsis	2.2%	2.7%
Septic shock	7.9%	2.0%
Acute Kidney Injury	7.9%	4.0%
Acute Respiratory Failure	4.5%	3.4%
Pulmonary embolism	3.4%	2.0%
Respiratory Failure	18.0%	8.7%

Laboratory Abnormalities

No laboratory abnormalities have been noted with sabizabulin 9 mg that were severe (Grade 3 or 4) or serious adverse reactions, or adverse reactions leading to death.

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to sabizabulin within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 300 (for information on how to access this form, see below). The FDA recommends that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "Sabizabulin use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, and clinical outcomes).
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
  - Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:

E-mail: Veru@medcominc.com or call Veru Inc. at 1-833-828-9283 to report adverse events

The prescribing healthcare provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with sabizabulin.

*Serious adverse events are defined as:

- Death or a life-threatening adverse event;
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly;
- Prolongation of existing hospitalization; or
- A congenital anomaly/birth defect.

7 DRUG INTERACTIONS

No clinical drug-drug interaction trials have been conducted with sabizabulin. Sabizabulin is not metabolized by cytochrome P450 (CYP) 3A4.

As sabizabulin may cause sensitivity to the sun, patients should avoid concomitant medications known to cause photosensitivity *[see Warnings and Precautions (5.2) and Animal Toxicology and/or Pharmacology (13.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Sabizabulin should not be used in pregnant individuals.

Risk Summary

There are no available human data on the use of sabizabulin during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on the mechanism of action and in vitro mutagenicity studies [*see Nonclinical Toxicology*

(13.1)], it is highly likely that the use of sabizabulin in a pregnant individual 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. Therefore, sabizabulin is not recommended during pregnancy. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy (*see Clinical Considerations*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo-fetal Risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to sabizabulin during pregnancy *[see MANDATORY REQUIREMENTS]*. Healthcare providers are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-828-9283 or by emailing Veru@medcominc.com.

8.2 Lactation

There are no data on the presence of sabizabulin or metabolites of sabizabulin in human milk. It is unknown if sabizabulin will have an effect on a breastfed infant. It is unknown if sabizabulin will affect milk production in a lactating patient taking sabizabulin. A lactating individual may consider interrupting breast feeding and may consider pumping and discarding the breast milk during treatment and for at least 7 days after last dose of sabizabulin.

8.3 Females and Males of Reproductive Potential

Based on the mechanism of action of sabizabulin and available in vitro data, sabizabulin is very likely to cause fetal harm if administered to a pregnant individual.

Pregnancy Testing
Prior to initiation of sabizabulin treatment in an individual of childbearing potential, a pregnancy test should be administered *[see Warnings and Precautions (5.1)]*.

Contraception
Females: In females of childbearing potential, a reliable method of contraception should be used correctly and consistently during treatment with sabizabulin and at least 7 days after last dose of sabizabulin *[see Warnings and Precautions (5.1)]*.

Males: In males with a female partner of childbearing potential, a reliable method of contraception should be used correctly and consistently during treatment with sabizabulin and at least 90 days after last dose of sabizabulin *[see Warnings and Precautions (5.1)]*.

8.4 Pediatric Use

Sabizabulin has not been studied in pediatric patients and is not authorized for use in pediatric patients.

8.5 Geriatric Use

In the clinical studies conducted with sabizabulin in hospitalized patients with COVID-19 at high risk for ARDS, there did not appear to be a difference in the observed safety profile of sabizabulin in patients ≥65 years of age compared to patients <65 years of age. The effect of age on the pharmacokinetics of sabizabulin has not been assessed *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Based on preclinical data, renal elimination appears to be a meaningful route of elimination for sabizabulin *[see Animal Toxicology and/or Pharmacology (13.2)]*. Patients with a creatinine clearance <60 mL/min were excluded from the clinical studies of sabizabulin. Therefore, sabizabulin should not be used in patients with a creatinine clearance <60 mL/min.

