FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
FDA Opening Remarks

EUA 113: Emergency Use Authorization of VERU-111 for the treatment of hospitalized subjects with COVID-19

Banu A. Karimi-Shah, MD
Deputy Director
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
U.S. Food and Drug Administration
November 9, 2022

Introduction

- VERU-111 is an oral tubulin inhibitor, not approved for any indication.
- Veru Inc., has submitted a request for Emergency Use Authorization (EUA) for VERU-111.
  - The proposed use: treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19, and who are at high risk for developing acute respiratory distress syndrome (ARDS).
- The proposed dose is 9 mg once daily for 21 days or until hospital discharge
  - oral or via nasogastric tube

Eligibility of VERU-111 for EUA

- The FDA EUA authority to authorize an unapproved product or unapproved uses of an approved product for emergency use exists during a public health emergency after a declaration by the Secretary of the Department of Health and Human Services.
- The Secretary has determined[1] that a public health emergency exists that involves the virus, SARS-CoV-2, that causes COVID-19, and declared circumstances exists justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic[2].
- Based on this declaration, FDA may issue an EUA after determining statutory requirements are met.

[1]pursuant to Section 564(b)(1)(C) of the Federal Food, Drug & Cosmetic Act (FD&C Act)
[2]pursuant to Section 564 of the FD&C Act (21 U.S.C. 360bbb-3)

Emergency Use Authorization (EUA)

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that –
  - the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2; and
  - The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product;
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

Emergency Use Authorization (EUA)

- FDA may require:
  - Appropriate conditions with respect to collection and analysis of information concerning the safety and effectiveness of the product with respect to the use of such product during the period when the authorization is in effect and a reasonable time following such period.
  - For example, FDA can require additional trial(s) as a condition of authorization

COVID-19 Pandemic

- Continued unmet medical need despite current standard of care therapies (dexamethasone, tocilizumab, remdesivir, baricitinib)

- Worldwide and US impact of COVID-19 pandemic
  - Worldwide: 623 million cases and 6.55 million deaths[1]
  - United States: 96.9 million cases and ~1.1 million deaths[2]
    - 37,052 reported new cases per day[2]
    - 3,257 new admissions for hospitalization per day[2]
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References:
1. https://covid19.who.int/. Accessed October 20, 2022.
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VERU-111 - COVID-19 Clinical Program

Study Identifier, Design, and Duration	Randomized Treatment	N	Characteristics of Enrolled Population	Primary and Key Secondary Efficacy Endpoints
V0211901 **(Study 901)** 1:1 R, DB, PC, MC, PG, 60-day duration *JUN 2020 – DEC 2020*	**VERU-111 18 mg** daily via PO/NG + SOC Pbo PO/NG daily + SOC *up to 21 days or hospital discharge*	20 19	Hospitalized adult PCR-confirmed SARS-CoV-2 infection WHO Category 5 or 6, or WHO Category 4 plus ≥1 comorbidity of the following: Hypertension, diabetes, BMI ≥ 40 kg/m², ≥65 years of age, immunocompromised, resides in a long-term care facility, asthma or chronic lung disease No hepatic or renal impairment	**Primary** • Alive and free of respiratory failure at Day 29 **Secondary** • All-cause mortality at Day 29 • Days in ICU • WHO Ordinal Scale for Improvement at Day 29 • Days on Mechanical Ventilation • Days in Hospital • Effect on CRP • Pharmacokinetic Endpoints
V3011902 **(Study 902)** 2:1 R, DB, PC, MC, PG, 60-day duration *MAY 2021 - JUN 2022*	**VERU-111 9 mg** daily via PO/NG + SOC Pbo PO/NG daily + SOC *up to 21 days or hospital discharge*	134 70	Hospitalized adult PCR-confirmed SARS-CoV-2 infection WHO Category 5 or 6, or WHO Category 4 plus ≥1 comorbidity of the following: Hypertension, diabetes, BMI ≥ 40 kg/m², ≥65 years of age, immunocompromised, resides in a long-term care facility, asthma or chronic lung disease No hepatic or renal impairment	**Primary** • All-cause mortality at Day 60 **Secondary** • Alive and free of respiratory failure at Day 29 • Days in ICU • WHO Ordinal Scale for Improvement at Day 29 • Days on Mechanical Ventilation • Days in Hospital • Change from baseline in viral load

Abbreviations: N: number of subjects, R: randomized, DB: double blind, PC: placebo controlled, MC: multicenter, PG: parallel group, JUN: June, PO: by mouth, NG: by nasogastric tube, SOC: standard of care, PCR: polymerase chain reaction assay, WHO: World Health Organization, BMI: body mass index; ICU: intensive care unit; CRP: C-reactive protein; Source: FDA Clinical Reviewer.

Study 902: Primary Endpoint Results

Proportion of Subjects Alive at Day 60 – ITT Set			
Analysis	**VERU-111**	**Placebo**	**Treatment Comparison***
Interim Analysis	79/98 (76.5) (4 missing**)	29/52 (53.8) (1 missing**)	OR (95% CI): 3.20 (1.43, 7.16) RD (95% CI): 23.1% (7.2, 38.9)
All 204 Subjects	109/134 (78.4) (4 missing**)	43/70 (58.6) (2 missing**)	OR (95% CI): 2.77 (1.37, 5.58) RD (95% CI): 19.0% (5.8, 32.2)

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

Abbreviations: OR: Odds Ratio, RD: Risk Difference, CI: Confidence Interval, ITT: Intention-to-treat

*From logistic regression model adjusting for sex, baseline WHO category, region, remdesivir use and dexamethasone use at baseline

**Imputation model for missing data included same covariates + treatment discontinuation status and discharge status

Issues for Consideration

- Uncertainties
  - High Placebo Mortality for Baseline Severity
  - Potential Unblinding Events with Enteral Tube Administration
  - Application of Standard of Care Therapies
  - Timing of Enrollment Compared to COVID-19 Clinical Course
  - Effects of Goals of Care on All-Cause Mortality
  - Efficacy Results of Other Microtubule Disruptors in COVID-19
  - Study Population Uncertainties
  - Limited Safety Database for this New Molecular Entity
- Appropriate population for potential authorization
- Assessment of known and potential benefit vs. known and potential risks.
- Additional clinical trial considerations

Considerations for Additional Trials

Study population

- Subjects with WHO 5 and 6 severity, or WHO 4 severity with additional selected comorbidities

Study design proposal

- Randomized, double-blind, fully matched placebo-controlled superiority design of VERU-111 + standard-of-care (SOC) versus placebo + SOC

Additional study elements

- Trial size and interim decision-making
- Placebo control, active control, or combinations of both
- Consideration of uncertainties raised by FDA in Study 902
  - Blinding, timing of enrollment, goals of care data, stratification of randomization by site, representation of baseline severity and comorbidities between arms
- Elements of SOC for COVID-19, pharmacological and non-pharmacological

Discussion Points and Voting Questions

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

Discussion Points and Voting Questions

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

Discussion Points and Voting Questions

3. **VOTE:** Do the known and potential benefits of VERU-111 when used for the treatment of adult patients hospitalized with COVID-19 at high risk of ARDS outweigh the known and potential risks of VERU-111?

   a. If yes, discuss the appropriate patient population in which VERU-111 should be authorized.

   b. If no, discuss what additional data would be necessary to assess the benefits vs. the risks of treatment.

Discussion Points and Voting Questions

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION

FDA Pulmonary-Allergy Drugs Advisory Committee Meeting

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Robert Busch, MD, MMSc
Medical Officer

Division of Pulmonology, Allergy, and Critical Care (DPACC)
Office of Immunology and Inflammation (OII)
Office of New Drugs (OND)

Sai Dharmarajan, PhD
Senior Mathematical Statistician

Division of Biometrics VII (DBVII)
Office of Biostatistics (OB)
Office of Translational Science (OTS)

Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)

November 9, 2022

Outline

- Overview of the Clinical Program and Review of Safety
  - Robert Busch, MD, MMSC
  - Medical Officer: DPACC, OII, OND, CDER, FDA
- Statistical Review of Efficacy
  - Sai Dharmarajan, PhD
  - Senior Mathematical Statistician: DBVII, OTS, CDER, FDA
- Uncertainties and Clinical Considerations
  - Sai Dharmarajan, PhD
  - Robert Busch, MD, MMSC

VERU-111

- New Molecular Entity
  - Oral tubulin inhibitor that binds to the “colchicine binding site” of microtubules and prevents cross-linking.
  - Not approved for any indication

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- Drug Substance
  - White or whitish to yellow-brown powder
- Drug Product (formulated capsule)
  - Intact off-white capsules with “V09” black print on cap filled with off-white to light tan to yellow granulate powder.

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- Proposed Dose
  - 9 mg orally (or via nasogastric tube) daily for up to 21 days or hospital discharge

WHO Ordinal Scale for Clinical Improvement

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

References:
1. https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis.

Abbreviations:
WHO: World Health Organization

VERU-111 Proposed Use

- Proposed Use
  - treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19, and who are at high risk for developing acute respiratory distress syndrome (ARDS).

VERU-111 Proposed Use Details

- High risk of ARDS
  - Represented in trials as a subject with WHO 5 or 6 severity.
  - Or a subject with WHO 4 severity and ≥1 comorbidity designated as a risk factor for 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

- Limitations of Use
  - Sabizabulin authorization excludes the following:
    - Use in patients less than 18 years of age, use in non-hospitalized patients, use in patients that are not on oxygen supplementation, use in pregnant women, or for prevention of COVID-19.

Abbreviations:
WHO: World Health Organization, BMI: body mass index

Overview of the Clinical Program and Review of Safety

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COVID-19: Background

COVID-19: Elements of Standard of Care

VERU-111 Development Program

V3011902 Trial Design and Endpoints

Patient Population Considerations

Review of Safety

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3. Iuliano, AD,, et al. 2022, Trends in Disease Severity and Health Care Utilization During the Early Omicron Variant Period Compared with Previous SARS-CoV-2 High Transmission Periods - United States, December 2020-January 2022, MMWR Morb Mortal Wkly Rep, 71(4):146-152.

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- Worldwide and US impact of COVID-19 pandemic
  - Worldwide: 623 million cases and 6.55 million deaths[1]
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- SARS-CoV-2 variants over time
  - Differences in transmissibility, virulence, and severity markers between wild-type, Delta, and Omicron variants[3]

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- COVID-19 clinical course in hospitalized patients characterized by both pulmonary and systemic manifestations.

