Title:
Intravenous Aviptadil and Remdesivir for Treatment of COVID-19-associated Hypoxemic Respiratory Failure: Randomized, Placebo-controlled Trials

Author:
ACTIV-3b / Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO) Study Group

Writing Committee:

Samuel M. Brown, MD, MS*
Department of Pulmonary/Critical Care Medicine, Intermountain Medical Center, Murray, Utah, USA. Division of Pulmonary/Critical Care Medicine, University of Utah, Salt Lake City, UT, USA
Christina Barkauskas, MD*
Division of Pulmonary/Critical Care Medicine, Duke Health, Durham, NC, USA
Birgit Grund, PhD
School of Statistics, University of Minnesota; Minneapolis, MN, USA
Shweta Sharma, MS
Division of Biostatistics, School of Public Health, University of Minnesota; Minneapolis, MN, USA
Andrew N. Phillips, PhD
Institute for Global Health, University College London, United Kingdom
Lindsay Leither, DO
Department of Pulmonary/Critical Care Medicine, Intermountain Medical Center, Murray, Utah, USA. Division of Pulmonary/Critical Care Medicine, University of Utah, Salt Lake City, UT, USA
Ithan D. Peltan, MD, MSc
Department of Pulmonary/Critical Care Medicine, Intermountain Medical Center, Murray, Utah, USA. Division of Pulmonary/Critical Care Medicine, University of Utah, Salt Lake City, UT, USA
Michael Lanspa, MD
Department of Pulmonary/Critical Care Medicine, Intermountain Medical Center, Murray, Utah, USA. Division of Pulmonary/Critical Care Medicine, University of Utah, Salt Lake City, UT, USA
Daniel Gilstrap, MD
Division of Pulmonary, Allergy and Critical Care Medicine, Duke Health, Durham, NC, USA
Ahmad Mourad, MD
Division of Infectious Diseases, Duke University School of Medicine, Durham, NC, USA
Kathleen Lane, RN
Surgical Office of Clinical Research, Cardiothoracic Surgical Division, Duke University School of Medicine, Durham, NC, USA
Jeremy R. Beitler, MD MPH
Columbia Respiratory Critical Care Trials Group and Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University. Center for Acute Respiratory Failure, New York-Presbyterian Hospital, New York, NY, USA

Alexis L. Serra, MD, MPH
Columbia Respiratory Critical Care Trials Group and Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University. Center for Acute Respiratory Failure, New York-Presbyterian Hospital, New York, NY, USA
Ivan Garcia, RRT
Columbia Respiratory Critical Care Trials Group and Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University. Center for Acute Respiratory Failure, New York-Presbyterian Hospital, New York, NY, USA
Eyad Almasri, MD
Department of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, UCSF Fresno, Fresno, CA, USA
Mohamed Fayed, MD
Department of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, UCSF Fresno, Fresno, CA, USA
Kinsley Hubel, MD
Department of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, UCSF Fresno, Fresno, CA, USA
Estelle S. Harris, MD
Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, UT, USA
Elizabeth A. Middleton, MD
Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, UT, USA
Macy AG Barrios
Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, UT, USA
Kusum S. Mathews, MD, MPH, MS
Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine; Department of Emergency Medicine; Icahn School of Medicine at Mount Sinai, New York, NY, USA
Neha N. Goel, MD, MS
Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine; Icahn School of Medicine at Mount Sinai, New York, NY, USA
Samuel Acquah, MD
Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine; Icahn School of Medicine at Mount Sinai, New York, NY, USA
Jarrod Mosier, MD
Department of Emergency Medicine and Division of Pulmonary, Allergy, Critical Care and Sleep, Department of Medicine, University of Arizona College of Medicine, Tucson, AZ, USA
Cameron Hypes, MD MPH
Department of Emergency Medicine and Division of Pulmonary, Allergy, Critical Care and Sleep, Department of Medicine, University of Arizona College of Medicine, Tucson, AZ, USA
Elizabeth Campbell, PhD
Department of Emergency Medicine, University of Arizona College of Medicine, Tucson, AZ, USA
Akram Khan, MD

Department of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Oregon Health & Science University, Portland, OR, USA
Catherine L. Hough, MD
Department of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Oregon Health & Science University, Portland, OR, USA
Jennifer G. Wilson, MD
Department of Emergency Medicine, Stanford University School of Medicine, Palo Alto, CA, USA
Joseph Levitt, MD
Department of Medicine, Stanford University School of Medicine, Palo Alto, CA, USA
Abhijit Duggal, MD
Department of Critical Care, Respiratory Institute, Cleveland Clinic, Cleveland OH, USA
Siddharth Dugar, MD
Department of Critical Care, Respiratory Institute, Cleveland Clinic, Cleveland OH, USA
Andrew J. Goodwin, MD, MSCR
Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, Charleston, SC, USA
Charles Terry, MD, MSCR
Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, Charleston, SC, USA
Peter Chen, MD
Women's Guild Lung Institute, Department of Medicine and Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA, USA
Sam Torbati, MD
Department of Emergency Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA
Nithya Iyer, MD
Division of Pulmonary/Critical Care, Baylor University Medical Center. Dallas, TX, USA
Uriel Sandkovsky, MD
Division of Infectious Diseases, Baylor University Medical Center. Dallas, TX, USA
Nicholas J. Johnson, MD
Department of Emergency Medicine and Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Washington/Harborview Medical Center, Seattle, WA, USA
Bryce RH Robinson, MD
Department of Surgery, University of Washington/Harborview Medical Center, Seattle, WA, USA
Michael Matthay, MD
Cardiovascular Research Institute and Departments of Medicine and Anesthesia, University of California-San Francisco, San Francisco, CA, USA
Neil Aggarwal, MD, MHSc
Department of Medicine, Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Ivor S. Douglas, MD
Department of Medicine, Denver Health Medical Center and Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
Jonathan D. Casey, MD, MSc
Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN, USA
, Manuel Hache-Marliere, MD
Jacobi Medical Center/Montefiore Medical Center - Albert Einstein College of Medicine, New York, NY, USA
J. Georges Youssef, M.D.
Department of Pulmonary/Critical Care Medicine, Weill Cornell Medical College. J. C. Walter Jr. Transplant Center Advanced Lung Diseases Program, Houston Methodist Hospital, Houston, TX , USA
William Nkemdirim MD, MPH
Montefiore Medical Center - Albert Einstein College of Medicine, New York, NY, USA
Brad Leshnower, MD
Division of Cardiothoracic Surgery, Emory University School of Medicine, Atlanta, GA, USA
Omar Awan, MD
Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Disorders Medicine, VA Medical Center and George Washington University, Washington, DC, USA
Sonal Pannu, MD
Department of Medicine, Division of Pulmonary Critical Care and Sleep, Ohio State University, Columbus, OH, USA
Darragh Shane O'Mahony, MD
Department of Acute Care Medicine, Swedish Medical Center, Seattle, WA, USA
Prasad Manian, MD
Division of Pulmonary and Critical Medicine, Baylor College of Medicine & Texas Heart Institute, Houston, TX, USA
J. W. Awori Hayanga MD MPH
Department of Cardiovascular and Thoracic Surgery. Heart and Vascular Institute, West Virginia University, Morgantown, WV, USA
Glenn W. Wortmann, MD
Infectious Diseases Section, MedStar Washington Hospital Center and Georgetown University, Washington, DC, USA
Bruno M. Tomazini, MD
Brazilian Research in Intensive Care Network (BRICNet), Brazil. HCor Research Institute, São Paulo, Brazil

