2 SYNOPSIS

Name of Sponsor/Company:	**Name of Finished Product:**	**Name of Active Ingredient:**
Veru Inc.	Sabizabulin	VERU-111

Title of Study:

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 Subjects at High Risk for Acute Respiratory Distress Syndrome (ARDS)

Protocol Number:

V3011902

Sponsor Scientific and Public Contact Points:

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Trial Registry Name and Number:

ClinicalTrials.gov: NCT04842747
EudraCT number: 2021-001194-24
IND number: 149282

Investigators:

A total of 57 investigators at 56 active sites in 6 countries.
The Coordinating Investigator was [redacted], MD in the United States.

Study Centers:

A total of 56 active sites in 6 countries (Argentina, Brazil, Bulgaria, Colombia, Mexico, and the United States); 37 sites recruited patients.

Publication(s) (Reference):

Barnette KG, Gordon MS, Rodriguez D, et al. Oral Sabizabulin for high-risk, hospitalized adults with Covid-19: Interim analysis. N Engl J Med Evid. 2022;1(9).
DOI: https://doi.org/10.1056/EVIDoa2200145.

Phase of Development:

Phase 3

Study Period:

Date of first patient enrollment: 19 May 2021 (first patient randomized)
Date of last patient's last visit: 03 June 2022 (last patient's last visit)

Reporting Period:

Final analysis: Initial database lock on 06 Jul 2022. The database was subsequently unlocked on 20 Jul 2022 and then relocked on 21 Jul 2022.

Background:

This is a multicenter, randomized, placebo-controlled, efficacy and safety study of sabizabulin for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients with SARS-CoV-2 at high risk for acute respiratory distress syndrome (ARDS) were randomly assigned (2:1) to the sabizabulin 9 mg or matching placebo, daily, for up to 21 days or until discharged from the hospital, whichever came first. The total planned study duration for a patient from Screening to Follow-up visit was 62 days.

Objectives and Endpoints:

Primary Study Objective/Endpoint:

- To demonstrate the efficacy of sabizabulin in the treatment of SARS-CoV-2 infection by assessing its effect on the proportion of patients who died on study (up to Day 60).
- The primary endpoint for the study was the proportion of patients who died on study (up to Day 60).

Secondary Study Objectives/Endpoints:

- The proportion of patients who were alive without respiratory failure at Day 15, Day 22, and Day 29. Day 29 was a key secondary endpoint. Respiratory failure was defined as endotracheal intubation and mechanical ventilation, extracorporeal membrane oxygenation, high-flow nasal cannula oxygen delivery, non-invasive positive pressure ventilation, clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision making was driven solely by resource limitation.
- Days in intensive care unit (ICU)

- World Health Organization (WHO) Ordinal Scale for Clinical Improvement change from Baseline to Day 15, Day 22, and Day 29 (see the table below)

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

Abbreviations: ECMO = extracorporeal membrane oxygenation; RRT = renal replacement therapy.

- Days on mechanical ventilation
- Days in hospital
- Proportion of patients who died on study at Day 15, Day 22, and Day 29
- Change from Baseline in viral load (Baseline to Day 9)

Safety Study Objective:

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

Methodology:

This randomized, double-blind, placebo-controlled clinical study consisted of 2 treatment groups. Patients with SARS-CoV-2 at high risk for ARDS were randomly assigned (2:1) to the sabizabulin 9 mg-treated group and placebo-treated group, respectively. Approximately 210 patients were planned to be randomly assigned (approximately 140 patients in the sabizabulin-treated group and approximately 70 patients in the placebo-treated group).

All patients received standard of care for the treatment of SARS-CoV-2 infection (coronavirus disease 2019 [COVID-19]). Randomization was stratified by Baseline WHO Ordinal Scale for Clinical Improvement score, such that patients with a WHO Ordinal Scale for Clinical Improvement score of 4, 5, or 6 at Baseline were approximately equally distributed between the treatment groups.

Each patient was to receive a 9 mg daily oral 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. The total duration per patient from Screening to Follow-up visit (approximately Day 60 on study) was approximately 62 days.