8.7 Hepatic Impairment

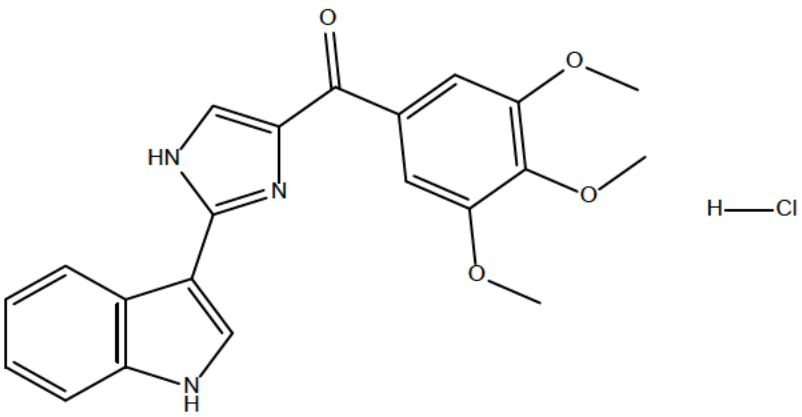
Based on preclinical data, hepatic elimination appears to be a meaningful route of elimination for sabizabulin *[see Animal Toxicology and/or Pharmacology (13.2)]*. Patients with ALT and/or AST levels >3 times the upper limit of normal and patients with total bilirubin greater than the upper limit of normal were excluded from the clinical studies of sabizabulin. Therefore, sabizabulin should not be used in patients with ALT and/or AST levels >3 times the upper limit of normal or patients with total bilirubin greater than the upper limit of normal.

10 OVERDOSAGE

Sabizabulin has been administered at doses of 32 mg daily for up to 36 months. There is no human experience with overdosage of sabizabulin. Treatment of overdosage with sabizabulin should be treated with general supportive care measures including monitoring of the clinical status of the patient. The elimination half-life of sabizabulin is approximately 5 hours. Therefore, circulating levels of sabizabulin should be essentially below detectable levels within 35 hours of dosing.

11 DESCRIPTION

Sabizabulin is a microtubule depolymerization agent. Sabizabulin has the empirical formula $C_{21}H_{20}ClN_3O_4$ representing a molecular weight of 413.89 (as a hydrochloride acid salt). The structural formula is:



The chemical name of sabizabulin is: (2-1H-indol-3-yl)-1H-imidazol-4-yl)(3,4,5-trimethoxyphenyl) methanone hydrochloride. It is a light yellow to yellow crystalline solid that is slightly soluble in water and soluble in ethanol.

Sabizabulin capsules, for oral use, are size 3 HPMC capsule containing 9 mg sabizabulin free base and the following inactive ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, and polyoxyl 40 hydrogenated castor oil. The white capsule is printed with a black iron oxide ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sabizabulin is an orally available, novel microtubule disruptor. Sabizabulin targets, binds, and crosslinks the α and β tubulin subunits to inhibit polymerization and to induce depolymerization of microtubules.

The components of the viral life cycle for the SARS-CoV-2 (COVID-19) virus that utilize microtubules include: virus-cell surface interactions, virus entry and internalization into the cell; virus intracellular transport to the perinuclear region of the cell; transport for viral assembly in the Golgi body, endoplasmic reticulum, microtubule organizing center, and then intracellular outbound trafficking to egress (release) infectious viral particles out of the cell.

Microtubule trafficking networks play a critical role in viral infection, replication, and spreading of new infectious viruses. Through inhibition of polymerization and depolymerization of microtubules, sabizabulin disrupts the microtubule trafficking networks making them unusable by the virus. This disrupts and suppresses the SARS-CoV-2 (COVID-19) viral life cycle.

Inhibition of microtubule polymerization and depolymerization of microtubules has been shown to suppress inflammasome activation and leucocyte mediated inflammatory activities including inhibition of leucocyte production of superoxides and release of various cytokines and pyrogens. Therefore, the mechanism of action of sabizabulin may also reduce the “cytokine storm” triggered by SARS-CoV-2 viral infection.

12.2 Pharmacodynamics

Clinical pharmacodynamic studies have not been conducted to assess the relationship of sabizabulin and either the anti-viral or anti-inflammatory activity.

12.3 Pharmacokinetics

The multiple dose pharmacokinetics of sabizabulin have been assessed at 9 mg dose per day in hospitalized COVID-19 patients and at 31.5 mg dose per day in men with advanced prostate cancer (Table 3). The elimination half-life of sabizabulin is approximately 5 hours. Therefore, drug is substantially eliminated from the body within 1.5 days after the last dose of study drug.

Administration of sabizabulin with a high fat meal has similar rate and extent of absorption compared to sabizabulin administered fasted. However, the time to reach C_{max} is delayed from an average of 1.7 hours to 4 hours when administered with a high fat meal. Based on these data, sabizabulin may be administered with or without food.