Robert F Miller MBBS FRCP
Institute for Global Health, University College London, UK
Jens-Ulrik Jensen, MD
Section of Respiratory Medicine, Department of Medicine, Herlev-Gentofte Hospital, Hellerup, Denmark. CHIP Center of Excellence for Health, Immunity, and Infections and Department of Infectious Diseases, Rigshospitalet;

Copenhagen, Denmark. Department of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Denmark
Daniel D. Murray, PhD
CHIP Center of Excellence for Health, Immunity, and Infections, Rigshospitalet; Copenhagen University Hospital; Copenhagen, Denmark
Nina Bickell, MD
Mount Sinai School of Medicine, New York, NY, USA
Jigna Zitakia, MD
Mount Sinai School of Medicine, New York, NY, USA
Sarah Burris, MHA
Mount Sinai School of Medicine, New York, NY, USA
Elizabeth S. Higgs, MD
National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA
Ven Natarajan, PhD
Frederick National Laboratory for Cancer Research, Frederick MD, USA
Robin L. Dewar, PhD
Frederick National Laboratory for Cancer Research, Frederick MD, USA
Adam Schechner
Frederick National Laboratory for Cancer Research, Frederick MD, USA
Nayon Kang, PharmD, MS
National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA
Alejandro Arenas-Pinto, MBBS, MSc, PhD
The Medical Research Council Clinical Trials Unit at UCL, University College London; London, UK. Institute for Global Health, University College London; London, UK
Fleur Hudson
The Medical Research Council Clinical Trials Unit at UCL, University College London; London, United Kingdom
Adit Ginde, MD
Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, USA
Wesley H. Self, MD, MPH
Department of Emergency Medicine, Vanderbilt University Medical Center; Nashville, TN, USA
Angela Rogers, MD
Stanford University, Palo Alto, CA, USA
Katie Oldmixon,
Massachusetts General Hospital, Boston, MA, USA
Haley Morin, BA
Stanford University, Palo Alto, CA, USA
Adriana Sanchez, MS
Veteran Affairs Medical Center, Washington, DC, USA
Amy C. Weintrob, MD
Infectious Diseases Section, Washington, DC VA Medical Center, Washington, DC, USA
Alexandre Biasi Cavalcanti, MD, PhD
HCor Research Institute, São Paulo, Brazil
Anne Davis-Karim, PharmD

Clinical Research Pharmacy Coordinating Center, Office of Research & Development, Department of Veterans Affairs, Albuquerque, NM, USA
Nicole Engen, MS
Division of Biostatistics, School of Public Health, University of Minnesota; Minneapolis, MN, USA
Eileen Denning, MPH
Division of Biostatistics, School of Public Health, University of Minnesota; Minneapolis, MN, USA
B. Taylor Thompson, MD
Division of Pulmonary and Critical Care, Department of Medicine, Massachusetts General Hospital and Harvard Medical School; Boston, MA, USA
Annetine C. Gelijns, PhD
Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai; New York, NY, USA
Virginia Kan, MD
Infectious Diseases Section, VA Medical Center, Washington, DC, USA
Victoria J. Davey, PhD
United States Department of Veterans Affairs; Washington, DC, USA
Jens D. Lundgren, MD
CHIP Center of Excellence for Health, Immunity, and Infections, Rigshospitalet; Copenhagen University Hospital; Copenhagen, Denmark
Abdel G. Babiker, PhD
The Medical Research Council Clinical Trials Unit at UCL, University College London; London, United Kingdom
James D. Neaton, PhD
Division of Biostatistics, School of Public Health, University of Minnesota; Minneapolis, MN, USA
H. Clifford Lane, MD
National Institute of Allergy and Infectious Diseases; Bethesda, MD, USA

*Dr. Brown and Dr. Barkauskas contributed equally to this work.

A full list of members of the ACTIV-3b/TESICO Study Group is provided in the Supplementary Appendix.

Corresponding author:
Samuel M. Brown
Shock Trauma ICU
5121 S. Cottonwood Street
Murray, UT 84107
Phone: (801) 507-6529
E-Mail: Samuel.Brown@imail.org

Funding:
Supported by the U.S. Operation Warp Speed program, the National Institute of Allergy and Infectious Diseases (NIAID), Division of Clinical Research (DCR) and Leidos Biomedical Research for the INSIGHT Network, and the National Heart, Lung, and

Blood Institute and the Research Triangle Institute for the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network and the Cardiothoracic Surgical Trials Network (CTSN). The NIAID, DCR funded this project through a subcontract,18X107C, from Leidos Biomedical Prime Contract HHSN261200800001E, NIH. The research was also, in part, funded by NIAID grant U01-AI136780 and the National Institutes of Health (NIH) Agreement 1OT2HL156812-01. Trial medication was donated by NRx Pharmaceuticals (aviptadil) and Gilead Sciences, Inc. (remdesivir). The views and conclusions contained in this document are those of the authors and should not be interpreted as representing the official policies, either expressed or implied, of the NIH.

ABSTRACT

Background: Aviptadil (vasoactive intestinal peptide) is a lung-protective neuropeptide and remdesivir is a nucleotide prodrug of an adenosine analog, both of which may improve outcomes for COVID-19 patients with acute hypoxemic respiratory failure.

Methods: Daily 12-hour infusions of aviptadil or placebo for three successive days and daily infusions of remdesivir or placebo for up to 10 successive days were studied using a master protocol for adults hospitalized for COVID-19 with acute hypoxemic respiratory failure. Participants could be randomized to both study treatments in a 2x2 factorial design or to just one of the agents. For both treatment comparisons, the primary outcome, assessed at Day 90, was a 6-category ordinal outcome ranging from return to home with liberation from supplemental oxygen (recovery) for ≥77 days to death. Mortality through Day 90 was a key secondary outcome. The independent data and safety monitoring board recommended stopping the aviptadil trial on May 25, 2022 for futility. On June 9, 2022, the sponsor stopped the trial of remdesivir due to slow enrollment.

