Supplementary Appendix

Contents:

Supplement to:

Intravenous Aviptadil and Remdesivir for Treatment of COVID-19-associated Hypoxemic Respiratory Failure

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

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

Contents

1 ACTIV-3b / TESICO Study Group

U.S. National Institute of Allergy and Infectious Diseases incl. Department of Clinical Research: H. Clifford Lane, M.D., Elizabeth S. Higgs, M.D., D.M.T.H., M.I.A., John Tierney, B.Sc.N., Susan E. Vogel, R.N., B.Sc.N., Laura A. McNay, M.Sc., Kelly Cahill, R.N., M.Sc., C.C.R.C., R.A.C., Page Crew, Pharm.D., M.P.H., B.C.P.S., Ratna Sardana, B.A., Sharon Segal Raim, M.P.H., Katy Shaw-Saliba Sc.M., Ph.D., Negin Atri, M.P.H., Mark Miller PharmD, B.C.P.S., R.A.C., David Vallee, PharmD, M.P.H., Lucy Chung, Pharm D., CCRP, Nayon Kang, PharmD, M.S., Yvette Delph, MBBS, D.A.

Foundation for the National Institutes of Health, The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) and Operation Warp Speed: Stacey J. Adam, Ph.D., Sarah Read, M.D., Ruxandra Draghia-Akli, M.D., Ph.D., Rachel Harrigan, M.D.

INSIGHT SDMC, Division of Biostatistics, School of Public Health and School of Statistics, University of Minnesota, Minneapolis, MN, USA: James D. Neaton, Ph.D., Amy Carlsen, R.N., Anita Carter, Eileen Denning, M.P.H., Alain DuChene, Kate Eckroth, M.P.H., Nicole Engen, M.S., Alex Frase, Birgit Grund, Ph.D., Merrie Harrison, Sue Meger, Shweta Sharma Mistry, M.S., Kien Quan, M.S., Siu Fun Quan, Cavan Reilly, Ph.D., Greg Thompson, Jamie Walski, M.H.A.

Cardiothoracic Surgical Trials Network (CTSN) International Coordinating Center (ICC).
Icahn School of Medicine at Mount Sinai, New York, USA: Annetine C. Gelijns, Ph.D., Alan J. Moskowitz, M.D., Emilia Bagiella, Ph.D., Ellen Moquete, R.N., B.S.N., Karen O'Sullivan, M.P.H., Mary E. Marks, R.N., B.S.N., Evan Accardi, B.A., Emily Kinzel, M.P.H., Sarah Burris M.H.A., Gabriela Bedoya, Lopa Gupta, M.P.H., Jessica R. Overbey, Dr.P.H., Maria L. Padillia, M.D., Milerva Santos, M.P.A.

CTSN Steering Committee Chair, Cleveland Clinic Foundation: Marc A. Gillinov, M.D.

U.S. National Heart Lung and Blood Institute: Marissa A. Miller, D.V.M., M.P.H., Wendy C. Taddei-Peters, Ph.D., Kathleen Fenton, M.D., M.S.

Duke University Health System: Peter K. Smith, M.D., Christina E. Barkauskas, M.D., Daniel L. Gilsreap, M.D., Andrew M. Vekstein, M.D., Emily R. Ko, M.D.,.PhD., Ahmad Mourad, M.D., Mashael S. Al-Hegelan, M.D., Kathleen Lane, B.Sc.N., R.N., Lauren M. McGowan, B.Sc., E.M.T.B., Mary Motta, B.Sc.N., R.N, Shauna Howell, B.Sc.N., R.N., Francine Bent, B.Sc.N., R.N., Rachel Kalager, B.Sc.N., R.N., Emmanuel Chan, M.H.E., Heather L. Aloor, M.Sc., S. Michelle Griffin, M. P. H., E.M.T.P., Anna Covington, B.Sc., Beth McLendon-Arvik, Pharm.D., Barbara Bussadori, R.Ph., Mary Miller-Bell, Pharm.D., Cathy Sampey, Pharm.D., Vincent Gaver, Pharm.D., B.C.P.S., Beth A. Hollister, B.Sc.N., R.N., Dana M. Giangiacomo, B.Sc., Alena Pauley, B.A., A.Sc., Aashay Patel, B.S.P.H., Chris Classon, B.A., A.Sc., Madison Frazier, B.Sc., Robyn Osborne, M.S., Debbi H. Conlon, A.A.S., H.T.(A.S.C.P.), Marybeth Joshi, M.P.H.

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Emory University: Brad Leshnower, M.D., F.A.C.S., William Bender, M.D., M.P.H., Jeffrey Miller, M.D., Katherine Nugent, M.D., Woodrow Farrington, M.D., Kim T. Baio, R.N., M.S.N., Mary K. McBride, R.N., B.S.N., M.A.S., Michele Fielding, R.N., B.S.N., C.C.R.C., Sonya Mathewson, R.N., B.S.N., C.C.R.C., Kristina Porte, B.A., C.C.R.C., Elizabeth Haley, R.N., B.S.N., C.C.R.N., Susan Rogers, R.Ph., Derrick Tyler, C.C.R.P.

Texas Heart Institute: Emerson Perin, M.D., Ph. D., Briana Costello, M.D., Prasad Manian, M.D., Alexander Postalian, M.D., M. Rizwan Sohail, M.D., Punit Hinsu, Pharm.D., Carolyn Watson, Casey Kappenman, M.S., James Chen, R.N., B.S.N., Kim Walker, Melyssa Fink, Gabrielle Phillip, Kim Mahon, Lydia Sturgis

Mount Sinai Medical Center: Kusum Mathews, M.D., Samuel Acquah, M.D., Neha Goel, M.D., Patrick Maher, M.D., Linda Rogers, M.D., Nicole Ng, M.D., Jason Marshall, PA-C, Adel Bassily-Marcus, M.D., Ivy Cohen, Shamini Ramoo, Aryan Malhotra, Jonathan Kessler, R.N., Rebekah Goetz

West Virginia University Medicine: Vinay Badhwar, M.D., Jeremiah Hayanga, M.D., Lisa Giblin Sutton, Roger Williams, Elizabeth Berry Bartolo, Dmitry Walker, Robin Bunner, Chad Glaze, Tanja Aucremanne, James Bishop, Macey Kelley, Autumn Peterson, Erica Sauerborn, Robin Reckart, Brittany Miller

Columbia University Irving Medical Center: Jeremy R. Beitler, M.D., M.P.H., Aaron Mittel, M.D., Anita Darmanian, M.D., Amanda Rosen, M.D., Purnema Madahar, M.D., John Schicchi, M.D., Katarzyna Gosek, Pharm.D., Amy Dzierba, Pharm.D., Romina Wahab, M.D., Ivan Garcia, Bsc-RRT, Connie Eng, Pharm.D., Alexis Serra, M.D., M.P.H.

Houston Methodist Hospital: Jihad Georges Youssef, M.D., Mukhtar Al-Saadi, M.D., Faisal Zahiruddin, D.O., Mohi Syed, M.D., Michael George Pharm.D., B.C.P.S., Varsha Patel, R.Ph., Chisom Onwunyi, Rosa Barroso da Costa

Prevention and Early Treatment of Acute Lung Injury Network (PETAL) ICC

Massachusetts General Hospital: B. Taylor Thompson M.D., Crystal North M.D., Cathryn Oldmixon R.N., Nancy Ringwood B.S.N., Laura Fitzgerald B.A./B.S., Haley D. Morin, B.S.N, Ariela Muzikansky R. N., B.A./B.S., Richard Morse B.A./B.S.

PETAL Steering Committee Chair, Johns Hopkins University: Roy G. Brower, M.D.

U.S. National Heart Lung and Blood Institute: Lora A, Reineck M.D., M.S., Karen Bienstock, PA-C, M.S.

ALIGNE SCC

SCC Lead Investigators: Baystate Medical Center: Jay S. Steingrub, M.D., Brigham and Women's Hospital: Peter Hou M.D.

Baystate Medical Center: Jay S. Steingrub M.D., Mark A. Tidswell M.D., Lori-Ann Kozikowski R.N., B.S.N., C.C.R.N., Cynthia Kardos R.N., B.S.N., C.C.R.N., Leslie De Souza

Boston SCC

SCC Lead Investigators: Beth Israel Deaconess Medical Center: Daniel Talmor M.D. and Nathan Shapiro M.D.

Massachusetts General Hospital: Kathryn Hibbert M.D., Kelsey Brait B.B.A., B.S., Mamary Kone, M.D. M.P.H.

California SCC

SCC Lead Investigators: University of California San Francisco: Michael A. Matthay M.D., David Geffen School of Medicine at UCLA: Gregory Hendey M.D.

University of California San Francisco, Mount Zion: Michael A, Matthay, M.D., Kirsten N. Kangelaris M.D., M.A.S., Kimia Ashktorab B.S., Rachel Gropper, BS, Anika Agrawal BA, Kelly Timothy, RN, Hanjing Zhuo M.P.H.

University of California Fresno: Eyad Almasri, M.D.; Mohamed Fayed, M.D.; Kinsley Hubel, M.D.; Alyssa Hughes, B.S. CRC; Rebekah Garcia, C.C.R.P.; Adrian Torres, B.S.; Maria Elena Hernandez- Almaraz

Stanford University: Angela Rogers M.D, Joseph Levitt M.D., M.S., Jennifer Wilson M.D., M.S., Rosemary Vojnik B.S, Cynthia Perez B.S., Jordan McDowell B.S., M.S.

UCLA Medical Center: Steven Y. Chang, MD, PhD; Julia Vargas, B.S.

Colorado SCC

SCC Lead Investigators: University of Colorado Hospital: Adit A. Ginde M.D., M.P.H, Marc Moss M.D.

University of Colorado Hospital: Neil Aggarwal M.D., Marc Moss M.D., Adit A. Ginde M.D., Jeffrey McKeehan M.S.N, Carrie Higgins B.S.N, Emily Johnson B.S.N., Suzanne Slaughter M.S.

Denver Health Medical Center: Ivor S. Douglas M.D., David Wyles M.D, Terra Hiller M.S.N., R.N., Judy Oakes Ph.D, Ana Garcia, B.S., Stephanie Gravitz M.P.H., Carolynn Lyle P.A., M.P.H., Diandra Swanson, B.S.

Montefiore-Sinai SCC

SCC Lead Investigators: Montefiore Medical Center: Michelle N. Gong M.D., Mount Sinai Hospital: Lynne D. Richardson, M.D.

Montefiore Medical Center Moses, Montefiore Medical Center Weiler: Michelle Ng Gong, MD, MS; Jen-Ting Chen, MD, MS; Ari Moskowitz, MD, MPH; Amira Mohamed, MD; William Nkemdirim, MD; Brenda Lopez, MD; Omowunmi Amosu, MA; Hiwet Tzehaie, BS; Sabah Boujid, BS.

University of Arizona/Banner University Medical Center Tucson: Jarrod M. Mosier M.D., Cameron D. Hypes M.D., Billie Bixby M.D., Elizabeth Salvagio Campbell PhD, Anitza A. Lopez B.S., JaVon Durley M.D., Boris Gilson B.S.

Ohio SCC

SCC Lead Investigators: University of Cincinnati: R. Duncan Hite M.D., Ohio State University: Henry Wang, M.D., Cleveland Clinic Foundation: Herbert P. Wiedemann, M.D., M.B.A.

Cleveland Clinic Foundation, Cleveland Clinic Fairview Hospital, Cleveland Clinic Marymount Hospital: Abhijit Duggal M.D., Siddharth Dugar M.D., Omar Mehkri M.D., Kiran Ashok, Alexander King, M.S, Connery Brennan, M.S

Ohio State University: Matthew C Exline M.D., MPH, Sonal R Pannu, M.D., MSc., Joshua A Englert M.D., Sarah Karow CCRP, Elizabeth Schwartz, Preston So, Madison So.

Pacific Northwest SCC

SCC Lead Investigators: Oregon Health and Science University: Catherine L. Hough M.D., University of Washington Medical Center: Bryce H. Robinson M.D.

Oregon Health and Science University: Catherine L. Hough M.D., Akram Khan M.D., Olivia F. Krol B.S., Genesis I. Briceno Parra M.D., Emmanuel Nii Lantei Mills M.D., Minn Oh, Ph.D., Jose Pena, M.D., Jesús Alejandro Martínez, B.S.

Cedars-Sinai Medical Center: Peter Chen M.D., Sam S. Torbati M.D., Susan E. Jackman B.S.N., M.S., Emad Bayoumi M.D., Ethan Pascual M.A., Antonina Caudill M.P.H., C.P.H., Po-En Chen, B.S.N., Tabia Richardson, Ph.D., M.P.H., Gregg J. Clapham M.A., Lisa Herrera, Cristabelle Ojukwu B.S., Devin Fine, B.S., Millie J. Gomez, M.D., Yunhee Choi-Kuaea, M.S.W., Gwendolyn Weissberg, B.S., Katherine Isip, B.S., Brittany Mattison, Dana Tran, B.S., Jennifer Emilov Dukov, B.S., Paul Chung, PharmD., Bo Ran Kang, PharmD., Lauren Escobar, PharmD., Trung Tran, B.S., Saba Baig, B.S.

Swedish Medical Center: D. Shane O'Mahony M.D, Julie A. Wallick B.A./B.S., Alexandria M. Duven, R.N., Dakota D. Fletcher B.S.

Harborview Medical Center: Nicholas J Johnson M.D., Bryce RH Robinson M.D., Stephanie Gundel B.S., Megan Fuentes B.S., Maranda Newton B.S., Emily Petersen B.A., Kelsey Jiang B.S.

Southeast SCC

SCC Lead Investigators: Wake Forest Baptist Health: D. Clark Files M.D., Chadwick Miller M.D.

Medical University of South Carolina: Andrew J. Goodwin M.D., Charles Terry M.D., Caitlin Lematty B.S., April Rasberry B.S., Ashley Warden B.S.

Utah SCC

SCC Lead Investigators: Intermountain Medical Center: Samuel Brown M.D., Joseph Bledsoe, M.D.

Intermountain Medical Center: Lindsay M. Leither M.D. Samuel M. Brown M.D., MS, Ithan D. Peltan M.D., M.Sc., Michael J. Lanspa M.D., Kirk Knowlton M.D., Daniel B. Knox M.D, Carolyn Klippel B.S., Brent P. Armbruster B.S., Darrin Applegate B.S., Karah Imel B.S., CCRC, Melissa Fergus MPS, Kasra Rahmati B.S., Hannah Jensen B.S., Valerie T Aston, MBA, CCRP, Joshua Jeppson B. S, J. Hunter Marshall B.S, Jenna Lumpkin A.S. CCRC, Cassie Smith, Tyler Burke B.S., Andrew Gray B.S.,

University of Utah Health: Estelle Harris, M.D., Elizabeth Middleton, M.D., Robert Paine, M.D., Sean Callahan, M.D., Misty Yamane, B.S., Macy Barrios, B.S., Lindsey Waddoups, M.S

Vanderbilt SCC

SCC Lead Investigators: Vanderbilt University Medical Center: Wesley H. Self M.D., M.P.H., Todd W. Rice M.D., M.S.C.I.

Vanderbilt University Medical Center: Wesley H. Self M.D., M.P.H., Todd W. Rice M.D., M.S.C.I., Jonathan D. Casey M.D., M.S.C.I., Jakea Johnson M.P.H, Christopher Gray R.N., Margaret Hays R.N., Megan Roth R.N., Sarah Musick R.N., Karen Miller R.N., Matthew W. Semler, M.D., M.Sc.

INSIGHT Washington ICC, Veterans Affairs (VA) Medical Center, Washington DC: Virginia L. Kan, M.D., Adriana Sánchez, M.S., Laura Popielski, M.P.H., Amy Kambo, M.P.H., Kimberly Viens, Melissa Turner, M.S.W., Michael J. Vjecha, M.D., Amy Weintrob, M.D.

Washington DC VA Medical Center: Omar Awan, M.D., Rachel Denyer, M.D., Rahul Khosla, M.D., Bindu Rajendran, Pharm.D.

MedStar Health Research Institute: Glenn Wortmann, M.D., Melissa Gonzales, B.S. and Theresa Moriarty, M.S.N., R.N., C.C.R.N.

Brazililian Research in Intensive Care Network (BRICNet), Brazil. HCor Research Instiutem Sao Paulo, Brazil: Alexandre Biasi, M.D. and Bruno Tomazini, M.D.

INSIGHT U.S. Department of Veterans Affairs (VA) ICC: Victoria J. Davey, Ph.D., M.P.H., Kousick Biswas, Ph.D., Cristin Harrington, B.A., Amanda Garcia, M.P.H., Tammy Bremer, Tara Burke, Brittany Koker, B.S., Anne Davis-Karim, Pharm.D., David Pittman, B.E., Shikha S. Vasudeva, M.D.

VA Loma Linda Healthcare System: James D. Anholm, MD, Lennard Specht, MD, Aimee Rodriguez, BS, RRT, Han Ngo, Pharm.D., Lien Duong, Pharm D., Matthew Previte, MLS ASCP^{CM}

INSIGHT Copenhagen ICC, CHIP (Centre of Excellence for Health, Immunity and Infections), Rigshospitalet, University of Copenhagen, Copenhagen, Denmark: Jens D. Lundgren, M.D., Ph.D. D.M.Sc., Andrew Phillips, Ph.D., Dorthe Raben, M.Sc., Daniel D. Murray, Ph.D., Charlotte B. Nielsen, Jakob Friis Larsen M.A., Lars Peters M.D., D.M.Sc.

INSIGHT Sydney ICC, The Kirby Institute, University of New South Wales, Sydney, Australia: Gail Matthews, M.B.Ch.B., Ph.D., Anthony Kelleher, M.B.B.S., Ph.D., Mark Polizzotto, M.D., Ph.D., Catherine Carey, B.A., M.Sc., Christina C. Chang, M.D., Ph.D., Nila J. Dharan, M.D., Ph.D., Sally Hough, B.Sc.,

Sophie Virachit, B.Sc., Ph.D., Sarah Davidson, B.N., Daniel J. Bice, B.MSc., Katherine Ognenovska, B.Sc., Ph.D., Gesalit Cabrera, B.MSc., M.I.P.H, Ruth Flynn, B.App. Sc., M.App. Sc.

INSIGHT London ICC, MRC Clinical Trials Unit at UCL, London, UK: Abdel G. Babiker, Ph.D., Alejandro Arenas-Pinto, MBBS, Ph.D, Robert F.Miller, F.R.C.P, Fleur.Hudson, BA.

Gilead Sciences, Foster City, CA, USA: Mazin Abdelghany, M.D.

Leidos Biomedical Research, Inc., Frederick, MD, USA: Beth Baseler, M.S., Marc Teitelbaum, M.D., Adam Schechner, M.D., H. Preston Holley, M.D., Shirley Jankelevich, M.D., Amy Adams, M.S., Nancy Becker, B.S.N., Suzanne Dolney, B.S.N., Debbie Hissey, Shelly Simpson, M.S., Mi Ha Kim, Ph.D., Joy Beeler, M.P.H, Liam Harmon, B.A., Sharon Vanderpuye, B.A., Lindsey Yeon, B.S., Leanna Frye, B.A., Erin Rudzinski, B.S., Molly Buehn, M.S., Vanessa Eccard-Koons, M.S., Sadie Frary, M.S., Leah MacDonald, M.S., Jennifer Cash, B.S., Lisa Hoopengardner, M.S., Jessica Linton, M.S., Michaela Nelson, B.S., Mary Spinelli-Nadzam, B.S., Calvin Proffitt, M.A., Christopher Lee, B.S., Theresa Engel, M.F.S., Laura Fontaine, B.S.N, CK Osborne, B.S., Matt Hohn, M.B.A., Michael Galcik, M.S., DeeDee Thompson, A.A., Jen Sandrus, Jon Marchand, M.S., Jiwan Giri, M.S., Stacy Kopka, M.S.

Frederick National Laboratory for Cancer Research/Leidos Biomedical Research, Inc., Frederick, MD.: Robin L. Dewar, Ph.D., Ven Natarajan, Ph.D., Weizhong Chang, Ph.D., Brad T. Sherman, M.S., Adam W. Rupert, BS, MT(ASCP), Helene Highbarger, M.S., Michael Baseler, Ph.D., Perrine Lallemand, B.S., Tauseef Rehman, M.A,, Tom Imamichi, Ph.D., Sylvain Laverdure, Ph.D., Sharada Paudel, Ph.D., Kyndal Cook, B.S., Kendra Haupt, B.S., Allison Hazen, M.S., Yunden Badralmaa, M.S, Jeroen Highbarger, B.S., Ashley McCormack, B.S.

Advanced Biomedical Laboratories, LLC., Cinnaminson, NJ, USA: Norman P. Gerry, Ph.D., Kenneth Smith, Bhakti Patel, Nadia Domeraski, Marie L. Hoover, Ph.D.

PCI Pharma Services: Nadine DuChateau, Adam Flosi, Rich Nelson, Jelena Stojanovic, Christine Wenner.

2 Supplementary Methods

This section is largely taken from the master protocol, appendices H-1 and H-2 for aviptadil and remdesivir, respectively, and the statistical analysis plan. There are three versions of the master protocol and appendix H-1 (aviptadil), dated March 15, 2021, August 11, 2021, and March 8, 2022. There was only one version of appendix H-2 (remdesivir), dated March 15, 2021. There was also only one version of the statistical analysis plan, dated August 5, 2021.

The major changes in the master protocol and appendix H-1 for each amendment are summarized below.

Version 2.0 (changes from Version 1.0)

- A new grading table for hypotension was added to the master protocol (Table 5 in section 10.1.4).
- Sections 5 and 6 of appendix H-1 were modified to change the criteria for grading hypotension and assessing its expectedness with aviptadil/placebo in the target population.

Version 3.0 (changes from Version 2.0)

- The master protocol was modified to 1) add specimen collection for all participants in the hospital at day 5 (previously, specimens were only collected for participants still in the ICU); and 2) to add the collection of additional health-related outcomes at day 90 and day 180. These changes were made to section 9.1.2 of the protocol.
- Appendix H1 was modified to add daily recording of hypotension through day 28.