References:
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COVID-19 Standard of Care Therapies

- **Pulmonary supportive care for COVID-19[1]**
  - Supplemental oxygen delivery methods
    - Simple nasal cannula, simple face mask
    - Heated, humidified, high-flow nasal cannula oxygen therapy (HFNC) or noninvasive positive pressure ventilation therapy (NiPPV)
    - Intubation and mechanical ventilation with low tidal volume ventilation
    - Extracorporeal membrane oxygenation for critical illness

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    - Intubation and mechanical ventilation with low tidal volume ventilation
    - Extracorporeal membrane oxygenation for critical illness

- **Extrapulmonary supportive care for COVID-19**
  - Volume resuscitation, pressors, antibiotics, anticoagulation, renal replacement

- **Additional elements of standard of care**
  - Physical therapy, nutrition, tracheostomy placement
  - Goals of care and decisions to withhold or withdraw life-sustaining treatments

References:
1. COVID-19 Treatment Guidelines Panel, 2022, Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, National Institutes of Health

COVID-19 Standard of Care Medications

- **FDA-approved SARS-CoV-2 vaccines**
  - Demonstrated safety and efficacy for prevention of infection with SARS-CoV-2, as well as prevention of severe disease and death from COVID-19[1,2]

References:
1. See https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccines
2. See https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccines
3. See VEKLURY (remdesivir) at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214787s014lbl.pdf

COVID-19 Standard of Care Medications

- **FDA-approved SARS-CoV-2 vaccines**
  - Demonstrated safety and efficacy for prevention of infection with SARS-CoV-2, as well as prevention of severe disease and death from COVID-19[1,2]

- **Remdesivir**
  - Approved: demonstrated reduction in time to recovery in subjects hospitalized with COVID-19
  - COVID-19 database: remdesivir exposure in 1592 subjects[3]

References:
1. See https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccines
2. See https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccines
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- **Dexamethasone**
  - NIH COVID-19 Treatment Guidelines recommend dexamethasone for subjects requiring supplemental oxygen for COVID-19[1] based on data suggesting a reduction in mortality.[2]
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1. COVID-19 Treatment Guidelines Panel, 2022, Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, National Institutes of Health
2. Horby, P, et al, 2021, Dexamethasone in Hospitalized Patients with Covid-19, N Engl J Med, 384(8):693-704.
3. See OLUMIANT (baricitinib) at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207924s007lbl.pdf
4. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19
5. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label platform trial. Lancet, 2022, May, 1:397. PMID: 33933206
6. Salama C, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. New England Journal of Medicine, 2021. Jan 7:384.

Abbreviations:
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- **Baricitinib**
  - Approved: demonstrated reduction in mortality in subjects hospitalized with COVID-19 requiring supplemental oxygen[3]
  - COVID-19 database: baricitinib exposure in 1,307 subjects[3]

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4. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19
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  - COVID-19 database: baricitinib exposure in 1,307 subjects[3]
- **Tocilizumab**
  - Authorized: available evidence suggests tocilizumab may be effective in reducing mortality among hospitalized subjects with COVID-19 requiring supplemental oxygen.[4]
  - COVID-19 EUA database: tocilizumab exposure in 3,016 subjects[5,6]

References:

1. COVID-19 Treatment Guidelines Panel, 2022, Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, National Institutes of Health
2. Horby, P, et al, 2021, Dexamethasone in Hospitalized Patients with Covid-19, N Engl J Med, 384(8):693-704.
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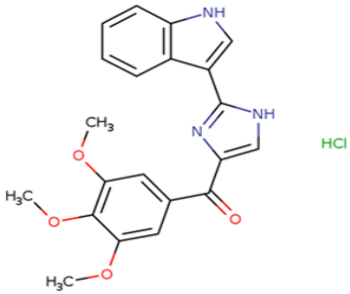
Review of Safety

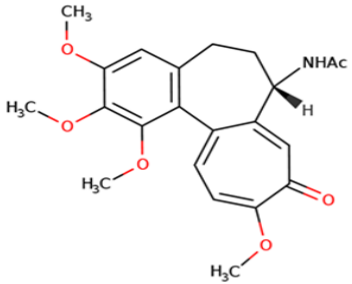
Proposed Mechanism of Action

- Tubulin inhibitor binding the “colchicine binding site”
- Sponsor proposes both anti-inflammatory and anti-viral activity of VERU-111 in COVID-19.

VERU-111



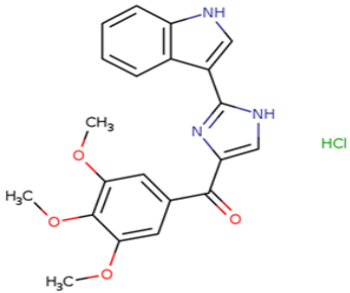
Colchicine



Proposed Mechanism of Action

- Tubulin inhibitor binding the “colchicine binding site”
- Sponsor proposes both anti-inflammatory and anti-viral activity of VERU-111 in COVID-19.
  - FDA review of anti-inflammatory data for VERU-111
    - Mechanistic rationale for VERU-111 in COVID-19 relies, in part, on assumptions of downstream anti-inflammatory actions similar to colchicine.
  - FDA review of anti-viral data for VERU-111
    - No direct evidence provided to support the antiviral activity of VERU-111.

VERU-111



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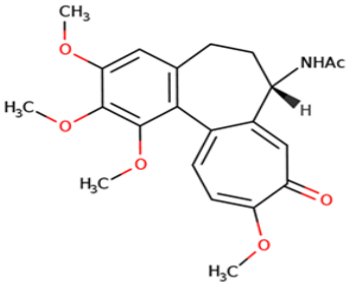

Regulatory History

Development outside COVID-19

- Prior IND 140406 for metastatic castration-resistant prostate cancer
  - Two ongoing studies in metastatic, castration-resistant, prostate cancer subtypes that are deemed not informative for the safety or efficacy of VERU111 in a hospitalized COVID-19 population.

Abbreviations:
IND: Investigational New Drug application, EUA: Emergency Use Authorization

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COVID-19 development program

- Opening IND 149282 for COVID-19 indication on April 24, 2020
- Randomized, double-blind, placebo-controlled clinical trials in COVID-19
  - V0211901 (Study 901): 39 subjects
  - V3011902 (Study 902): planned for 300 subjects

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  - V0211901 (Study 901): 39 subjects
  - V3011902 (Study 902): planned for 300 subjects
- Sample size change and interim analysis
  - Sample size changed from initially planned 300 to 210 subjects based on slow enrollment.
  - Interim analysis of the first 150 subjects met pre-specified bounds for efficacy.
  - Study 902 stopped after 204 subjects enrolled.
- EUA Submission

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COVID-19 Clinical Program

Study Identifier, Design, and Duration	Randomized Treatment	N	Characteristics of Enrolled Population	Primary and Key Secondary Efficacy Endpoints
V0211901 **(Study 901)** 1:1 R, DB, PC, MC, PG, 60-day duration *JUN 2020 – DEC 2020*	**VERU-111 18 mg** daily via PO/NG + SOC Pbo PO/NG daily + SOC *up to 21 days or hospital discharge*	20 19	Hospitalized adult PCR-confirmed SARS-CoV-2 infection WHO Category 5 or 6, or WHO Category 4 plus ≥1 comorbidity of the following: Hypertension, diabetes, BMI ≥ 40 kg/m², ≥65 years of age, immunocompromised, resides in a long-term care facility, asthma or chronic lung disease No hepatic or renal impairment	**Primary** • Alive and free of respiratory failure at Day 29 **Secondary** • All-cause mortality at Day 29 • Days in ICU • WHO Ordinal Scale for Improvement at Day 29 • Days on Mechanical Ventilation • Days in Hospital • Effect on CRP • Pharmacokinetic Endpoints
V3011902 **(Study 902)** 2:1 R, DB, PC, MC, PG, 60-day duration *MAY 2021 - JUN 2022*	**VERU-111 9 mg** daily via PO/NG + SOC Pbo PO/NG daily + SOC *up to 21 days or hospital discharge*	134 70	Hospitalized adult PCR-confirmed SARS-CoV-2 infection WHO Category 5 or 6, or WHO Category 4 plus ≥1 comorbidity of the following: Hypertension, diabetes, BMI ≥ 40 kg/m², ≥65 years of age, immunocompromised, resides in a long-term care facility, asthma or chronic lung disease No hepatic or renal impairment	**Primary** • All-cause mortality at Day 60 **Secondary** • Alive and free of respiratory failure at Day 29 • Days in ICU • WHO Ordinal Scale for Improvement at Day 29 • Days on Mechanical Ventilation • Days in Hospital • Change from baseline in viral load

Abbreviations: N: number of subjects, R: randomized, DB: double blind, PC: placebo controlled, MC: multicenter, PG: parallel group, JUN: June, PO: by mouth, NG: by nasogastric tube, SOC: standard of care, PCR: polymerase chain reaction assay, WHO: World Health Organization, BMI: body mass index; ICU: intensive care unit; CRP: C-reactive protein

COVID-19 Clinical Program

Study Identifier, Design, and Duration	Randomized Treatment	N	Characteristics of Enrolled Population	Primary and Key Secondary Efficacy Endpoints
V0211901 **(Study 901)** 1:1 R, DB, PC, MC, [illegible], 60-day duration *JUN 2020 – DEC 2020*	**VERU-111 18 mg** daily via PO/NG + SOC Pbo PO/NG daily + SOC *up to 21 days or hospital discharge*	20[illegible] 19[illegible]	Hospitalized adult PCR-confirmed SARS-CoV-2 infection WHO Category 5 or 6, or WHO Category 4 plus ≥1 comorbidity of the following: Hypertension, diabetes, BMI ≥ 40 kg/m², ≥65 years of age, immunocompromised, resides in a long-term care facility, asthma or chronic lung disease No hepatic or renal impairment	**Primary** • Alive and free of respiratory failure at Day 29 **Secondary** • All-cause mortality at Day 29 • Days in ICU • WHO Ordinal Scale for Improvement at Day 29 • Days on Mechanical Ventilation • Days in Hospital • Effect on CRP • Pharmacokinetic Endpoints
V3011902 **(Study 902)** 2:1 R, DB, PC, MC, [illegible], 60-day duration *MAY 2021 - JUN 2022*	**VERU-111 9 mg** [illegible] daily via PO/NG + SOC Pbo PO/NG daily + SOC *up to 21 days or hospital discharge*	134[illegible] 70[illegible]	Hospitalized adult PCR-confirmed SARS-CoV-2 infection WHO Category 5 or 6, or WHO Category 4 plus ≥1 comorbidity of the following: Hypertension, diabetes, BMI ≥ 40 kg/m², ≥65 years of age, immunocompromised, resides in a long-term care facility, asthma or chronic lung disease No hepatic or renal impairment	**Primary** • All-cause mortality at Day 60 **Secondary** • Alive and free of respiratory failure at Day 29 • Days in ICU • WHO Ordinal Scale for Improvement at Day 29 • Days on Mechanical Ventilation • Days in Hospital • Change from baseline in viral load