Findings: Four hundred seventy-one of the 640 planned participants were randomized to aviptadil/placebo, among whom 461 participants (231 allocated to aviptadil and 230 to placebo) received any infusion of blinded aviptadil. For the aviptadil/placebo comparison, at entry, 271 (59%) were on high flow nasal oxygen or non-invasive ventilation and 190 (41%) on mechanical ventilation or ECMO. The odds ratio (aviptadil/placebo) of being in a better outcome category at Day 90 was 1.11 (95% CI: 0.80-1.55; p=0.54). Cumulative mortality through Day 90 was 38% (n=86) for aviptadil and 36% (n=83) for placebo (HR 1.04; 95% CI: 0.77-1.41). A composite safety outcome including death, organ failure, serious infection, serious adverse events, and grade 3 or

4 adverse events through Day 5 occurred in 63% (n=146) of aviptadil and 56% (n=129) of placebo participants (OR 1.40; 95% CI: 0.94-2.08). Eighty-seven participants were randomized to remdesivir/placebo.

Interpretation: Among patients with COVID-19-associated acute hypoxemic respiratory failure, aviptadil, compared to placebo, did not significantly improve clinical outcomes through Day 90. The smaller than planned sample size for the remdesivir trial does not permit definitive conclusions regarding safety or efficacy.

(Funded by the National Institutes of Health (NIH) and others. TESICO ClinicalTrials.gov number, NCT04843761)

INTRODUCTION

SARS-CoV-2 infection may lead to acute hypoxemic respiratory failure, including acute respiratory distress syndrome (ARDS), which is often lethal. Even with adherence to current treatment guidelines, 60-day mortality remains 30–50% among COVID-19 patients with acute hypoxemic respiratory failure.[1,2] [3]

Aviptadil, the synthetic form of the 28-amino acid neuropeptide vasoactive intestinal peptide (VIP), has been proposed as a treatment for acute hypoxemic respiratory failure based on pleoiotropic lung-protective effects including increases in surfactant production, decreased cytopathy, and modulated inflammatory response in monocytes.[4,5] A Phase 2/3 randomized trial suggested possible efficacy in COVID-19 respiratory failure.[6] Remdesivir, a small molecule antiviral, improves outcomes among hospitalized patients in general, but data among critically ill patients are less robust.[7]

ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines / Therapeutics for Inpatients with COVID-19) is an NIH-led public/private partnership established in April 2020 to advance COVID-19 therapeutics and vaccines. ACTIV-3b, Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO), which focuses on patients with COVID-19 critical illness with hypoxemic respiratory failure, is one of several ACTIV therapeutic master protocols enabling simultaneous evaluation of multiple agents.[8] The ACTIV agent selection committee selected aviptadil for study within TESICO.[9] We report here the results of the trials comparing intravenous aviptadil and intravenous remdesivir each with placebo among patients with COVID-19 acute hypoxemic respiratory failure.

METHODS

Trial Design and Oversight

For the TESICO trial of aviptadil and remdesivir, depending on eligibility, consenting participants could be randomized to both study treatments or matching placebo in a 2x2 factorial design or to just one of the agents (details in the Supplementary Appendix, Section 2 and Figure S1). A factorial design was used for sample size efficiency because an interaction was considered unlikely. Randomization to only one of the two factors was permitted in order to include participants who were not eligible for one of the investigational agents.

The TESICO protocol was approved by a governing institutional review board for each enrolling site. Written informed consent for trial participation was obtained from each enrolled participant or a legally authorized representative. The trial was overseen by an independent data and safety monitoring board (DSMB) and conducted under an investigational new drug protocol with the U.S. Food and Drug Administration.

Target Population

Hospitalized adult patients were eligible if they had acute hypoxemic respiratory failure due to confirmed SARS-CoV-2 infection and were within four days of onset of respiratory failure. Acute hypoxemic respiratory failure was defined pragmatically as hypoxemia (defined clinically, with no specific threshold required) caused by COVID-19 pneumonia plus receipt of high-flow nasal oxygen (HFNO), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO).[10,11]

Agent-specific exclusion criteria for aviptadil included refractory hypotension, severe diarrhea, or end-stage liver disease. Participants were excluded from the

factorial randomization if they did not meet the eligibility criteria for both aviptadil and remdesivir. If eligible for one of the treatments, participants could be randomized separately to that active agent/placebo. A full list of eligibility criteria is provided in the Supplementary Appendix (Section 2).

Randomization and Blinding

Participants were randomized with a web-based application. For each site, randomization was stratified by disease severity (HFNO/NIV or IMV/ECMO), and four strata defined by remdesivir and aviptadil eligibility: 1) eligible for randomization to aviptadil and remdesivir in the 2x2 factorial; participants were equally randomized to either intravenous aviptadil, aviptadil matching placebo, intravenous remdesivir, or remdesivir matching placebo (1:1:1:1), with participants in the factorial receiving blinded infusions of both agents; 2) eligible for randomization to aviptadil only because remdesivir was started prior to randomization; 3) eligible for randomization to aviptadil only because remdesivir was contraindicated; and 4) eligible for randomization to remdesivir only because aviptadil was contraindicated (Figure S1). For participants in strata 2 through 4, randomization was (1:1) to the active agent or matching placebo. Permuted block randomization was used to generate the randomization schedules for each site (see Supplementary Appendix Section 2). Research staff, clinical personnel, and participants were blinded to trial group assignment; an unblinded pharmacist prepared blinded study product for infusion on site.

Interventions/Treatments

Aviptadil acetate was administered as a daily 12-hour infusion for three days, targeting 600 pmol/kg on infusion day 1, 1200 pmol/kg on infusion day 2, and 1800 pmol/kg on

infusion day 3. Remdesivir was administered as a 200 mg loading dose, followed by 100 mg daily maintenance doses for up to a 10-day total course. For participants assigned placebo for either agent, matched saline placebo was administered in identical volumes.

All infusions of aviptadil/placebo were administered in an intensive care or step-down unit; participants discharged from intensive care or step-down unit did not continue dosing of aviptadil/placebo. If respiratory failure had resolved on or before Day 5, clinical teams were allowed to stop blinded remdesivir/placebo after 5 doses. Neither agent was continued after hospital discharge if the treatment course had not been completed.

Expected side effects of aviptadil included hypotension and diarrhea. Aviptadil/matching placebo was contraindicated on a given infusion day for participants receiving ≥ 0.1 mcg/kg/min of norepinephrine or equivalent vasopressor or with > 3 liquid stools in the preceding 24 hours. Blood pressure was monitored per local clinical guidelines but at least every 2 hours for the duration of the aviptadil infusion and for 2 hours thereafter. Study management guidelines stipulated responses to worsening hypotension with pauses, decreases, or discontinuation of the aviptadil/placebo infusion and to substantial diarrhea with oral loperamide and/or changes in the infusion. The grading system used for hypotension and other adverse events is given in the Supplemental Appendix (Section 2).

Sites were strongly encouraged to administer glucocorticoids per NIH treatment guidelines.[12] By design, participants were either receiving remdesivir prior to

randomization or were randomized to remdesivir versus remdesivir placebo, unless contraindicated. Use of antiplatelet/anticoagulant treatment and immunomodulators were at the discretion of treating clinicians.