Number of Patients (Planned and Analyzed):

Planned: Approximately 210 patients

Enrolled: 244 patients (Screening failed in 40 patients)

Intent-to-Treat (ITT) Set (all randomized patients): 204 patients (134 patients in the sabizabulin 9 mg group and 70 patients in the placebo group)

Modified Intent-to-Treat (mITT) Set: 198 patients (129 patients in the sabizabulin 9 mg group and 69 patients in the placebo group)

Safety Set: 199 patients (130 patients in the sabizabulin 9 mg group and 69 patients in the placebo group)

Diagnosis and Main Criteria for Inclusion and Exclusion:

Male and female adult patients (aged ≥18 years) with SARS-CoV-2 infection confirmed by polymerase chain reaction test, hospitalized with moderate to severe COVID-19 (WHO Ordinal Scale score 4 with a comorbidity, or WHO Ordinal Scale scores of 5 or 6 regardless of presence of comorbidities) and at high risk of ARDS.

Test Product, Dose, Mode of Administration, and Batch Numbers:

Sabizabulin, 9 mg, once daily, orally or through a nasogastric tube

Bulk capsule batch numbers: 21173 and 21096

Duration of Treatment:

Up to 21 days or until the patient was discharged from the hospital (whichever occurred first)

Reference Therapy, Dose, Mode of Administration, and Batch Numbers:

Placebo for sabizabulin, 0 mg, once daily, orally or through a nasogastric tube

Placebo capsule batch numbers: 21098 and 21174

Statistical Methods:

Efficacy Analyses:

All statistical tests were performed using a 2-tailed 5% overall significance level, unless otherwise stated. All comparisons between treatments were reported with 95% confidence intervals (CI) for the difference.

The primary endpoint for the study was the proportion of patients that died on study (up to Day 60). Responders were patients who were alive at Day 60. Mortality rates were analyzed using a logistic regression model. The model was fitted using logit link function. The primary analysis was performed on the ITT Set. A sensitivity analysis using the tipping-point approach was conducted to assess the robustness of the primary analysis approach.

The primary endpoint was also assessed in the mITT Set and the Safety Set as secondary analyses. Risk differences between treatment groups were calculated using an identity link function. Mortality rates were summarized using Kaplan-Meier survival curves, and equality of treatment groups were tested using log-rank test. Hazard ratios were calculated using the Cox proportional hazards model. Subgroup analyses were performed for region, standard of care, and WHO Ordinal Scale for Clinical Improvement score at Baseline.

Secondary efficacy analyses included the proportion of patients alive without respiratory failure at Day 15, Day 22, and Day 29; days in ICU; WHO Ordinal Scale for Clinical Improvement change from Baseline to Day 15, Day 22, and Day 29; days on mechanical ventilation; days in hospital; the proportion of patients who died on study at Day 15, Day 22, and Day 29; and change from Baseline in viral load.

An efficacy interim analysis of the primary endpoint, all-cause mortality at Day 60, was conducted when approximately 71.4% of the patients (~150 patients) had completed Day 60, died, or withdrew for other reasons. The first 150 patients randomized into the study were included in the planned interim analysis. On 08 Apr 2022, the Independent Data Monitoring Committee for the study reviewed the efficacy and safety data of this interim analysis and recommended to stop the study due to overwhelming efficacy and no safety concerns.

Safety Analyses:

Safety was assessed in the Safety Set. All adverse events were listed and treatment-emergent adverse event (TEAEs) were summarized according to the Medical Dictionary for Regulatory Activities (version 24.0) System Organ Class (SOC) and Preferred Term (PT). Individual results of laboratory tests (eg, hematology, chemistry, and urinalysis), vital signs and weight, quantitative electrocardiogram (ECG) parameters from 12-lead safety ECGs, and physical examination findings were listed, and observed values and changes from baseline were summarized.

Analysis Sets:

- Enrolled Set: All patients who gave informed consent.
- ITT Set: All randomized patients.
- mITT Set: All randomized patients who completed the efficacy portion of the study and who did not have any major protocol deviations. Patients who were randomized but did not receive study drug were excluded from the mITT Set. Note: All protocol deviations were assessed and documented on a case-by-case basis before the database lock.

Deviations considered to have a serious impact on the efficacy results led to the relevant patient being excluded from the mITT.

- Safety Set: All randomized patients who received at least 1 dose of study drug (sabizabulin or placebo).