Trial design and Randomization

Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO) is a master protocol for carrying out adaptive, randomized, double-blind placebo-controlled trials of investigational agents. Aviptadil and remdesivir were the initial agents studied in TESICO.

The initial studies employed a 2x2 factorial design for patients eligible to receive aviptadil versus matched placebo and remdesivir versus matched placebo. Participants who were not eligible to be randomized to the factorial were randomized 1:1 to either aviptadil versus matched placebo or to remdesivir versus matched placebo depending on eligibility. All participants received standard of care (SOC) plus the randomized treatment assignment.

Randomization was carried out within strata defined by aviptadil/remdesivir eligibility, disease severity and by site pharmacy. Some clinical sites in close proximity to one another planned to share a pharmacy but this did not occur. Thus the randomization scheme can be considered as one in which stratification was by site. Permuted block randomization was used to generate the randomization schedules for each stratum.

The 4 randomization strata defined by aviptadil and remdesivir eligibility were:

Stratum 1: Participants who were eligible for aviptadil and remdesivir, and had not received any remdesivir prior to randomization. These participants were randomized (1:1:1:1) in a 2x2 factorial to the four possible combinations of aviptadil, remdesivir, and the matching placebos for these drugs: 1) aviptadil + remdesivir placebo; 2) aviptadil placebo + remdesivir; 3) aviptadil + remdesivir; and 4) aviptadil placebo + remdesivir placebo. See Figure S1.

Stratum 2: Participants who were not eligible to receive remdesivir (contraindication). These participants were randomized to aviptadil versus aviptadil placebo only.

Stratum 3: Participants who were not eligible to receive aviptadil (contraindication). These participants were randomized to remdesivir versus remdesivir placebo only.

Stratum 4: Participants who have received remdesivir prior to randomization and were eligible for aviptadil. These participants were randomized to aviptadil versus aviptadil placebo only.

Randomization was also stratified by disease severity in 2 strata:

1. Participants receiving high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV).
2. Participants receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO).

After confirming eligibility and obtaining informed consent, designated individuals at the clinical sites used a web-based randomization application to verify eligibility to obtain a study identification (SID) number for blinded agent/matching placebo. This “prescription” was sent to the site pharmacy. The site pharmacist used a web-based pharmacy application to determine which agent/placebo the SID corresponds to. The pharmacist was unblinded and prepared the infusion bags for the patient.

Study Population

According to the statistical analysis plan (version 1.0), comparisons of safety outcomes were to be analyzed by modified intention to treat (mITT), defined as the population of participants who received a complete or partial infusion of the respective blinded study agent. Participants who did not receive any of the aviptadil/matching placebo were excluded from the mITT population for that comparison. All other participants, including those who did not meet strict eligibility criteria (3 participants), those who received a

partial infusion volume on one of the 3 days due to staff error or equipment malfunction (22 participants), and one participant who received a 4th dose of blinded aviptadil are included in the mITT analysis for aviptadil/placebo. Similarly, those who did not receive any of the remdesivir/matching placebo for that comparison were to be excluding from mITT population for that comparison. All other participants, including those who did not meet strict eligibility criteria (2 of the 3 participants also in the aviptadil/placebo comparison), and those who did not receive a dose or received incomplete volume of an expected infusion of blinded remdesivir due to staff error or equipment malfunction (6 participants) were included in the mITT analysis for remdesivir/placebo.

For the comparison of efficacy outcomes, the analysis was to be by intention to treat (all randomized participants) with sensitivity analyses carried out by modified intention to treat.

Ten participants did not receive any infusion of aviptadil/placebo. Six of the 10 participants withdrew consent prior to the infusion; two participants exceeded the vasopressor limit each day on which the infusion was to be given; one participant died before the infusion; and one participant improved prior to infusion.

Considering the reasons why these 10 participants randomized to aviptadil/matching placebo did not receive any of the infusions, a mITT analysis is carried out for both safety and efficacy outcomes. The risk of bias resulting from the exclusion of these 10 patients was considered low in this double-blind trial and this approach allowed potential risks and benefits to be evaluated in the same population.

All of the participants randomized to remdesivir/matching placebo received at least one infusion.

The complete inclusion and exclusion criteria from the protocol are given below.

Inclusion Criteria

1. Age ≥ 18 years;

2. Informed consent by the patient or the patient's legally-authorized representative (LAR);

3. Requiring admission for inpatient hospital acute medical care for clinical manifestations of COVID-19, per the responsible investigator, and NOT for purely public health or quarantine purposes.

4. Current respiratory failure (i.e., receipt of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO used to treat acute hypoxemic respiratory failure).

5. SARS-CoV-2 infection, documented by a nucleic acid test (NAT) or equivalent testing with most recent test within 14 days prior to randomization. (For non-NAT tests, only those deemed to have equivalent specificity to NAT by the protocol team will be allowed. A central list of allowed non-NAT tests will be maintained.)

6. Respiratory failure is believed to be due to SARS-CoV-2 pneumonia.

Exclusion Criteria

1. Known allergy to investigational agent or vehicle
2. More than 4 days since initiation of support for respiratory failure (i.e., receipt of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or ECMO used to treat acute hypoxemic respiratory failure).
3. Chronic/home mechanical ventilation (invasive or non-invasive) for chronic lung or neuromuscular disease (non-invasive ventilation used solely for sleep-disordered breathing is not an exclusion).
4. Moribund patient (i.e., not expected to survive 24 hours)
5. Active use of “comfort care” or other hospice-equivalent standard of care
6. Expected inability to participate in study procedures;
7. In the opinion of the responsible investigator, any condition for which, participation would not be in the best interest of the participant or that could limit protocol-specified assessments;
8. Previous enrollment in TESICO

In addition to these exclusion criteria specified in the master protocol that applied to all investigational agents, additional exclusion criteria could be specified in the appendix for each investigational agent studied.

Agent specific exclusion criteria for aviptadil and remdesivir are given below.

Aviptadil-specific exclusion criteria (see also Protocol Appendix H-1)

- *Refractory hypotension*, defined as infusion of vasopressors at or above norepinephrine equivalent of 0.1 mcg/kg/min (or infusion of more than one simultaneous vasopressor) in prior 4 hours to maintain MAP > 65 mmHg OR systolic blood pressure <90 mmHg or MAP < 65 mmHg at time of enrollment (or randomization, if the patient had already been enrolled) confirmed on two consecutive measurements at least 5 minutes apart (if a single measurement meets those criteria, a second measurement was required). Since aviptadil may induce hypotension, as noted above, patients with critical hypotension were considered to have a different risk:benefit profile that is less likely to favor aviptadil, even where aviptadil is efficacious.

- *Severe diarrhea*, defined as 3 or more liquid bowel movements within the last 24 hours. Since diarrhea is a common side effect of aviptadil, if patients already had severe diarrhea, they were considered to have a different risk:benefit profile that is less likely to favor aviptadil.
- *Current C. difficile infection (CDI)*. CDI generally causes diarrhea, its severity is often gauged in part by the volume of diarrhea, and anti-motility agents that may be used to manage aviptadil-associated diarrhea are contraindicated in CDI. These factors suggested that the risk:benefit ratio in patients with CDI may not be favorable.
- *Pregnancy or current breast-feeding*. Aviptadil was associated with involution of embryos in animal models and may be associated with changes in visceral and/or placental perfusion. It was thus felt not appropriate to infuse aviptadil in pregnant patients or in women who were breastfeeding.
- *End-stage liver disease (ESLD)*, defined as hepatic decompensation in a person with or without cirrhosis, usually associated with ascites (fluid in the peritoneal cavity), jaundice, variceal hemorrhage or hepatic encephalopathy (confusion, change in behavior, forgetfulness). Liver function tests and/or coagulation profile are usually abnormal. An isolated elevation in serum bilirubin did not meet criteria for end-stage liver disease.

Remdesivir-specific exclusion criteria (see also Protocol Appendix H-2)

- Prior receipt of any dose of remdesivir during the present illness.
- GFR <30 ml/min and not receiving dialysis.
- ALT or AST > 10 times the upper limit of normal.
- Unwillingness to commit to avoid sex that may result in pregnancy for at least 7 days after completion of remdesivir or placebo.

Study Treatment Management Guidelines For Blinded Aviptadil Infusion

Pre-Infusion Check to Verify Administration

On days 0, 1, and 2, prior to beginning infusion of blinded aviptadil, sites were to check blood pressure, vasopressor use/dosage, and use of anti-diarrheal medications to determine if the participant was able to receive the blinded infusion.

If hypotensive, i.e., (1) two consecutive SBP measures < 90mmHg or two consecutive MAP readings < 65mmHg, or (2) using two vasopressors or being administered a vasopressor at or higher than 0.1 µg/kg/min norepinephrine equivalent dose, then the participant was not eligible to be infused. If hypotension was expected to be temporary and resolved within an appropriate timeframe, the participant was able to be infused.

The participant was not eligible for infusion that day if, in the opinion of the bedside clinician or site investigator, the participant had had clinically significant and uncontrolled liquid stool within the 24 hours before infusion.

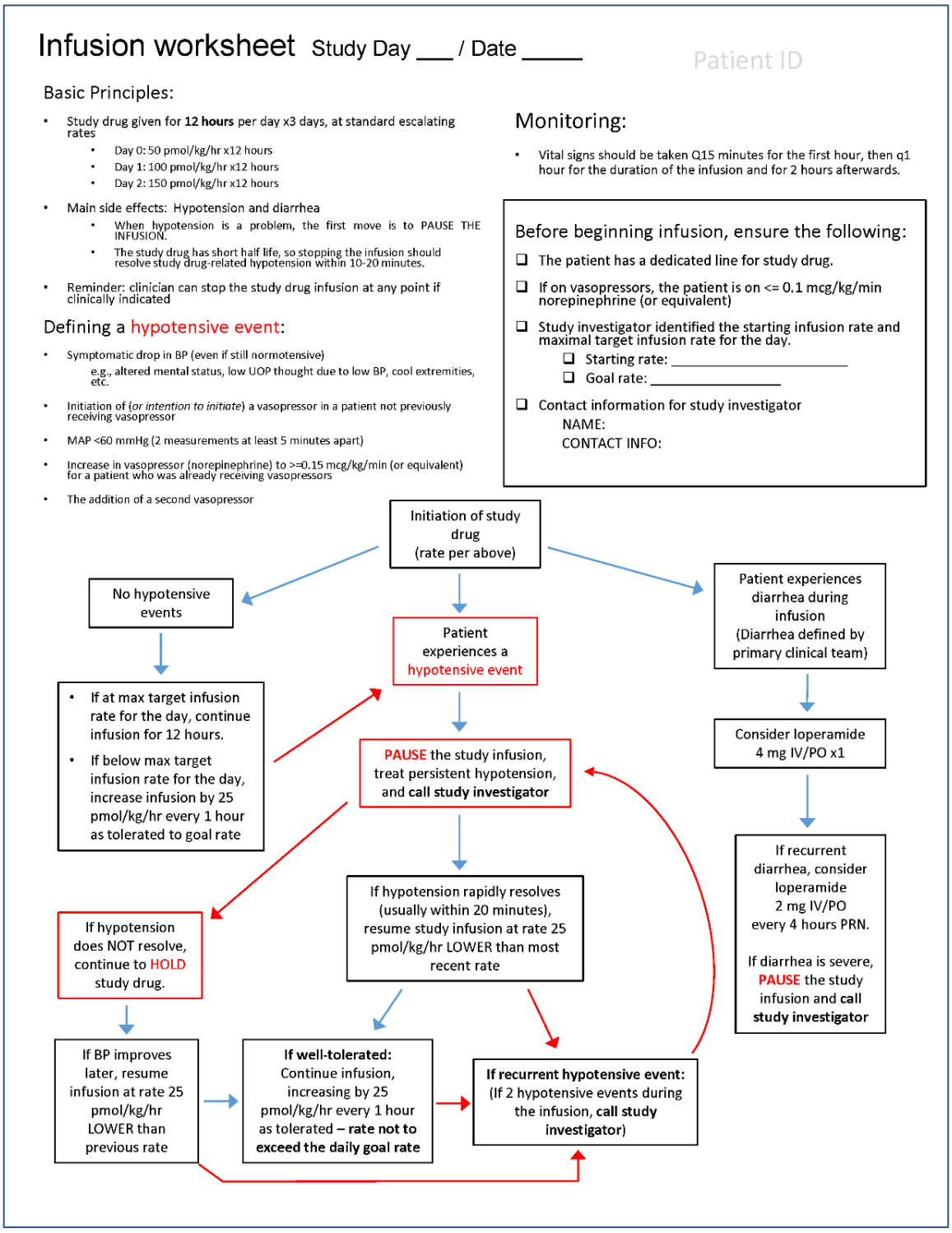
Infusion was also not required once discharged.

Basic Principles for Infusion

- Study drug was given for **12 hours** per day x3 days, at standard escalating rates
  - Day 0: 50 pmol/kg/hr x12 hours
  - Day 1: 100 pmol/kg/hr x12 hours
  - Day 2: 150 pmol/kg/hr x12 hours
- Due to the 12-hour infusion period, it was recommended that the infusion ideally start between 8.00am-noon each day, and at least 4-6 hours after the previous infusion monitoring period.
- Under the direction of the investigator, the proposed starting infusion rate for the day could be reduced or the infusion could be paused and restarted due to infusion reactions or participant circumstances.
- The infusion rate was not to exceed the daily goal infusion rate.
- Main side effects: Hypotension and diarrhea
  - When hypotension was a problem, the first move was to **PAUSE THE INFUSION**.
  - The study drug has a short half-life, so it was considered that stopping the infusion should resolve study drug-related hypotension within 10-20 minutes.
  - Defining a hypotensive event during the infusion:
    - Symptomatic drop in BP (even if still normotensive) e.g., altered mental status, low UOP thought due to low BP, cool extremities, etc.
    - Initiation of (*or intention to initiate*) a vasopressor in a patient not previously receiving vasopressor
    - MAP <60 mmHg (2 measurements at least 5 minutes apart)
    - Increase in vasopressor (norepinephrine) to $\geq$0.15 mcg/kg/min (or equivalent) for a patient who was already receiving vasopressors
    - The addition of a second vasopressor
- Vital signs were to be taken Q15 minutes for the first hour, then q1 hour for the duration of the infusion and for 2 hours afterwards. Starting in October 2021, BP monitoring was allowed to be at the 30 minute mark, 2 hour mark, and every two hours after then.

Infusion Management Worksheet

Below is the infusion management worksheet used by sites to help manage hypotensive events or diarrhea during the infusion.



Study Treatment Management Guidelines For Blinded Remdesivir Infusion

Blinded remdesivir infusions were a 10-day course, with a 200mg loading dose on Day 0 and 100mg doses on subsequent days for those with active assignment. Remdesivir/matched placebo infusions were discontinued upon completion of the course or discharge. Per the treating clinical team, infusions could be discontinued after 5 days if the participant was no longer requiring respiratory support (high flow oxygen, noninvasive ventilation or invasive mechanical ventilation). Participants were to be monitored closely for infusion-related or anaphylactic reactions and eGFR and transaminases were to be monitored as clinically appropriate, per institutional policy. Infusion reactions during the infusion, and within 2 hours after the infusion ended were recorded on a daily infusion checklist.

Primary and Secondary Endpoints

Primary Endpoint

The primary endpoint for both the aviptadil versus placebo and the remdesivir versus placebo comparisons is a 6-category ordinal outcome assessed at day 90 following randomization. The 6 categories of this primary endpoint are defined below.

Category	**Status at 90 days**
1 (Best)	At home and off oxygen. No. of consecutive days at Day 90 ≥ 77
2	49-76
3	1-48
4	Not hospitalized AND either at home on oxygen OR not at home
5	Hospitalized for medical care OR in hospice care
6 (Worst)	Dead

Categories 1-3 define 3 ranked categories of the number of days alive, at home, and not receiving new supplemental oxygen at Day 90 (77 or more consecutive days, 49–76 days, or 1–48 days). Home is defined as the level of residence or facility where the participant was residing prior to onset of COVID-19 which led to the hospital admission (index hospitalization) that led to enrollment in this protocol. Residence or facility groupings to define home are: 1) **Independent/community dwelling** with or without help, including house, apartment, undomiciled/homeless, shelter, or hotel; 2) **Residential care facility** (e.g., assisted living facility, group home, other non-medical institutional setting); 3) **Other healthcare facility** (e.g., skilled nursing facility, acute

rehab facility); and 4) **Long-term acute care hospital** (hospital aimed at providing intensive, longer term acute care services, often for more than 28 days). Lower (less intensive) level of residence or facility will also be considered as home. By definition, "home" cannot be a "short-term acute care" facility. Participants previously residing in a "long-term acute care" hospital recover when they return to the same or lower level of care.

Since some patients might have been receiving supplemental oxygen before their COVID-19 illness, the protocol defined new supplemental oxygen as any supplemental oxygen in participants who were not receiving supplemental oxygen before their COVID-19 illness or an increase in supplemental oxygen above pre-COVID-19 baseline among patients who were receiving supplemental oxygen before their COVID-19.

Only participants who are "recovered" at Day 90 (returned home, free of new supplemental oxygen) enter categories 1-3, and "days recovered" count only the consecutive time period between the last time the participant entered the "recovered" state and Day 90. This means, re-hospitalization, change of residence from home to a higher level of care or re-instating of supplemental oxygen above pre-COVID levels would change the participant's status to "not recovered" and reset the clock.

Categories 4-6 are for patients who are not recovered at Day 90:

- discharged from the hospital but either not yet home, or home but receiving new supplemental oxygen;
- still hospitalized or receiving hospice care; and
- dead.

The worst status at Day 90 defines the ordinal outcome. Therefore, participants who recover (are discharged home, and not receiving new supplemental oxygen) but who require supplemental oxygen at Day 90, are hospitalized at Day 90 or who die at or before Day 90 are categorized in categories 4-6.

Secondary Efficacy Outcomes

Time to recovery through Day 90, defined as alive, at home, and off new supplemental oxygen, and time to death through Day 90, the two major components of the primary ordinal outcome, are key secondary outcomes for both the aviptadil and remdesivir comparisons with placebo.

Several pre-specified secondary efficacy outcomes and outcomes reported in other COVID-19 trials for hospitalized participants are summarized in the main paper or this supplemental appendix. They are listed below.

- Death (death is also considered as component of safety outcomes)
- A 3-category ordinal outcome at Day 90: 1) recovered; 2) alive not recovered; and 3) dead at Day 90
- Time to discharge from the index (initial) hospitalization
- Time to be discharged home (first event)

- Time to be discharged home and off supplemental oxygen (first event)
- Time to sustained recovery through Day 90, defined as being discharged from the index hospitalization, followed by being alive and home for 14 consecutive days
- Composite of death, clinical organ failure, or serious infection through day 90
- Composite of death or worsening of respiratory dysfunction (this and other clinical organ failure events and serious infections are defined in the Safety Outcomes section which follows). These outcomes are considered secondary efficacy outcomes and are also considered as components of the composite safety outcomes specified.
- A 7-category ordinal outcome that assesses the patient's clinical status and oxygen support as defined below:
    - Can independently undertake usual activities with minimal or no symptoms
    - Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
    - Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
    - Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen)
    - Non-invasive ventilation or high-flow oxygen (high flow nasal cannula)
    - Invasive ventilation, extracorporeal membrane oxygenation (ECMO), mechanical circulatory support, or new receipt of renal replacement therapy
    - Death

Safety Outcomes

Adverse events of any grade during each infusion and 2 hours post infusion completion were collected on daily agent-specific checklists (over days 0, 1, and 2 for aviptadil/placebo and over days 0-9 for remdesivir/placebo). Infusion reactions on the remdesivir checklist were used for the remdesivir comparison, and infusion reactions on the aviptadil checklist were used for the aviptadil comparison.

Composite safety outcomes were defined through Days 5, 28 and 90. The composite safety outcome through days 5 and 28 was defined as a composite of five components: i) death, ii) serious adverse events, iii) incident grade 3 or 4 adverse events, including those during and post-infusion, iv) incident organ failure, or v) serious co-infection. The

composite safety outcome through Day 90 included all of the components except grade 3 or 4 adverse events. Definitions for each component of the primary safety outcome are detailed below.

Components of the composite safety outcomes:

i) Death from any cause (collected through Day 90)

ii) Serious adverse event (collected through Day 90)

Definition of serious adverse event (SAE): an untoward or unfavorable medical occurrence in a study participant that resulted in any of the following:

- Death
- Life-threatening (i.e., an immediate threat to life)
- Hospitalization or prolongation of hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital abnormalities/birth defects
- Other important medical events that may jeopardize the participant and/or may require intervention to prevent one of the outcomes listed above

iii) Grade 3 or 4 adverse event (collected through Day 28)

With the exception of hypotension which was graded as explained in the table at the end of this section, adverse events were graded for severity using a toxicity table of the Division of AIDS, NIAID [NIAID Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 2017 (https://rsc.niaid.nih.gov/clinical-research-sites/grading-severity-adult-pediatric-adverse-events-corrected-version-two-one).

For adverse events not in the Division of AIDS table, a generic grading scheme was used. Adverse events were categorized according to codes in the Medical Dictionary for Regulatory Activities (MedDRA®), version 25.1.

The generic definitions for grade 3 and 4 adverse events are below.