Primary and Secondary Outcomes for Each Treatment Comparison

The primary outcome was a 6-category ordinal outcome defining the participant's status at Day 90: (1) at home (defined as the type of residence before hospitalization) and off oxygen (recovered) for at least 77 days, (2) at home and off oxygen for 49–76 days, (3) at home and off oxygen for 1–48 days, (4) not hospitalized but either on supplemental oxygen or not at home, (5) hospitalized or in hospice care, or (6) dead (see Supplementary Appendix Section 2). Mortality through Day 90 was a secondary endpoint; all participants were also followed for mortality through Day 180. Adverse events of any grade severity were collected during each infusion and 2 hours after infusion completion. Composite safety outcomes were assessed through Day 5, Day 28, and Day 90. These outcomes are defined in the Supplementary Appendix (Section 2).

Baseline Serologic and Virologic Assays

Serostatus (Genscript cPass and Quanterix HD-X) and antigen (Quanterix Simoa) testing were performed centrally on cryopreserved plasma obtained at baseline, while viral strain was determined using strain-specific PCR for Delta or Omicron variants on mid-turbinate samples obtained at baseline. Further details of laboratory methods are presented in the Supplementary Appendix (Section 2).

Statistical Analysis

The enrollment target was 640 participants for both the aviptadil versus matched placebo comparison and for the remdesivir versus matched placebo comparison. With the planned factorial design, it was assumed that the total sample size for the two trials would be substantially less than 1,280. This sample size target for each trial provided 80% power to detect a common odds ratio (OR) of 1.5 for the primary ordinal outcome at the (two-sided) 0.05 level of significance. More detailed sample size assumptions are provided in the Supplemental Appendix (Section 2).

The independent DSMB regularly reviewed interim analyses; on May 25, 2022 the DSMB reviewed a pre-specified futility analysis using conditional power estimates which were based on 70% of the planned number of participants in the aviptadil/placebo group with the Day 90 primary outcome. Following this review, the DSMB recommended stopping randomization of aviptadil versus placebo because it was highly unlikely that statistical significance would be achieved with full enrollment (conditional power was 12.4%, assuming an OR of 1.5 for the as-yet unobserved data). Randomization to the aviptadil trial of the master protocol was stopped at the time of this recommendation. At this review, the DSMB also noted that while there were no safety concerns for the remdesivir/placebo comparison, given the slow enrollment there may be operational reasons to close that trial as well. The investigator and sponsor agreed to end the remdesivir/placebo trial on June 9, 2022. Guidelines given to the DSMB for the futility assessment by the blinded investigator team are provided in the Supplementary Appendix (Section 2).

The analysis cohort for treatment comparisons of aviptadil versus matching placebo was randomized participants who received any amount of aviptadil or placebo (modified intention-to-treat). The primary analysis used a proportional odds model to

estimate the OR of a better outcome on aviptadil compared to placebo for the 6-category ordinal outcome at Day 90.[13] The model was stratified by disease severity (HFNO/NIV or IMV/ECMO) at study entry. Treatment comparisons for the primary outcome were based on participants for whom the Day 90 outcome was ascertained. An analysis that considered missing Day 90 outcome data was also carried out and is described in the Supplementary Appendix (Section 2). Death through Day 90 and through Day 180 and composite safety outcomes through Days 28 and 90 were compared between treatment groups using Cox proportional hazards models stratified by disease severity; hazard ratios (HRs) and 95% confidence intervals (CIs) are cited. Follow-up was censored using the date of withdrawal/loss-to-follow-up, or Day 90 (or 180), whichever was earlier. Treatment groups were also compared using Fine-Gray models stratified by disease severity at study entry to estimate sub-hazard ratios (sHR) for secondary outcomes that have been used in other trials, including time to discharge, time to discharge home, and time to discharge home for 14 days; cumulative incidence was estimated using the Aalen and Johansen method and compared using Gray's method.[14-17] Twenty-three exploratory subgroup analyses (15 of which were prespecified) were performed to assess treatment effect heterogeneity by baseline characteristics. The heterogeneity of ORs and HRs for subgroups were assessed by including an interaction term in the corresponding regression models. One of the subgroups considered for the aviptadil comparison was defined according to whether remdesivir was randomized as part of the 2x2 factorial, whether remdesivir was initiated prior to randomization, or whether remdesivir was contraindicated. For participants enrolled in the 2x2 factorial, the effect of aviptadil versus matched placebo was also compared for those randomly assigned remdesivir with those assigned matching

placebo for remdesivir. Results of the subgroup analyses should be interpreted with caution because there was no adjustment for type 1 error.

Analyses for remdesivir versus matching placebo were carried out with similar methods.

For both the aviptadil and remdesivir efficacy comparisons, an OR >1 for the primary endpoint and a sHR >1 for Fine-Gray models indicate superiority of the active treatment compared to placebo. Treatment comparisons for safety outcomes that include death are presented such that HRs <1 or ORs <1 indicate a more favorable outcome for the active treatment. Statistical analyses were performed using SAS (version 9.4) or R (version 4.1).

Role of the funding source

Investigators from NIH were directly involved in all aspects of this study, including study design, data collection, data analysis, data interpretation, and writing of the report. All analyses of biological material were done in a blinded manner at laboratories affiliated with the funding source; data were sent to the statistical and data management center at the University of Minnesota for linkage to the trial database. Several representatives from NIH are part of the writing group for the manuscript. The views and conclusions contained in this document are those of the authors and should not be interpreted as representing official policies, either expressed or implied, of the National Institutes of Health or Department of Veterans Affairs.

RESULTS

Participants

From April 21, 2021 to May 24, 2022, participants were enrolled at 28 sites in the United States (Table S1). For the aviptadil comparison, 471 participants were randomized to aviptadil or matched placebo. The mITT population comprised 461 participants (Figures S1 and S2) who received at least a partial infusion of aviptadil (n=231) or aviptadil matched placebo (n=230).

For the remdesivir comparison, 87 participants (Figures S1 and S3) were randomized to remdesivir or matched placebo and all received some infusion of remdesivir (n=44) or remdesivir matched placebo (n=43). Eighty-five participants, i.e., those enrolled in the 2x2 factorial, were included in the mITT analyses for both agents. Reasons for not receiving any infusion of blinded aviptadil are presented in Table S2.

Baseline characteristics for the aviptadil/placebo comparison by treatment group are summarized in Table 1 and Tables S3–S11 for the mITT population. Overall, for the 461 participants in the mITT population, median age was 57 (IQR 46, 66) years; 39% (n=178) were female; 53% (n=246) reported non-White race or Hispanic ethnicity. Ninety-four percent (n=431) were in an intensive care unit at baseline, with 59% (n=271) receiving HFNO or NIV, 40% (n=185) receiving IMV, and 1% (n=5) ECMO. Median times from hospital admission and from onset of respiratory failure to randomization were 2 (IQR: 2,4) days and 2 (IQR: 2, 3) days, respectively, 39% (n=179) met Berlin criteria for ARDS, while 97% (n=445) of participants met modified Berlin criteria (bilateral infiltrates and SF ratio <315).[11] Ninety-five percent (n=440) of participants were prescribed glucocorticoids, and 95% (n=436) were prescribed

antiplatelet/anticoagulant treatment at baseline. Most (74%, n=305/414) participants were infected with the Delta variant.