Abbreviations: N: number of subjects, R: randomized, DB: double blind, PC: placebo controlled, MC: multicenter, PG: parallel group, JUN: June, PO: by mouth, NG: by nasogastric tube, SOC: standard of care, PCR: polymerase chain reaction assay, WHO: World Health Organization, BMI: body mass index; ICU: intensive care unit; CRP: C-reactive protein

COVID-19 Clinical Program

Study Identifier, Design, and Duration	Randomized Treatment	N	Characteristics of Enrolled Population	Primary and Key Secondary Efficacy Endpoints
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V3011902 **(Study 902)** 2:1 R, DB, PC, MC, PG, 60-day duration *MAY 2021 - JUN 2022*	**VERU-111 9 mg** daily via PO/NG + SOC Pbo PO/NG daily + SOC *up to 21 days or hospital discharge*	134 70	Hospitalized adult PCR-confirmed SARS-CoV-2 infection WHO Category 5 or 6, or WHO Category 4 plus ≥1 comorbidity of the following: Hypertension, diabetes, BMI ≥ 40 kg/m², ≥65 years of age, immunocompromised, resides in a long-term care facility, asthma or chronic lung disease No hepatic or renal impairment	**Primary** • All-cause mortality at Day 60 **Secondary** • Alive and free of respiratory failure at Day 29 • Days in ICU • WHO Ordinal Scale for Improvement at Day 29 • Days on Mechanical Ventilation • Days in Hospital • Change from baseline in viral load

Abbreviations: N: number of subjects, R: randomized, DB: double blind, PC: placebo controlled, MC: multicenter, PG: parallel group, JUN: June, PO: by mouth, NG: by nasogastric tube, SOC: standard of care, PCR: polymerase chain reaction assay, WHO: World Health Organization, BMI: body mass index; ICU: intensive care unit; CRP: C-reactive protein

COVID-19 Clinical Program

Study Identifier, Design, and Duration	Randomized Treatment	N	Characteristics of Enrolled Population	Primary and Key Secondary Efficacy Endpoints
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V3011902 **(Study 902)** 2:1 R, DB, PC, MC, PG, 60-day duration *MAY 2021 - JUN 2022*	**VERU-111 9 mg** daily via PO/NG + SOC Pbo PO/NG daily + SOC *up to 21 days or hospital discharge*	**134** **70**	Hospitalized adult PCR-confirmed SARS-CoV-2 infection WHO Category 5 or 6, or WHO Category 4 plus ≥1 comorbidity of the following: Hypertension, diabetes, BMI ≥ 40 kg/m², ≥65 years of age, immunocompromised, resides in a long-term care facility, asthma or chronic lung disease No hepatic or renal impairment	**Primary** • All-cause mortality at Day 60 **Secondary** • Alive and free of respiratory failure at Day 29 • Days in ICU • WHO Ordinal Scale for Improvement at Day 29 • Days on Mechanical Ventilation • Days in Hospital • Change from baseline in viral load

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COVID-19 Clinical Program

Study Identifier, Design, and Duration	Randomized Treatment	N	Characteristics of Enrolled Population	Primary and Key Secondary Efficacy Endpoints
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Abbreviations: N: number of subjects, R: randomized, DB: double blind, PC: placebo controlled, MC: multicenter, PG: parallel group, JUN: June, PO: by mouth, NG: by nasogastric tube, SOC: standard of care, PCR: polymerase chain reaction assay, WHO: World Health Organization, BMI: body mass index; ICU: intensive care unit; CRP: C-reactive protein

Overview of the Clinical Program and Review of Safety

COVID-19: Background

COVID-19: Elements of Standard of Care

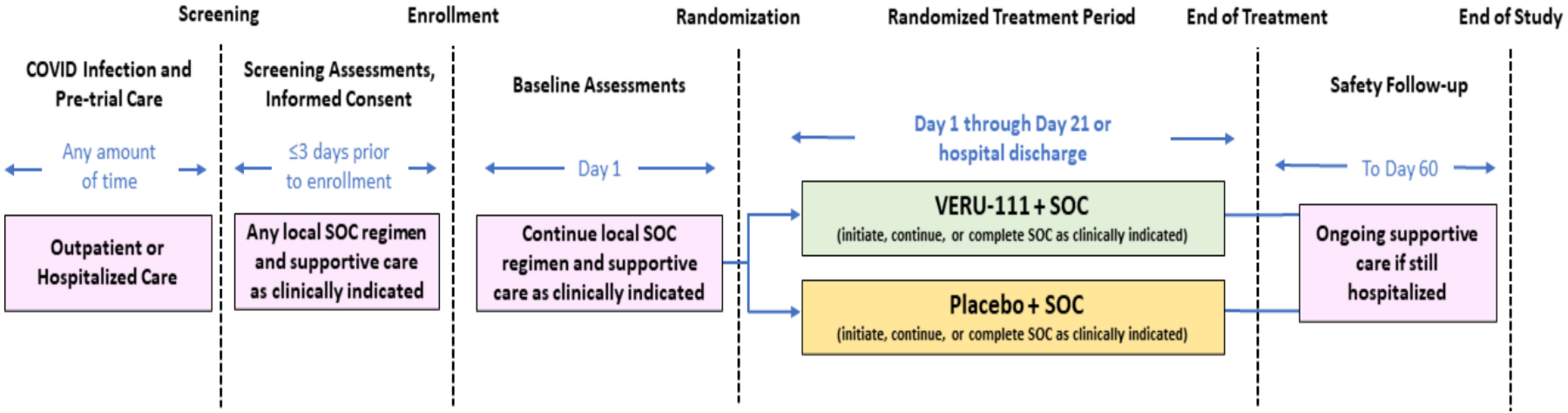
VERU-111 Development Program

V3011902 Trial Design and Endpoints

Patient Population Considerations

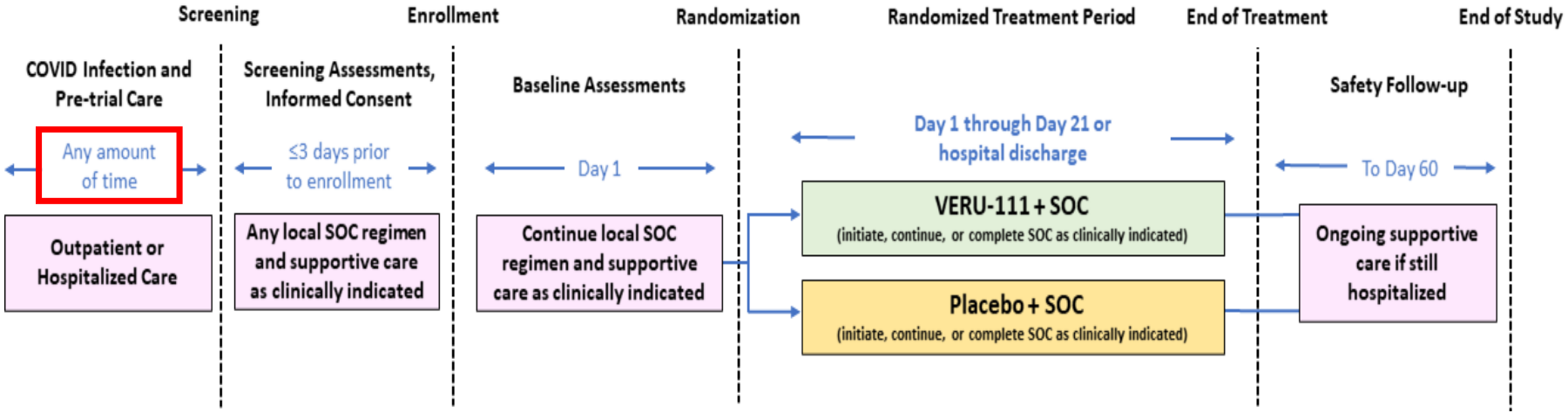
Review of Safety

Efficacy Trial: V3011902



Source: Reviewer. Abbreviations: SOC = Standard of care

Efficacy Trial: V3011902



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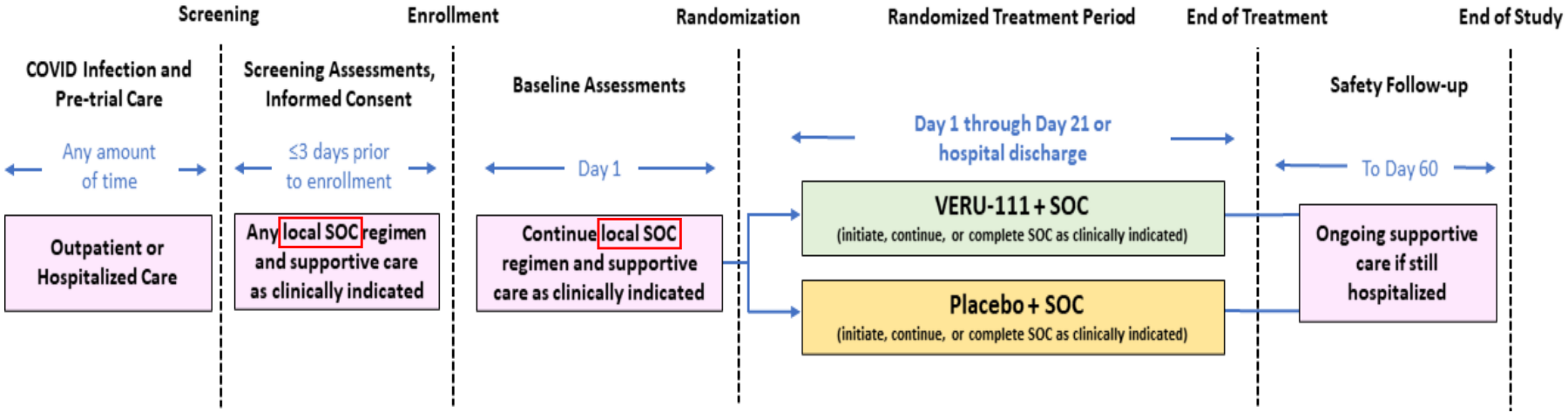