Sample Size Justification:

Approximately 210 patients were planned to be randomized at a 2:1 ratio into 2 treatment groups (approximately 140 patients in the sabizabulin-treated group and approximately 70 patients in the placebo-treated group). Randomization was stratified by Baseline WHO Ordinal Scale for Clinical Improvement score, such that patients with a WHO Ordinal Scale for Clinical Improvement of 4, 5 and 6 at Baseline were approximately equally distributed between the treatment groups. Assuming a rate of mortality of 5% in the sabizabulin-treated group and 25% in the placebo-treated group, the above sample sizes were expected to yield a 95% CI of (-0.308, -0.092) for the risk difference between treatment groups.

Summary of Results:

Study Patients:

- A total of 244 patients were enrolled in the study, of whom 204 were randomly assigned to sabizabulin 9 mg (134 patients) or placebo (70 patients). A total of 125 (93.3%) patients in the sabizabulin 9 mg group and 66 (94.3%) patients in the placebo group completed the study.
    - Of the 199 patients included in the Safety Set, 105 (80.8%) in the sabizabulin 9 mg group and 57 (82.6%) patients in the placebo group discontinued study drug prior to Day 21. The most common reasons for discontinuation of study drug prior to Day 21 were discharge from hospital (84 [80.0%] and 39 [68.4%] patients, respectively) and death (13 [12.4%] and 15 [26.3%] patients, respectively).
    - Nine (6.7%) patients in the sabizabulin 9 mg group withdrew from the study early (primary reasons were withdrawal by patient in 6 [66.7%] patients, and lost to follow-up, physician decision, and other, each in 1 [11.1%] patient).
    - Four (5.7%) patients in the placebo group withdrew from the study early (primary reasons were withdrawal by patient and lost to follow-up, each in 2 [50.0%] patients).
- Major protocol deviations were reported in a similar percentage of patients in the sabizabulin 9 mg and placebo groups (19 deviations in 18 [13.4%] patients and 14 deviations in 7 [10.0%] patients, respectively). The most common major protocol deviations were in the "safety" category (9 deviations in 8 [6.0%] patients and 9 deviations in 4 [5.7%] patients, respectively), mostly related to the late reporting of serious adverse events. The overall impact of important protocol deviations on the study results and conclusions was considered minor.

- A total of 204 patients were included in the ITT Set, of whom 5 (3.7%) patients in the sabizabulin 9 mg group and 1 (1.4%) patient in the placebo group were excluded from the mITT Set. Reasons for exclusion from the mITT Set were:
    - Three patients in the sabizabulin 9 mg group and 1 patient in the placebo group were excluded because they did not receive study drug.
    - One patient in the sabizabulin 9 mg group was excluded due to a major protocol deviation related to study drug and because they did not receive study drug.
    - One patient in the sabizabulin 9 mg group was excluded due to a major protocol deviation related to study drug.
- All 199 patients who received at least 1 dose of study drug (sabizabulin or placebo) were included in the Safety Set.
- The majority of patients in the ITT Set were male (134 [65.7%] patients), most were of White race (178 [87.3%] patients), and the mean (standard deviation [SD]) age at study start was 61.8 (14.04) years. Demographic characteristics were generally well-balanced between the sabizabulin 9 mg and placebo groups. Demographic characteristics in the mITT Set and Safety Set were similar to the ITT Set.
- In the ITT Set, the most common Baseline comorbidities were respiratory issues (153 [75.0%] patients), hypertension (131 [64.2%] patients), and pneumonia (127 [62.3%] patients). Baseline comorbidities of cancer and respiratory issues were more commonly reported in the sabizabulin 9 mg group compared with placebo; diabetes and pneumonia were more commonly reported in the placebo group.
- Overall, the most common previous medical histories, by PT, were dyspnea (35 [17.2%] patients), cough (34 [16.7%] patients), and pyrexia (27 [13.2%] patients). Previous medical history was broadly similar between groups.
- The most common ongoing medical histories, by PT, were hypertension (126 [61.8%] patients), obesity (74 [36.3%] patients), and COVID-19 pneumonia (67 [32.8%] patients). Differences in ongoing medical histories between the sabizabulin 9 mg and placebo groups were noted for the SOCs gastrointestinal disorder (25 [18.7%] and 22 [31.4%] patients, respectively) and infections and infestations (74 [55.2%] and 46 [65.7%] patients, respectively), and the PT obesity (55 [41.0%] and 19 [27.1%] patients, respectively).
- Overall, the majority of patients had prior medications, including 116 (86.6%) patients in the sabizabulin 9 mg group and 62 (88.6%) patients in the placebo group.
    - The most common prior medications by Anatomical Therapeutic Chemical Level 2 were corticosteroids for systemic use (79 [38.7%] patients), most commonly dexamethasone (57 [27.9%] patients), vaccines (74 [36.3%] patients), most commonly