Seventy-six percent (n=349) of participants assigned aviptadil or placebo were receiving remdesivir prior to randomization.

Baseline characteristics for the remdesivir/placebo comparison by treatment group are summarized in Section 5 of the Supplemental Appendix (Tables S12–S20).

Aviptadil

Adherence to Infusions and Concomitant Treatments

Infusions of aviptadil or matching placebo were closely monitored (Table S21). On the first infusion day (600 pmol/kg), 91% (n=211 aviptadil and n=210 placebo) participants received a full dose (defined as at least 90% of the prescribed volume), with no difference by treatment group. On subsequent infusion days (1200–1800 pmol/kg), fewer participants received a full dose (83% (n=190) for aviptadil vs. 91% (n=208) for placebo on the second day, 75% (n=170) vs. 88% (n=197) on the third day), with participants in the aviptadil group consistently receiving less study infusion than the placebo group.

The great majority of participants in both treatment groups continued glucocorticoids through Day 5 and antiplatelet/anticoagulant treatment through Day 7 (Table S22).

Efficacy Summary

The OR for being in a better category of the primary efficacy endpoint for aviptadil vs. placebo at Day 90, from a model stratified by baseline disease severity, was 1.11 (95% CI: 0.80-1.55; p=0.54) (Figure 1). The p-value corresponding to the test of proportional odds was 0.078; ORs for dichotomized outcomes for the 6 categories of the primary ordinal outcome are summarized in Table 2. The cumulative distribution of supplemental oxygen-free days at home through Day 90 ("days recovered") is shown in Figure S4. The unadjusted OR for the 6-category Day 90 outcome, and the ORs after adjustment for other randomization stratification variables were consistent with the primary analysis (Table S23).

Eleven participants (2% of the mITT population) with follow-up through Day 90 (6 assigned aviptadil and 5 placebo) had an unknown status for the Day 90 ordinal primary outcome. Sensitivity analyses that imputed the outcome category for participants with unknown Day 90 status were consistent with the primary analysis (OR=1.10; 95% CI: 0.79-1.52; Figure S5).

Through Day 90, 86 participants in the aviptadil group and 83 in the placebo group died. The cumulative percent who died through Day 90 was 38% and 36% in the aviptadil and placebo groups respectively (Figure 2) with a HR for aviptadil compared to placebo of 1.04 (95% CI: 0.77-1.41). By Day 180, the percentages who died were 39% (90 deaths) and 38% (86 deaths), respectively with a corresponding HR of 1.06 (95% CI: 0.79, 1.42).

Secondary efficacy outcomes are further summarized in Table 2, Figures S6-S13 and Table S24. For each of these measures, the 95% CI for the relative treatment difference includes 1.0.

Safety Summary

Infusion reactions were significantly more common for participants treated with aviptadil compared to placebo (Table 3 and Tables S25-S32). Twenty-four (10%) aviptadil and 13 (6%) placebo participants had an infusion discontinued due to an adverse event; 71 (31%) and 35 (15%) experienced an infusion pause due to an adverse event (Table 3). Most adverse events during or within 2 hours of completing the infusion were grade 1 or 2. Diarrhea, facial flushing, tachycardia and hypotension occurred more frequently on aviptadil than placebo; these events were more common for aviptadil than placebo on the second and third infusion days, when higher aviptadil doses were targeted (Table 3).

On average, on the second and third infusion days, mean arterial pressure (MAP) was 5–7mmHg lower among aviptadil vs. placebo participants during each infusion ($p<0.001$), but returned to parity by 2 hours after completing the infusion (Figure 3). Further details on hypotension adverse events associated with the infusion are provided in Table S32.

The primary safety outcome of death, serious adverse events, organ failure, serious infection, or grade 3 or 4 adverse events through Day 5 (Tables 3 and S33-S46) was experienced by 63% (n=146) of participants in the aviptadil compared to 56% (n=129) in the placebo groups, OR 1.40 (95% CI 0.94-2.08), p=0.10. Using data through Day 28, the percentages were 78% (n=181) versus 75% (n=172) in the aviptadil and placebo groups, respectively, with HR 1.17 (95% CI 0.95-1.44), p=0.15 (Tables 3 and S47-S61 and Figure S14). While hypotension was more common in the aviptadil than placebo groups during the infusion, the percentage of participants with potentially serious renal complications of hypotension through Day 28, among those without

dialysis at entry, were similar for the aviptadil and placebo groups, 19% (n=41/213) and 18% (n=40/223), respectively (Table 3).

Summaries of serious adverse events, including organ failure and serious infections, and cardiovascular events through Day 90, and laboratory abnormalities through Day 5 are in the Supplemental Appendix (Tables S62-S66).

Subgroup Analyses

The estimated OR (aviptadil/placebo) for the primary ordinal outcome did not vary according to disease severity (Figure S15). ORs for those receiving HFNO or NIV at entry and IMV or ECMO at entry were 1.04 (95% CI: 0.67-1.60) and 1.21 (95% CI: 0.73-2.04), respectively (p=0.71 for interaction). ORs for the primary endpoint varied across four subgroups defined by use (or nonuse) of remdesivir (p=0.038). Among the 84 participants enrolled in the factorial, ORs (aviptadil/placebo) were 2.11 (95% CI: 0.69-6.46) for those randomized to remdesivir and 3.78 (95% CI: 1.17-12.24) for those randomized to the remdesivir placebo. For those for whom remdesivir was contraindicated (n=22), the OR was 0.64 (95% CI: 0.10-4.08); and for those from whom remdesivir had been started prior to randomization (n=344), the majority of participants, the OR was 0.93 (95% CI: 0.64-1.36). For the 84 participants in the factorial study, ORs (aviptadil/placebo) for those also assigned remdesivir as compared to placebo for remdesivir did not vary (p=0.33) (Figure S15).

There was also possible evidence of heterogeneity for subgroups defined by race/ethnicity. This apparent heterogeneity arose because of an OR (2.71, 95% CI: 1.37–5.33) indicating a possible favorable effect of aviptadil for those of non-Black Hispanic ethnicity and ORs indicating possible unfavorable effects (OR 0.78, 95% CI:

0.34–1.83 for Blacks, and OR 0.76, 95% CI: 0.46–1.23 for Whites) for other race/ethnicity groups (Figure S15). Subgroup analyses for Day 90 mortality (Figure S16 and Table S67) and the Day 5 and 28 composite safety outcomes are summarized in Figures S17–S18.

Follow-up results for the 84 participants randomized to remdesivir vs. placebo are presented in Section 7 of the Supplementary Appendix.