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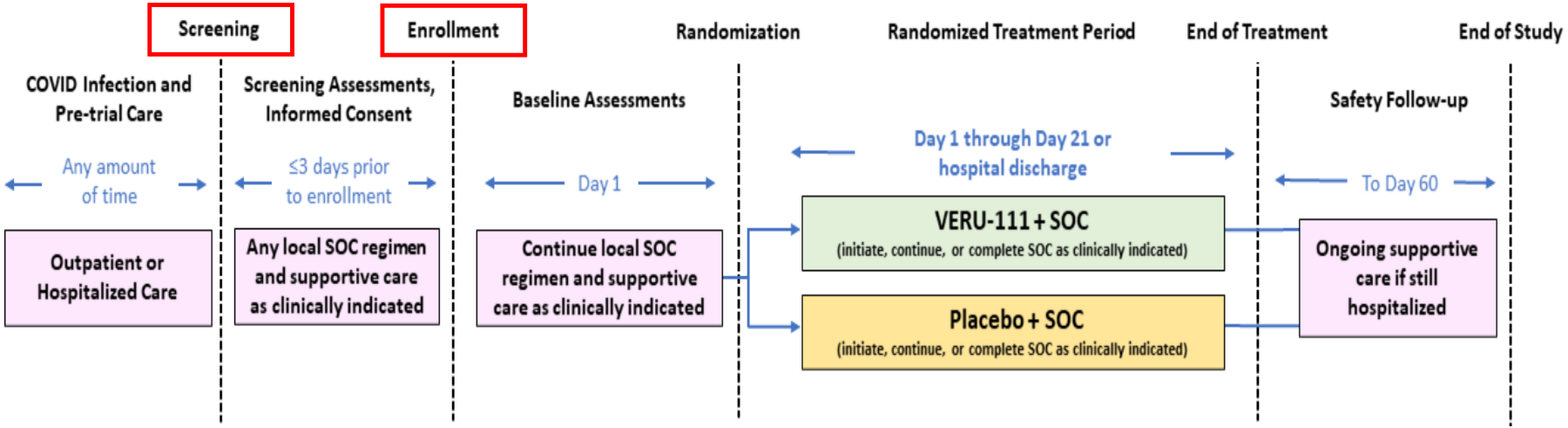
Efficacy Trial: V3011902



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V3011902: Patient Selection

- **Inclusion:**
  - ≥18 years of age
  - Peripheral capillary oxygen saturation ≤ 94% on room air at screening
  - SARS-CoV-2 infection confirmed by PCR
  - WHO score of 5 or 6
  - WHO score of 4 with ≥ 1 designated comorbidity:

Abbreviations: PCR: polymerase chain reaction assay, WHO: World Health Organization, BMI: body mass index, PRN: as needed

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  - Peripheral capillary oxygen saturation ≤ 94% on room air at screening
  - SARS-CoV-2 infection confirmed by PCR
  - WHO score of 5 or 6
  - WHO score of 4 with ≥ 1 designated comorbidity:
    - 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

Abbreviations: PCR: polymerase chain reaction assay, WHO: World Health Organization, BMI: body mass index, PRN: as needed

WHO Ordinal Scale for Severity

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

References:
1. https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis.

WHO Ordinal Scale for Severity

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	Limitation of activities	2
Hospitalized, Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs: **subset with ≥ 1 designated comorbidity**	4
Hospitalized, Severe disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
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    - 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

- **Exclusion:**
  - Requiring ventilation and additional organ support (e.g. pressors, renal replacement therapy, extracorporeal membrane oxygenation (WHO Ordinal Scale score of 7).
    - NOTE: short term (PRN) use of pressors is allowed.

Abbreviations: PCR: polymerase chain reaction assay, WHO: World Health Organization, BMI: body mass index, PRN: as needed

V3011902: Randomization and Blinding

Randomization

- Randomization stratified by WHO score 4, 5, or 6.
  - Randomization not stratified by site.

V3011902: Randomization and Blinding

Randomization

- Randomization stratified by WHO score 4, 5, or 6.
  - Randomization not stratified by site.

Blinding

- VERU-111 drugs product and placebo supplied in identical capsules for PO administration.
  - NG Tube administration required opening the capsule and mixing contents with water.

V3011902: Endpoints

- **Primary**
  - All-cause mortality
    - “Proportion of subjects alive on-study at Day 60”

V3011902: Endpoints

- **Primary**
  - All-cause mortality
    - "Proportion of subjects alive on-study at Day 60"

- **Secondary**
  - Proportion of subjects alive and free of respiratory failure at Day 29
  - Days in ICU
  - Days in Hospital
  - Mean change in WHO ordinal scale

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Study 902: Disposition

- **Analysis Sets**
  - Intention-to-treat
  - Safety
  - Modified intention-to-treat

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

Source: Statistical Reviewer Analysis; adsl.xpt

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

Study 902: Disposition

- **Analysis Sets**
  - Intention-to-treat
  - Safety
  - Modified intention-to-treat
- **Study Medication Discontinuation**
  - ~82% discontinued early across study arms

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Study 902: Disposition

- **Analysis Sets**
  - Intention-to-treat
  - Safety
  - Modified intention-to-treat
- **Study Medication Discontinuation**
  - ~82% discontinued early across study arms
- **Withdrawals**
  - Similar across study arms

	VERU-111 9 mg N=134	Placebo N=70	Total N=204
Safety Population – received a least one dose of study drug, n (%)			
Number of Subjects (%)	130 (97.0)	69 (98.6)	199 (97.5)
mITT Population – completed efficacy portion and do not have major protocol violations, n (%)			
Number of Subjects (%)	129 (96.3)	69 (98.6)	198 (97.1)
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Source: Statistical Reviewer Analysis; adsl.xpt

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

Study 902: Demographics

- **Clinically relevant imbalance in age**
  - CDC Treatment Guidelines suggest that age remains strongest risk factor for severe COVID-19 outcomes

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

Source: Statistical Reviewer Analysis; adsl.xpt

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

Study 902: Baseline Disease Characteristics

- **Small imbalances in clinically relevant baseline characteristics**
  - WHO 6 severity
  - Remdesivir use
  - Dexamethasone use
  - Hospitalization despite prior vaccination

Characteristic	VERU-111 9 mg N=134	Placebo N=70	Total N=204
Baseline WHO Ordinal Scale, n (%)			
4*. Hospitalized, Moderate disease: Oxygen by mask or nasal prongs	59 (44.0)	29 (41.4)	88 (43.1)
5. Hospitalized, Severe disease: Non-invasive ventilation or high-flow oxygen	63 (47.0)	33 (47.1)	96 (47.1)
6. Hospitalized, Severe disease: Intubation and mechanical ventilation	12 (9.0)	8 (11.4)	20 (9.8)
Standard of Care Agents at Baseline (Day 1)			
Remdesivir, n (%)	40 (29.9)	17 (24.3)	57 (27.9)
Dexamethasone, n (%)	108 (80.6)	54 (77.1)	162 (79.4)
Tocilizumab, n (%)	8 (6.0)	7 (10.0)	15 (7.4)
Baricitinib or Tofacitinib, n (%)	9 (6.7)	8 (11.4)	17 (8.3)
COVID-19 Vaccination Prior to Baseline, n (%)			
Y	47 (35.1)	27 (38.6)	74 (36.3)

Source: Statistical Reviewer Analysis; adsl.xpt; adapted with additional Sponsor information provided as Responses to Information Request
Standard of Care Medications for COVID-19 includes corticosteroids or remdesivir for COVID-19.
Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; ITT, Intention-to-treat population; N, number of subjects; n, number of subjects within specific characteristics; SD, standard deviation; WHO, World Health Organization ordinal scale for clinical severity; VERU-111, sabizabulin

Study 902: Baseline Disease Characteristics

- **Small imbalances in clinically relevant baseline characteristics**
  - WHO 6 severity
  - Remdesivir use
  - Dexamethasone use
  - Hospitalization despite prior vaccination

- **Not depicted:**
  - 38.1% of subjects in ICU at baseline in VERU-111 group versus 44.3% in placebo group

Characteristic	VERU-111 9 mg N=134	Placebo N=70	Total N=204
Baseline WHO Ordinal Scale, n (%)			
4*. Hospitalized, Moderate disease: Oxygen by mask or nasal prongs	59 (44.0)	29 (41.4)	88 (43.1)
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Study 902: Baseline Disease Characteristics

- **Small imbalances in clinically relevant baseline characteristics**
  - Diabetes
  - Heart Failure
  - Pneumonia
  - Acute Respiratory Failure
  - ARDS

Characteristic	VERU-111 9 mg N=134	Placebo N=70	Total N=204
Baseline Comorbidities, n (%)			
Number of comorbidities, Mean (SD)	1.7 (1.17)	1.7 (1.12)	1.7 (1.15)
Subjects with no comorbidities, n (%)	22 (16.4)	9 (12.9)	31 (15.2)
Subjects with 2 or more comorbidities, n (%)	72 (53.7)	36 (51.4)	108 (52.9)
Diabetes, n (%)	45 (33.6)	28 (40.0)	73 (35.8)
Hypertension, n (%)	85 (63.4)	46 (65.7)	131 (64.2)
Heart Failure, n (%)	8 (6.0)	7 (10.0)	15 (7.4)
Asthma, n (%)	14 (10.4)	3 (4.3)	17 (8.3)
COPD**, n (%)	13 (9.7)	3 (4.3)	16 (7.8)
Interstitial Lung Disease, n (%)	8 (6)	5 (7.1)	13 (6.4)
Cancer, n (%)	11 (8.2)	1 (1.4)	12 (5.9)
Resides Primarily in Nursing Home***	***	***	***
Immunocompromised****	****	****	****
Pneumonia, n (%)	81 (60.4)	46 (65.7)	127 (62.3)
Acute Respiratory Failure, n (%)	28 (20.9)	18 (25.7)	46 (22.5)
Acute Respiratory Distress Syndrome, n (%)	3 (2.2)	3 (4.3)	6 (2.9)

Source: Statistical Reviewer Analysis; adsl.xpt; adapted with additional Sponsor information provided as Responses to Information Request
Notes: *All subjects randomized with WHO 4 COVID-19 were required to also have ≥1 comorbidity from the list noted in the inclusion criteria of Study 902.
**Per the Sponsor: "Veru notes that 'chronic obstructive pulmonary disease' is the only preferred term in the database for "Chronic Lung Disease."
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Standard of Care Medications for COVID-19 includes corticosteroids or remdesivir for COVID-19.