COVID-19 vaccine inact (vero) CZ02 (30 [14.7%] patients), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) in (19 [9.3%] patients), COVID-19 vaccine (16 [7.8%] patients), and tozinameran (12 [5.9%] patients), antibacterials for systemic use (67 [32.8%] patients), most commonly azithromycin (29 [14.2%] patients) and ceftriaxone (22 [10.8%] patients), antithrombotic agents (62 [30.4%] patients), most commonly enoxaparin (21 [10.3%] patients) and enoxaparin sodium (12 [5.9%] patients), analgesics (59 [28.9%] patients), most commonly paracetamol (34 [16.7%] patients) and metamizole sodium (17 [8.3%] patients), and antivirals for systemic use (43 [21.1%] patients), most commonly remdesivir (40 [19.6%] patients).

- Prior medications were broadly similar in the sabizabulin 9 mg and placebo groups, with the exception of agents acting on the renin-angiotensin system (15 [11.2%] and 4 [5.7%] patients, respectively), antithrombotic agents (38 [28.4%] and 24 [34.3%] patients, respectively), blood substitutes and perfusion solutions (22 [16.4%] and 8 [11.4%] patients, respectively), drugs for acid related disorders (17 [12.7%] and 4 [5.7%] patients, respectively), lipid modifying agents (9 [6.7%] and 1 [1.4%] patients, respectively), antihistamines for systemic use (0 [0%] and 4 [5.7%] patients, respectively), and muscle relaxants (11 [8.2%] and 2 [2.9%] patients, respectively).

- Overall, the most common concomitant treatments included antithrombotic agents (196 [96.1%] patients), corticosteroids for systemic use (191 [93.6%] patients), antibacterials for systemic use (158 [77.5%] patients), drugs for acid related disorders (155 [76.0%] patients), analgesics (139 [68.1%] patients), psycholeptics (110 [53.9%] patients), drugs used in diabetes (108 [52.9%] patients, and blood substitutes and perfusion solutions (106 [52.0%] patients).

  - Concomitant medications were generally well-balanced in the sabizabulin 9 mg and placebo groups, with the exception of blood substitutes and perfusion solutions (62 [46.3%] and 44 [62.9%] patients, respectively), cardiac therapy (35 [26.1%] and 32 [45.7%], respectively), diuretics (59 [44.0%] and 38 [54.3%] patients, respectively), drugs for constipation (40 [29.9%] and 28 [40.0%] patients, respectively), drugs used in diabetes (66 [49.3%] and 42 [60.0%] patients, respectively), and lipid modifying agents (31 [23.1%] and 24 [34.3%] patients, respectively).

- Background remdesivir and background dexamethasone were reported in 40 (29.9%) and 108 (80.6%) patients, respectively, in the sabizabulin 9 mg group and 17 (24.3%) and 54 (77.1%) patients, respectively, in the placebo group. A total of 47 (35.1%) patients in the sabizabulin 9 mg group and 27 (38.6%) patients in the placebo group were vaccinated against COVID-19 (at least 1 shot). Regional differences in background standard of care were noted.

- All patients had a treatment compliance within the range of 81.0% to 100%.

- Mean (SD) exposure (ie, days on study drug) was similar between the sabizabulin 9 mg and placebo groups (11.4 [6.56] and 11.6 [6.01] days, respectively).