DISCUSSION

In this multicenter phase III trial of participants hospitalized for COVID-19-associated respiratory failure, treatment with aviptadil did not improve the primary ordinal outcome or survival at Day 90 compared to placebo. Other secondary endpoints also did not demonstrate efficacy for aviptadil. Safety analyses were largely consistent with the known safety profile of aviptadil—hypotension, diarrhea, and facial flushing were the most common and prominent events associated with infusion.

This trial specifically addresses patients with critical COVID-19 acute hypoxemic respiratory failure, who suffer the highest COVID-19-related mortality.[18-20] In vitro, aviptadil has four potential mechanisms of action relevant to COVID-19 acute hypoxemic respiratory failure, including suppression of SARS-CoV-2 replication, decrease in viral cytopathy, modulation of monocyte-derived inflammation, and increases in surfactant production.[5] Based on multiple complementary mechanisms of action, experience with pre-pandemic ARDS, and an exploratory efficacy signal from a previous Phase 2/3 randomized trial,[6] aviptadil was a logical lung-specific agent for

investigation in COVID-19 acute hypoxemic respiratory failure. While in the present study aviptadil infusion appeared safe in a closely monitored, largely ICU, setting in which on-treatment hypotension can be promptly addressed, we found no evidence to suggest that aviptadil has a therapeutic role for patients with COVID-19 acute hypoxemic respiratory failure.

Although more than half of enrolled participants reported Hispanic ethnicity or non-White race, the trial had limited power to explore subgroups based on race/ethnicity. A possible favorable effect of aviptadil observed among Hispanic participants (and a possibly similar effect among patients in the remdesivir factorial, who were more often Hispanic) must be interpreted with caution, due to the absence of an overall treatment effect as well as the large number of subgroups assessed.

Strengths and limitations

This trial demonstrates the feasibility of robust trials specific to critical COVID-19 acute hypoxemic respiratory failure, with enhanced safety monitoring adapted to the specific patient population. Study drug was infused with intensive monitoring, structured management guidance for hypotension, and specific grading tables for hypotension.

The safety protocols used within this trial aimed to balance potential risks and benefits, emphasizing infusion pauses and dose reduction rather than substantial increases in vasopressor therapy and/or fluid loading to counter the hypotensive effects of aviptadil, an investigational agent with unproven clinical benefit. This approach resulted in 24% of assigned participants not receiving the full prescribed dose of aviptadil across the three infusion days, although 97% of participants received 50% or more of the target dose. While it is therefore possible that the dose or duration of

aviptadil used (3 days of escalating doses, 12 hours per day) was not ideal, we employed dosing conventions used in prior studies at the time of study launch that pharmacokinetic modeling suggests achieve adequate lung concentrations.[5,21,22] Furthermore, the average decrease in MAP of 5-7 mmHg on the second and third days of infusion suggests that a higher dose of aviptadil would not be well tolerated. Given the lack of efficacy and increasing intolerance on later dosing days, we believe it unlikely that longer courses of treatment would have a benefit.

Methodological innovations include use of a novel, patient-centered endpoint and a pragmatic definition of respiratory failure that included patients receiving HFNO.[10,11] The primary endpoint combined mortality and the speed with which survivors recovered; the definition of recovery was patient-centered given the substantial burden of new supplemental oxygen and/or failure to return home. The inclusion of patients receiving HFNO is justified based on the homogeneity of this population (all had COVID-19 pneumonia as the cause of their hypoxemic respiratory failure), the fact that 40% of patients receiving HFNO at baseline subsequently underwent invasive mechanical ventilation, and the concordance of results between patients receiving HFNO or invasive mechanical ventilation at baseline.

Additional strengths of this trial include rigorous safety protocols for the study of a vasodilating agent in patients with or at risk for hypotension, the racial/ethnic diversity of participants, use of evidence-based standard of care therapy, and standardized ascertainment of endpoints. Specifically, ascertainment of the primary, patient-centered endpoint through Day 90 was >95%, suggesting that (with appropriate resources and training) outcomes beyond hospital mortality can be reliably measured in this complex and critically ill population.

Our trial has other limitations. First, the trial has limited power for subgroup analyses. Second, while the trial was performed after SARS-CoV-2 vaccines were generally available, most participants had not been vaccinated, limiting generalization to a more vaccinated population. Third, while the vast majority of trial participants received corticosteroids, second-line immune-suppression was added to NIH COVID-19 treatment guidelines for hospitalized patients with rapidly worsening hypoxemia during the conduct of the TESICO trial, and only 34% of trial participants received second-line immune-suppression. Fourth, enrollment in the remdesivir factor of the 2x2 factorial was limited by extensive pretreatment in the patient population, and as a consequence, planned comparisons of remdesivir with placebo are substantially underpowered. Fifth, we did not collect formal screening logs from enrolling sites, although we enrolled with broad eligibility criteria at diverse sites, and the enrolled trial population was ethnically diverse, suggesting good generalizability.

In summary, we found no evidence that intravenous aviptadil improved clinical outcomes among patients with COVID-19-associated acute hypoxemic respiratory failure; inferences regarding remdesivir are limited by sample size.

Research in Context

Evidence before this study

Mortality remains high among hospitalized patients with COVID-19 who experience critical hypoxemic respiratory failure. While certain immunomodulators (especially glucocorticoids and perhaps baricitinib and tocilizumab) have suggested efficacy in this critically ill population, mortality remains high. Lung-specific therapies are an important priority for patients with this condition, given the strong association between the severity of lung failure and ultimate patient outcomes. Aviptadil, the synthetic form of Vasoactive Intestinal Peptide, is a neuropeptide hormone with positive pleiotropic effects in pre-clinical models. A phase 2/3 trial of intravenous aviptadil among hospitalized patients with COVID-19 and respiratory failure suggested the possibility of efficacy for intravenous aviptadil in this population. In addition, prior trials suggested the possibility that the antiviral remdesivir may have efficacy in this population, although this is not certain. We serially searched MEDLINE in English from 1970 to 2021 for (“aviptadil” or “remdesivir”) and (“COVID” or “novel coronavirus” or SARS-CoV-2).

Added value of this study

In this multicenter Phase 3 trial, we evaluated three daily infusions of intravenous aviptadil vs. placebo and/or 10 days of intravenous remdesivir in the setting of standard care (including glucocorticoid therapy). Aviptadil did not improve the primary endpoint of recovery status at Day 90; nor did aviptadil improve any other endpoint. The anticipated safety profile was confirmed—flushing, hypotension, and diarrhea were all more common in the aviptadil-assigned group. Few patients were randomized to the remdesivir vs. placebo comparison.

Implications of all the available evidence

Aviptadil does not appear to have a role in the treatment of critical respiratory failure among patients hospitalized with COVID-19. Other lung-related therapies should be sought in this severely underserved population.