ı, number of subjects within specific characteristics; SD, standard deviation; WHO, World Health Organization ordinal scale for clinical severity; VERU-111, sabizabulin

Study 902: Baseline Disease Characteristics

- **Small imbalances in clinically relevant baseline characteristics**
  - Diabetes
  - Heart Failure
  - Pneumonia
  - Acute Respiratory Failure
  - ARDS
- **No formal baseline data collection**
  - Immunocompromise
  - Nursing home residence

Characteristic	VERU-111 9 mg N=134	Placebo N=70	Total N=204
Baseline Comorbidities, n (%)			
Number of comorbidities, Mean (SD)	1.7 (1.17)	1.7 (1.12)	1.7 (1.15)
Subjects with no comorbidities, n (%)	22 (16.4)	9 (12.9)	31 (15.2)
Subjects with 2 or more comorbidities, n (%)	72 (53.7)	36 (51.4)	108 (52.9)
Diabetes, n (%)	45 (33.6)	28 (40.0)	73 (35.8)
Hypertension, n (%)	85 (63.4)	46 (65.7)	131 (64.2)
Heart Failure, n (%)	8 (6.0)	7 (10.0)	15 (7.4)
Asthma, n (%)	14 (10.4)	3 (4.3)	17 (8.3)
COPD**, n (%)	13 (9.7)	3 (4.3)	16 (7.8)
Interstitial Lung Disease, n (%)	8 (6)	5 (7.1)	13 (6.4)
Cancer, n (%)	11 (8.2)	1 (1.4)	12 (5.9)
Resides Primarily in Nursing Home***	***	***	***
Immunocompromised****	****	****	****
Pneumonia, n (%)	81 (60.4)	46 (65.7)	127 (62.3)
Acute Respiratory Failure, n (%)	28 (20.9)	18 (25.7)	46 (22.5)
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Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; ITT, Intention-to-treat population; N, number of subjects; n, number of subjects within specific characteristics; SD, standard deviation; WHO, World Health Organization ordinal scale for clinical severity; VERU-111, sabizabulin

Study 902: Pre-randomization Therapy and Pre-randomization Duration of Hospitalization

- **Pre-randomization standard of care COVID-19 therapy**
  - Higher proportion of subjects with >14 days of therapy for VERU-111

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

Source: Statistical Reviewer Analysis; adsl.xpt

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

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

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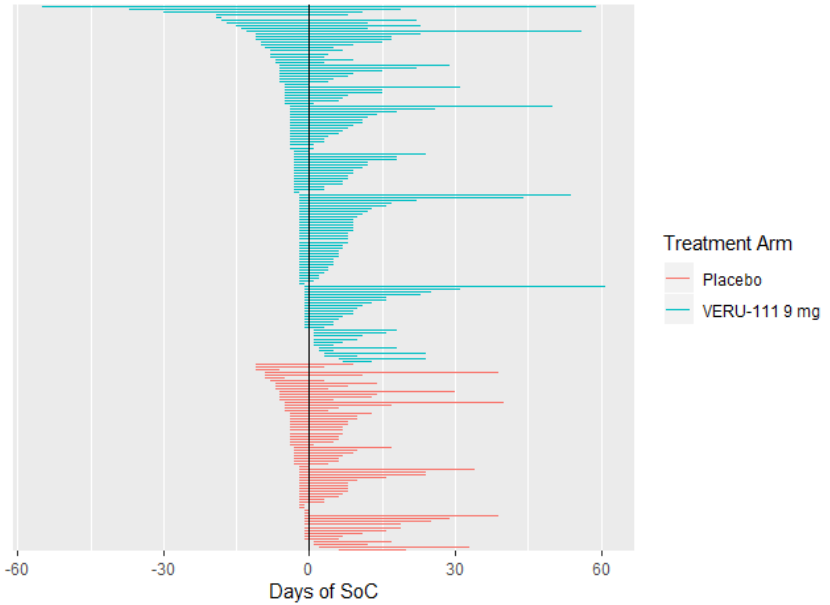
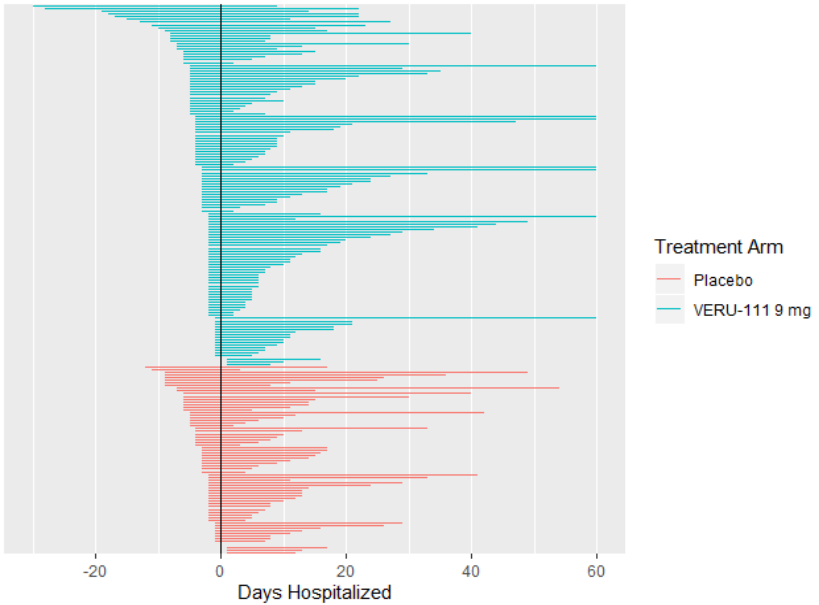
Study 902: Pre-randomization Therapy and Pre-randomization Duration of Hospitalization

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



Study 902: Pre-randomization and Post-randomization Days in Hospital by Treatment Arm (ITT)



Source: Reviewer based on Sponsor-submitted data. Note: For this analysis standard of care therapy was defined as concomitant medication data for remdesivir or dexamethasone attributed to COVID-19 therapy

Abbreviations: COVID-19, coronavirus disease 2019; ITT, intention to treat population; SoC, standard of care

Overview of the Clinical Program and Review of Safety

COVID-19: Background

COVID-19: Elements of Standard of Care

VERU-111 Development Program

V3011902 Trial Design and Endpoints

Patient Population Considerations

Review of Safety

Safety

- Safety results are presented for evaluation of benefit-risk and in the context of a potential efficacy on all-cause mortality.

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- Characterization of VERU-111's safety profile in COVID-19 is limited by the small sample size of Studies 901 and 902.
  - Total safety database of 149 subjects exposed to VERU-111 in the COVID-19 program.

- Primary data for safety characterization are from Study 902 safety analysis set.
  - 130 subjects randomized to VERU-111 and 69 subjects randomized to placebo.
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- The content and frequency of safety assessments in Study 901 and Study 902 were adequate in the setting of trials considered safe to proceed during the COVID-19 pandemic.

Safety: Adverse Events

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    - Overarching event term in 2.3% of subjects on VERU-111 versus 0% placebo
  - Gastrointestinal motility AEs and diarrhea
    - Diarrhea event term in 3.8% of subjects on VERU-111 versus 1.4% placebo
  - Gastrointestinal symptom AEs and nausea/vomiting
    - Signs and symptoms overarching term in 6.9% of subjects on VERU-111 versus 0% placebo
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- **Skin conditions and dermatologic adverse events**
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- **Skin conditions and dermatologic adverse events**
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- **Venous thromboembolism adverse events**
  - Adverse event term deep vein thrombosis 2.3% versus 1.4% among other small imbalances in related terms

Safety: Serious Adverse Events

- Characterization of serious adverse event (SAE) profile of VERU-111 limited by small sample size of Study 902.

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- SAE review for potential signals identified in AE review
  - Imbalance in urinary tract infection terms recapitulated with small imbalance in SAEs.
  - Review inconclusive for other AE signals

Summary of the Clinical Development Program

- Efficacy and safety data rely primarily on Study 902, a 2:1 randomized, double blind, placebo controlled, efficacy and safety trial of VERU-111 in COVID-19 that randomized 204 subjects.

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- Size of available safety database is smaller than other medications for other EUA products.
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- Overall impact of these potential safety signals on benefit-risk is dependent on the level of confidence for the potential efficacy signal for mortality.

Outline

- Overview of the Clinical Program and Review of Safety
  - Robert Busch, MD, MMSC
  - Medical Officer: DPACC, OII, OND, CDER, FDA
- Statistical Review of Efficacy
  - Sai Dharmarajan, PhD
  - Biometrics Reviewer: DBVII, OTS, CDER, FDA
- Uncertainties and Clinical Considerations
  - Sai Dharmarajan, PhD
  - Robert Busch, MD, MMSC

Statistical Review of Efficacy

Interim Analysis and Decision Making

- Study 902 followed a group sequential design allowing for one interim look and with the overall type I error controlled at 5% (two-sided $\alpha = 0.05$)
- Interim analysis was to include first 150 randomized subjects who had completed all evaluations through Day 60
  - Initially planned to occur at 50% information fraction
  - As maximum sample size was reduced from 300 to 210, occurred at 71.4%
- The criterion for efficacy at interim analysis was a two-sided p-value of 0.016
- If the criterion was not met, the trial was to continue to the final analysis including all 210 subjects

Stopping at Interim

- The p-value (p = 0.0045) at interim analysis was lower than the threshold p-value of 0.016
  - The statistical boundary for efficacy was crossed
- Independent Data Monitoring Committee recommended stopping for efficacy
- An additional 54 subjects were already enrolled at the time of stopping and were allowed to complete the study period
- Thus, information is available on 204 randomized subjects and is provided in the results to follow

Primary Endpoint Results

Proportion of Subjects Alive at Day 60 – ITT Set			
Analysis	**VERU-111**	**Placebo**	**Treatment Comparison***
Interim Analysis	79/98 (76.5) (4 missing**)	29/52 (53.8) (1 missing**)	OR (95% CI): 3.20 (1.43, 7.16) RD (95% CI): 23.1% (7.2, 38.9)
All 204 Subjects	109/134 (78.4) (4 missing**)	43/70 (58.6) (2 missing**)	OR (95% CI): 2.77 (1.37, 5.58) RD (95% CI): 19.0% (5.8, 32.2)