Efficacy Results:

- **Primary endpoint:** the proportion of patients who died on study (up to Day 60):
  - The percentage of patients in the ITT Set 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 mITT Set (18.1% and 38.8%, respectively).
  - 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 tipping-point sensitivity analysis of the primary analysis was consistently in favor of sabizabulin versus placebo.
- **Secondary Endpoints:** analyses of secondary endpoints were consistently in favor of sabizabulin versus placebo, including:
  - The percentage of patients in the ITT Set who were alive at Day 60 and the OR for mortality were consistently in favor of sabizabulin versus placebo across subgroups of region, standard of care, and WHO Ordinal Scale score at Baseline.
  - The proportion of patients who were alive without respiratory failure at Day 15 (71.8% and 58.0%, respectively; OR: 1.86 [95% CI: 0.92, 3.77], $P = 0.0863$), Day 22 (73.3% and 56.5%, respectively; OR: 2.22 [95% CI: 1.10, 4.51], $P = 0.0269$), Day 29 (73.8% and 55.9%, respectively; OR: 2.39 [95% CI: 1.16, 4.92], $P = 0.0186$), and Day 60 (80.0% and 60.3%; OR: 2.65 [95% CI: 1.31, 5.36], $P = 0.0066$).
  - The mean (SD) number of days in ICU was 16.0 (23.50) and 26.3 (28.11) days, respectively, and the median (range) number of days in ICU was 2.0 (0, 60) and

9.0 (0, 60) days, respectively (least squares [LS] mean difference: -9.9 [95% CI: -16.7, -3.1], *P* = 0.0045).

- The mean (SD) number of days on mechanical ventilation was 13.7 (23.57) and 24.6 (29.00) days, respectively, and the median (range) number of days on mechanical ventilation was 0.0 (0, 60) and 0.0 (0, 60) days, respectively (LS mean difference: -10.4 [95% CI: -17.5, -3.4], *P* = 0.0038).

- The mean (SD) number of days in hospital was 24.0 (21.78) and 31.0 (24.61) days, respectively, and the median (range) number of days in hospital was 13.0 (2, 60) and 16.5 (3, 60), respectively (LS mean difference: -6.3 [95% CI: -12.4, -0.1], *P* = 0.0463).

- The proportion of patients who were alive at Day 15 (91.6% and 78.3%, respectively; OR: 2.59 [95% CI: 1.10, 6.08], *P* = 0.0291), Day 22 (87.0% and 76.8%, respectively; OR: 1.75 [95% CI: 0.80, 3.82], *P* = 0.1621), and Day 29 (84.6% and 70.6%, respectively; OR: 2.15 [95% CI: 1.01, 4.54], *P* = 0.0459).

- The proportion of patients with a WHO Ordinal Scale score of 0 or 1 at Day 15 (9.0% and 12.9%, respectively; OR: 0.70 [95% CI: 0.29, 1.68], *P* = 0.4216), Day 22 (35.1% and 30.0%, respectively; OR: 1.26 [95% CI: 0.65, 2.44], *P* = 0.4989), Day 29 (38.8% and 32.9%, respectively; 1.27 [95% CI: 0.66, 2.45], *P* = 0.4692), and Day 60 (54.5% and 42.9%, respectively; 1.65 [95% CI: 0.87, 3.15], *P* = 0.1269).

  - There was clear separation between the sabizabulin 9 mg and placebo groups, in the mean profile and mean change from Baseline profile for WHO Ordinal Scale for Clinical Improvement, at Days 22, 29, 45, and 60.

- From Baseline to Day 9, mean viral load decreased by 25.2% for sabizabulin and increased by 573.8% for placebo. From Baseline to last on-study, mean viral load decreased by 42.9% for sabizabulin and increased by 412.1% for placebo.

Pharmacokinetics Results:

- Mean sabizabulin predose (trough) concentrations increased from Day 1 to Day 3 and remained stable up to Day 9.

Safety Results:

- TEAEs were reported in 136 (68.3%) patients overall, including 82 (63.1%) patients in the sabizabulin 9 mg group and 54 (78.3%) patients in the placebo group.

  - The most common TEAEs, by SOC, were infections and infestations (39 [30.0%] and 28 [40.6%] patients, respectively) and respiratory, thoracic, and mediastinal disorders (33 [25.4%] and 32 [46.4%] patients, respectively).

- The most common TEAEs, by PT, were respiratory failure (13 [10.0%] and 14 [20.3%] patients, respectively), acute kidney injury (11 [8.5%] and 8 [11.6%] patients, respectively), and pneumonia (8 [6.2%] and 9 [13.0%]) patients, respectively).
  - The PT COVID-19 was reported in 5 (3.8%) and 3 (4.3%) patients, respectively.
  - The PT COVID-19 pneumonia was reported in 1 (0.8%) and 3 (4.3%) patients, respectively.
  - The PT pneumonia acinetobacter was reported in 1 (0.8%) and 0 patients, respectively.
  - The PT pneumonia bacterial was reported in 2 (1.5%) and 5 (7.2%) patients, respectively.