Table 3: The Steady State Pharmacokinetics of Sabizabulin Capsule Under Fasted and Fed Conditions

	31.5 mg (fasted)	31.5 mg (fed)	9 mg
N	6	6	4
C_{max} (ng/mL)	182.2±32.6	169.9±104.2	57.5±12.87
T_{max} (hr)	1.67±1.21	4.08±2.69	NA
$AUC_{0\text{-}24h}$ (ng*hr/mL)	973.58±307.87	1011.27±512.54	455.4±34.0
$T_{½}$ (hr)	5.11±1.24	4.89±1.09	4.29±1.43

Specific Populations

The effect of age, sex, race, ethnicity, or disease severity on the pharmacokinetics of sabizabulin has not been assessed.

Pediatric

Sabizabulin is not indicated for and has not been studied in pediatric patients.

Gender

Sabizabulin is indicated for use in hospitalized males and females. However, no comparative pharmacokinetics have been done between genders with sabizabulin.

Geriatric

Sabizabulin is indicated for use in hospitalized patients 18 years of age and older and has been used in patients up to 92 years of age. However, no comparative pharmacokinetics have been done to compare older patients with younger patients.

Patients with Renal Impairment

The PK of sabizabulin has not been evaluated in patients with moderate and severe renal impairment, however preclinical data indicate that renal elimination is a meaningful route of elimination for sabizabulin *[see Animal Toxicology and/or Pharmacology (13.2)]*.

Patients with Hepatic Impairment

The PK of sabizabulin has not been evaluated in patients with moderate and severe hepatic impairment, however preclinical data indicate that hepatic elimination may be a meaningful route of elimination for sabizabulin *[see Animal Toxicology and/or Pharmacology (13.2)]*.

12.4 Microbiology

Anti-viral and Anti-inflammatory Activities

A high throughput screen for anti-viral activity revealed inhibition of SARS-CoV-2 viral cytopathic activity in Vero E6 cells (EC_{50} of <3nM). In a separate viral titer assay, the $TCID_{50}$ was not reached in Vero E6 cells treated with supernatant from SARS-CoV-2 infected cells treated with 1nM or 10nM sabizabulin. Both the 1nM and 10nM sabizabulin treated cells were >90% viable indicating that there was a marked reduction of detectable infectious SARS-CoV-2 virus particles from the supernatant.

In vitro studies to determine if sabizabulin can suppress toxic shock levels of these key cytokines of the cytokine storm were conducted. The effects of sabizabulin on cytokine production was assessed by stimulating isolated mouse spleen cells with an endotoxin that causes shock called lipopolysaccharide (LPS). The cells were stimulated with 5 μg/ml LPS for 1 hour and then incubated overnight (approximately 21 hours) with sabizabulin to mimic the clinical situation, and cytokine levels were analyzed. At a concentration that represents the blood levels of sabizabulin observed in clinically dosed patients, sabizabulin (40 nM) significantly reduced the production of key cytokines known to be involved with COVID-19 cytokine storm: TNFα (-31%) ($p=0.006$), IL-1α (-123%) ($p=0.0005$), IL-1β (-97%) ($p=0.0003$), IL-6 (-85%) ($p<0.00008$), and IL-8 homologue (-96%) ($p<0.0000007$). This reduction was similar to, or greater than, depending on the specific cytokine, to that observed with dexamethasone (10nM), a steroid and a known inhibitor of cytokine production during inflammation.

Activity against SARS-CoV-2 in animal models

In a mouse model of ARDS, BALB/c mice infected with mouse-adapted SARS-CoV-2, administered sabizabulin via oral gavage once daily (3 mg/kg and 9 mg/kg) demonstrated a reduction in deaths as well as pathologic assessments of bronchointerstitial inflammation and global pneumonia severity.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
A carcinogenicity study with sabizabulin has not been conducted.

Mutagenesis
Sabizabulin was negative for mutagenicity in the AMES test. Sabizabulin was positive for aneugenic activity in the *in vitro* micronucleus test with and without metabolic activation with no indication of structural aberrations observed. These results are consistent with the mechanism of action of sabizabulin (inhibition of microtubule polymerization and depolymerization of the microtubules). Specifically, per the mechanism of action of sabizabulin, through the inhibition of

microtubule polymerization, chromosomal segregation is impacted resulting in an abnormal number of chromosomes in daughter cells. Sabizabulin is not considered to be clastogenic.