ACKNOWLEDGMENTS

We thank the participants and families whose collaborative spirit and dedication to science at a time of great personal stress made this trial possible. We also thank the members of the ACTIV-3b / TESICO data and safety monitoring board — Graeme A. Meintjes, M.B., Ch.B., Ph.D. (chair), Wendy Armstrong, M.D., David Glidden, Ph.D., Jesse Hall, M.D., Yvonne Maldonado, Ph.D., Barbara E. Murray, M.D., Stuart Campbell Ray, M.D., Valeria Cavalcanti Rolla, M.D., Ph.D., Haroon Saloojee, M.B., B.Ch., Anastasios A. Tsiatis, Ph.D., Paul A. Volberding, M.D., Rieke van der Graaf, Ph.D., and Sally Hunsberger, Ph.D. (executive secretary) — for their review of the protocol and their guidance based on interim reviews of the data.

DATA SHARING STATEMENT

Deidentified data and supporting documentation, including the protocol, statistical analysis plan, informed consent document, and data dictionary will be made available to researchers after approval of a proposal for use of the data. Proposals for data use should be submitted by means of the research proposal form on the INSIGHT website (www.insight-trials.org).

Contributions of Writing Committee Members

Responsible for decision to submit the manuscript: Brown, Neaton, Lane, Barkauskas.

Directly accessed and verified the underlying data: Sharma, Grund.

Composed the initial manuscript: Brown, Barkauskas (no outside medical writer was used).

Conceptualization: Lundgren, Lane, Neaton, Gelijns, Thompson, Kan, Davey, Babiker, Polizzotto, Brown, Ginde, Barkauskas.

Investigation: Brown, Barkauskas, Grund, Sharma, Phillips, Leither, Peltan, Lanspa, Gilstrap, Mourad, Lane, Beitler, Serra, Garcia, Almasri, Fayed, Hubel, Harris, Middleton, Barrios, Mathews, Goel, Acquah, Mosier, Hypes, Campbell, Khan, Hough, Wilson, Levitt, Duggal, Dugar, Goodwin, Terry, Chen, Torbati, Iyer, Sandkovsky, Johnson, Robinson, Matthay, Aggarwal, Douglas, Casey, Hache-Marliere, Youssef, Knemdirim, Leshnower, Awan, Pannu, O'Mahony, Manian, Hayanga, Wortmann, Tomazini, Miller, Jensen, Murray, Bickell, Zitakia, Burris, Higgs, Natarajan, Dewar, Schechner, Kang, Arenas-Pinto, Hudson, Ginde, Self, Rogers, Oldmixon, Morin, Sanchez, Weintrob, Cavalcanti, Davis-Karim, Engen, Denning, Thompson, Gelijns, Kan, Davey, Lundgren, Babiker, Neaton, Lane.

Data curation: Sharma, Grund, Neaton.

Formal analysis: Phillips, Sharma, Grund, Babiker, Neaton.

Funding acquisition: Lundgren, Lane, Neaton, Gelijns, Thompson, Kan, Davey, Babiker.

Supervision: Lane, Lundgren, Neaton, Gelijns, Thompson, Kan, Davey, Babiker, Higgs.

Review & editing manuscript: Brown, Barkauskas, Grund, Sharma, Phillips, Leither, Peltan, Lanspa, Gilstrap, Mourad, Lane, Beitler, Serra, Garcia, Almasri, Fayed, Hubel, Harris, Middleton, Barrios, Mathews, Goel, Acquah, Mosier, Hypes, Campbell, Khan, Hough, Wilson, Levitt, Duggal, Dugar, Goodwin, Terry, Chen, Torbati, Iyer, Sandkovsky, Johnson, Robinson, Matthay, Aggarwal, Douglas, Casey, Hache-Marliere, Youssef, Knemdirim, Leshnower, Awan, Pannu, O'Mahony, Manian, Hayanga, Wortmann, Tomazini, Miller, Jensen, Murray, Bickell, Zitakia, Burris, Higgs, Natarajan, Dewar, Schechner, Kang, Arenas-Pinto, Hudson, Ginde, Self, Rogers, Oldmixon, Morin, Sanchez, Weintrob, Cavalcanti, Davis-Karim, Engen, Denning, Thompson, Gelijns, Kan, Davey, Lundgren, Babiker, Neaton, Lane.

Declaration of Interests

CEB reports funding from the National Institutes of Health (NIH) for the Aviptadil study, during the conduct of the study. BG reports grants from the NIH, during the conduct of the study. SS reports a grant from the NIH, during the conduct of the study. ANP reports grants from the William T. Grant Foundation (WT), the National Institute for Health and Care Research (NIHR), UK Research and Innovation (UKRI), and the Bill and Melinda Gates Foundation (BMGF) and consulting fees from BMGF, outside of the submitted work. IDP reports funding from NIH and the National Institute of General Medical Sciences (NIGMS), during the conduct of the study, a grant from Janssen for the study of influenza patient reported outcomes and a contract with Regeneron for a COVID-19 therapy trial, outside of the submitted work. JRB reports a grant from the NIH, during the conduct of the study, grants from the NIH, Quantum Leap Healthcare Collaborative, and Sedana Medical, consulting fees from Sedana Medical, and compensation from Hamilton Medical for participation as a Medical Monitor, outside of the submitted work. ESH reports study materials from NeuroRx, Inc. and Gilead through the National Heart, Lung, and Blood Institute (NHLBI) subcontract, during the conduct of the study, subcontracts with Bristol Meyers Squibb (BMS), Allergan, Gilead, and Janssen for Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-1) clinical trial, subcontracts with Astra Zeneca, Brii Biosciences, Vir Biotechnology, Inc., and Eli Lilly for Therapeutics for Inpatients with COVID-19 (TICO) clinical trial, and additional subcontracts with Rigel, APEIRON Biologics AG and Trevena for Novel Experimental COVID-19 Therapies Affecting Host Response (NECTAR) clinical trial, outside of the submitted work. EM reports study materials from NeuroRx, Inc. and Gilead through NHLBI subcontract, during the conduct of the study, subcontracts with BMS, Allergan, Gilead, and Janssen for ACTIV-1 clinical trial, subcontracts with Astra Zeneca, Brii Biosciences, Vir Biotechnology, Inc., and Eli Lilly for TICO clinical trial, and additional subcontracts with Rigel, APEIRON Biologics AG and Trevena for NECTAR clinical trial, outside of the submitted work. MAGB reports study materials from NeuroRx, Inc. and Gilead through NHLBI subcontract, during the conduct of the study, subcontracts with BMS, Allergan, Gilead, and Janssen for ACTIV-1 clinical trial, subcontracts with Astra Zeneca, Brii Biosciences, Vir Biotechnology, Inc., and Eli Lilly for TICO clinical trial, and subcontracts with Rigel, APEIRON Biologics AG and Trevena for NECTAR clinical trial, outside of the submitted work. KSM reports grants and contracts from NIH, NHLBI, and the Society for Critical Care Medicine, participation as a steering committee member for Roivant/Kinevant Sciences, and employment as a Clinical Research Physician at Chiesi USA, Inc., outside of the submitted work. JM reports receiving study materials and funding from the Albert Einstein College of Medicine for the study protocol, during the conduct of the study. CH reports funding from the National Institute of Allergy and Infectious Diseases (NIAID) in the form of per patient payments for “A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with Acute Respiratory Distress Syndrome Associated with COVID-19”, during the conduct of the study. AK reports grants from Eli Lilly, AstraZeneca, 4D Medical, United Therapeutics, Regeneron Pharmaceuticals, and Dompe Pharmaceuticals and consulting fees from Dompe Pharmaceuticals for clinical trial design, outside of the submitted work. AD reports grants from NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) network and the Centers for Disease Control and Prevention (CDC) and Data Safety Monitoring Board (DSMB) or Advisory Board participation for Alung Technologies, outside of the submitted work. SD reports a grant from Chest Sonosite Ultrasound to