- Grade 3: Events causing inability to perform usual social and functional activities; some assistance usually required; medical intervention/therapy required.
- Grade 4: Events causing inability to perform basic self-care functions; medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

iv) Organ failure (collected through Day 90)

Organ failure is defined by development of any of the following clinical events:

1. Worsening respiratory dysfunction:
    a. Increase in the level of respiratory support from high-flow nasal cannula or non-invasive mechanical ventilation at baseline to invasive mechanical ventilation or ECMO, or from invasive mechanical ventilation at baseline to ECMO.
2. Cardiac and vascular dysfunction:
    a. Myocardial infarction
    b. Myocarditis or pericarditis
    c. Congestive heart failure (CHF): new onset NYHA class III or IV, or worsening to class III or IV
    d. Hypotension treated with vasopressor therapy
    e. Atrial or ventricular tachyarrhythmias
3. Renal dysfunction:
    a. New requirement for renal replacement therapy
4. Hepatic dysfunction:
    a. Hepatic decompensation
5. Neurological dysfunction
    a. Acute delirium
    b. Cerebrovascular event (stroke, cerebrovascular accident [CVA])
    c. Transient ischemic events (i.e., CVA symptomatology resolving <24 hrs)
    d. Encephalitis, meningitis or myelitis
6. Hematological dysfunction:
    a. Disseminated intravascular coagulation
    b. New arterial or venous thromboembolic events, including pulmonary embolism and deep vein thrombosis
    c. Major bleeding events [>2 units of blood within 24 hours, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding].

v) Serious co-infection (collected through Day 90)

Serious co-infection is defined as: intercurrent, at least probable, documented serious disease caused by an infection other than SARS-CoV-2, requiring antimicrobial administration and care within an acute-care hospital.

As indicated in section 10.2.3 of the protocol, end organ dysfunction and serious infections were defined as “protocol-specified exempt serious events”. Those events were systematically reported during follow-up but not reported on SAE forms with narratives unless they were considered related to the study agent. These events are listed below.

- Death
- Stroke
- Meningitis
- Encephalitis
- Myelitis
- Myocardial infarction
- Myocarditis
- Pericarditis
- New onset of worsening of CHF (NYHA class 3 or 4)
- Arterial or deep vein thromboembolic events
- Worsening respiratory failure
- Hypotension treated with vasopressor therapy
- Atrial or ventricular arrhythmias
- Renal dysfunction requiring renal replacement therapy
- Hepatic decompensation
- Neurologic dysfunction, including acute delirium and transient ischemic events
- Disseminated intravascular coagulation
- Major bleeding events
- Serious infections

Other than all-cause death, the above list of “protocol-specified exempt serious events” is identical to the “organ failure and serious infections” component in the composite safety outcomes. Most of these events are considered of similar severity as SAEs.

<u>Collection and Grading of Hypotension AEs</u>

Hypotension AEs were graded centrally according to the table below. This grading table was introduced in Version 2.0 of the protocol. Hypotension AEs reported under protocol Version 1.0 were re-graded centrally using information that had been obtained as part of the regular study data collection, augmented by additional information submitted by chart abstraction where required.

Table: Hypotension AE Grading in TESICO protocol version 2.0

AE GRADING	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 LIFE-THREATENING
SERIOUSNESS GUIDANCE*	N	N	N (usually)	Y
Hypotension criteria that apply to all assessments	No intervention or complication meeting criteria for higher grade.	IVF ≥500 mL **OR** low-dose vasopressor (e.g. <0.1 NE [or equivalent])	Moderate-dose vasopressor (e.g. ≥0.1 NE [or equivalent]) **OR** ≥2 vasopressors **OR** multiple interventions	Life-threatening or clinically significant complications **OR** *persistent* clinically significant deterioration.
Additional hypotension criteria for aviptadil/placebo infusion days	No infusion change for hypotension	Decrease infusion rate *for hypotension* **OR** pause infusion with resumption *for hypotension*	Study drug discontinued for day *for hypotension* **OR** study drug not given for day *for hypotension* **OR** study drug discontinued permanently *for hypotension*	No additional criteria

* Guidance provides suggested seriousness alignment with AE grade but does not overrule investigator judgment. In particular, the presence of critical illness influences the threshold for considering a given hypotension AE 'life-threatening' or an 'important medical event.' Evaluation of other factors, including the intensity of intervention required and the event's impact on the patient, are required to determine event seriousness.

Hypotension AEs that occurred *peri-infusion* (during the infusion and up to 2 hours after the infusion) were collected via a checklist of potential infusion reactions on each infusion day. In addition, during the infusion of blinded aviptadil, the peri-infusion mean arterial pressure (MAP) and systolic blood pressure (SBP) values (reported every 2 hours) were used to identify Grade 1 hypotension. Incidence of MAP <65 or SBP <90 mmHg was counted as a grade 1 hypotension AE, unless criteria for a higher grade were met.

During the time between infusions and after the last infusion was completed, hypotension AEs were collected as part of the protocol-specified reporting of grade 3 and 4 AEs.

Serologic and Virologic Assays

Laboratory specimens were collected for consenting participants and stored by clinical sites and periodically sent to a central biorepository, Advanced BioMedical Laboratories (ABML), for use in future research.

A nasal mid-turbinate swab was collected at baseline. Swabs were immediately placed into tubes containing 3 mL of sterile Universal Transport Medium (UTM). Samples were aliquoted into 3 cryovials, frozen, and shipped on a regular basis to ABML.

Four 1.0 mL aliquots of serum and four 1 mL aliquots of plasma were collected at baseline, and on follow-up days 3 and 5. On day 3, samples were only collected if still hospitalized, and on day 5, samples were only collected for participants who were still in the intensive care unit. Two 9 mL tubes, one SST and one EDTA of blood was drawn to obtain the 8 aliquots.

Qualitative RT-PCR analysis of SARS-CoV-2

Extraction, master mix preparation, and RT-PCR were performed as described in the CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel. RNA from the nasal swab samples was isolated on either a Qiagen EZ1 Advanced XL using EZ1 Virus Mini Kits or a Thermo Fisher KingFisher Flex using a MagMAX Viral/Pathogen Nucleic Acid Isolation Kit. RT-PCR mastermix was prepared using Thermo Fisher TaqPath™ 1-Step RT-qPCR Master Mix, CG and the IDT 2019-nCov CDC EUA Kit. RT-PCR was performed on an Applied Biosystems QuantStudio 7 Flex. Ct scores of less than 40 for both nCoV N1 and nCoV N2 probe sets indicated presence of SARS-CoV-2 RNA. These qualitative RNA measurements were centrally determined by ABML, blinded to treatment group.

Quantitative RT-PCR analysis of SARS-CoV-2

Quantitative RT-PCR analysis of the nasal swab samples was performed using the same RNA extracts prepared for the qualitative assay. The assay conditions were the same as outlined in the CDC protocol except the RNaseP probe set was not used. A five-point standard curve with known concentrations (copies/mL) of the SARS-CoV-2 nucleocapsid gene was included in each plate. The reported concentration of each sample was the average of the calculated concentrations from both probes. The lower limit of quantification (LLoQ) for this measurement is 100 copies/mL. These quantitative measurements were centrally determined by ABML, blinded to treatment group.

SARS-CoV-2 Variants.

The presence of the Delta variant versus other variants was determined using an RTPCR assay specifically designed to amplify nucleocapsid of SARS-CoV-2 and N-terminal domain of the Spike gene of the Delta variant. Thus, specimens that were positive for both nucleocapsid and N-terminal domain of the Spike gene of the Delta variant were designated as Delta. Samples dated between November 2021 and May 2022 that were positive by PCR for nucleocapsid of SARS-CoV-2 and negative for Delta

variant were tested for the Omicron variant using a Taqman SARS-CoV-2 mutation panel assay from Thermofisher. Viral RNA sequences using the nasal swab material are being determined for all participants; sequences and PCR test results are available for 329 participants. Agreement between PCR and sequencing was 99% for Delta and 100% for Omicron.

Antibody Levels

Stored plasma specimens were used to measure total anti-SARS-CoV-2 antibody levels. Antibody levels were determined using the BioRad Platelia SARS-CoV-2 Total Ab assay (BioRad, Hercules, California) (anti-N antibodies). Results of this assay are reported as "specimen ratios". Specimen ratios are defined as the specimen optical density (OD) divided by the OD of the control R4 (ODMR4). Specimen ratios ≥ 1.0 are considered positive, those between 0.8 and 1.0 equivocal, and those < 0.8 negative. In this report, we refer to those with levels < 1.0 specimen ratios as having "negative" anti-N Abs and those with specimen ratios ≥ 1.0 as having positive anti-N Abs.

Levels of neutralizing antibodies (nAbs) directed against the SARS-CoV-2 receptor binding domain (RBD) were determined using the GenScript SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) assay (GenScript, Piscataway, NJ) (nAbs). nAbs are expressed as percent binding inhibition; levels ≥ 30% are considered positive for nAbs as recommended by the manufacturer, and those < 30% are considered negative for nAbs.

Antibody determinations were made centrally at the Frederick National Laboratory, Frederick, MD, blinded to the treatment group.

Antigen Levels

SARS-CoV-2 nucleocapsid antigen levels were determined in 90 µL plasma in duplicate using a Quanterix assay (Quanterix, Billerica, MA). The LLoQ was determined to be 3 ng/L. Results below that level were imputed as 2.9 ng/L. The antigen determinations were made centrally at the Frederick National Laboratory, blinded to the treatment group.

Sample Size Assumptions

- The primary analysis will be intention to treat.
- A proportional odds model will be used to compare recovery at Day 90.
- Patients will be assigned the worst category that applies at Day 90.
- The "last-off" method (for return to home and liberation from new supplemental oxygen) is used to calculate days of recovery among those who are recovered on Day 90.
- Approximately 80% of patients will enter the trial on high-flow nasal oxygen, while approximately 20% will enter with non-invasive or invasive mechanical ventilation or ECMO. Control-group event rates for these patients are based on findings from ACTT-1 (see reference 9 of the main paper), and unpublished data from the Intermountain Prospective COVID Registry (IPOC), ISARIC, and other data sources. This includes estimates

of the percentage of patients in each category of respiratory support (i.e., high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO) at baseline.

- Most patients will be discharged in the first month after randomization; based on ACTT-1 and unpublished PETAL Network data, we estimate 25% will be discharged to their home and stay home for 14 days by day 28 following randomization; half of these patients will be discharged to their home on oxygen; and most will receive oxygen for 3-4 weeks. Thus, the category 1 percentage is approximately 12% considering re-initiation of home oxygen and re-hospitalization.
- Categories 2 and 3 are wider and also consider home oxygen re-initiation and re-hospitalization.
- Three categories of time at home off oxygen were considered because an intervention that shortened time on new supplemental oxygen and also decreased mortality was considered clinically relevant.
- Based on unpublished data from the PETAL Network and Intermountain Healthcare, 33% of participants will die by Day 90. A single category is used for death at Day 90 instead of time of death given the target population and planned follow-up.
- At Day 90, < 10% of patients will be in the hospital; and about 10% will be on oxygen or not at home.
- With type 1 error of 0.05 (2-sided) and 80% power to detect the OR of 1.5, sample size is 602. This was increased to 640 (320 in each group) to allow for a small percentage of patients who withdraw consent or are lost to follow-up before Day 90.

The estimated control and treatment arm distribution of endpoint categories used to calculate sample size and power is displayed in the table below.

Estimated Distribution of Endpoint Categories Used for Power Calculation

Category	Status at 90 days	Investigational Agent (%)	Control (%)
1	At home and off oxygen. No. consecutive days at Day 90 ≥ 77	17.0	12.0
2	49-76	27.7	23.0
3	1-48	17.2	17.0
4	Not hospitalized AND either at home on oxygen OR not at home	9.1	10.0
5	Hospitalized for medical care OR in hospice care	4.3	5.0
6	Dead	24.7	33.0
	Total	100.0	100.0

Interim Analysis for Futility

The TESICO protocol and the statistical analysis plan did not specify an interim futility assessment. In part, this was because the primary endpoint requires 90 days of follow-up, and it was anticipated that many randomized participants would not yet have achieved 90 days of follow-up at the time futility analyses would be carried out. That changed in early 2022 when there was a substantial slow-down in enrollment due to new variants that led to less severe infections.

Therefore, on May 1, 2022, a futility plan was defined for the DSMB to be carried out at their next meeting on May 25, 2022. That plan, which was developed by blinded statisticians and clinical investigators, is included as an addendum to the statistical analysis plan and summarized below.

We proposed that futility be assessed at the May 25, 2022 DSMB meeting using conditional power estimates for the primary 6-category ordinal outcome. We also proposed that the recommendation by the DSMB on futility consider the time required to complete enrollment in the trial in addition to conditional power. For example, if enrollment could be completed in 3 months, then conditional power > 0.10 might be acceptable for continuing the trial; if the completion of enrollment required another 12 months, then conditional power of > 0.50 might be more appropriate.

For the May 25 review the blinded investigators made the following assumptions:

- Outcome data would be available for 70% of the 640 planned patients.
- By the time of the meeting, the number enrolled to the aviptadil/placebo group would be 472. This would leave an additional 168 patients to enroll.

- Enrollment would be completed in 7 months by December 31, 2022 (an average of 24 patients per month from June through December). This assumption was based on steady enrollment at 15 new sites in Brazil which were scheduled to begin enrollment in July or August 2022, enrollment in Europe which was to begin in September 2022, and an increase in enrollment in the U.S. The rate required to complete enrollment by the end of 2022 would have been similar to that for the month of February 2022 when 22 patients were enrolled.

We proposed that conditional power be estimated assuming the following two scenarios for future data (for patients not enrolled and those enrolled who had not yet been followed for 90 days):

1. Assume an odds ratio (OR) of 1.5 as hypothesized in the design.
2. Assume the currently observed OR.

As a guideline, it was recommended that conditional power be at least 0.20 based on either of the 2 scenarios to continue the trial.

We also asked the DSMB to consider the following other information in making their recommendation:

- The magnitude of the OR required for the remaining 30% of patients in order to obtain a significant result.
- The observed mortality differences between treatment groups (mortality is an important secondary endpoint).
- Subgroup findings for the primary endpoint for the two disease strata by oxygen requirement at baseline (high flow nasal cannula and non-invasive ventilation versus mechanical ventilation and ECMO).
- The primary safety outcome at day 28.
- A repeat of the aforementioned analyses, excluding participants who were not infused in the event a modified intention to treat (mITT) analysis is carried out instead of an ITT analysis.

Results of Futility Analysis

Following the DSMB review of interim data on May 25, 2022, the DSMB recommended stopping the aviptadil portion of TESICO for futility. At the time of their review the odds ratio (OR) (aviptadil versus placebo) for the primary endpoint was 1.10 (95% CI: 0.79-1.54). This was based on 70% of the planned information for the primary endpoint. Both of the planned estimates of conditional power were less than 20%. Conditional power assuming the protocol specified OR of 1.50 for future data was 12.4%; assuming the observed OR of 1.10, conditional power was 1.4%.

The DSMB also recommended that the remdesivir component of TESICO could continue but indicated that given the slow accrual (87 of the planned 640 patients were enrolled at the time) there may be operational reasons for closing enrollment to the remdesivir study.

On June 9, 2022, it was determined that the remdesivir trial would close to enrollment.

Statistical Analyses

This section supplements the Statistical Analysis section in the Methods section of the main paper. The modified intention to treat (mITT) analysis population is described in more detail, and methods used for sensitivity analyses of the primary endpoint and secondary endpoint are described.

Aviptadil Analysis Population

The mITT analysis population for the aviptadil versus placebo comparison includes 461 participants, of whom 231 were assigned aviptadil and 230 placebo (Figure S1). For these 461 participants, those with data available for efficacy and safety outcomes are included in analyses given in the main paper and the supplement.

Eleven of the 461 participants (6 randomly assigned aviptadil and 5 placebo) are missing the day 90 ordinal outcome. Two of the 11 participants withdrew consent while hospitalized. The other 9 participants were lost to follow-up for the primary endpoint after being discharged. Six of the 9 participants were lost after being followed for at least 60 days; for 1 participant, the primary endpoint status was not known after 29 days of follow-up; and for 2 participants, the primary endpoint status was not known after day 7. The last known endpoint status for these 11 participants is summarized below.

Table: Last known status for 11 participants with missing primary efficacy outcome (6-category ordinal recovery outcome ascertained at Day 90)

Treatment Group	Participant Number	Last known status	Study day on which status last known	Number of follow-up days spent in last known status
Aviptadil	1	Discharged but not home, or home but not off oxygen	76	6
	2	Home and off oxygen	80	66
	3	Home and off oxygen	7	3
	4	Home and off oxygen	63	10
	5	Hospitalized	5 (withdrawn consent)	5
	6	Discharged but not home, or home but not off oxygen	63	23
Placebo	1	Home and off oxygen	29	22
	2	Discharged but not home, or home but not off oxygen	77	60
	3	Home and off oxygen	61	22
	4	Hospitalized	2 (withdrawn consent)	2
	5	Home and off oxygen	7	4

For the treatment comparison of the primary endpoint, a sensitivity analysis was carried out which included the 11 participants in the table above. In this analysis, the last known status for each participant was carried forward to day 90. Sensitivity analyses were also carried out with stratification by site and with stratification by the 4 randomization strata that defined aviptadil and remdesivir eligibility. These analyses were carried out with and without the inclusion of disease severity stratification.

Remdesivir Analysis Population

All participants randomized to receive blinded remdesivir (n=87) received some amount of infusion. One participant in the remdesivir group is missing Day 90 status and is not included in the analysis for the primary endpoint. That participant was randomized to also receive active aviptadil and is participant number 1 (first row) in the table above.

Methods for Secondary Efficacy Endpoints and Subgroups

Proportional odds models were used for summarizing ordinal outcomes; proportional hazards regression models were used for mortality and for outcomes that include death as part of a composite outcome; and Fine-Gray models, which accounted for the competing risk of death, were used to summarize outcomes based on hospital discharge (recovery models). Sub-hazard ratios (sHRs) are reported for the recovery models. All of the regression models were stratified by disease severity (2 strata). Time-to-event

models censor follow-up at the last known alive date prior to Day 90 for participants lost to follow-up or who withdrew consent.

The results of the subgroup analyses for aviptadil versus placebo should be interpreted with caution because there was no overall treatment difference and there was no adjustment made to type 1 error. The subgroup results are shown to guide future COVID-19 research in this target population. Given the small sample size for those randomized to remdesivir or matching placebo, subgroup analyses are not reported.

3 Supplementary Tables and Figures: Trial Enrollment, Schematic, and Consort Diagrams: Aviptadil and Remdesivir Comparisons

Below is a summary of the tables and figures in the supplement related to enrollment, the trial design, and consort diagrams for participants in both the aviptadil and remdesivir comparisons. The tables and figures included in the supplement are shown in the order that they are referred to in the main text. Summaries are below.

Table S1. Enrollment by site - 28 sites, all in the United States, enrolled 473 participants across both agents. Twenty of the 28 sites enrolled 5 or more participants.

Eight-five participants were randomized to both aviptadil and remdesivir in the 2x2 factorial. These participants were enrolled by 19 of the 28 sites.

Most participants randomized to aviptadil/placebo (363/471) were in stratum 4 (prior/current use of remdesivir); 85 of 87 participants randomized to remdesivir/placebo were in stratum 1 (2x2 factorial).

Figure S1. Trial design schematic– 473 participants were randomized across the 4 eligibility strata. Treatment groups, aviptadil vs. placebo and remdesvir vs. placebo were balanced within these strata. Participants in stratum 1 (i.e., the factorial) were included in analyses for both agents.

Figure S2. Consort diagram for the aviptadil comparison– 471 participants were randomized, 234 to aviptadil and 237 to placebo.

Four hundred sixty-one participants (231 aviptadil and 230 placebo) received some study treatment and are in the mITT analysis cohort.

For 450 participants (225 aviptadil and 225 placebo), the day 90 ordinal outcome status was known.

Figure S3. Consort diagram for the remdesivir comparison– 87 participants were randomized, 44 to remdesivir and 43 to placebo.

All randomized participants received some study treatment and are in the mITT analysis cohort.

For 86 participants (43 aviptadil and 43 placebo), the primary ordinal outcome status at Day 90 was known.

Table S2. Participants excluded from the aviptadil/placebo mITT analysis cohort – 10 participants (3 aviptadil and 7 placebo) excluded from the mITT analysis cohort are listed with the reason no study treatment was infused. Six withdrew consent prior to the infusion (2 aviptadil and 4 placebo); 1 participant died before the infusion; 2 participants exceeded the vasopressor limit on each day the infusion was to be given; and 1 participant improved and transitioned to conventional oxygen.