Impairment of Fertility
Sabizabulin has not been evaluated for impairment of fertility.

13.2 Animal Toxicology and/or Pharmacology

In a mass balance study in dogs, the mean total recovery of radiolabeled sabizabulin was 84.5% ± 6.88% with a mean fecal recovery of 60.7% ± 12.0%, a mean urine recovery of 15.6% ± 5.66%. These results indicate that both renal and hepatic routes of elimination are meaningful for sabizabulin.

In rats, the no adverse effect level for sabizabulin was 3 mg/kg/day with a C_{max} of 137 ng/mL. The 10 mg/kg/day was deemed to be severely toxic with an average C_{max} of 628 ng/mL.

In dogs, the no adverse effect level for sabizabulin was 4 mg/kg/day due to adverse body weight losses and a lengthening of the PR, QT, and QTc intervals observed in animals administered 8 mg/kg/day.

In an *in vitro* study with BALB/c 3T3 mouse fibroblasts sabizabulin demonstrated phototoxic potential, with a photoirritancy factor (PIF) of approximately 121 to 148 and mean photo effect (MPE) of 0.661 to 0.741.

14 CLINICAL STUDIES

Clinical data supporting this Emergency Use Authorization are based on data from 204 randomized subjects in the Phase 3 clinical trial (NCT04842747). The Phase 3 clinical trial was a multicenter, multinational, randomized, double-blind, placebo-controlled clinical trial of sabizabulin 9 mg treatment in hospitalized patients diagnosed with COVID-19 at high risk for ARDS. Eligible subjects were 18 years of age or older, required oxygen supplementation (oxygen saturation less than 94% on room air), with one or more pre-defined risk for factors for disease progression: Asthma (moderate to severe), Chronic Lung Disease, Diabetes, Hypertension, Severe Obesity (BMI ≥40), 65 years of age or older, primarily reside in a nursing home or long-term care facility, immunocompromised, or require non-invasive ventilation or high-flow oxygen or intubation and mechanical ventilation. Subjects were allowed to receive the current standard of care including vaccination for COVID-19. Subjects were randomized 2:1 to receive sabizabulin 9 mg or placebo once daily for up to 21 days or until discharge from the hospital.

The primary efficacy endpoint in the study was proportion of patients that die up to Day 60 on the study (Table 4).

Table 4: Primary Efficacy Endpoint – Mortality up to Day 60 (Intent to Treat Population)

Result	Sabizabulin 9mg	Placebo	% Relative Reduction
Proportion of patients that died by Day 60 (ITT population)	25/130 (19.2%)	27/68 (39.7%)	51.6%
Treatment Comparison	**Odds Ratio**	**95% CI**	**p-value**
Sabizabulin 9mg vs. Placebo	2.74	(1.36, 5.53)	0.0049

Model effects are displaying median of the p-values for imputed analyses. Odds Ratio and associated 95% Confidence Interval (CI) is presented for the probability of survival at Day 60. An odds ratio > 1 indicates benefit in sabizabulin group. Multiple imputation used for missing vital status at Day 60. Imputation model included treatment, region, sex, remdesivir use, dexamethasone use and WHO strata, and additionally subject's discharge status and early treatment discontinuation status.

The key secondary efficacy endpoints are days in ICU, days on mechanical ventilation, and proportion of patients alive and free of respiratory failure at Day 29. These parameters are presented in Table 5, 6, and 7. A clinically meaningful and statistically significant reduction in days in the ICU, days in hospital and days on mechanical ventilation was observed in the sabizabulin treated group compared to placebo.

Table 5: Days in ICU

Treatment	Mean (days)	SD	Median (days)	Min, Max
Sabizabulin 9 mg (n=134)	16.0	23.50	2.0	0, 60
Placebo (n=70)	26.3	28.11	9.0	0, 60
Treatment Comparison	**LS mean**	**SE**	**95% CI**	**p-value**
Sabizabulin 9mg vs. Placebo	-9.9	3.44	(-16.7, -3.1)	0.0045

'Days in ICU' is the number of days in ICU up to Day 60. All subjects who died at any time got 60 days in ICU (even those subjects who were never in ICU).