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

Abbreviations: OR: Odds Ratio, RD: Risk Difference, CI: Confidence Interval, ITT: Intention-to-treat

*From logistic regression model adjusting for sex, baseline WHO category, region, remdesivir use and dexamethasone use at baseline

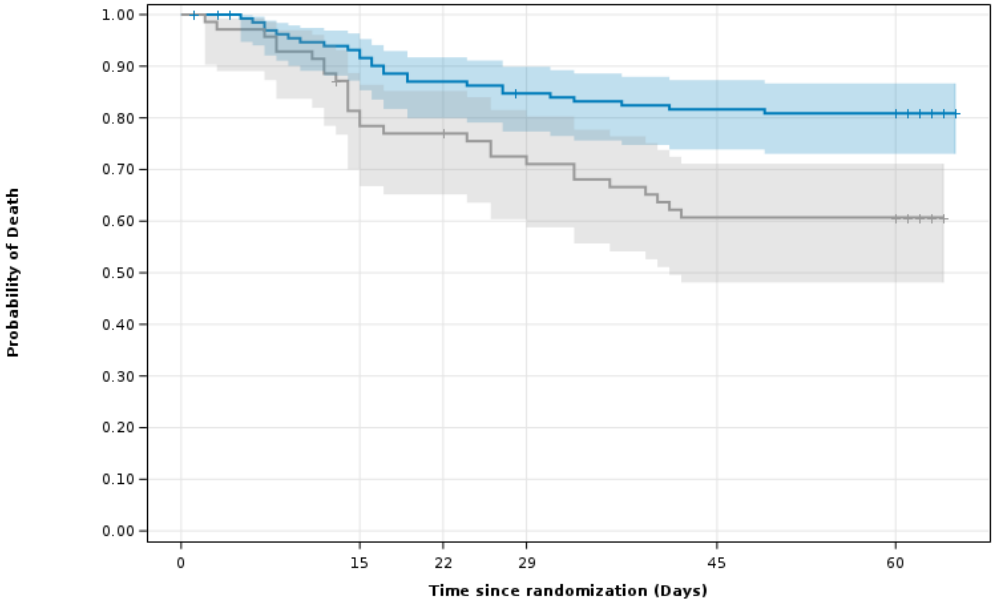
**Imputation model for missing data included same covariates + treatment discontinuation status and discharge status

Sensitivity to Missing Data

- Sensitivity analysis considered the full range of possible response rates in the subjects with missing data
  - Response defined as being alive at Day 60
- Primary findings remained robust even to missing data assumptions
- Results from tipping point analysis:
  - In the most extreme unfavorable case for treatment:
    OR: 2.63, 95% CI: (1.27, 5.44); RD: 17.7%, 95% CI: (4.3%, 31.4%)

All-Cause Mortality at Day 29 and other timepoints

- At Day 29, 110 (82.1%) and 48 (68.6%) subjects remained alive in the VERU-111 and placebo arms, respectively
- The proportion of subjects alive was higher in the VERU-111 arm
  - Odds Ratio at Day 29: 2.15, 95% CI: 1.02, 4.56
  - Risk Difference at Day 29: 11.9% 95% CI: -0.3%, 24.2%



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

Exploring Impact of Baseline Imbalances

- Baseline imbalances were observed in the timing of enrollment into the study with respect to clinical course and duration of standard of care
- The potential effect of these imbalances on study findings were explored using:
  - Sensitivity analyses that adjusted for these baseline factors as additional covariates in the primary analysis of the primary endpoint
  - Subgroup analyses defined by the timing of enrollment into the study with respect to clinical course and receipt of standard of care

Revised Models Including Additional Baseline Factors

Proportion of Subjects Alive at Day 60 – ITT Set		
Model*	**Odds Ratio** (95% CI)**	**Risk Difference** (95% CI)**
Primary Analysis Model	2.77 (1.37, 5.58)	19.0 (5.8, 32.2)
Primary Analysis Model + Days Hospitalized before Randomization	2.58 (1.30, 5.14)	19.5 (6.9, 32.1)
Primary Analysis Model + Days from Standard of Care*** Start to Randomization	2.65 (1.32, 5.33)	18.7 (5.6, 31.9)

Abbreviations: OR: Odds Ratio, RD: Risk Difference, CI: Confidence Interval, ITT: Intention-to-treat

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

**Odds ratio, 95% CI and Risk Difference, 95% CI are calculated using corresponding logistic regression model

***Standard of Care defined as corticosteroids for COVID-19 or remdesivir

Subgroup Analyses by Days Hospitalized and Duration of SoC

Proportion of Subjects Alive at Day 60 – ITT Set				
Subgroup	**VERU-111**	**Placebo**	**Risk Difference* (95% CI)**	**Odds Ratio* (95% CI)**
Days of Hospitalization Prior to Randomization				
< 10 Days	97/121 (80.2)	40/66 (60.6)	19.3 (5.6, 33.0)	2.51 (1.25, 5.04)
< 5 Days	73/90 (81.1)	28/46 (60.9)	20.2 (4.0, 36.4)	4.18 (1.63, 10.70)
Duration of SoC** Prior to Randomization				
< 10 Days	89/110 (80.9)	39/63 (61.9)	18.8 (4.8, 32.8)	2.38 (1.15, 4.92)
< 5 Days	74/91 (81.3)	32/49 (65.3)	15.8 (0.3, 31.3)	2.88 (1.19, 6.99)

Abbreviations: OR: Odds Ratio, RD: Risk Difference, CI: Confidence Interval, ITT: Intention-to-treat

*Odds ratio, 95% CI and Risk Difference, 95% CI are calculated using a logistic regression model with covariates for treatment group, region, sex, baseline WHO category, remdesivir use and dexamethasone use at baseline

**Standard of Care defined as corticosteroids for COVID-19 or remdesivir

Discussion of Exploratory Analyses of Baseline Imbalances

- Addition of covariates had minimal impact on the primary efficacy results
- Subgroup analyses results were consistent with the primary efficacy analysis
- These post-hoc analyses were simplistic explorations using available data
  - Do not completely eliminate uncertainty caused by these imbalances
- A larger study where such imbalances are less likely to occur after randomization would confirm lack of influence of baseline imbalances

Secondary Endpoints

- A positive trend for efficacy seen in secondary endpoints of:
  - Alive and Free of Respiratory Failure at Day 29
  - Days in ICU, in Hospital, on Mechanical Ventilation
  - Clinical Improvement on WHO Scale
- While supportive, these results were influenced by results in mortality
  - Imbalances in timing of enrollment may also influence the clinical interpretation of some secondary endpoints (e.g., Days in Hospital)

Statistical Efficacy Summary

- Study met statistical criterion for stopping at the interim analysis
- Data in all 204 subjects completing study indicate treatment benefit for all cause mortality at Day 60
- Results robust to missing data assumptions
- Exploratory analyses indicate minimal impact of baseline imbalances in timing of enrollment and duration of SoC
- Positive numerical trend consistent across subgroups defined by age, baseline WHO category, region, SoC use at baseline

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Uncertainties and Clinical Considerations

Uncertainties and Clinical Considerations

- High Placebo Mortality for Baseline Severity
- Potential Unblinding Events with Enteral Tube Administration
- Application of Standard of Care Therapies
- Timing of Enrollment Compared to COVID-19 Clinical Course
- Effects of Goals of Care on All-Cause Mortality
- Efficacy Results of Other Microtubule Disruptors in COVID-19
- Study Population Uncertainties

Uncertainty: Placebo Mortality

- Placebo Day 60 mortality 39.7%; 45.1% at interim, 63.6% within North America
- Higher than expected based on data from prior[1,2,3] studies and concurrent[4,5] studies in similar population calls into question interpretability of results

Study Drug	**Baricitinib**	**Tocilizumab**	**Sarulimab**	**Infliximab**	**Aviptadil**	**Veru-111**	**Veru-111**
Study	COV-BARRIER[1]	REMDACTA[2]	Lescure et al.[3]	ACTIV-1 IM[4]	ACTIV-3b[5]	V3011902	V3011902 Interim
Distribution of Baseline Severity (WHO OS Category)	3: 13% 4: 62% 5: 25%	4: 6.2% 5: 83.3% 6: 4.3% 7: 6.2%	4: 76% 5: 13% 6-7: 11%	3: 3.7% 4: 52.3% 5: 33.7% 6-7: 10.3%	5-6: 100%	4*: 41.4% 5: 47.1% 6: 11.4%	4*: 34.6% 5: 53.8% 6: 11.5%
Day 60 Mortality	**15%**	**25%**	**11%**	**16.5%**	**35%****	**39.7%**	**45.1%**
Date of Study	June 2020 to January 2021	June 2020 to March 2021	March 2020 to Sep 2020	Oct 2020 to Dec 2021	April 2021 to May 2022	June 2021 to May 2022	June 2021 to May 2022

**Day 90 results *With additional risk factors

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Uncertainty: Placebo Mortality

- We have focused our discussion on Day 60 mortality as this is the primary endpoint and the results of which were used to justify stopping early
- A few studies had a similar Day 29 mortality rate in the placebo group, but these studies were
  - Conducted earlier in the pandemic (with potential differences in SoC therapies and viral variants)
- Treatment difference at Day 29, OR: 2.15 (1.02, 4.56), RD: 11.9% (-0.3%, 24.2%), was lower than Day 60
  - Differentiation between treatment arms occurred after Day 29

Uncertainty: Potential Unblinding

- VERU-111 or matching placebo capsules were opened and contents mixed with water for enteral tube administration.