Table S1: Enrollment by Site: Both Agents

	Eligibility Stratum							
Site	*Factorial, Both Agents N (%)*	*VIP Only, RDV Contra-indicated N (%)*	*RDV Only, VIP Contra-indicated N (%)*	*VIP Only, Prior/ Current RDV Use N (%)*	*Total Rand N.*	*Any VIP or RDV mITT N.*	*VIP mITT N.*	*RDV mITT N.*
Banner University Medical Center Tucson	9 (43)	3 (14)	2 (10)	7 (33)	21	20	18	11
Baylor, Scott and White Health	0 (0)	2 (18)	0 (0)	9 (82)	11	11	11	0
Cedars-Sinai Medical Center	1 (8)	0 (0)	0 (0)	11 (92)	12	12	12	1
Cleveland Clinic Foundation	1 (6)	0 (0)	0 (0)	16 (94)	17	17	17	1
Columbia University Irving Medical Center	10 (22)	1 (2)	0 (0)	34 (76)	45	44	44	10
Denver Health Hospital and Authority	1 (13)	0 (0)	0 (0)	7 (88)	8	8	8	1
Duke University Hospital	9 (15)	2 (3)	0 (0)	49 (82)	60	60	60	9
Emory University	0 (0)	0 (0)	0 (0)	3 (100)	3	2	2	0
Harborview Medical Center	0 (0)	0 (0)	0 (0)	10 (100)	10	10	10	0
Houston Methodist Research Insitiute	1 (20)	0 (0)	0 (0)	4 (80)	5	5	5	1
Intermountain Medical Center	2 (2)	2 (2)	0 (0)	78 (95)	82	79	79	2
MUSC Research Nexus Clinic	10 (59)	3 (18)	0 (0)	4 (24)	17	16	16	10
MedStar Health Research Institute	0 (0)	0 (0)	0 (0)	1 (100)	1	1	1	0
Montefiore Medical Center - Weiler campus	0 (0)	0 (0)	0 (0)	6 (100)	6	6	6	0
Montefiore Medical Center Moses Hospital	2 (67)	0 (0)	0 (0)	1 (33)	3	3	3	2
Mount Sinai Medical Center	7 (28)	3 (12)	0 (0)	15 (60)	25	25	25	7
Ohio State University Wexner Medical Center	0 (0)	0 (0)	0 (0)	2 (100)	2	1	1	0
Oregon Health and Science University	6 (30)	5 (25)	0 (0)	9 (45)	20	20	20	6
Stanford University Hospital & Clinics	0 (0)	0 (0)	0 (0)	18 (100)	18	18	18	0
Swedish Hospital First Hill	1 (50)	0 (0)	0 (0)	1 (50)	2	2	2	1
Texas Heart Institute	1 (50)	0 (0)	0 (0)	1 (50)	2	2	2	1
UCSF Fresno	8 (21)	2 (5)	0 (0)	29 (74)	39	39	39	8
UCSF Medical Center	0 (0)	0 (0)	0 (0)	9 (100)	9	9	9	0
University of Colorado Hospital	2 (25)	0 (0)	0 (0)	6 (75)	8	8	8	2
University of Utah Hospital	12 (32)	0 (0)	0 (0)	25 (68)	37	35	35	12
Vanderbilt University Medical Center	0 (0)	0 (0)	0 (0)	6 (100)	6	6	6	0
Washington DC VA Medical Center	1 (33)	0 (0)	0 (0)	2 (67)	3	3	3	1
West Virginia University Medicine	1 (100)	0 (0)	0 (0)	0 (0)	1	1	1	1
Total Enrolling Sites (n=28)	***85 (18)***	***23 (5)***	***2 (0)***	***363 (77)***	***473***	***463***	***461***	***87***

No. sites registered=51, No. sites open=40.
RDV=remdesivir; VIP=aviptadil; mITT=modified intention to treat (received some blinded infusion)

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Figure S1: Trial Design Schematic

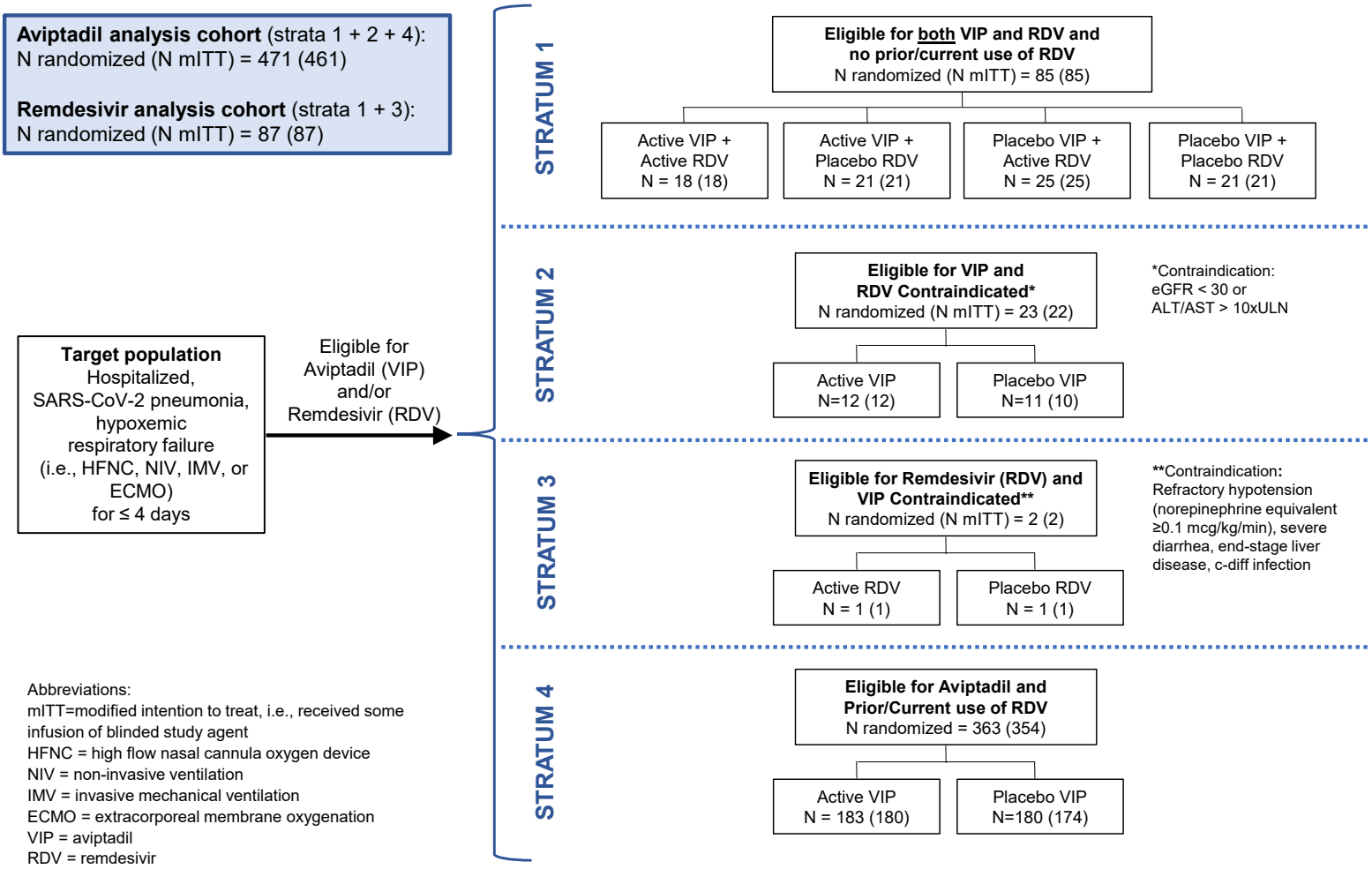
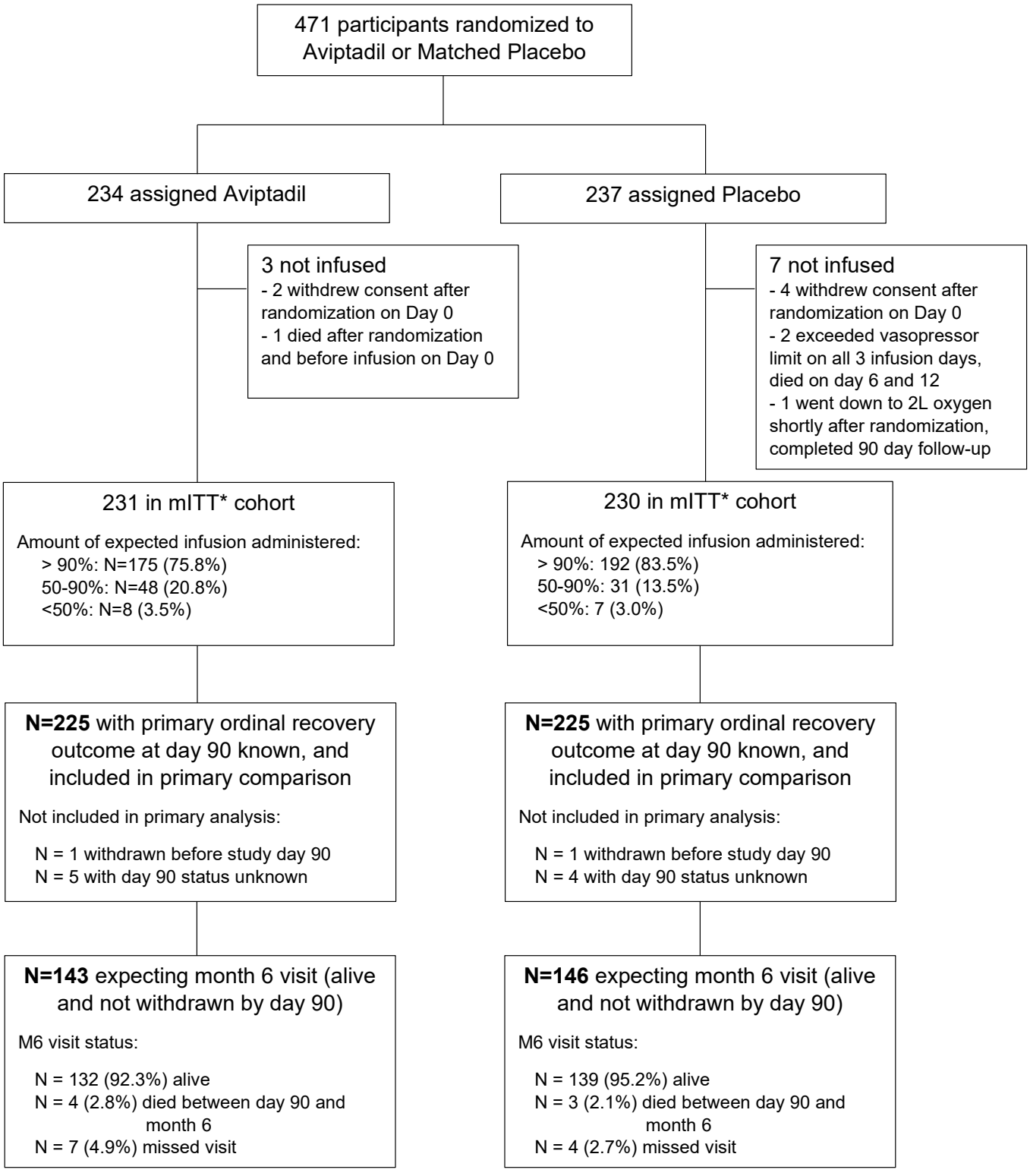
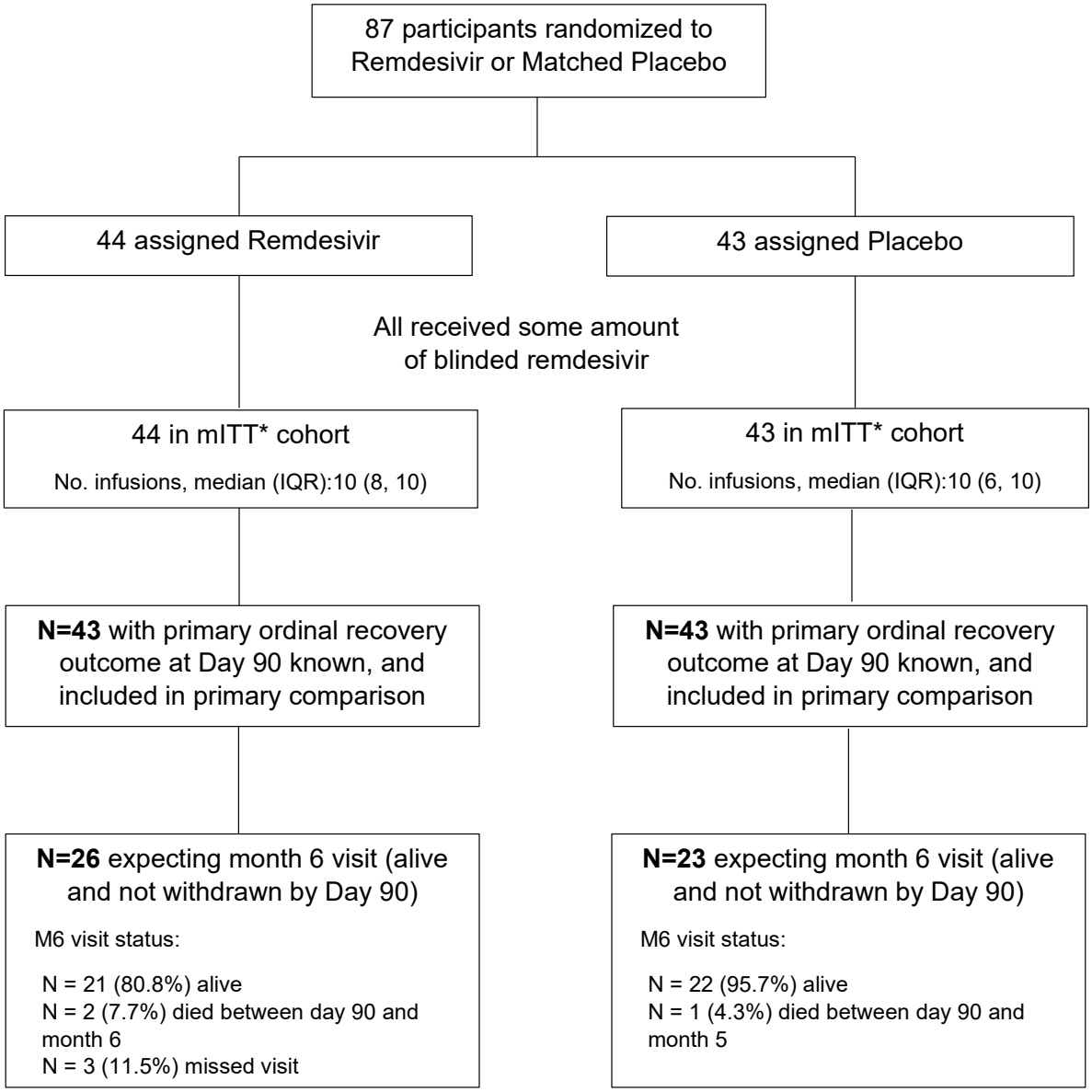


Figure S2: CONSORT Diagram: Aviptadil Comparison



* mITT = modified intention to treat, i.e., received some infusion of blinded study agent. Treatment group comparisons for safety outcomes at day 5, day 28, day 90, and death through day 180 (month 6) include all participants in the mITT cohort.

Figure S3: CONSORT Diagram: Remdesivir Comparison



* mITT = modified intention to treat, i.e., received some infusion of blinded study agent. Treatment group comparisons for safety outcomes at Day 5, Day 28, Day 90, and death through Day 180 (Month 6) include all participants in the mITT cohort.

Table S2: Participants Excluded from the mITT Cohort, Reasons for Not Receiving Any Blinded Aviptadil/Placebo

Treatment Assignment	Participant Number	Design Strata	Severity Stratum	Comments
Aviptadil	1	Stratum 4 – prior or current use	Severe (HFNC)	Withdrew consent on Day 0 prior to infusion.
	2	Stratum 4 – prior or current RDV use	Severe (HFNC)	Withdrew consent on Day 0 prior to infusion.
	3	Stratum 4 – prior or current RDV use	Critical (IMV)	Died on Day 0 after randomization and before infusion.
Placebo	1	Stratum 4 – prior or current RDV use	Severe (HFNC)	Withdrew consent on Day 0 prior to infusion.
	2	Stratum 4 – prior or current RDV use	Severe (HFNC)	Withdrew consent on Day 0 prior to infusion.
	3	Stratum 4 – prior or current RDV use	Critical (IMV)	Withdrew consent on Day 0 prior to infusion.
	4	Stratum 4 – prior or current RDV use	Severe (HFNC)	Withdrew consent on Day 0 prior to infusion.
	5	Stratum 2 – RDV contraindicated	Critical (IMV)	Exceeded vasopressor limit on Days 0-2, not infused per protocol, remained under followup and died on Day 6.
	6	Stratum 4 – prior or current RDV use	Severe (HFNC)	Exceeded vasopressor limit on Days 0-2, not infused per protocol, remained under followup and died on Day 12.
	7	Stratum 4 – prior or current RDV use	Severe (IMV)	Shortly after randomization on Day 0 participant improved and switched to 2L conventional oxygen, not infused, remained under follow-up through Day 90.

RDV = remdesivir; HFNC: high flow nasal cannula; IMV = invasive mechanical ventilation

4 Supplementary Tables and Figures: Baseline Characteristics for the Aviptadil Comparison

In this section, a summary of the tables and figures in the supplement related to baseline characteristics for participants in the aviptadil comparison is given. The tables and figures included in the supplement are shown in the order that they are referred to in the main text. Summaries are below.

Table S3-S11. Baseline characteristics for the aviptadil comparison; mITT comparisons – prior to randomization, a medical history was obtained, including concomitant treatments. Local laboratory tests were recorded. These and other baseline characteristics by treatment group are summarized in these tables. In each of these supplementary tables, baseline characteristics are given for all participants in the mITT cohort for the aviptadil comparisons (last column) and separately for those assigned aviptadil or aviptadil placebo.

Use of remdesivir and disease severity were design strata considered in the randomization (see Section 2. Methods). In the mITT cohort, for 349 participants remdesivir had been started prior to randomization (stratum 4) (Table S5). Of the 112 participants who had not started taking remdesivir, 1 began taking it on the day of randomization, 85 were randomized to the 2x2 factorial (stratum 1), for 22 participants, remdesivir was contraindicated (stratum 2), and 4 participants were randomized under stratum 4 (prior/current use) but never took any remdesivir.

Two hundred seventy one participants (59%) are in the HFNO/NIV disease severity stratum; 190 (41%) are in the IMV/ECMO disease severity stratum. The respiratory support at entry defining the disease severity strata is summarized in Table S5.

Table S11 summarizes concomitant medications at baseline. Corticosteroids and antiplatelets/anticoagulants were prescribed for over 94% of participants.

Table S3: Baseline Demographics: Aviptadil Comparison

	Aviptadil No. (%)	Aviptadil Placebo No. (%)	Total No. (%)
No. participants	***231***	***230***	***461***
Age [median (IQR)]	*58 (46, 67)*	*57 (46, 66)*	*57 (46, 66)*
18-39 years	34 (14.7)	33 (14.3)	67 (14.5)
40-49 years	39 (16.9)	39 (17.0)	78 (16.9)
50-59 years	55 (23.8)	62 (27.0)	117 (25.4)
60-69 years	54 (23.4)	56 (24.3)	110 (23.9)
70-79 years	37 (16.0)	28 (12.2)	65 (14.1)
≥ 80 years	12 (5.2)	12 (5.2)	24 (5.2)
Sex at Birth			
Male	137 (59.3)	146 (63.5)	283 (61.4)
Female	94 (40.7)	84 (36.5)	178 (38.6)
Race/Ethnicity			
Asian	7 (3.0)	10 (4.3)	17 (3.7)
Black	40 (17.3)	33 (14.3)	73 (15.8)
Hispanic	62 (26.8)	57 (24.8)	119 (25.8)
White	102 (44.2)	113 (49.1)	215 (46.6)
Other	20 (8.7)	17 (7.4)	37 (8.0)
Pre-COVID Residence (home)			
Long-term acute care	1 (0.4)	2 (0.9)	3 (0.7)
Other health care facility	0 (0.0)	0 (0.0)	0 (0.0)
Residential care facility	1 (0.4)	0 (0.0)	1 (0.2)
Community dwelling	1 (0.4)	0 (0.0)	1 (0.2)
Independent living, with medical help	6 (2.6)	8 (3.5)	14 (3.0)
Independent living, without medical help	222 (96.1)	220 (95.7)	442 (95.9)
Hospital Location at Entry			
ICU	218 (94.4)	213 (92.6)	431 (93.5)
Stepdown/intermediate care unit	13 (5.6)	16 (7.0)	29 (6.3)
General ward	0 (0.0)	0 (0.0)	0 (0.0)
Emergency department (ED/ER)	0 (0.0)	1 (0.4)	1 (0.2)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Eligibility Stratum			
Factorial	39 (16.9)	46 (20.0)	85 (18.4)
VIP only, RDV contraindicated	12 (5.2)	10 (4.3)	22 (4.8)
RDV only, VIP contraindicated	0 (0.0)	0 (0.0)	0 (0.0)
VIP only, current/prior RDV	180 (77.9)	174 (75.7)	354 (76.8)

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Table S4: Baseline Vital Signs: Aviptadil Comparison

	Aviptadil No. (%)	Aviptadil Placebo No. (%)	Total No. (%)
No. participants	***231***	***230***	***461***
Respiratory rate (bmp) median (IQR)	24 (20, 28)	24 (20, 29)	24 (20, 29)
< 20	54 (23.4)	46 (20.0)	100 (21.7)
≥ 20	177 (76.6)	184 (80.0)	361 (78.3)
Oxygen saturation (SpO_2, %) median (IQR)	94 (92, 96)	94 (92, 97)	94 (92, 97)
< 92	41 (17.7)	40 (17.4)	81 (17.6)
92-96	133 (57.6)	129 (56.1)	262 (56.8)
>96	57 (24.7)	61 (26.5)	118 (25.6)
Fraction of inspired O_2 (FiO_2) median (IQR)	0.7 (0.6, 1.0)	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)
<0.30	0 (0.0)	2 (0.9)	2 (0.4)
0.30-0.40	22 (9.6)	33 (14.3)	55 (12.0)
0.41-0.70	109 (47.4)	82 (35.7)	191 (41.5)
> 0.70	99 (43.0)	113 (49.1)	212 (46.1)
SF ratio (SpO_2/FiO_2) median (IQR)	134 (100, 176)	131 (98, 186)	133 (99, 182)
<315	228 (99.1)	227 (98.7)	455 (98.9)
≥ 315	2 (0.9)	3 (1.3)	5 (1.1)
PF ratio* (PaO_2/FiO_2, computed) median (IQR)	83 (43, 133)	79 (40, 145)	74 (64, 86)
<300	228 (99.1)	227 (98.7)	455 (98.9)
≥ 300	2 (0.9)	3 (1.3)	5 (1.1)
Temperature (˚C) median (IQR)	36.7 (36.4, 37.0)	36.7 (36.3, 37.0)	36.7 (36.4, 37.0)
< 38	223 (97.4)	221 (96.1)	444 (96.7)
≥ 38	6 (2.6)	9 (3.9)	15 (3.3)
Heart rate (bmp) median (IQR)	75 (65, 85)	73 (62, 88)	121 (109, 134)
<100	210 (90.9)	210 (91.3)	420 (91.1)
≥ 100	21 (9.1)	20 (8.7)	41 (8.9)
Systolic BP (SBP, mmHg) median (IQR)	123 (111, 135)	118 (107, 134)	69 (62, 78)
<90	2 (0.9)	2 (0.9)	4 (0.9)
90-110	55 (23.8)	77 (33.5)	132 (28.6)
>110	174 (75.3)	151 (65.7)	325 (70.5)
Diastolic BP (DBP, mmHg) median (IQR)	70 (63, 78)	68 (61, 77)	86 (77, 94)
Mean arterial pressure (MAP, mmHg) median (IQR)	86 (79, 96)	84 (76, 94)	86 (79, 96)
< 65 with vasopressor	0 (0.0)	0 (0.0)	0 (0.0)
< 65 without vasopressor	2 (0.9)	1 (0.4)	3 (0.7)
≥ 65 with vasopressor	35 (15.2)	29 (12.6)	64 (13.9)
≥ 65 without vasopressor	194 (84.0)	200 (87.0)	394 (85.5)
Vasopressor dose, NE equivalent µg/kg/min median (IQR), on vasopressor at entry	0.03 (0.02, 0.05)	0.04 (0.03, 0.06)	0.04 (0.02, 0.05)

*PF ratio derived from: SF ratio=64 + 0.84 *(PF ratio). Per Rice et al, Chest 2007.