study of incidence of Deep Vein Thrombosis (DVT) in COVID-19 patients, during the conduct of the study. AJG reports payment from Sound Pharmaceuticals for participation as a Medical Monitor for a COVID therapeutic trial, outside of the submitted work. USS reports consulting fees from Shionogi, Paratek, and ViiV Healthcare for participation on Advisory Boards and speaking fees from Shionogi and Paratek, outside of the submitted work. NJJ reports grants from CDC, Department of Defense (DOD), and NIH and participation on a DSMB, outside of the submitted work. MAM reports grants from NIH and NIAID, during the conduct of the study. NA reports funding from NIH, during the conduct of the study. JDC reports grants from NIH and DOD, outside of the submitted work. DDM reports funding from the Danish National Research Foundation (DNRF126), during the conduct of study. AAG reports funding from NIH, during the conduct of the study, grants or contracts from NIH, DOD, CDC, Faron Pharmaceuticals, and Abbvie and participation on a DSMB or Advisory Board for NIH, outside of the submitted work. WHS reports funding from NIH and NIAID, during the conduct of the study. CFO reports contracts with NIH and NHLBI, outside of the submitted work. BTT reports a grant from NHLBI, consulting fees from Bayer, Genetec, and Novartis, and participation on a DSMB or Advisory Board for Aperion, outside of the submitted work. VK reports subcontracts with University of Minnesota, NIAID, and NIH for the TICO and Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO) platform trials, outside of the submitted work. AGB reports a grant from University of Minnesota, during the conduct of the study, grants from the Medical Reserve Corps (MRC) and UKRI, payment from NIAID for participation on a COVID-19 Vaccines DSMB, and participation on the World Health Organization (WHO) Trial Data and Safety Monitoring Committee (DSMC), outside of the submitted work. JDN reports grants from NIAID, NIH, and Leidos Biomedical, outside of the submitted work. HCL reports employment from NIAID, during the conduct of study.

REFERENCES

1. Peltan ID, Caldwell E, Admon AJ, et al. Characteristics and Outcomes of US Patients Hospitalized With COVID-19. *American journal of critical care : an official publication, American Association of Critical-Care Nurses* 2022; **31**(2): 146-57.
2. Hasan SS, Capstick T, Ahmed R, et al. Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroids use: a systematic review and meta-analysis. *Expert review of respiratory medicine* 2020; **14**(11): 1149-63.
3. Merchant HA, Kow CS, Hasan SS. COVID-19 first anniversary review of cases, hospitalization, and mortality in the UK. *Expert review of respiratory medicine* 2021; **15**(8): 973-8.
4. Said SI. Vasoactive intestinal peptide. *Journal of endocrinological investigation* 1986; **9**(2): 191-200.
5. Temerozo JR, Sacramento CQ, Fintelman-Rodrigues N, et al. VIP plasma levels associate with survival in severe COVID-19 patients, correlating with protective effects in SARS-CoV-2-infected cells. *J Leukoc Biol* 2022; **111**(5): 1107-21.
6. Youssef JG, Lavin P, Schoenfeld DA, et al. The Use of IV Vasoactive Intestinal Peptide (Aviptadil) in Patients With Critical COVID-19 Respiratory Failure: Results of a 60-Day Randomized Controlled Trial. *Critical care medicine* 2022; **50**(11): 1545-54.
7. Amstutz A, Speich B, Mentré F, et al. Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. *Lancet Respir Med* 2023, https://doi.org/10.1016/S2213-2600(22)00528-8.
8. LaVange L, Adam SJ, Currier JS, et al. Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV): Designing Master Protocols for Evaluation of Candidate COVID-19 Therapeutics. *Ann Intern Med* 2021; **174**(9): 1293-300.
9. Buchman TG, Draghia-Akli R, Adam SJ, et al. Accelerating Coronavirus Disease 2019 Therapeutic Interventions and Vaccines-Selecting Compounds for Clinical Evaluation in Coronavirus Disease 2019 Clinical Trials. *Critical care medicine* 2021; **49**(11): 1963-73.
10. Matthay MA, Thompson BT, Ware LB. The Berlin definition of acute respiratory distress syndrome: should patients receiving high-flow nasal oxygen be included? *Lancet Respir Med* 2021; **9**(8): 933-6.
11. Brown SM, Peltan ID, Barkauskas C, et al. What Does Acute Respiratory Distress Syndrome Mean during the COVID-19 Pandemic? *Ann Am Thorac Soc* 2021; **18**(12): 1948-50.
12. National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. 2022. https://www.covid19treatmentguidelines.nih.gov/ (accessed 5/25/2022.
13. McCullagh P. Regression models for ordinal data. *Journal of the Royal Statistical Society: Series B (Methodological)* 1980; **42**(2): 109-27.
14. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94**(446): 496-509.

15. Zhou B, Latouche A, Rocha V, Fine J. Competing risks regression for stratified data. *Biometrics* 2011; **67**(2): 661-70.
16. Aalen OO, Johansen S. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. *Scandinavian Journal of Statistics* 1978: 141-50.
17. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *The Annals of statistics* 1988: 1141-54.
18. Group RC, Horby PW, Mafham M, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv* 2021: 2021.06.15.21258542.
19. RECOVERY Investigators. Dexamethasone in Hospitalized Patients with Covid-19. *New England Journal of Medicine* 2020; **384**(8): 693-704.
20. ACTIV-3–Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Tixagevimab-cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. *Lancet Respir Med* 2022; **10**(10): 972-84.
21. Kane MG, O'Dorisio TM, Krejs GJ. Production of secretory diarrhea by intravenous infusion of vasoactive intestinal polypeptide. *N Engl J Med* 1983; **309**(24): 1482-5.
22. Virgolini I, Raderer M, Kurtaran A, et al. Vasoactive intestinal peptide-receptor imaging for the localization of intestinal adenocarcinomas and endocrine tumors. *N Engl J Med* 1994; **331**(17): 1116-21.