Table 6: Days on Mechanical Ventilation

Treatment	Mean (days)	SD	Median (days)	Min, Max
Sabizabulin 9 mg (n=134)	13.7	23.57	0.0	0, 60
Placebo (n=70)	24.6	29.00	0.0	0, 60
Treatment Comparison	**LS mean**	**SE**	**95% CI**	**p-value**
Sabizabulin 9mg vs. Placebo	-10.4	3.56	(-17.5, -3.4)	0.0038

'Days on Mechanical Ventilation (MV)' is the number of days on MV up to Day 60. All subjects who died at any time got 60 days on MV (even those subjects who were never on MV).

Table 7: Proportion of Patients Alive and Free of Respiratory Failure at Day 29 (Intent to Treat Population)

Result	**Sabizabulin 9mg**	**Placebo**	**% Relative Increase**
Proportion of patients alive and free of respiratory failure at Day 29 (ITT population)	96/130 (73.8%)	38/68 (55.9%)	32.0%
Treatment Comparison	**Odds Ratio**	**95% CI**	**p-value**
Sabizabulin 9mg vs. Placebo	2.34	(1.14, 4.80)	0.0208

Responders are subjects who are alive and has Grade 0-4 on the WHO Ordinal Scale for Clinical Improvement at the visit. Non-responders are subjects who died before the visit or has Grade 5-8 on the WHO Ordinal Scale for Clinical Improvement at the visit. Missing vital status was handled using multiple imputation methods. Imputation model included treatment, region, sex, remdesivir use, dexamethasone use and WHO strata, and additionally subject's discharge status and early treatment discontinuation status. Model effects are displaying median of the p-values for the imputed analyses. An odds ratio > 1 indicates benefit in sabizabulin group.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Sabizabulin capsules are supplied as follows:

Contents	Description	How Supplied	NDC
9 mg sabizabulin	White size 3 capsule imprinted with V09	30-count bottle	NDC-69681-119-30

16.2 Storage and Handling

Sabizabulin capsules should be stored in a dry location at 20°C to 25°C (68°F -76°F) with excursions permitted between 15°C-30°C (59°F- 86°F). Do not remove the desiccant package from the bottle after opening.

Keep out of reach of children.

Sabizabulin capsules should not be handled, crushed, or opened without gloves. Sabizabulin capsules should not be handled at all by a woman who is pregnant or may potentially be pregnant because of the potential risk of fetal harm *[see MANDATORY REQUIREMENTS, Warnings and Precautions (5.1), Use in Specific Populations (8.1) and Patient Counseling Information (17)]*.

17 PATIENT COUNSELING INFORMATION

As a prescribing healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS AND CAREGIVERS" and document that information was provided. A copy of this Fact Sheet should be provided to the patient and/or caregiver prior to receiving sabizabulin [see *MANDATORY REQUIREMENTS*].

Risk of Fetal Toxicity
Physicians should discuss with patients the contraindication of sabizabulin in pregnant individuals *[see MANDATORY REQUIREMENTS, Warnings and Precautions (5.1), and Use in Specific Populations (8.1)]*.

Advise female patients of childbearing potential of the requirement to use effective contraception while receiving sabizabulin and at least 7 days after last dose of sabizabulin. A female partner of a male patient of childbearing potential should be advised of the requirement to use effective contraception while receiving sabizabulin and at least 90 days after last dose of sabizabulin *[see Use in Specific Populations (8.1)]*.

Pregnancy Surveillance Program
If a woman is exposed to sabizabulin while pregnant or if a female partner of a male patient that was exposed to sabizabulin becomes pregnant within 90 days of last dose of sabizabulin, the outcomes of these pregnancies will be monitored by Veru Inc. Patients should be advised to contact Veru Inc. at 1-833-828-9283 or Veru@medcominc.com *[see Use in Specific Populations (8.1)]*

Lactation
The effect of sabizabulin on a breastfeeding baby is unknown. It is recommended that the patient consider interrupting breast feeding and pumping and discarding the breast milk for at least 7 days after last dose of sabizabulin *[see Use in Specific Populations (8.2)]*.

Administration Instructions
Sabizabulin should be administered orally with or without food at approximately the same time every day. Up to 21 doses of sabizabulin may be administered to a patient. If the dose of sabizabulin is missed, the dose may be administered within 12 hours of the target dosing time. If a patient vomits after administration of sabizabulin, do not administer another dose of sabizabulin on that day. Return to the dosing schedule the next day. Sabizabulin should only be administered to patients who are admitted to the hospital. Sabizabulin should be administered only by hospital personnel. Sabizabulin capsules may be opened and administered via a nasogastric feeding tube *[see Dosage and Administration (2.1)]*.