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Table S5: Baseline COVID-19 Characteristics and Respiratory Status: Aviptadil Comparison

	Aviptadil No. (%)	Aviptadil Placebo No. (%)	Total No. (%)
No. participants	***231***	***230***	***461***
COVID-19 Characteristics			
Days since hospital admission *median (IQR)*	*2 (2, 3)*	*2 (2, 4)*	*2 (2, 4)*
Days latest +ve SARS-CoV-2 test *median (IQR)*	*3 (2, 4)*	*2 (2, 5)*	*3 (2, 4)*
Days since symptom onset *median (IQR)*	*9 (7, 13)*	*10 (7, 13)*	*10 (7, 13)*
0-6 days	55 (23.8)	37 (16.1)	92 (20.0)
7-14 days	141 (61.0)	155 (67.4)	296 (64.2)
>14 days	35 (15.2)	38 (16.5)	73 (15.8)
SARS-CoV-2 vaccination, n (%)			
mRNA, 3 doses (last ≥ 14 days from symptoms)	12 (5.2)	11 (4.8)	23 (5.0)
mRNA, 2 doses (last ≥ 14 days from symptoms)	37 (16.0)	36 (15.7)	73 (15.8)
J&J, 2 doses (last ≥ 14 days from symptoms)	0 (0.0)	0 (0.0)	0 (0.0)
J&J, 1 dose (last ≥ 14 days from symptoms)	4 (1.7)	5 (2.2)	9 (2.0)
Other/Partial*	23 (10.0)	15 (6.5)	38 (8.2)
No vaccination	149 (64.5)	151 (65.7)	300 (65.1)
Unknown	6 (2.6)	12 (5.2)	18 (3.9)
Blinded vaccination	0 (0.0)	0 (0.0)	0 (0.0)
Remdesivir before randomization** *median doses (IQR)*	*2 (2, 4)*	*2 (2, 4)*	*2 (2, 4)*
No prior use	54 (23.4)	58 (25.2)	112 (24.3)
1-2 doses	91 (39.4)	94 (40.9)	185 (40.1)
3-5 doses	83 (35.9)	75 (32.6)	158 (34.3)
6-8 doses	3 (1.3)	3 (1.3)	6 (1.3)
9+ doses	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory Status			
Days since respiratory failure *median (IQR)*	*2 (2, 3)*	*2 (2, 3)*	*2 (2, 3)*
0-1 day	53 (23.0)	50 (21.7)	103 (22.4)
2-3 days	151 (65.7)	150 (65.2)	301 (65.4)
4 days	26 (11.3)	30 (13.0)	56 (12.2)
Days since lung imaging results *median (IQR)*	*1 (1, 2)*	*1 (1, 2)*	*1 (1, 2)*
Lung Infiltrate, n (%)s			
No imaging	0 (0.0)	1 (0.4)	1 (0.2)
No infiltrates	0 (0.0)	0 (0.0)	0 (0.0)
Unilateral	4 (1.7)	5 (2.2)	9 (2.0)
Bilateral	227 (98.3)	224 (97.4)	451 (97.8)
Bilateral infiltrates & SF ratio < 315, n (%)	224 (97.4)	221 (96.1)	445 (96.7)
ARDS by Berlin criteria*, n (%)	89 (38.7)	90 (39.1)	179 (38.9)
Current mode of respiratory support, n (%)			
High-flow nasal cannula (HFNC) oxygen device	127 (55.0)	118 (51.3)	245 (53.1)
Non-invasive ventilation (NIV)	9 (3.9)	17 (7.4)	26 (5.6)
Invasive mechanical ventilation (IMV)	93 (40.3)	92 (40.0)	185 (40.1)
Extracorporeal membrane oxygenation (ECMO)	2 (0.9)	3 (1.3)	5 (1.1)
HFNC flow rate, L/min *median (IQR)* among those on HFNC at entry	*50 (40, 50)*	*50 (40, 50)*	*50 (40, 50)*

* recd. 1 of 2 dose series, last vaccination < 14 days before symptoms, 1-2 vaccinations but unknown dates

** median RDV use presented for those with prior receipt of RDV.

*** bilateral infiltrates and PF ratio<300 (per Rice et al) and IMV or ECMO

Table S6: Baseline Medical History: Aviptadil Comparison

	Aviptadil No. (%)	Aviptadil Placebo No. (%)	Total No. (%)
No. participants	***231***	***230***	***461***
Medical History*			
Asthma	26 (11.3)	29 (12.6)	55 (11.9)
Cerebrovascular event	4 (1.7)	4 (1.7)	8 (1.7)
COPD	5 (2.2)	17 (7.4)	22 (4.8)
Diabetes mellitus requiring medication	82 (35.5)	71 (30.9)	153 (33.2)
Heart failure	24 (10.4)	15 (6.5)	39 (8.5)
Hepatic impairment	3 (1.3)	1 (0.4)	4 (0.9)
HIV or other immune suppression	17 (7.4)	17 (7.4)	34 (7.4)
Hypertension requiring medication	99 (42.9)	92 (40.0)	191 (41.4)
Malignancy	9 (3.9)	17 (7.4)	26 (5.6)
MI or other acute coronary syndrome	8 (3.5)	8 (3.5)	16 (3.5)
Renal impairment	45 (19.5)	38 (16.5)	83 (18.0)
Any of above	*153 (66.2)*	*155 (67.4)*	*308 (66.8)*
Pre-COVID Requirements			
Pre-morbid continuous suppl. oxygen	4 (1.7)	6 (2.6)	10 (2.2)
Pre-morbid renal replacement Rx (RRT)	7 (3.0)	3 (1.3)	10 (2.2)
BMI, kg/m^2 [median (IQR)]	*32.9 (28.0, 39.4)*	*33.4 (28.6, 40.4)*	*33.0 (28.3, 40.0)*
<30	81 (35.5)	78 (34.2)	159 (34.9)
30-39.9	92 (40.4)	89 (39.0)	181 (39.7)
≥ 40	55 (24.1)	61 (26.8)	116 (25.4)
Composites			
Compromised immune system**	36 (15.6)	32 (13.9)	68 (14.8)
Metabolic co-morbidity***	94 (40.7)	83 (36.1)	177 (38.4)
Renal impairment or need for RRT	46 (19.9)	38 (16.5)	84 (18.2)
No hypertension, no metabolic condition	103 (44.6)	110 (47.8)	213 (46.2)
Hypertension, no metabolic condition	34 (14.7)	37 (16.1)	71 (15.4)
No hypertension, metabolic condition	29 (12.6)	28 (12.2)	57 (12.4)
Hypertension and metabolic condition	65 (28.1)	55 (23.9)	120 (26.0)

* Diagnoses requiring regular follow-up, medication, or hospitalization within the previous 12 months.

** current use of antirejection medication, cytotoxic chemotherapy, trt. with biologic medication, HIV or other immunosuppresive disorder

*** history of diabetes req. Rx, cerebrovascular event, heart failure, MI or other acute coronary syndrome

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Table S7: Current Medical Conditions During Index Hospitalization, at Baseline: Aviptadil Comparison

	Aviptadil No. (%)	Aviptadil Placebo No. (%)	Total No. (%)
No. participants	***231***	***230***	***461***
Cardiac and Vascular	**64 (27.7)**	**55 (23.9)**	**119 (25.8)**
Myocardial infarction	7 (3.0)	4 (1.7)	11 (2.4)
Congestive heart failure (I/II/III/IV)	4 (1.7)	6 (2.6)	10 (2.2)
Class I/II	2 (0.9)	3 (1.3)	5 (1.1)
Class III/IV	2 (0.9)	2 (0.9)	4 (0.9)
Myocarditis	0 (0.0)	1 (0.4)	1 (0.2)
Pericarditis	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension requiring vasopressor	51 (22.1)	39 (17.0)	90 (19.5)
Atrial tachyarrhythmias	10 (4.3)	14 (6.1)	24 (5.2)
Ventricular tachyarrhythmias	4 (1.7)	2 (0.9)	6 (1.3)
Hematological	**16 (6.9)**	**7 (3.0)**	**23 (5.0)**
Bleeding	1 (0.4)	0 (0.0)	1 (0.2)
Disseminated intravascular coagulation (DIC)	0 (0.0)	0 (0.0)	0 (0.0)
Thromboembolic events (arterial/venous)	15 (6.5)	7 (3.0)	22 (4.8)
DVT	6 (2.6)	3 (1.3)	9 (2.0)
Pulmonary embolism	8 (3.5)	4 (1.7)	12 (2.6)
Arterial thrombosis/embolism	2 (0.9)	0 (0.0)	2 (0.4)
Hepatic			
Hepatic decompensation*	0 (0.0)	0 (0.0)	0 (0.0)
Infection			
Intercurrent disease, non SARS-CoV-2	30 (13.0)	25 (10.9)	55 (11.9)
Primarily respiratory	23 (10.0)	18 (7.8)	41 (8.9)
Neurological	**16 (6.9)**	**12 (5.2)**	**28 (6.1)**
Acute delirium	13 (5.6)	11 (4.8)	24 (5.2)
Cerebrovascular event	1 (0.4)	0 (0.0)	1 (0.2)
Ischemic	0 (0.0)	0 (0.0)	0 (0.0)
Hemorrhagic	1 (0.4)	0 (0.0)	1 (0.2)
Both	0 (0.0)	0 (0.0)	0 (0.0)
Encephalitis	0 (0.0)	0 (0.0)	0 (0.0)
Meningitis	0 (0.0)	0 (0.0)	0 (0.0)
Myelitis	0 (0.0)	1 (0.4)	1 (0.2)
Transient ischemic event	1 (0.4)	0 (0.0)	1 (0.2)
Renal			
New need for renal replacement Tx (RRT)**	11 (4.9)	4 (1.8)	15 (3.3)
Any of above	***94 (40.7)***	***83 (36.1)***	***177 (38.4)***

* Exclusionary for randomization to aviptadil/placebo

** Participants with pre-COVID need for dialysis excluded from denominator

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Table S8: SARS-CoV-2 Antibodies, Antigen, and Viral Load Levels, at Baseline: Aviptadil Comparison

BioRad Antinucleocapsid Ab [a] Sample/Cutoff Ratio	Aviptadil	Aviptadil Placebo	Total
N. in group	***231***	***230***	***461***
N. with data	***222***	***223***	***445***
Positive, n (%)	171 (77.0)	182 (81.6)	353 (79.3)
Equivocal, n (%)	3 (1.4)	3 (1.3)	6 (1.3)
Negative, n (%)	48 (21.6)	38 (17.0)	86 (19.3)
GenScript Anti-Spike Neutralizing Ab[b] Binding Inhibition(%)	**Aviptadil**	**Aviptadil Placebo**	**Total**
N. with data	***222***	***223***	***445***
Positive, n (%)	157 (70.7)	156 (70.0)	313 (70.3)
Negative, n (%)	65 (29.3)	67 (30.0)	132 (29.7)
Quanterix Antigen[c] Concentration (pg/mL)	**Aviptadil**	**Aviptadil Placebo**	**Total**
N. with data	***222***	***223***	***445***
Positive, n (%)	211 (95.0)	211 (94.6)	422 (94.8)
Negative, n (%)	11 (5.0)	12 (5.4)	23 (5.2)
min*, max	2.9, 66296	2.9, 77791	2.9, 77791
median (IQR)	1246 (95, 6114)	1502 (224, 6406)	1294 (150, 6200)
mean ± SD	5275 ± 9680	5492 ± 9472	5384 ± 9566
$\log_{10}$, median (IQR)	3.10 (1.98, 3.79)	3.18 (2.35, 3.81)	3.11 (2.18, 3.79)
$\log_{10}$, mean ± SD	2.8 ± 1.2	3.0 ± 1.1	2.9 ± 1.2
≥ 1000, n (%)	115 (51.8)	122 (54.7)	237 (53.3)
* 2.9 is imputed for antigen < LOQ (<3)			
Quanterix Antibody[d] (ng/mL)	**Aviptadil**	**Aviptadil Placebo**	**Total**
N. with data	***222***	***223***	***445***
Positive, n (%)	163 (73.4)	161 (72.2)	324 (72.8)
Negative, n (%)	59 (26.6)	62 (27.8)	121 (27.2)
min*, max	8, 6157524	0, 9009149	0, 9009149
median (IQR)	4901 (608, 45436)	3287 (619, 26341)	3848 (619, 35847)
mean ± SD	235431 ± 711961	191720 ± 748613	213526 ± 730063
$\log_{10}$, median (IQR)	3.69 (2.78, 4.66)	3.52 (2.79, 4.42)	3.59 (2.79, 4.55)
$\log_{10}$, mean ± SD	3.8 ± 1.4	3.6 ± 1.3	3.7 ± 1.3

[a] BioRad Platelia anti-nucleocapsid assay (total antibody): positive: ≥ 1.0 sample/cutoff ratio

[b] GenScript cPass surrogate SARS-CoV-2 neutralization assay (anti-spike); positive: ≥ 30% binding inhibition

[c] Quanterix Simoa nucleocapsid antigen; positive: ≥ 3 pg/mL

[d] Quanterix Simoa anti-spike assay (immunoglobulin G); positive: ≥ 770 ng/mL

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Table S9: SARS-CoV-2 Midturbinate Nasal Swab Viral Load, at Baseline: Aviptadil Comparison

Nasal Swab Fluid [a]	Aviptadil	Aviptadil Placebo	Total
N. in group	***231***	***230***	***461***
Viral RNA			
Qualitative, N. with data	***226***	***226***	***452***
Positive, n (%)	208 (92.0)	200 (88.5)	408 (90.3)
Equivocal, n (%)	1 (0.4)	1 (0.4)	2 (0.4)
Negative, n (%)	17 (7.5)	25 (11.1)	42 (9.3)
Quantitative, N with data[b]	***208***	***200***	***408***
min, max $x10^3$ copies/mL	0.1, 214355.3	0.1, 745032.1	0.1, 745032.1
median (IQR), $x10^3$ copies/mL	25.1 (1.8, 395.5)	64.5 (4.1, 710.6)	43.9 (2.5, 472.1)
mean ± SD, $x10^3$ copies/mL	3614.0 ± 21394.0	10617.0 ± 71149.0	7046.8 ± 52155.5
log_{10}, median (IQR)	4.40 (3.24, 5.59)	4.80 (3.61, 5.85)	4.64 (3.39, 5.67)
log_{10}, mean ± SD	4.4 ± 1.5	4.8 ± 1.5	4.6 ± 1.5
Variant			
N. tested for variant	***227***	***225***	***452***
Positive nucleocapsid PCR, n (%)	207 (91.2)	207 (92.0)	414 (91.6)
Undetermined nucleocapsid PCR, n (%)	20 (8.8)	18 (8.0)	38 (8.4)
N. with positive PCR	***207***	***207***	***414***
Delta, n (%)	155 (74.9)	150 (72.5)	305 (73.7)
Omicron[c], n (%)	25 (12.1)	25 (12.1)	50 (12.1)
Other[d], n (%)	27 (13.0)	32 (15.5)	59 (14.3)

[a] Midturbinate swab specimen

[b] Among those with positive qualitative result. Lower limit of quantification is 100 copies/mL

[c] Determined among those with specimens collected Nov 2021 or later that were positive for the nucleocapsid PCR but not positive for delta PCR

[d] Positive for the nucleocapsid PCR but not positive for delta or omicron

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Table S10: Baseline Lab Measures: Aviptadil Comparison

Laboratory Measure*	Aviptadil Med [IQR]	Aviptadil Placebo Med [IQR]	Total Med [IQR]
No. participants	***231***	***230***	***461***
Metabolic Panel			
Sodium (mEq/L)	140 (136, 142)	139 (137, 142)	139 (136, 142)
Potassium (mEq/L)	4.3 (3.9, 4.7)	4.3 (3.9, 4.7)	4.3 (3.9, 4.7)
Chloride (mEq/L)	105 (102, 108)	104 (101, 108)	105 (101, 108)
Bicarbonate/CO_2 (mEq/L)	23.0 (20.0, 26.0)	23.0 (21.0, 26.0)	23.0 (21.0, 26.0)
BUN, mg/dL	30 (21, 43)	30 (21, 42)	30 (21, 42)
Serum creatinine (mg/dL)	0.97 (0.70, 1.58)	0.99 (0.75, 1.30)	0.98 (0.73, 1.44)
Total bilirubin (mg/dL)	0.5 (0.4, 0.8)	0.5 (0.4, 0.7)	0.5 (0.4, 0.7)
AST/SGOT (U/L)**	48 (29, 74)	46 (31, 65)	47 (30, 68)
ALT/SGPT (U/L)**	35 (21, 68)	36 (22, 61)	36 (21, 64)
Complete Blood Count			
WBC (10^9/L)	8.7 (6.2, 12.7)	8.7 (6.1, 11.8)	8.7 (6.2, 12.1)
Hemoglobin (g/dL)	12.8 (11.4, 14.1)	13.1 (11.6, 14.4)	12.9 (11.6, 14.3)
Platelets (10^9/L)	251 (194, 322)	252 (204, 325)	252 (201, 324)
Neutrophils (10^9/L)	7.25 (4.87, 10.71)	7.00 (4.57, 10.10)	7.13 (4.74, 10.34)
Lymphocytes (10^9/L)	0.70 (0.40, 1.01)	0.63 (0.44, 1.02)	0.66 (0.41, 1.01)
Other			
CRP, mg/L	70.2 (31.6, 121.7)	72.1 (34.3, 131.5)	71.6 (33.2, 128.3)
Ferritin (µg/mL)	1057 (523, 1773)	1001 (570, 1959)	1005 (532, 1881)
INR, from PT (seconds)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)
D-dimer (µg/mL)	1.44 (0.81, 4.00)	1.48 (0.82, 3.65)	1.46 (0.81, 3.84)

BUN=blood urea nitrogen, WBC=white blood count, CRP=C-reactive protein, PT=prothrombin time

*As collected on case report forms.

**AST/SGOT and/or ALT/SGPT can be reported

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Table S11: Baseline Concomitant Medications: Aviptadil Comparison

	Aviptadil No. (%)	Aviptadil Placebo No. (%)	Total No. (%)
No. participants	***231***	***230***	***461***
Antibiotics	116 (50.2)	124 (53.9)	240 (52.1)
IV antibiotic	110 (47.6)	119 (51.7)	229 (49.7)
Oral antibiotic	19 (8.2)	21 (9.1)	40 (8.7)
Antifungals	8 (3.5)	14 (6.1)	22 (4.8)
Antidiarrheal agent	1 (0.4)	0 (0.0)	1 (0.2)
ACE inhibitors	2 (0.9)	4 (1.7)	6 (1.3)
ARBs	4 (1.7)	3 (1.3)	7 (1.5)
Beta blockers	26 (11.3)	25 (10.9)	51 (11.1)
Antiplatelets/anticoagulants	220 (95.2)	216 (93.9)	436 (94.6)
Aspirin	35 (15.2)	31 (13.5)	66 (14.3)
Other antiplatelet	10 (4.3)	13 (5.7)	23 (5.0)
Heparin, prophylactic dose	133 (57.6)	123 (53.5)	256 (55.5)
Heparin, intermediate dose	33 (14.3)	42 (18.3)	75 (16.3)
Heparin therapeutic dose	38 (16.5)	28 (12.2)	66 (14.3)
Warfarin	2 (0.9)	0 (0.0)	2 (0.4)
DOAC	7 (3.0)	7 (3.0)	14 (3.0)
Other anticoagulant	21 (9.1)	19 (8.3)	40 (8.7)
Pulmonary vasodilators	18 (7.8)	17 (7.4)	35 (7.6)
Phosphodiesterase	0 (0.0)	0 (0.0)	0 (0.0)
Prostanoids	4 (1.7)	5 (2.2)	9 (2.0)
Nitric oxide	8 (3.5)	8 (3.5)	16 (3.5)
Other pulm. vasodilator	6 (2.6)	4 (1.7)	10 (2.2)
SARS-CoV-2 antiviral (excl RDV)	2 (0.9)	3 (1.3)	5 (1.1)
Antirejection meds	20 (8.7)	17 (7.4)	37 (8.0)
Corticosteroids	219 (94.8)	221 (96.1)	440 (95.4)
Biologics, cancer/autoimmune	3 (1.3)	3 (1.3)	6 (1.3)
Cytotoxic chemotherapy	0 (0.0)	2 (0.9)	2 (0.4)
Immune modulators	78 (33.8)	78 (33.9)	156 (33.8)
IL-1 inhibitor	0 (0.0)	0 (0.0)	0 (0.0)
IL-6 inhibitor	30 (13.0)	23 (10.0)	53 (11.5)
Interferons	0 (0.0)	0 (0.0)	0 (0.0)
JAK inhibitor	45 (19.5)	53 (23.0)	98 (21.3)
TNF inhibitor	1 (0.4)	0 (0.0)	1 (0.2)
Other immune modulator	4 (1.7)	3 (1.3)	7 (1.5)
Sedatives	117 (50.6)	112 (48.7)	229 (49.7)
Benzodiazepines	42 (18.2)	43 (18.7)	85 (18.4)
Opiods	98 (42.4)	95 (41.3)	193 (41.9)
Propofol	82 (35.5)	83 (36.1)	165 (35.8)
Dexmedetomidine	18 (7.8)	22 (9.6)	40 (8.7)
Other sedative	24 (10.4)	17 (7.4)	41 (8.9)
NSAIDs (at least 7 days)	10 (4.3)	9 (3.9)	19 (4.1)

Concomitant medications in past 24 hours, including long-acting medications for underlying conditions received on a regular basis.