- TEAEs considered related to study drug were reported in 21 (10.6%) patients overall, including 13 (10.0%) patients in the sabizabulin 9 mg group and 8 (11.6%) patients in the placebo group.
  - The most common TEAEs considered related to study drug, by SOC, in the sabizabulin 9 mg group were gastrointestinal disorders (6 [4.6%] patients) and investigations (5 [3.8%] patients) and in the placebo group were investigations (4 [5.8%] patients) and respiratory, thoracic, and mediastinal disorders (3 [4.3%] patients).
  - The most common TEAEs considered related to study drug, by PT, in the sabizabulin 9 mg group were transaminases increased (3 [2.3%] patients), dyspepsia (2 [1.5%] patients), and diarrhea (2 [1.5%] patients) and in the placebo group were respiratory failure (2 [2.9%] patients) and hepatic enzyme increased (2 [2.9%] patients).
- Most TEAEs were Common Terminology Criteria for Adverse Events Grade 1 or 2.
- Serious TEAEs were reported in 70 (35.2%) patients overall, including 38 (29.2%) patients in the sabizabulin 9 mg group and 32 (46.4%) patients in the placebo group.
  - The most common serious TEAEs, by SOC, were respiratory, thoracic, and mediastinal disorders (23 [17.7%] and 23 [33.3%] patients, respectively) and infections and infestations (20 [15.4%] and 15 [21.7%] patients, respectively)
  - The most common serious TEAEs, by PT, were respiratory failure (13 [10.0%] and 14 [20.3%] patients, respectively) and acute kidney injury (6 [4.6%] and 6 [8.7%] patients, respectively).

- 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 common TEAE leading to study drug discontinuation, by SOC, was investigations (2 [1.5%] and 2 [2.9%] patients, respectively).
    - All TEAEs leading to study drug discontinuation, by PT, were reported in 1 patient each (dysphagia, COVID-19, endocarditis staphylococcal, alanine aminotransferase increased, liver function test increased, acute kidney injury, and respiratory failure in the sabizabulin 9 mg group; hepatic enzyme increased, liver function test abnormal, and dyspnea in the placebo group).
- There were 48 (24.1%) patients with fatal TEAEs in this study, including 23 (17.7%) patients in the sabizabulin 9 mg group and 25 (36.2%) patients in the placebo group.
    - The most common fatal TEAEs, by SOC, were infections and infestations (10 [7.7%] and 7 [10.1%] patients, respectively) and respiratory, thoracic, and mediastinal disorders (8 [6.2%] and 10 [14.5%] patients, respectively).
    - The most common fatal TEAEs, by PT, were respiratory failure (5 [3.8%] and 4 [5.8%] patients, respectively), acute respiratory failure (2 [1.5%] and 3 [4.3%] patients), COVID-19 (3 [2.3%] and 2 [2.9%] patients, respectively), and pneumonia (1 [0.8%] and 3 [4.3%] patients, respectively).
- There were no clinically meaningful findings in laboratory assessments or vital sign evaluations that could be directly related to the study drug.

Conclusions:

- Sabizabulin demonstrated a statistically significant 20.5 percentage point absolute reduction in all-cause mortality by Day 60, the primary efficacy endpoint of the study. The Kaplan-Meier analysis showed that the reduction in deaths with sabizabulin started within the first week of treatment.
    - This efficacy was further supported by the consistency of the subgroup analyses of the primary endpoint: a reduction in deaths with sabizabulin treatment compared with placebo regardless of region, standard of care treatment received, or Baseline WHO ordinal scale score.
    - The secondary efficacy endpoints demonstrated that sabizabulin treatment resulted in a significant reduction in days in the ICU, days on mechanical ventilation, and days in the hospital compared with placebo.

- The trough PK values indicate that steady state is reached with 3 days of dosing, consistent with the previously observed 5-hour elimination half-life of sabizabulin, as the trough levels of sabizabulin did not increase from Day 3 to Day 9.

- Sabizabulin treatment was well-tolerated in patients hospitalized with moderate to severe COVID-19 and at high risk of ARDS. There were no clinically relevant safety observations in the sabizabulin group compared with placebo.

Document Date and Version Number:

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