18 MANUFACTURER INFORMATION

For additional information visit: www.verupharma.com or https://sabizabulin.com

If you have questions, please contact:

1-833-828-9283

Manufactured by:

Veru Inc., 2916 North Miami Ave, Suite 1000, Miami, FL 33127

Fact Sheet For Patients And Caregivers

Emergency Use Authorization (EUA) Of Sabizabulin Capsules For Coronavirus Disease 2019 (COVID-19)

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you with SABIZABULIN for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in hospitalized adult patients with moderate to severe COVID-19 infection who are at high risk for Acute Respiratory Distress Syndrome (ARDS) and for whom other COVID-19 treatment options approved or authorized by the FDA are not accessible or clinically appropriate. This Fact Sheet contains information to help you understand the risks and benefits of taking the Sabizabulin you have received or may receive.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make SABIZABULIN available during the COVID-19 pandemic (for more details about an EUA please see "**What is an Emergency Use Authorization?**" at the end of this document). SABIZABULIN is not an FDA-approved medicine in the United States. Read this Fact Sheet for information about SABIZABULIN. Talk to your healthcare provider about your options or if you have any questions. It is your choice to take SABIZABULIN or stop it at any time.

What is COVID-19?

COVID-19 is caused by a virus called a coronavirus. You can get COVID-19 through close contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. Older people and people of all ages with severe, long lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example seem to be at higher risk of being hospitalized for COVID-19.

What is SABIZABULIN?

SABIZABULIN is an investigational medicine used to treat SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 infection, with positive results of direct SARS-CoV-2 viral testing, who are at high risk for acute respiratory distress syndrome (ARDS) and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or are not clinically appropriate. SABIZABULIN is investigational because it is still being studied.

There is limited information about the safety and effectiveness of using SABIZABULIN to treat hospitalized people with moderate to severe COVID-19 who are at high risk for ARDS. Available results from clinical trials in adults indicate that treatment with SABIZABULIN may decrease the risk of dying in hospitalized patients with COVID-19 who are at high risk of ARDS.

The FDA has authorized the emergency use of SABIZABULIN for the treatment of SARS-CoV-2 infection in hospitalized adult patients with moderate to severe COVID-19 infection, with positive results of direct SARS-CoV-2 viral testing, who are at high risk for acute ARDS under

an EUA. For more information on EUA, see the **"What is an Emergency Use Authorization (EUA)?"** section at the end of this Fact Sheet.

SABIZABULIN is not authorized:

- For use in people less than 18 years of age.
- For prevention of COVID-19.
- For non-hospitalized patients with COVID-19.
- For use in patients that are not on oxygen supplementation.
- For use in patients that are pregnant.

What should I tell my healthcare provider before I take SABIZABULIN?

Tell your healthcare provider if you:

- Have any allergies
- Have liver or kidney disease
- Are pregnant or plan to become pregnant
- Are breastfeeding a child
- Have any serious illness other than COVID-19

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive SABIZABULIN?

- SABIZABULIN is given orally or via nasogastric tube, one time each day for up to 21 days, as determined by your healthcare provider.

What are the important possible side effects of SABIZABULIN?

- SABIZABULIN may cause harm to your unborn baby. It is not known if SABIZABULIN will harm your baby if you take SABIZABULIN during pregnancy. Talk to your healthcare provider if you have questions or concerns about how SABIZABULIN may affect your unborn baby.
- SABIZABULIN may cause sensitivity to the sun. Until SABIZABULIN is eliminated from the body (approximately 2 days after last dose), you should avoid or minimize exposure to sunlight (including sunlamps), use a sunblock (SPF 50 or higher), and wear clothing that protects against sun exposure. Additionally, you should avoid concomitant medications known to cause photosensitivity. Talk to your healthcare provider if you have questions about medications that may make you sensitive to the sun.

The most common side effect of SABIZABULIN is urinary tract infection.

At doses higher than 9 mg per day, the most common side effects were diarrhea, nausea, vomiting, and fatigue.

These are not all the possible side effects of SABIZABULIN. Serious and unexpected side effects may happen. This medicine is still being studied, so it is possible that all of the risks are not known at this time.