5 Supplementary Tables and Figures: Baseline Characteristics for the Remdesivir Comparison

In this section, a summary of the tables and figures in the supplement related to baseline characteristics for participants in the remdesivir comparison is given. The tables and figures included in the supplement are shown in the order that they are referred to in the main text. Summaries are below.

Tables S12-S20. Baseline characteristics for the remdesivir comparison; mITT comparisons – tables presented are a parallel set to the aviptadil comparison. In this cohort, the median age was 57 years (IQR: 46, 65), 33% female, 98% randomized to the factorial (Table S12).

Thirteen participants were taking vasopressors at entry (Table S13), 40 (46%) participants are in the HFNO/NIV disease severity stratum and 47 (54%) are in the IMV/ECMO disease severity stratum (Table S14). Most participant were infected with the delta variant (71%, Table S18), 95% of participants were taking corticosteroids and 91% were prescribed antiplatelets/anticoagulants (Table S20).

Table S12: Baseline Demographics: Remdesivir Comparison

	Remdesivir No. (%)	Remdesivir Placebo No. (%)	Total No. (%)
No. participants	***44***	***43***	***87***
Age [median (IQR)]	*54 (45, 66)*	*58 (47, 65)*	*57 (46, 65)*
18-39 years	9 (20.5)	5 (11.6)	14 (16.1)
40-49 years	5 (11.4)	10 (23.3)	15 (17.2)
50-59 years	13 (29.5)	8 (18.6)	21 (24.1)
60-69 years	11 (25.0)	15 (34.9)	26 (29.9)
70-79 years	5 (11.4)	4 (9.3)	9 (10.3)
≥ 80 years	1 (2.3)	1 (2.3)	2 (2.3)
Sex at Birth			
Male	30 (68.2)	28 (65.1)	58 (66.7)
Female	14 (31.8)	15 (34.9)	29 (33.3)
Race/Ethnicity			
Asian	3 (6.8)	0 (0.0)	3 (3.4)
Black	6 (13.6)	4 (9.3)	10 (11.5)
Hispanic	14 (31.8)	16 (37.2)	30 (34.5)
White	17 (38.6)	18 (41.9)	35 (40.2)
Other	4 (9.1)	5 (11.6)	9 (10.3)
Pre-COVID Residence (home)			
Long-term acute care	1 (2.3)	0 (0.0)	1 (1.1)
Other health care facility	0 (0.0)	0 (0.0)	0 (0.0)
Residential care facility	0 (0.0)	1 (2.3)	1 (1.1)
Community dwelling	0 (0.0)	0 (0.0)	0 (0.0)
Independent living, with medical help	0 (0.0)	1 (2.3)	1 (1.1)
Independent living, without medical help	43 (97.7)	41 (95.3)	84 (96.6)
Hospital Location at Entry			
ICU	42 (95.5)	40 (93.0)	82 (94.3)
Stepdown/intermediate care unit	2 (4.5)	3 (7.0)	5 (5.7)
General ward	0 (0.0)	0 (0.0)	0 (0.0)
Emergency department (ED/ER)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Eligibility Stratum			
Factorial	43 (97.7)	42 (97.7)	85 (97.7)
VIP only, RDV contraindicated	0 (0.0)	0 (0.0)	0 (0.0)
RDV only, VIP contraindicated	1 (2.3)	1 (2.3)	2 (2.3)
VIP only, current/prior RDV	0 (0.0)	0 (0.0)	0 (0.0)

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Table S13: Baseline Vital Signs: Remdesivir Comparison

	Remdesivir No. (%)	Remdesivir Placebo No. (%)	Total No. (%)
No. participants	***44***	***43***	***87***
Respiratory rate (bmp) median (IQR)	26 (20, 29)	23 (17, 28)	24 (18, 29)
< 20	9 (20.5)	16 (37.2)	25 (28.7)
≥ 20	35 (79.5)	27 (62.8)	62 (71.3)
Oxygen saturation (SpO_2, %) median (IQR)	94 (93, 97)	95 (92, 97)	94 (92, 97)
< 92	8 (18.2)	7 (16.3)	15 (17.2)
92-96	23 (52.3)	25 (58.1)	48 (55.2)
>96	13 (29.5)	11 (25.6)	24 (27.6)
Fraction of inspired O_2 (FiO_2) median (IQR)	0.7 (0.5, 0.9)	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)
<0.30	1 (2.3)	0 (0.0)	1 (1.1)
0.30-0.40	8 (18.2)	5 (11.6)	13 (14.9)
0.41-0.70	16 (36.4)	18 (41.9)	34 (39.1)
> 0.70	19 (43.2)	20 (46.5)	39 (44.8)
SF ratio (SpO_2/FiO_2) median (IQR)	140 (102, 194)	133 (96, 184)	137 (99, 192)
<315	43 (97.7)	42 (97.7)	85 (97.7)
≥ 315	1 (2.3)	1 (2.3)	2 (2.3)
PF ratio* (PaO_2/FiO_2, computed) median (IQR)	90 (45, 155)	82 (38, 143)	73 (61, 85)
<300	43 (97.7)	42 (97.7)	85 (97.7)
≥ 300	1 (2.3)	1 (2.3)	2 (2.3)
Temperature (˚C) median (IQR)	37.0 (36.7, 37.4)	36.8 (36.2, 37.1)	36.9 (36.3, 37.3)
< 38	42 (95.5)	42 (97.7)	84 (96.6)
≥ 38	2 (4.5)	1 (2.3)	3 (3.4)
Heart rate (bmp) median (IQR)	75 (62, 90)	71 (61, 77)	117 (106, 134)
<100	39 (88.6)	40 (93.0)	79 (90.8)
≥ 100	5 (11.4)	3 (7.0)	8 (9.2)
Systolic BP (SBP, mmHg) median (IQR)	120 (111, 134)	117 (106, 133)	65 (60, 74)
<90	0 (0.0)	0 (0.0)	0 (0.0)
90-110	11 (25.0)	17 (39.5)	28 (32.2)
>110	33 (75.0)	26 (60.5)	59 (67.8)
Diastolic BP (DBP, mmHg) median (IQR)	65 (59, 74)	67 (62, 76)	82 (76, 91)
Mean arterial pressure (MAP, mmHg) median (IQR)	86 (74, 89)	82 (76, 92)	86 (74, 89)
< 65 with vasopressor	0 (0.0)	0 (0.0)	0 (0.0)
< 65 without vasopressor	0 (0.0)	0 (0.0)	0 (0.0)
≥ 65 with vasopressor	8 (18.2)	5 (11.6)	13 (14.9)
≥ 65 without vasopressor	36 (81.8)	38 (88.4)	74 (85.1)
Vasopressor dose, NE equivalent µg/kg/min median (IQR), on vasopressor at entry	0.05 (0.03, 0.08)	0.04 (0.01, 0.04)	0.04 (0.02, 0.06)

*PF ratio derived from: SF ratio=64 + 0.84 *(PF ratio). Per Rice et al, Chest 2007.

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Table S14: Baseline COVID-19 Characteristics and Respiratory Status: Remdesivir Comparison

	Remdesivir No. (%)	Remdesivir Placebo No. (%)	Total No. (%)
No. participants	***44***	***43***	***87***
COVID-19 Characteristics			
Days since hospital admission *median (IQR)*	*2 (2, 3)*	*2 (1, 3)*	*2 (2, 3)*
Days latest +ve SARS-CoV-2 test *median (IQR)*	*2 (2, 4)*	*2 (2, 4)*	*2 (2, 4)*
Days since symptom onset *median (IQR)*	*10 (7, 14)*	*11 (8, 16)*	*10 (7, 15)*
0-6 days	9 (20.5)	7 (16.3)	16 (18.4)
7-14 days	26 (59.1)	21 (48.8)	47 (54.0)
>14 days	9 (20.5)	15 (34.9)	24 (27.6)
SARS-CoV-2 vaccination, n (%)			
mRNA, 3 doses (last ≥ 14 days from symptoms)	3 (6.8)	0 (0.0)	3 (3.4)
mRNA, 2 doses (last ≥ 14 days from symptoms)	5 (11.4)	7 (16.3)	12 (13.8)
J&J, 2 doses (last ≥ 14 days from symptoms)	0 (0.0)	0 (0.0)	0 (0.0)
J&J, 1 dose (last ≥ 14 days from symptoms)	3 (6.8)	3 (7.0)	6 (6.9)
Other/Partial*	3 (6.8)	5 (11.6)	8 (9.2)
No vaccination	29 (65.9)	26 (60.5)	55 (63.2)
Unknown	1 (2.3)	2 (4.7)	3 (3.4)
Blinded vaccination	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory Status			
Days since respiratory failure *median (IQR)*	*2 (2, 3)*	*2 (1, 3)*	*2 (2, 3)*
0-1 day	6 (13.6)	14 (32.6)	20 (23.0)
2-3 days	30 (68.2)	28 (65.1)	58 (66.7)
4 days	8 (18.2)	1 (2.3)	9 (10.3)
Days since lung imaging results *median (IQR)*	*1 (0, 2)*	*1 (1, 2)*	*1 (0, 2)*
Lung Infiltrate, n (%)s			
No imaging	0 (0.0)	0 (0.0)	0 (0.0)
No infiltrates	0 (0.0)	0 (0.0)	0 (0.0)
Unilateral	2 (4.5)	1 (2.3)	3 (3.4)
Bilateral	42 (95.5)	42 (97.7)	84 (96.6)
Bilateral infiltrates & SF ratio < 315, n (%)	41 (93.2)	41 (95.3)	82 (94.3)
ARDS by Berlin criteria*, n (%)	24 (54.5)	20 (46.5)	44 (50.6)
Current mode of respiratory support, n (%)			
High-flow nasal cannula (HFNC) oxygen device	19 (43.2)	20 (46.5)	39 (44.8)
Non-invasive ventilation (NIV)	0 (0.0)	1 (2.3)	1 (1.1)
Invasive mechanical ventilation (IMV)	23 (52.3)	22 (51.2)	45 (51.7)
Extracorporeal membrane oxygenation (ECMO)	2 (4.5)	0 (0.0)	2 (2.3)
HFNC flow rate, L/min *median (IQR)* among those on HFNC at entry	*45 (40, 50)*	*50 (40, 55)*	*50 (40, 50)*

* recd. 1 of 2 dose series, last vaccination < 14 days before symptoms, 1-2 vaccinations but unknown dates
*** bilateral infiltrates and PF ratio<300 (per Rice et al) and IMV or ECMO

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Table S15: Baseline Medical History: Remdesivir Comparison

	Remdesivir No. (%)	Remdesivir Placebo No. (%)	Total No. (%)
No. participants	***44***	***43***	***87***
Medical History*			
Asthma	5 (11.4)	3 (7.0)	8 (9.2)
Cerebrovascular event	0 (0.0)	0 (0.0)	0 (0.0)
COPD	2 (4.5)	3 (7.0)	5 (5.7)
Diabetes mellitus requiring medication	12 (27.3)	14 (32.6)	26 (29.9)
Heart failure	0 (0.0)	1 (2.3)	1 (1.1)
Hepatic impairment	1 (2.3)	1 (2.3)	2 (2.3)
HIV or other immune suppression	4 (9.1)	2 (4.7)	6 (6.9)
Hypertension requiring medication	21 (47.7)	17 (39.5)	38 (43.7)
Malignancy	1 (2.3)	2 (4.7)	3 (3.4)
MI or other acute coronary syndrome	4 (9.1)	0 (0.0)	4 (4.6)
Renal impairment	7 (15.9)	4 (9.3)	11 (12.6)
Any of above	*30 (68.2)*	*26 (60.5)*	*56 (64.4)*
Pre-COVID Requirements			
Pre-morbid continuous suppl. oxygen	1 (2.3)	2 (4.7)	3 (3.4)
Pre-morbid renal replacement Rx (RRT)	1 (2.3)	0 (0.0)	1 (1.1)
BMI, kg/m^2 [median (IQR)]	*33.4 (28.3, 41.3)*	*33.3 (28.9, 38.5)*	*33.4 (28.4, 39.8)*
<30	17 (39.5)	13 (31.0)	30 (35.3)
30-39.9	13 (30.2)	22 (52.4)	35 (41.2)
≥ 40	13 (30.2)	7 (16.7)	20 (23.5)
Composites			
Compromised immune system**	5 (11.4)	4 (9.3)	9 (10.3)
Metabolic co-morbidity***	15 (34.1)	15 (34.9)	30 (34.5)
Renal impairment or need for RRT	7 (15.9)	4 (9.3)	11 (12.6)
No hypertension, no metabolic condition	18 (40.9)	21 (48.8)	39 (44.8)
Hypertension, no metabolic condition	11 (25.0)	7 (16.3)	18 (20.7)
No hypertension, metabolic condition	5 (11.4)	5 (11.6)	10 (11.5)
Hypertension and metabolic condition	10 (22.7)	10 (23.3)	20 (23.0)

* Diagnoses requiring regular follow-up, medication, or hospitalization within the previous 12 months.

** current use of antirejection medication, cytotoxic chemotherapy, trt. with biologic medication, HIV or other immunosuppresive disorder

*** history of diabetes req. Rx, cerebrovascular event, heart failure, MI or other acute coronary syndrome

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Table S16: Current Medical Conditions During Index Hospitalization, at Baseline: Remdesivir Comparison

	Remdesivir No. (%)	Remdesivir Placebo No. (%)	Total No. (%)
No. participants	***44***	***43***	***87***
Cardiac and Vascular	**15 (34.1)**	**11 (25.6)**	**26 (29.9)**
Myocardial infarction	3 (6.8)	2 (4.7)	5 (5.7)
Congestive heart failure (I/II/III/IV)	0 (0.0)	0 (0.0)	0 (0.0)
Class I/II	0 (0.0)	0 (0.0)	0 (0.0)
Class III/IV	0 (0.0)	0 (0.0)	0 (0.0)
Myocarditis	0 (0.0)	0 (0.0)	0 (0.0)
Pericarditis	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension requiring vasopressor	13 (29.5)	7 (16.3)	20 (23.0)
Atrial tachyarrhythmias	1 (2.3)	2 (4.7)	3 (3.4)
Ventricular tachyarrhythmias	0 (0.0)	0 (0.0)	0 (0.0)
Hematological	**0 (0.0)**	**3 (7.0)**	**3 (3.4)**
Bleeding	0 (0.0)	0 (0.0)	0 (0.0)
Disseminated intravascular coagulation (DIC)	0 (0.0)	0 (0.0)	0 (0.0)
Thromboembolic events (arterial/venous)	0 (0.0)	3 (7.0)	3 (3.4)
DVT	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	0 (0.0)	2 (4.7)	2 (2.3)
Arterial thrombosis/embolism	0 (0.0)	1 (2.3)	1 (1.1)
Hepatic			
Hepatic decompensation*	0 (0.0)	1 (2.3)	1 (1.1)
Infection			
Intercurrent disease, non SARS-CoV-2	5 (11.4)	4 (9.3)	9 (10.3)
Primarily respiratory	5 (11.4)	4 (9.3)	9 (10.3)
Neurological	**5 (11.4)**	**3 (7.0)**	**8 (9.2)**
Acute delirium	5 (11.4)	1 (2.3)	6 (6.9)
Cerebrovascular event	0 (0.0)	0 (0.0)	0 (0.0)
Ischemic	0 (0.0)	0 (0.0)	0 (0.0)
Hemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)
Both	0 (0.0)	0 (0.0)	0 (0.0)
Encephalitis	0 (0.0)	1 (2.3)	1 (1.1)
Meningitis	0 (0.0)	0 (0.0)	0 (0.0)
Myelitis	0 (0.0)	1 (2.3)	1 (1.1)
Transient ischemic event	0 (0.0)	0 (0.0)	0 (0.0)
Renal			
New need for renal replacement Tx (RRT)**	1 (2.3)	1 (2.3)	2 (2.3)
Any of above	***18 (40.9)***	***15 (34.9)***	***33 (37.9)***

* Exclusionary for randomization to aviptadil/placebo

** Participants with pre-COVID need for dialysis excluded from denominator

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Table S17: SARS-CoV-2 Antibodies, Antigen, and Viral Load Levels, at Baseline: Remdesivir Comparison

BioRad Antinucleocapsid Ab [a] Sample/Cutoff Ratio	Remdesivir	Remdesivir Placebo	Total
N. in group	***44***	***43***	***87***
N. with data	***42***	***43***	***85***
Positive, n (%)	36 (85.7)	39 (90.7)	75 (88.2)
Equivocal, n (%)	0 (0.0)	1 (2.3)	1 (1.2)
Negative, n (%)	6 (14.3)	3 (7.0)	9 (10.6)
GenScript Anti-Spike Neutralizing Ab[b] Binding Inhibition(%)	**Remdesivir**	**Remdesivir Placebo**	**Total**
N. with data	***42***	***43***	***85***
Positive, n (%)	29 (69.0)	37 (86.0)	66 (77.6)
Negative, n (%)	13 (31.0)	6 (14.0)	19 (22.4)
Quanterix Antigen[c] Concentration (pg/mL)	**Remdesivir**	**Remdesivir Placebo**	**Total**
N. with data	***42***	***43***	***85***
Positive, n (%)	37 (88.1)	41 (95.3)	78 (91.8)
Negative, n (%)	5 (11.9)	2 (4.7)	7 (8.2)
min*, max	2.9, 77791	2.9, 13119	2.9, 77791
median (IQR)	721 (37, 5156)	998 (55, 5364)	876 (52, 5327)
mean ± SD	5775 ± 12922	3064 ± 3743	4404 ± 9506
$\log_{10}$, median (IQR)	2.85 (1.57, 3.71)	3.00 (1.74, 3.73)	2.94 (1.72, 3.73)
$\log_{10}$, mean ± SD	2.7 ± 1.3	2.7 ± 1.1	2.7 ± 1.2
≥ 1000, n (%)	20 (47.6)	21 (48.8)	41 (48.2)
* 2.9 is imputed for antigen < LOQ (<3)			
Quanterix Antibody[d] (ng/mL)	**Remdesivir**	**Remdesivir Placebo**	**Total**
N. with data	***42***	***43***	***85***
Positive, n (%)	32 (76.2)	37 (86.0)	69 (81.2)
Negative, n (%)	10 (23.8)	6 (14.0)	16 (18.8)
min*, max	8, 1973322	13, 2708505	8, 2708505
median (IQR)	6579 (1176, 38817)	10453 (1415, 161E3)	6899 (1328, 59770)
mean ± SD	140327 ± 414644	212447 ± 499337	176811 ± 458151
$\log_{10}$, median (IQR)	3.82 (3.07, 4.59)	4.02 (3.15, 5.21)	3.84 (3.12, 4.78)
$\log_{10}$, mean ± SD	3.8 ± 1.3	4.1 ± 1.3	3.9 ± 1.3

[a] BioRad Platelia anti-nucleocapsid assay (total antibody): positive: ≥ 1.0 sample/cutoff ratio

[b] GenScript cPass surrogate SARS-CoV-2 neutralization assay (anti-spike); positive: ≥ 30% binding inhibition

[c] Quanterix Simoa nucleocapsid antigen; positive: ≥ 3 pg/mL

[d] Quanterix Simoa anti-spike assay (immunoglobulin G); positive: ≥ 770 ng/mL

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Table S18: SARS-CoV-2 Midturbinate Nasal Swab Viral Load, at Baseline: Remdesivir Comparison

Nasal Swab Fluid [a]	Remdesivir	Remdesivir Placebo	Total
N. in group	***44***	***43***	***87***
Viral RNA			
Qualitative, N. with data	***43***	***42***	***85***
Positive, n (%)	39 (90.7)	39 (92.9)	78 (91.8)
Equivocal, n (%)	2 (4.7)	0 (0.0)	2 (2.4)
Negative, n (%)	2 (4.7)	3 (7.1)	5 (5.9)
Quantitative, N with data[b]	***39***	***39***	***78***
min, max $x10^3$ copies/mL	0.1, 130392.4	0.1, 12915.8	0.1, 130392.4
median (IQR), $x10^3$ copies/mL	191.0 (1.2, 768.5)	53.5 (3.4, 464.9)	96.8 (2.5, 559.6)
mean ± SD, $x10^3$ copies/mL	5908.0 ± 22455.8	1246.8 ± 3027.1	3577.4 ± 16089.8
log_{10}, median (IQR)	5.28 (3.08, 5.88)	4.72 (3.52, 5.66)	4.98 (3.40, 5.74)
log_{10}, mean ± SD	4.8 ± 1.7	4.7 ± 1.4	4.7 ± 1.6
Variant			
N. tested for variant	***43***	***42***	***85***
Positive nucleocapsid PCR, n (%)	41 (95.3)	42 (100.0)	83 (97.6)
Undetermined nucleocapsid PCR, n (%)	2 (4.7)	0 (0.0)	2 (2.4)
N. with positive PCR	***41***	***42***	***83***
Delta, n (%)	27 (65.9)	32 (76.2)	59 (71.1)
Omicron[c], n (%)	7 (17.1)	3 (7.1)	10 (12.0)
Other[d], n (%)	7 (17.1)	7 (16.7)	14 (16.9)

[a] Midturbinate swab specimen

[b] Among those with positive qualitative result. Lower limit of quantification is 100 copies/mL

[c] Determined among those with specimens collected Nov 2021 or later that were positive for the nucleocapsid PCR but not positive for delta PCR

[d] Positive for the nucleocapsid PCR but not positive for delta or omicron

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Table S19: Baseline Lab Measures: Remdesivir Comparison

Laboratory Measure*	Remdesivir Med [IQR]	Remdesivir Placebo Med [IQR]	Total Med [IQR]
No. participants	***44***	***43***	***87***
Metabolic Panel			
Sodium (mEq/L)	139 (136, 142)	138 (136, 141)	138 (136, 141)
Potassium (mEq/L)	4.3 (4.0, 4.8)	4.4 (4.0, 4.7)	4.3 (4.0, 4.7)
Chloride (mEq/L)	106 (100, 108)	104 (101, 107)	104 (100, 107)
Bicarbonate/CO_2 (mEq/L)	24.0 (22.0, 26.0)	23.0 (21.0, 26.0)	24.0 (22.0, 26.0)
BUN, mg/dL	25 (21, 43)	29 (22, 36)	27 (21, 38)
Serum creatinine (mg/dL)	0.90 (0.77, 1.31)	0.98 (0.70, 1.20)	0.90 (0.73, 1.20)
Total bilirubin (mg/dL)	0.5 (0.4, 0.7)	0.5 (0.4, 0.9)	0.5 (0.4, 0.8)
AST/SGOT (U/L)**	48 (33, 69)	43 (30, 60)	47 (31, 65)
ALT/SGPT (U/L)**	41 (23, 85)	39 (26, 61)	40 (23, 65)
Complete Blood Count			
WBC (10^9/L)	8.7 (7.3, 11.5)	9.4 (6.0, 11.4)	9.0 (7.2, 11.4)
Hemoglobin (g/dL)	12.9 (11.2, 14.4)	13.7 (12.0, 14.1)	13.0 (11.8, 14.3)
Platelets (10^9/L)	259 (210, 350)	253 (191, 298)	257 (204, 315)
Neutrophils (10^9/L)	7.39 (5.85, 10.07)	8.39 (5.37, 10.20)	7.50 (5.78, 10.15)
Lymphocytes (10^9/L)	0.62 (0.40, 0.92)	0.50 (0.33, 0.77)	0.53 (0.36, 0.88)
Other			
CRP, mg/L	73.4 (36.9, 112.8)	92.0 (47.0, 160.9)	82.4 (42.4, 125.4)
Ferritin (µg/mL)	956 (642, 1945)	1306 (651, 2197)	1078 (643, 2010)
INR, from PT (seconds)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)
D-dimer (µg/mL)	1.64 (0.97, 4.00)	2.11 (0.94, 5.39)	1.92 (0.97, 5.09)

BUN=blood urea nitrogen, WBC=white blood count, CRP=C-reactive protein, PT=prothrombin time

*As collected on case report forms.