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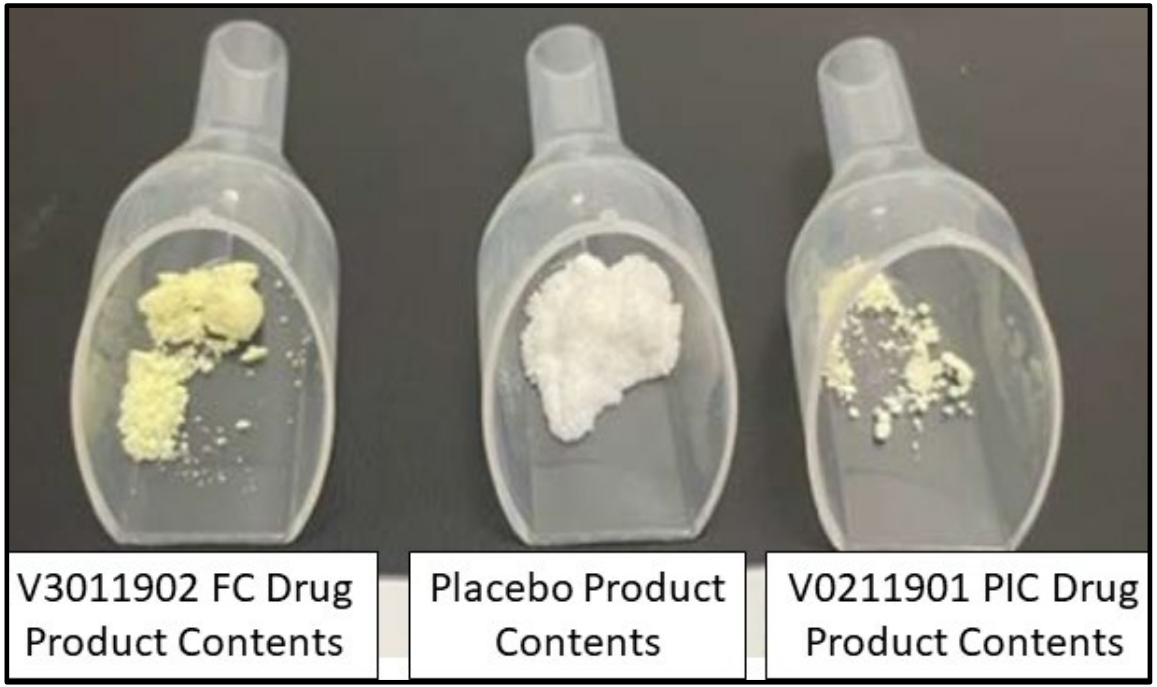
Visual Comparison of VERU-111 Drug Product and Placebo Powder (Capsule Contents)

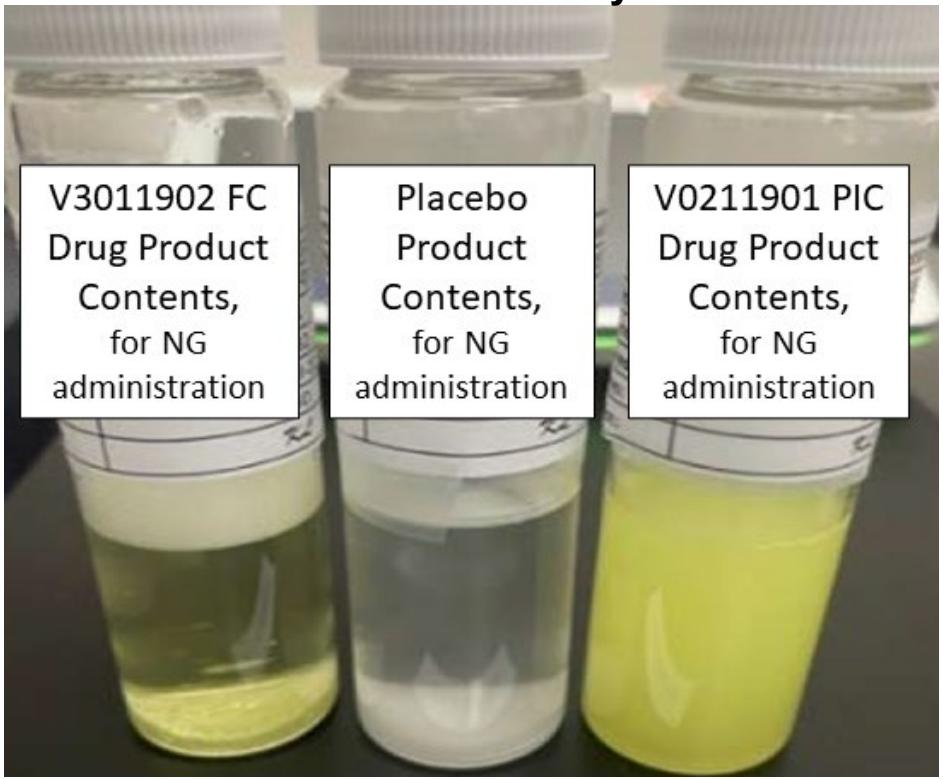


Source: photograph by Sponsor, labels adapted from Sponsor-submitted materials. Abbreviations: FC = formulated capsule formulation; PIC = powder in capsule formulation;

Uncertainty: Potential Unblinding

- Differences in appearance and dissolution properties of capsule contents

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

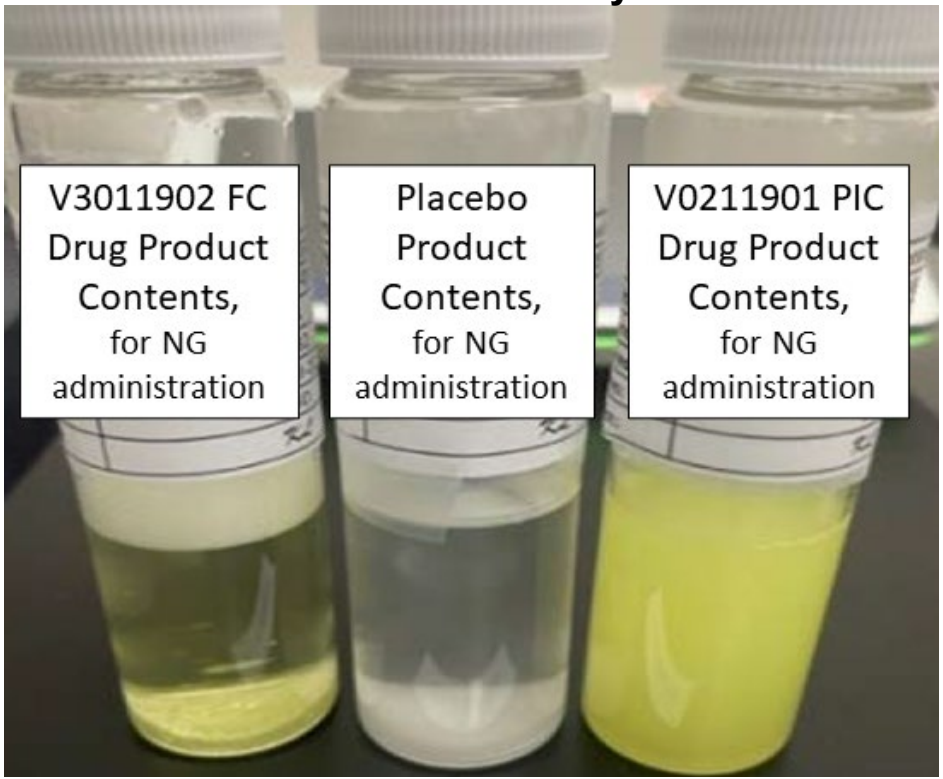


Source: photograph by Sponsor, labels adapted from Sponsor-submitted materials

Uncertainty: Potential Unblinding

- Differences in appearance and dissolution properties of capsule contents
  - Study 902 VERU-111 capsule contents
    - Yellow transparent solution with many visible yellow particulates present
  - Study 902 placebo capsule contents
    - Clear transparent solution with many visible white particulates present

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



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Uncertainty: Potential Unblinding

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  - Performance bias
  - Prior studies may suggest that inadequately blinded mortality trials overestimate efficacy.

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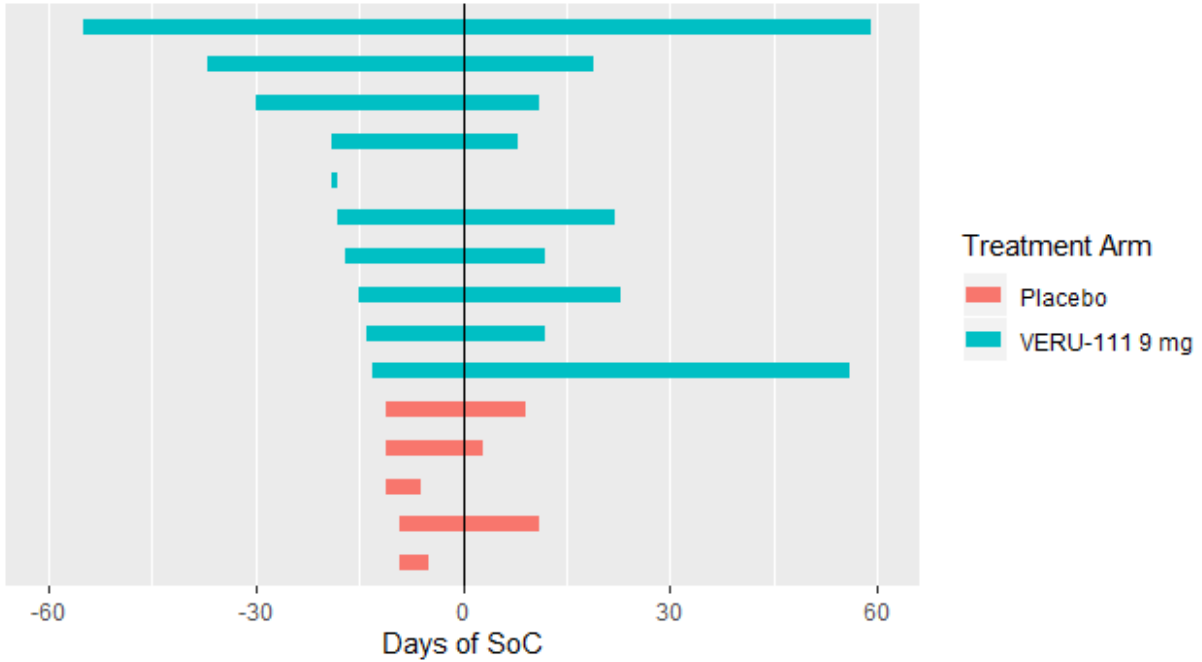
- Features of Study 902 and potential vulnerability to performance bias after unblinding
  - Frequent, clinically relevant interventions in critically ill subjects
  - Available prior information regarding VERU-111 efficacy endorsed mortality benefit
  - Clinical decision-making in the setting of pandemic
- Limited data collection to mitigate these concerns (e.g., elements of ventilation strategy, fluid strategy, goals of care)

Uncertainties: Application of Standard of Care

- Uncertainty in applicability of data to US healthcare decision-making
  - Local standard of care (SOC) at some Study 902 sites may differ from general COVID-19 SOC in the US.