What other treatment choices are there?

Olumiant (baricitinib) is FDA-approved as an oral tablet for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Veklury (remdesivir) is FDA-approved as an intravenous (IV) infusion for the treatment of mild-to-moderate COVID-19 in certain adults and children

Talk with your doctor to see if Olumiant or Veklury are appropriate for you.

Like SABIZABULIN, FDA may also allow for the emergency use of other medicines to treat people with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on the emergency use of other medicines that are authorized by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials for which you may be eligible.

It is your choice to be treated or not to be treated with SABIZABULIN. Should you decide not to take it, it will not change your standard medical care.

What if I am pregnant or breastfeeding?

Pregnancy

- There is no experience treating pregnant women or breastfeeding mothers with SABIZABULIN. SABIZABULIN has not been studied in pregnant women.
- Based on findings from studies of cells, **SABIZABULIN may cause harm to your unborn baby when administered during pregnancy.**
- SABIZABULIN is not recommended for use in pregnancy.
- If you and your healthcare provider decide that you should take SABIZABULIN during pregnancy if there are no other COVID-19 treatment options approved or authorized by the FDA that are accessible or clinically appropriate for you, this would be considered off label use and is not recommended.
- If you and your healthcare provider decide that you should take SABIZABULIN during pregnancy, you and your healthcare provider should discuss the known and potential benefits and the potential risks of taking SABIZABULIN during pregnancy. Talk to your healthcare provider if you have questions or concerns about how SABIZABULIN may affect your unborn baby.

For individuals who are able to become pregnant:

- Your healthcare provider may do a pregnancy test to see if you are pregnant before starting treatment with SABIZABULIN.
- Tell your healthcare provider right away if you think you may be pregnant during treatment with SABIZABULIN.
- You should use a reliable method of birth control (contraception) during treatment with SABIZABULIN. It is not known if SABIZABULIN can affect sperm. Males who are sexually active with females who are able to become pregnant should use a reliable method of contraception correctly and consistently during SABIZABULIN treatment and for at least 3 months (90 days) after the last dose. The risk to sperm beyond 3 months is not known. Talk to your healthcare provider about reliable birth control methods. Talk to your healthcare provider if you have questions or concerns about how SABIZABULIN may affect sperm.

Pregnancy Surveillance Program:

- There is a pregnancy surveillance program for individuals who take SABIZABULIN during pregnancy or become pregnant while taking or shortly after taking SABIZABULIN. The purpose of this program is to collect information about the health of you and your baby. Talk to your healthcare provider about how to take part in this program.
- If you take SABIZABULIN during pregnancy and you agree to participate in in the pregnancy surveillance program and allow your healthcare provider to share your information with Veru Inc., then your healthcare provider will report your use of SABIZABULIN during pregnancy to Veru Inc. by calling 1-833-828-9283 or emailing Veru@medcomminc.com.

Breastfeeding

There is no experience treating breastfeeding mothers with SABIZABULIN. Breastfeeding is not recommended during treatment with SABIZABULIN and for 7 days after the last dose of SABIZABULIN. If you are breastfeeding or plan to breastfeed, talk to your healthcare provider about your options and specific situation before taking SABIZABULIN.

How do I report side effects with SABIZABULIN?

Contact your healthcare provider if you have any side effects that bother you or do not go away.

Report side effects to FDA MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088 (1-800-332-1088) or you can report side effects to Veru Inc. at the contact information provided below.

Email	Telephone number
Veru@medcomminc.com	1-833-828-9283

How can I learn more about COVID-19?

- Ask your healthcare provider.
- Visit https://www.cdc.gov/COVID-19.
- Contact your local or state public health department.
- Visit https://sabizabulin.com

What is an Emergency Use Authorization?

The United States FDA has made SABIZABULIN available under and emergency access mechanism called an Emergency Use Authorization (EUA). The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify emergency use of drugs and biological products during the COVID-19 pandemic. SABIZABULIN 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, who are at high risk for acute respiratory distress syndrome (ARDS), has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA has determined, among other things, that based on the total amount of scientific evidence available including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved, and available alternatives**.**

All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic. The EUA for SABIZABULIN is in effect for the duration of the COVID-19 declaration justifying emergency use of SABIZABULIN, unless terminated or revoked (after which SABIZABULIN may no longer be used under the EUA).

Additional Information

For general questions visit the website below.

https://sabizabulin.com

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