**AST/SGOT and/or ALT/SGPT can be reported

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Table S20: Baseline Concomitant Medications: Remdesivir Comparison

	Remdesivir No. (%)	Remdesivir Placebo No. (%)	Total No. (%)
No. participants	***44***	***43***	***87***
Antibiotics	29 (65.9)	21 (48.8)	50 (57.5)
IV antibiotic	28 (63.6)	21 (48.8)	49 (56.3)
Oral antibiotic	2 (4.5)	1 (2.3)	3 (3.4)
Antifungals	2 (4.5)	1 (2.3)	3 (3.4)
Antidiarrheal agent	0 (0.0)	0 (0.0)	0 (0.0)
ACE inhibitors	0 (0.0)	1 (2.3)	1 (1.1)
ARBs	0 (0.0)	2 (4.7)	2 (2.3)
Beta blockers	2 (4.5)	5 (11.6)	7 (8.0)
Antiplatelets/anticoagulants	40 (90.9)	39 (90.7)	79 (90.8)
Aspirin	12 (27.3)	4 (9.3)	16 (18.4)
Other antiplatelet	3 (6.8)	4 (9.3)	7 (8.0)
Heparin, prophylactic dose	19 (43.2)	24 (55.8)	43 (49.4)
Heparin, intermediate dose	2 (4.5)	3 (7.0)	5 (5.7)
Heparin therapeutic dose	9 (20.5)	6 (14.0)	15 (17.2)
Warfarin	0 (0.0)	0 (0.0)	0 (0.0)
DOAC	0 (0.0)	0 (0.0)	0 (0.0)
Other anticoagulant	8 (18.2)	7 (16.3)	15 (17.2)
Pulmonary vasodilators	4 (9.1)	1 (2.3)	5 (5.7)
Phosphodiesterase	0 (0.0)	0 (0.0)	0 (0.0)
Prostanoids	1 (2.3)	1 (2.3)	2 (2.3)
Nitric oxide	1 (2.3)	0 (0.0)	1 (1.1)
Other pulm. vasodilator	2 (4.5)	0 (0.0)	2 (2.3)
SARS-CoV-2 antiviral (excl RDV)	0 (0.0)	0 (0.0)	0 (0.0)
Antirejection meds	2 (4.5)	2 (4.7)	4 (4.6)
Corticosteroids	41 (93.2)	42 (97.7)	83 (95.4)
Biologics, cancer/autoimmune	0 (0.0)	0 (0.0)	0 (0.0)
Cytotoxic chemotherapy	0 (0.0)	0 (0.0)	0 (0.0)
Immune modulators	10 (22.7)	14 (32.6)	24 (27.6)
IL-1 inhibitor	0 (0.0)	0 (0.0)	0 (0.0)
IL-6 inhibitor	3 (6.8)	10 (23.3)	13 (14.9)
Interferons	0 (0.0)	0 (0.0)	0 (0.0)
JAK inhibitor	6 (13.6)	3 (7.0)	9 (10.3)
TNF inhibitor	0 (0.0)	0 (0.0)	0 (0.0)
Other immune modulator	1 (2.3)	1 (2.3)	2 (2.3)
Sedatives	26 (59.1)	24 (55.8)	50 (57.5)
Benzodiazepines	11 (25.0)	11 (25.6)	22 (25.3)
Opiods	24 (54.5)	19 (44.2)	43 (49.4)
Propofol	22 (50.0)	19 (44.2)	41 (47.1)
Dexmedetomidine	5 (11.4)	2 (4.7)	7 (8.0)
Other sedative	6 (13.6)	9 (20.9)	15 (17.2)
NSAIDs (at least 7 days)	1 (2.3)	2 (4.7)	3 (3.4)

Concomitant medications in past 24 hours, including long-acting medications for underlying conditions received on a regular basis.

6 Supplementary Tables and Figures: Follow-up for the Aviptadil Comparison

Below is a summary of the tables and figures in the supplement related to follow-up, including efficacy and safety for participants in the aviptadil comparison. The tables and figures included in the supplement are shown in the order that they are referred to in the main text.

Table S21. Adherence to aviptadil infusion – the percentage of the planned infusion of aviptadil and placebo given on each day is summarized. On days 1 and 2 the percentage given was less for those in the aviptadil compared to the placebo group. The average over the 3 days was 75.8% full (>90%), 20.8% most (50-90%), and some (<50%) 3.5%. Corresponding percentages for the placebo group are 83.5%, 13.5%, and 3.0%.

Table S22. Concomitant medication at days 1, 3, 5 and 7 of follow-up – with a few exceptions, concomitant medication use was similar for each treatment group on each day of follow-up; antidiarrheal agents were given to participants assigned aviptadil more often than those assigned placebo on days 1 and 3; corticosteroids, antiplatelets/anticoagulants, sedatives, and antibiotics were the most commonly prescribed medications in each treatment group on each day.

Figure S4. Cumulative Percent of Supplemental Oxygen-Free Days at Home by Day 90 - Figure S4 gives the cumulative distribution of supplemental-oxygen free days at home at Day 90 (supplemental oxygen-free days at home correspond to the "number of days recovered" used to define categories of the ordinal primary endpoint), an ordered categorical outcome with 93 categories. Categories 1-90 denote the ranked categories for the number of supplemental-oxygen free days. Deaths, hospitalization, and being discharged from the hospital but not recovered (this means, being at home on oxygen or discharged to a location with higher level of care than the pre-COVID-19 home) are considered the worst possible outcomes at day 90 and are shown before day 1. Higher categories are better. Each point of the curve for each treatment group gives the cumulative percentage of participants whose Day 90 recovery status was in the given category or a worse category. For example, at day 20, 54.2% of participants assigned aviptadil and 62.2% assigned placebo had died, were not recovered, or were "recovered" for less than or equal to 20 days; at day 60 these percentages were 75.1% and 75.6%, respectively, for the aviptadil and placebo groups. Here, the recovery category "20" includes the participants who had 20 continuous "oxygen-free days at home" by Day 90; these participants had returned to home and discontinued supplemental oxygen use on Day 70. The vertical dashed lines denote the boundaries for the ordinal primary outcome, and the values of the red-solid (aviptadil) and blue-dashed (placebo) lines where they cross the vertical dashed lines denote the cumulative

percentages of participants according to the dichotomized ordered categories of the primary outcome. There was no difference between treatment groups for the worst two categories (death or hospitalized on Day 90); the difference between the curves favored aviptadil among those who were discharged but not recovered by Day 90, and the treatment difference declined through about 50 days; afterwards, the curves were superimposed. Only participants with known primary outcome were included.

Figure S5. Sensitivity analysis for the primary endpoint, imputing the day 90 outcome using last value carried forward for the 11 participants with missing the primary ordinal endpoint at day 90 – categories for the 11 participants with missing day 90 status were imputed using last value carried forward. With this imputation, the OR was 1.10 (95% CI: 0.79-1.52). The p-value corresponding to the test for proportional odds was 0.11. See Section 2 of this appendix for a line listing of the last known status for these 11 participants.

Table S23. Summary table presenting the odds ratio for the aviptadil versus placebo group for the day 90 outcome after varying adjustment factors – the statistical analysis plan defined several sensitivity analyses concerning stratification factors used in the primary endpoint analysis. We pre-specified that the primary analysis would include only disease severity as a stratifying variable. As sensitivity analyses, we planned an unstratified analysis, an analysis stratified by design stratum (as shown in Figure S1), an analysis stratified by disease severity and design stratum, and an analysis stratified by geographical region. The latter was planned in anticipation of sites in other countries enrolling patients. This enrollment outside of the U.S. was never realized due the inability to provide study treatment to sites outside of the U.S. prior to ending the trial.

All of the sensitivity analyses carried out yielded similar ORs to that estimated for the pre-specified primary analysis which only stratified on disease severity. These ORs, 95% CIs, and p-values are given in Table S23.

Figure S6. Four-category ordinal outcome by day – the distribution of participants across 4 ordinal categories on each day of follow-up (0 to 90) are shown. The four ordinal categories shown correspond to categories 4, 5 and 6 of the primary ordinal outcome and to a category that merges categories 1, 2 and 3 into a single category. The percentage of participants in each category is shown with a different color. From left to right, the 4 categories are:

- Death
- Hospitalized or receiving hospice care
- Discharged, but not at home off oxygen, or at home requiring oxygen
- At home and off oxygen

While categories 5 (hospitalized or receiving hospice care) and 6 (death) are similar for the aviptadil and placebo groups over time, more participants assigned aviptadil than placebo move from category 4 (discharged, but not at home, or at home requiring supplemental oxygen) to categories 1-3 (at home and not requiring supplemental oxygen) over time.

Figure S7. Time to discharge – the subhazard ratio (sHR) for time to discharge was 0.99 (95% CI: 0.78-1.24). Cumulative incidence after 90 days was 60.4% for aviptadil and 60.3% for placebo and after 28 days (a time period used in other trials with this endpoint) was 46.1% and 48.5% for the aviptadil and placebo groups, respectively. The median time to discharge (95% CI) was 36 days for the aviptadil group and 31 days for the placebo group.

Among participants with known outcome status at day 90 (n=225 aviptadil and n=225 placebo), using the "last-off method", the median hospital-free days through day 90 was 45 days for the aviptadil group and 40 for the placebo group; deaths before day 90 assigned a value of -1 (p=0.98 for test of difference between groups using a Wilcoxon test stratified by disease severity).

Figure S8. Time to discharge home – the sub-hazard ratio (sHR) for time to discharge home (ignoring oxygen requirement after discharge) was 0.97 (95% CI: 0.77-1.23). The median time to discharge home was 47 days for the aviptadil group and 52 days for the placebo group.

Figure S9. Time to discharge home for at least 14 days – the sub-hazard ratio (sHR) for time to discharge home for at least 14 cumulative days (an endpoint referred to as sustained recovery in other trials) was 0.97 (95% CI: 0.76-1.23). The median time to discharge home for at least 14 days was 61 days for the aviptadil group and 69 days for the placebo group.

Table S24. 3-category ordinal outcome at day 90 - a 3-category ordinal outcome was also defined at day 90. This ordinal outcome combines the first 3 categories (discharged home and off supplemental oxygen) into a single category and combines the two categories for surviving participants who have not been discharged home off supplemental oxygen in a single category. The OR for this ordinal outcome was 1.17 (95% CI: 0.82-1.66). The p-value corresponding to the proportional odds assumption was 0.006. The ORs comparing category 1 versus 2 and 3 and comparing categories 1 and 2 versus 3 can be found in Table 2 of the manuscript and are 1.38 (95% CI: 0.95-2.00) and 0.95 (95% CI: 0.64-1.38), respectively.

Figure S10. 7-category pulmonary ordinal outcome on day 7, 14 and 28 – an ordinal outcome used in other ACTIV-3 trials is summarized. This ordinal outcome takes into account oxygen requirements and ranges from "can independently undertake usual activities with minimal/no symptoms" to "death". ORs, none of which favored

aviptadil, and 95% CIs on day 7, 14 and 28 are 0.93 (95%CI: 0.67-1.31), 0.97 (95% CI: 0.70-1.35), and 0.94 (95%CI: 0.68-1.32), respectively. On each day there were fewer participants assigned aviptadil compared to placebo in the best category (category 1) and more participants in the worst category (category 7).

Figure S11. Time to clinical organ failure, serious infection or death – The hazard ratio (HR) (aviptadil versus placebo) for the incidence of the composite outcome of clinical organ failure, serious infection, or death through Day 90 was 1.13 (95% CI 0.91-1.40). A HR > 1.0 indicates a more favorable result for placebo. The most common organ failure events were hypotension treated with vasopressor therapy and respiratory failure (see Table S64).

Figure S12. Time to respiratory worsening or death - the HR (aviptadil versus placebo) for respiratory worsening or death through Day 90 was 1.00 (95% CI 0.77-1.31). This HR was 0.99 (95% CI: 0.70-1.40) for those receiving oxygen from a high-flow nasal cannula or non-invasive mechanical ventilation at baseline; the HR was 1.02 (95% CI: 0.67-1.57) for those on invasive mechanical ventilation or ECMO at entry.

Figure S13. Time to rehospitalization or death after initial discharge– Among participants who were discharged, 139 in the aviptadil group and 138 in the placebo group, the hazard ratio (HR) comparing the aviptadil to the placebo group for time to hospital readmission or death after discharge was 0.66 (95% CI: 0.30-1.24). The cumulative incidence through 90 days was 7.8% for aviptadil and 11.2% for placebo.

Tables S25-S31. Infusion reactions by treatment group – infusion reactions reported on a checklist on the 3 days the infusion of aviptadil or placebo was to be given are summarized over all 3 days on which the infusion was given in Tables S25-S28. For participants who reported the same reaction on more than one day, the one with highest severity grade is counted. Tables S29-S31 summarize infusion reactions by day. Hypotension and diarrhea adverse events occurred more often on aviptadil compared to placebo. This was more evident on Days 1 and 2, when the dose of aviptadil was increased, than Day 0.

Table S32. Peri-infusion hypotension summary – this table summarizes peri-infusion hypotension (during and up to 2 hours after the infusion), infusion modifications due to hypotension, and vasopressor and IV fluid use. The majority of hypotension AEs were grade 1 or 2. Forty-six participants (20%) in the aviptadil group experienced grade 3 or 4 hypotension during the peri-infusion period compared to 28 participants (12%) assigned placebo.

Tables S33-S46. Safety outcomes through day 5 – Table S33 summarizes the day 5 composite safety outcome. Tables S34-S46 provide additional details on the components of the day 5 composite safety outcome. The OR (aviptadil versus placebo) for the composite of grade 3 or 4 adverse events, SAEs, end organ failure, serious infections or

death was 1.40 (95% CI: 0.94-2.08). Each component of the composite outcome occurred more frequently for those randomized to aviptadil compared to placebo.

MedDRA system organ class (SOC) for the 13 SAEs that were reported on the SAE form (i.e., with narratives) through day 5 (8 on aviptadil and 5 on placebo) are summarized in Table S34.

End organ dysfunction and serious infections through day 5 are summarized in Table S35. As noted in the Methods section of this appendix, these events were defined as "protocol-specified exempt serious events". These exempt events were systematically reported during follow-up but not reported as a SAE unless they were considered related to study agent. Over 43% of participants in each treatment group experienced at least one of these events of organ dysfunction and serious infection. The most common events were hypotension, intercurrent disease other than SARS-CoV-2, and worsening respiratory failure.

Table S36 gives incident grade 3 and 4 events by SOC through day 5. Tables S37-S46 summarize AEs by MedDRA preferred terms (PTs) for SOCs for which there were at least 5 events.

Table S47, Figure S14, and Tables S48-S61. Safety outcomes through day 28 – Table S47 summarizes the day 28 composite safety outcome. Figure S14 gives the Kaplan-Meier plot for time to the day 28 composite safety outcome, and Tables S48-S61 provide additional details on the components of the day 28 composite safety outcome.

The HR (aviptadil versus placebo) for the composite of grade 3 or 4 adverse events, SAEs, end organ failure, serious infections or death was 1.17 (95% CI: 0.95-1.44) (Table S47). Each component of the composite outcome occurred more frequently for those randomized to aviptadil compared to placebo. Most events occurred in the first 5 days of follow-up (63% for aviptadil and 56% for placebo; at day 28 these cumulative percentages were 79% and 75% (Figure S14).

MedDRA SOCs for the 38 SAEs (reported on the SAE form) that occurred through day 28 (19 on aviptadil and 19 on placebo) are summarized in Table S48.

End organ dysfunction and serious infections through day 28 are summarized in Table S49. Over 63% of participants in each treatment group experienced at least one of these events. Several events occurred in more than 10% of participants.

Table S50 gives incident grade 3 and 4 events by SOC through day 28. Most incident grade 3 and 4 adverse events were in the vascular SOC (120 aviptadil and 111 placebo). Tables S51-S61 summarize AEs by MedDRA PT for SOCs for which there were at least 5 events. Most of the vascular events were due to hypotension (105 aviptadil and 100 placebo) (Table S61).

Tables S62-S65. Safety outcomes through day 90. Composite safety outcome through day 90 – Table S62 summarizes the day 90 composite safety outcome, and Tables S63-S65 provide additional details on the components of the day 90 composite safety outcome. The HR (aviptadil versus placebo) for the composite of SAEs, end organ failure, serious infections or death was 1.11 (95% CI 0.89-1.38).

MedDRA SOCs for the 48 SAEs (reported on the SAE form) that occurred through day 90 (25 on aviptadil and 23 on placebo) are summarized in Table S63. End organ dysfunction and serious infections through day 90 are summarized in the Table S64. Eight (3.5%) participants randomized to aviptadil and 1 (0.4%) randomized to placebo had a myocardial infarction; congestive heart failure occurred among 2 (0.9%) participants assigned aviptadil and 7 (3.0%) assigned placebo. The most common event was hypotension requiring a vasopressor occurred in 38% randomized to aviptadil and 39% randomized to placebo. Worsening respiratory failure occurred in 25% randomized to aviptadil and 27% randomized to placebo.

Cardiovascular events reported are further summarized in Table S65. The most common cardiovascular events were deep vein thrombosis (DVT) and pulmonary embolism (PE). Through day 90, 29 participants developed a DVT among those randomized to aviptadil compared to 36 participants randomized to placebo. PE occurred in 8 participants randomized to aviptadil and 7 randomized to placebo.

Table S66. Grade 3 or 4 laboratory abnormalities – local laboratory tests were evaluated on days 1 and 2 of follow-up for all participants, and on days 3 and 5 if clinically available. This table considers grade 3 or 4 test results on these days; 42% assigned aviptadil and 40% assigned placebo had a least one grade 3 or 4 laboratory test result. Low lymphocyte count was the most common abnormal test in both groups.

Figures S15-S18. Subgroup analyses for the primary ordinal outcome, death through day 90, the composite safety outcome through day 5, and the composite safety outcome through day 28 -subgroups for major outcomes exhibited little heterogeneity according to baseline subgroups. Of the 24 subgroups considered for each of the 4 outcomes, two subgroups, remdesivir stratum and race/ethnicity, suggested possible heterogeneity of the treatment effect for the primary endpoint ($p=0.038$ and $p=0.02$ for interaction based on 3 df chi-square statistic, respectively). The subgroup of participants of Hispanic race/ethnicity had a more favorable outcome on aviptadil for the primary endpoint than other race/ethnicity groups (Figure S15) and the subgroups of participants randomized to the factorial (both agents) had more favorable outcomes on aviptadil compared to those with prior/current remdesivir use. These should be interpreted cautiously since there was no adjustment to type 1 error for the number of subgroups examined.

Table S67. Cumulative incidence of death through study days 5, 28, 90, and 180 according to baseline oxygen requirements – death rates in both treatment groups

increased substantially between days 5 and 28. Death rates across treatment groups according to baseline oxygen requirements were similar over time, except for some imbalance between treatment groups among those who required NIV at study entry (9 deaths in the aviptadil group versus 17 in the placebo group).