Uncertainties: Application of Standard of Care

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



Source: Reviewer based on Sponsor-submitted data. Note: For this analysis standard of care therapy was defined as concomitant medication data for remdesivir or corticosteroids attributed to COVID-19 therapy

Abbreviations: COVID-19, coronavirus disease 2019; ITT, intention to treat population; SoC, standard of care

Uncertainties: Application of Standard of Care

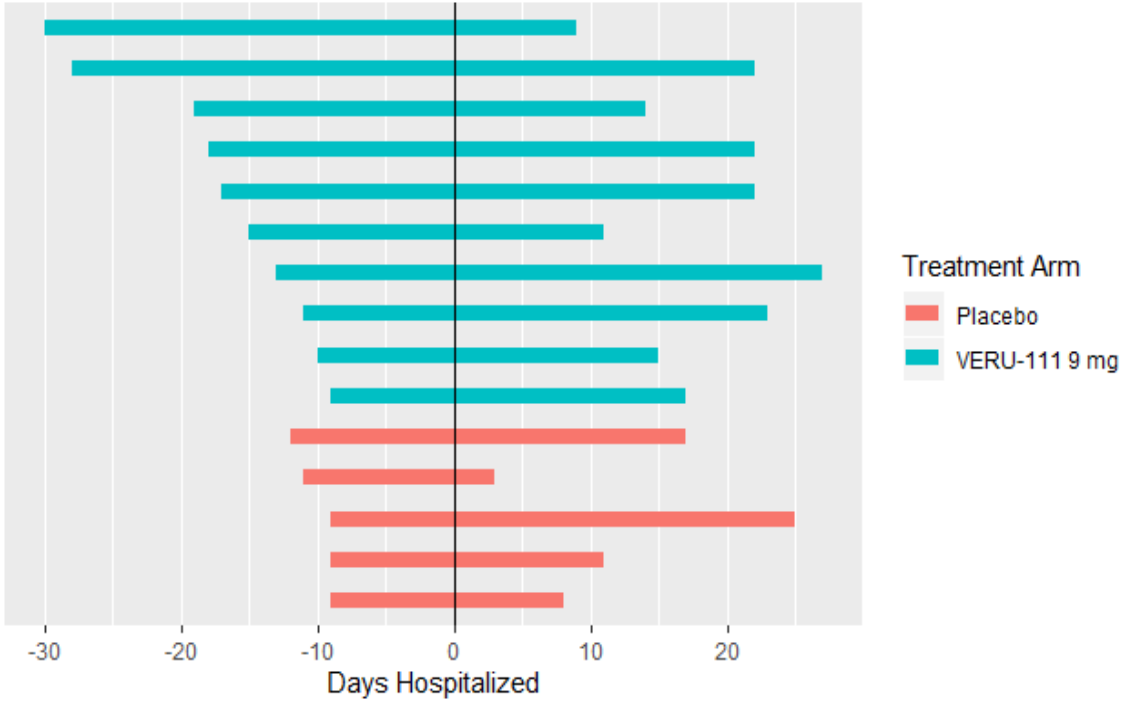
- Uncertainty in applicability of data to US healthcare decision-making
  - Local standard of care (SOC) at some Study 902 sites may differ from general COVID-19 SOC in the US.

- Small, but clinically relevant baseline imbalances in standard of care (SOC) pharmacologic therapies between arms
  - Limited data after randomization to better assess impact of SOC during the trial

- Limited data on non-pharmacologic elements of SOC in Study 902 that could impact mortality.

Uncertainties: Timing of Enrollment

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



Source: Reviewer based on Sponsor-submitted data.
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  - Limited available data suggest some subjects were improving prior to randomization.

- Scope and impact of these uncertainties are not possible to determine based on limited available data.

Uncertainties: Goals of Care

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  - Evidence from narratives that it did occur

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  - Evidence from narratives that it did occur

- Goals of care decision-making may play a direct role in mortality endpoints.

- High variability in goals of care decision-making

- Goals of care decision-making occurred more frequently during COVID-19 pandemic.

Uncertainties: Goals of Care

- Uncertainty in how variability in goals of care decision-making may have influenced mortality outcomes

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PLEASE NOTE: These uncertainties in the interpretation of the trial endpoint do not imply that goals of care decision-making in Study 902 was ethically or medically inappropriate.

Uncertainties: Colchicine Trials

- The totality of evidence does not support the efficacy of colchicine (a tubulin inhibitor) on clinically meaningful endpoints in COVID-19.

References:
1. Deftereos, SG, et al., 2020, Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial, JAMA Netw Open, 3(6):e2013136.
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- Early small trial enrolling 105 subjects suggested potential efficacy on mortality.[1]

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Uncertainties: Colchicine Trials

- The totality of evidence does not support the efficacy of colchicine (a tubulin inhibitor) on clinically meaningful endpoints in COVID-19.
- Early small trial enrolling 105 subjects suggested potential efficacy on mortality.[1]
- Cochrane Database of Systematic Reviews meta-analysis in COVID-19 did not suggest a mortality benefit for colchicine.[2]
  - Meta-analysis risk ratio for all-cause mortality of 1.00 with a 95% CI of 0.93 to 1.08, based on 11,445 hospitalized participants at Day 28
  - The authors conclude that “colchicine plus standard care probably results in little to no difference in all-cause mortality up to 28 days compared to standard care alone”.

References:
1. Deftereos, SG, et al., 2020, Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial, JAMA Netw Open, 3(6):e2013136.
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  - Unclear whether each component and comorbidity is adequately represented in Study 902 to provide confidence in results in this specific subgroup

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- High risk of ARDS definition used in Study 902 included many discrete comorbidities.
  - Unclear whether each component and comorbidity is adequately represented in Study 902 to provide confidence in results in this specific subgroup
    - WHO 4 population comprised 88 subjects
    - Asthma and COPD each <10% of the entire enrolled population
    - Data on “immunocompromised” category not formally collected

Summary of Uncertainties and Clinical Considerations

- High Placebo Mortality for Baseline Severity
- Potential Unblinding Events with Enteral Tube Administration
- Application of Standard of Care Therapies
- Timing of Enrollment Compared to COVID-19 Clinical Course
- Effects of Goals of Care on All-Cause Mortality
- Efficacy Results of Other Microtubule Disruptors in COVID-19
- Study Population Uncertainties

Small sample size and lack of additional data collection limit further exploration of these uncertainties

Considerations for Additional Trials

Study population

- Subjects with WHO 5 and 6 severity, or WHO 4 severity with additional selected comorbidities

Design proposal

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

Considerations

- Fitness of efficacy and safety data for interpretation
- Trial size and interim decision-making
- Choice of primary endpoint
- Placebo control, active control, or combinations of both
- Consideration of uncertainties raised by FDA in Study 902
    - Elements of SOC for COVID-19, pharmacological and non-pharmacological
    - Blinding and methods to prevent unblinding events
    - Time of enrollment and COVID-19 clinical course
    - Standards or data recording for goals of care decision-making
    - Stratification of randomization by site
    - Representation of baseline severity class and comorbidities between arms
- Equipoise


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FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
Charge to the Committee

EUA 113: VERU-111 for the treatment of hospitalized subjects with COVID-19

Banu A. Karimi-Shah, MD
Deputy Director
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
U.S. Food and Drug Administration
November 9, 2022

Proposed Use: VERU-111

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

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

Benefit-Risk Considerations

Proportion of Subjects Alive at Day 60 – ITT Set			
Analysis	**VERU-111**	**Placebo**	**Treatment Comparison***
Interim Analysis	79/98 (76.5) (4 missing**)	29/52 (53.8) (1 missing**)	OR (95% CI): 3.20 (1.43, 7.16) RD (95% CI): 23.1% (7.2, 38.9)
All 204 Subjects	109/134 (78.4) (4 missing**)	43/70 (58.6) (2 missing**)	OR (95% CI): 2.77 (1.37, 5.58) RD (95% CI): 19.0% (5.8, 32.2)

Statistical boundary was crossed for efficacy at interim analysis in N = 150 patients with p-value 0.0045 (compare with an allocated α of 0.016)
Abbreviations: OR: Odds Ratio, RD: Risk Difference, CI: Confidence Interval, ITT: Intention-to-treat
*From logistic regression model adjusting for sex, baseline WHO category, region, remdesivir use and dexamethasone use at baseline
**Imputation model for missing data included same covariates + treatment discontinuation status and discharge status

Benefit-Risk Considerations

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Benefit-Risk Considerations

- Limited safety database when compared to other products that have been granted EUA
  - 149 subjects received VERU-111 for COVID-19
- VERU-111 is a new molecular entity
  - Limited relevant previous human experience

Emergency Use Authorization (EUA)

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that –
  - the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2; and
  - The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product;
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

Emergency Use Authorization (EUA)

- FDA may require:
  - Appropriate conditions with respect to collection and analysis of information concerning the safety and effectiveness of the product with respect to the use of such product during the period when the authorization is in effect and a reasonable time following such period.

Considerations for Additional Trials

Study population

- Subjects with WHO 5 and 6 severity, or WHO 4 severity with additional selected comorbidities

Study design proposal

- Randomized, double-blind, fully matched placebo-controlled superiority design of VERU-111 + SOC versus placebo + SOC

Additional study elements

- Trial size and interim decision-making
- Placebo control, active control, or combinations of both
- Consideration of uncertainties raised by FDA in Study 902
  - Blinding, timing of enrollment, goals of care data, stratification of randomization by site, representation of baseline severity and comorbidities between arms
- Elements of SOC for COVID-19, pharmacological and non-pharmacological

EUA Considerations

- FDA's authorization of a medical product under EUA is not the same as the Agency's approval or licensure of a product.
- For an EUA, the Agency authorizes a Health Care Provider Fact Sheet and a Patient Fact Sheet. These are similar to Prescribing Information and Patient Labeling or a Medication Guide for approved products.
- As part of its authorization, FDA will establish, to the extent practicable, conditions in the EUA that it finds necessary to protect the public health.
- FDA will periodically review the circumstances and appropriateness of the EUA.

Discussion Points and Voting Questions

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

Discussion Points and Voting Questions

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

Discussion Points and Voting Questions

3. **VOTE:** Do the known and potential benefits of VERU-111 when used for the treatment of adult patients hospitalized with COVID-19 at high risk of ARDS outweigh the known and potential risks of VERU-111?

   a. If yes, discuss the appropriate patient population in which VERU-111 should be authorized.

   b. If no, discuss what additional data would be necessary to assess the benefits vs. the risks of treatment.

Discussion Points and Voting Questions

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


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