Table S21: Adherence, Percent of Planned Infusion Administered: Aviptadil Comparison

	Aviptadil		Placebo	
	N Exp.[1]	No. (%)	N Exp.[1]	No. (%)
Average of planned infusion volume administered				
Mean percent across Days 0-2[2]				
Full (> 90%)	231	175 (75.8)	230	192 (83.5)
Most (50-90%)		48 (20.8)		31 (13.5)
Some (< 50%)		8 (3.5)		7 (3.0)
Day 0				
Full (> 90%)	231	211 (91.3)	230	210 (91.3)
Most (50-90%)		9 (3.9)		17 (7.4)
Some (< 50%)		9 (3.9)		2 (0.9)
None (0%)		2 (0.9)		1 (0.4)
Day 1				
Full (> 90%)	230	190 (82.6)	228	208 (91.2)
Most (50-90%)		27 (11.7)		12 (5.3)
Some (< 50%)		11 (4.8)		3 (1.3)
None (0%)		2 (0.9)		5 (2.2)
Day 2				
Full (> 90%)	227	170 (74.9)	225	197 (87.6)
Most (50-90%)		30 (13.2)		9 (4.0)
Some (< 50%)		11 (4.8)		6 (2.7)
None (0%)		16 (7.0)		13 (5.8)

[1] If participant died/withdrew prior to the day's infusion, that day and any subsequent infusion days were not considered expected. If infusion not administered on an expected day, administered volume set to 0.

[2] Distribution of each participants average volume administered across study days 0-2.

Note - Percent volume administered each day computed from estimated volume administered divided by expected volume to administer as reported on CRFs.

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Table S22: Concomitant Medications At Days 1, 3, 5, and 7: Aviptadil Comparison

	Day 1		Day 3		Day 5		Day 7	
	Aviptadil No. (%)	Placebo No. (%)	Aviptadil No. (%)	Placebo No. (%)	Aviptadil No. (%)	Placebo No. (%)	Aviptadil No. (%)	Placebo No. (%)
No. participants	***230***	***229***	***225***	***224***	***222***	***221***	***214***	***215***
Antibiotics	104 (45)	110 (48)	98 (44)	99 (44)	94 (42)	91 (41)	92 (43)	89 (41)
IV antibiotic	98 (43)	108 (47)	95 (42)	93 (42)	86 (39)	84 (38)	88 (41)	82 (38)
Oral antibiotic	15 (7)	12 (5)	10 (4)	12 (5)	13 (6)	11 (5)	8 (4)	12 (6)
Antifungals	14 (6)	12 (5)	19 (8)	14 (6)	23 (10)	22 (10)	27 (13)	22 (10)
Antidiarrheal agent	31 (13)	6 (3)	13 (6)	7 (3)	3 (1)	2 (1)	2 (1)	2 (1)
ACE inhibitors	3 (1)	0 (0)	2 (1)	2 (1)	5 (2)	3 (1)	7 (3)	4 (2)
ARBs	3 (1)	3 (1)	1 (0)	6 (3)	4 (2)	5 (2)	6 (3)	9 (4)
Beta blockers	24 (10)	23 (10)	32 (14)	18 (8)	29 (13)	17 (8)	26 (12)	21 (10)
Antiplatelets/anticoagulants	217 (94)	220 (96)	215 (96)	211 (94)	202 (91)	200 (90)	179 (84)	184 (86)
Aspirin	40 (17)	34 (15)	37 (16)	33 (15)	32 (14)	27 (12)	30 (14)	31 (14)
Other antiplatelet	11 (5)	10 (4)	10 (4)	11 (5)	10 (5)	11 (5)	8 (4)	11 (5)
Heparin, prophylactic dose	108 (47)	119 (52)	109 (48)	108 (48)	99 (45)	97 (44)	79 (37)	88 (41)
Heparin, intermediate dose	39 (17)	39 (17)	35 (16)	38 (17)	30 (14)	38 (17)	27 (13)	29 (13)
Heparin therapeutic dose	48 (21)	38 (17)	42 (19)	33 (15)	40 (18)	34 (15)	34 (16)	35 (16)
Warfarin	2 (1)	0 (0)	1 (0)	1 (0)	2 (1)	1 (0)	2 (1)	1 (0)
DOAC	7 (3)	8 (3)	8 (4)	8 (4)	10 (5)	9 (4)	14 (7)	10 (5)
Pulmonary vasodialators	21 (9)	13 (6)	17 (8)	14 (6)	17 (8)	18 (8)	12 (6)	15 (7)
Phosphodiesterase	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Prostanoids	6 (3)	3 (1)	5 (2)	4 (2)	5 (2)	6 (3)	2 (1)	3 (1)
Nitric oxide	10 (4)	8 (3)	8 (4)	8 (4)	8 (4)	9 (4)	6 (3)	9 (4)
Other pulm. vasodilator	5 (2)	2 (1)	4 (2)	2 (1)	4 (2)	3 (1)	4 (2)	2 (1)
SARS-CoV-2 antivirals (excl RDV)	0 (0)	2 (1)	2 (1)	2 (1)	1 (0)	2 (1)	2 (1)	2 (1)
Antirejection meds	20 (9)	16 (7)	23 (10)	13 (6)	24 (11)	16 (7)	21 (10)	17 (8)
Corticosteroids	217 (94)	222 (97)	199 (88)	199 (89)	182 (82)	174 (79)	107 (50)	116 (54)
Biologics, cancer/autoimmune	4 (2)	2 (1)	4 (2)	3 (1)	3 (1)	3 (1)	2 (1)	1 (0)
Cytotoxic chemotherapy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Immune modulators	54 (23)	54 (24)	52 (23)	53 (24)	42 (19)	49 (22)	39 (18)	41 (19)
IL-1 inhibitor	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
IL-6 inhibitor	3 (1)	2 (1)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Interferons	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
JAK inhibitor	49 (21)	50 (22)	48 (21)	49 (22)	40 (18)	47 (21)	35 (16)	40 (19)
TNF inhibitor	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other immune modulator	2 (1)	2 (1)	3 (1)	5 (2)	2 (1)	3 (1)	4 (2)	2 (1)
Sedatives	126 (55)	123 (54)	127 (56)	121 (54)	116 (52)	117 (53)	109 (51)	116 (54)
Benzodiazepines	49 (21)	42 (18)	55 (24)	46 (21)	48 (22)	49 (22)	45 (21)	50 (23)
Opiods	110 (48)	107 (47)	108 (48)	107 (48)	100 (45)	103 (47)	100 (47)	101 (47)
Propofol	85 (37)	83 (36)	71 (32)	82 (37)	64 (29)	73 (33)	55 (26)	61 (28)
Dexmedetomidine	28 (12)	25 (11)	30 (13)	26 (12)	26 (12)	32 (14)	30 (14)	31 (14)
Other sedative	19 (8)	16 (7)	20 (9)	18 (8)	19 (9)	23 (10)	17 (8)	23 (11)
NSAIDs	7 (3)	10 (4)	9 (4)	8 (4)	6 (3)	9 (4)	9 (4)	9 (4)

Concomitant medications in past 24 hours excluding long-acting medications taken previously that may still have therapeutic levels in the body.

Program Name =vip fupconmeds Create date=17-NOV-2022 Cut date=08-NOV-2022

Figure S4: Cumulative Percent of Supplemental Oxygen-Free Days at Home by Day 90: Aviptadil Comparison

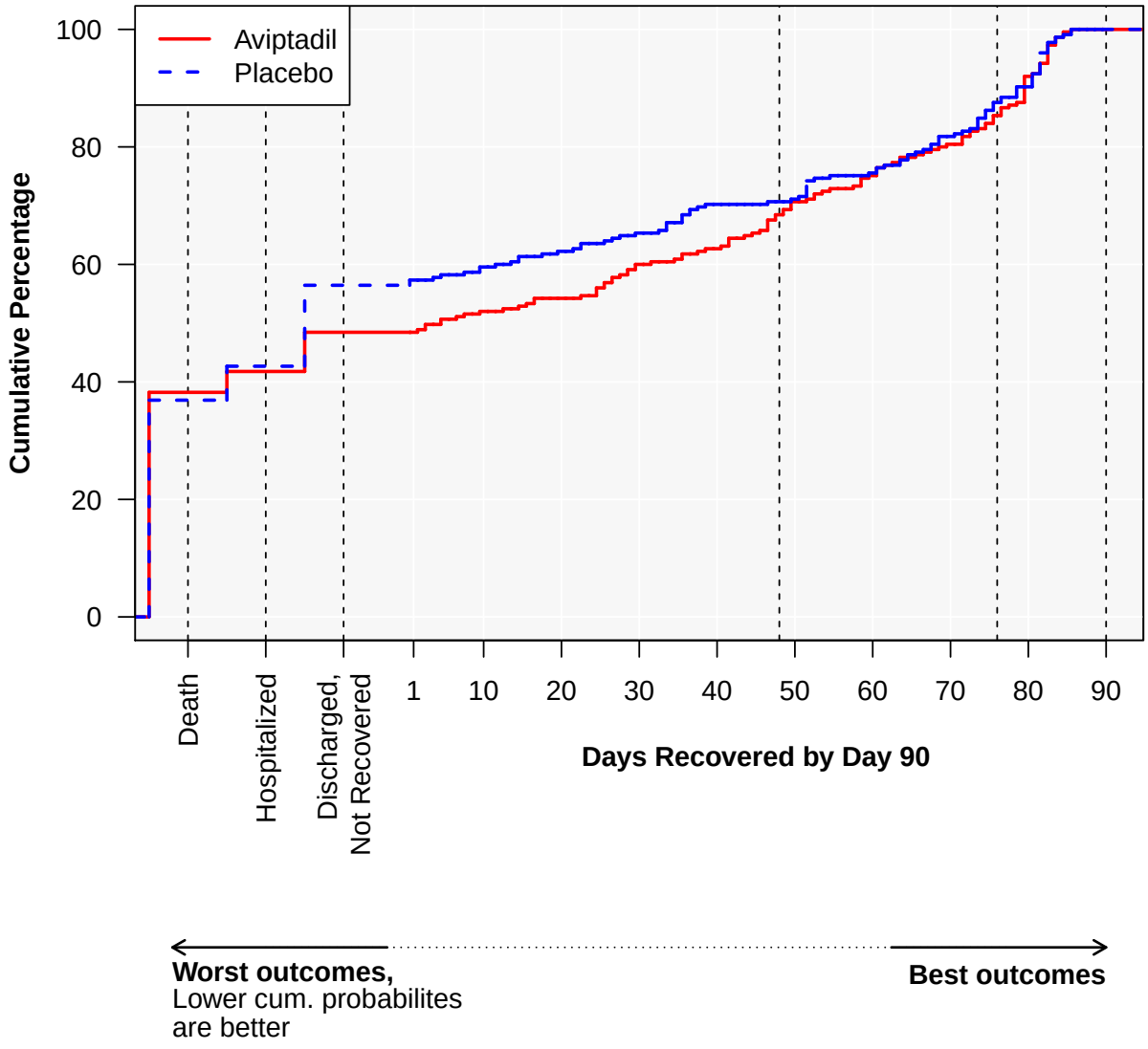

Figure S5: Sensitivity Analysis for the Ordinal Primary Outcome: Outcome imputed for Unknown Outcome Status at Day 90: Aviptadil Comparison

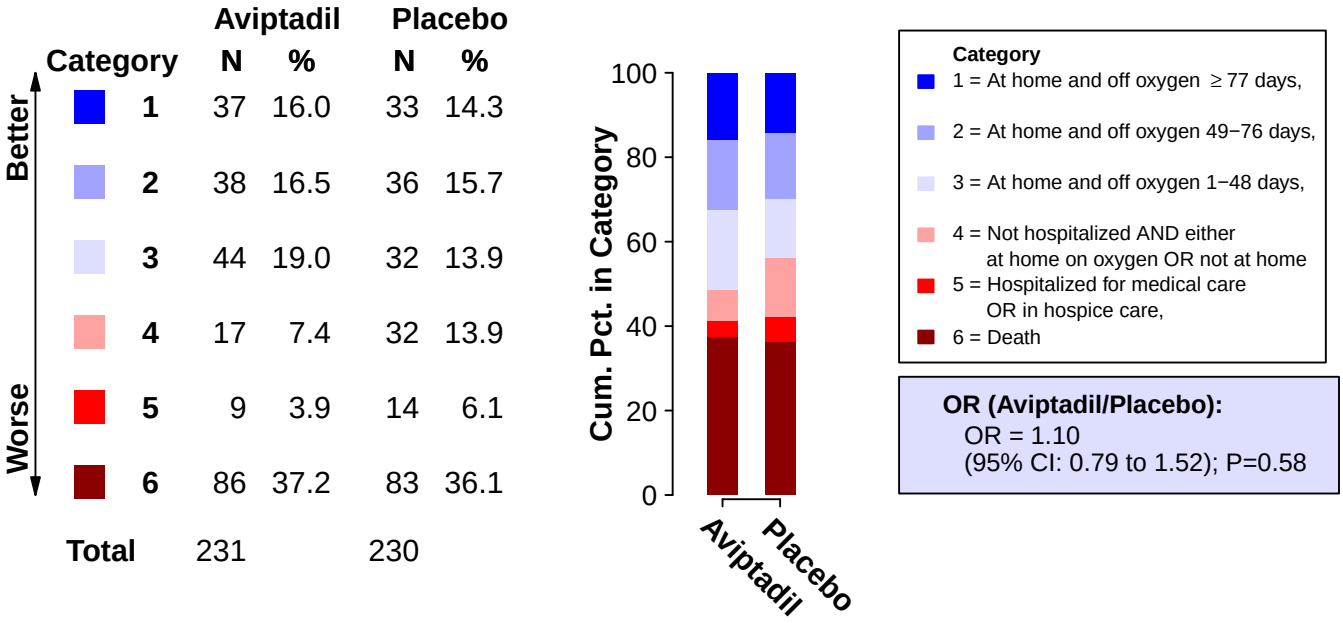

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Table S23: 6-Category Ordinal Outcome: Odds Ratio Comparing Treatment Groups by Varying Adjustment: Aviptadil Comparison

6-category Ordinal Outcome at Day 90	No. in mITT cohort	Odds Ratio[a] (OR) for Aviptadil/Placebo (95% CI)	p value
Primary[b]			
OR, adjusted for disease severity	450	1.11 (0.80-1.55)	0.54
Sensitivity[b]			
OR, unadjusted	450	1.12 (0.80-1.55)	0.52
OR, adjusted for clinical site[c]	450	1.07 (0.77-1.50)	0.68
OR, adjusted for disease severity and clinical site	450	1.07 (0.76-1.49)	0.71
OR, adjusted for randomization stratum[d]	450	1.12 (0.80-1.57)	0.50
OR, adjusted for disease severity and randomization stratum	450	1.11 (0.80-1.56)	0.51
Imputed[e]			
OR, adjusted for disease severity	461	1.10 (0.79-1.52)	0.58

mITT=modified intention to treat (i.e., received some infusion)

[a] Summary odds ratio for being in a better category at day 90 (aviptadil vs. placebo). Proportional odds regression model.

Category 1: At home and off oxygen ≥ 77 days (best)
Category 2: At home and off oxygen 49-76 days
Category 3: At home and off oxygen 1-48 days
Category 4: Discharged, but not at home, or at home requiring supplemental oxygen
Category 5: Hospitalized or receiving hospice care
Category 6: Died (worst)

[b] Analysis cohort is limited to participants in the mITT cohort with known status at day 90

[c] 21 distinct sites; 20 sites with ≥ 5 participants enrolled (97% of total), and 8 sites with < 5 participants pooled into one group (3% of total)

[d] Randomization stratum based on eligibility for both aviptadil and remdesivir (see Figure S1)

[e] Day 90 status for the 11 participants with missing status included using last known status carried forward.

Figure S6: Ordinal Outcome with 4 Categories, Distribution over Time: Aviptadil Comparison

Abbr.: N_{exp} = expected number of pts with known status; N_{obs} = number of pts with known status.

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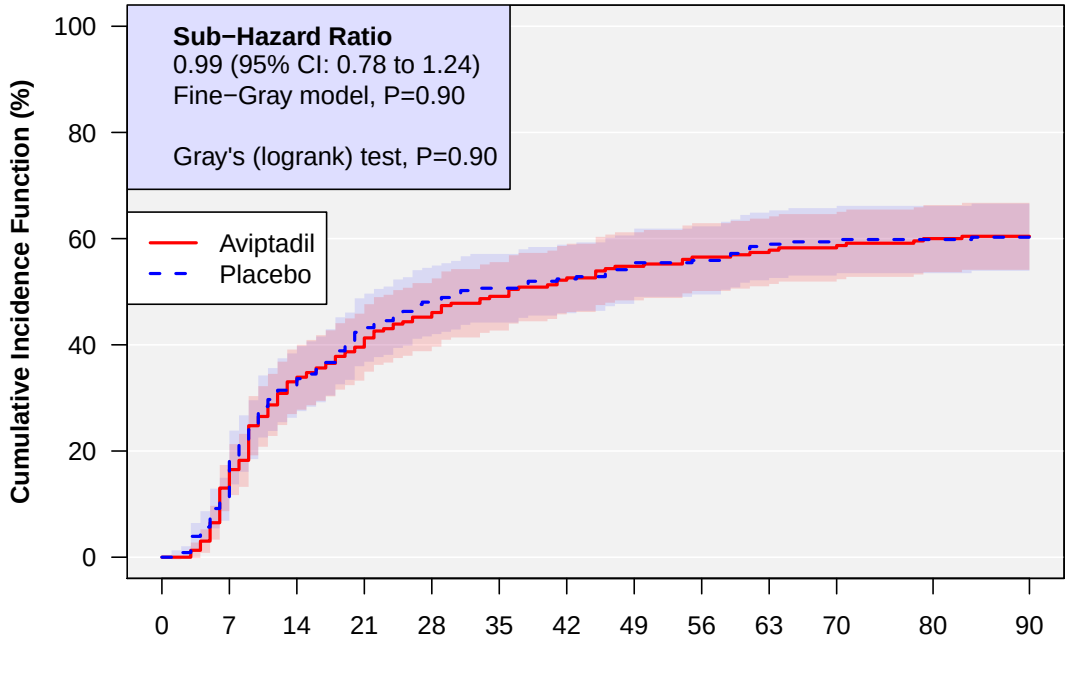
Figure S7: Time to Hospital Discharge: Aviptadil Comparison



Number at Risk:

A:	231	185	119	86	60	41	32	24	18	15	13	8	7
P:	230	191	127	79	56	41	34	26	22	14	12	11	10

Estimated Cumulative Pct. With Event:

A:		16.5	33.9	41.3	46.1	49.1	52.6	54.8	56.5	57.8	58.7	60.0	60.4
P:		18.8	33.6	43.2	48.5	50.7	52.4	55.5	55.9	59.0	59.8	59.8	60.3

Note: Tests are stratified by disease severity.

fig_t2discharge File created=11/17/22 Data cutoff=11/08/22

Status	Aviptadil (n= 231) No.	Aviptadil (n= 231) Pct	Placebo (n= 230) No.	Placebo (n= 230) Pct.	DRR[a] (A/P)	95% CI	P-value
Discharged	139	60.2	138	60.0	0.99	0.78, 1.24	0.90
Censored	8	3.5	11	4.8			
Died[b]	84	36.4	81	35.2			
Days to discharge[c] median (95% CI)	36 (24, 55)		31 (22, 58)				

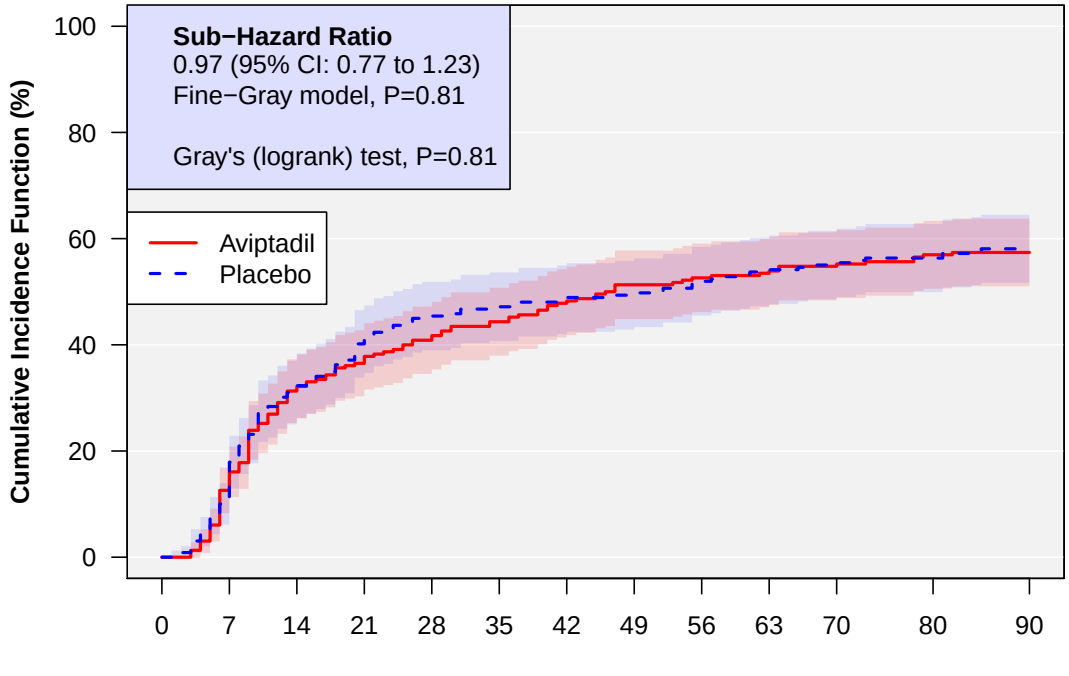
[a] Discharge rate ratio (A vs P) for time to discharge from the index hospitalization using the Fine-Gray method for considering death as a competing risk; stratified by disease severity (severe or critical). DRR > 1 indicates benefit to the Aviptadil group.

[b] Death before discharge from hospital considered a competing risk.

[c] Modified Kaplan-Meier estimate where follow-up for participants who died prior to discharge was carried forward to the administrative censoring date (cut date for this current report).

Program Name =mitt vip t2discharge90 Create date=17-NOV-2022 Cut date=08-NOV-2022

Figure S8: Time to Hospital Discharge and First Return Home: Aviptadil Comparison



Number at Risk:

A:	231	186	122	92	69	51	41	31	26	23	20	14	13
P:	230	192	129	83	61	48	42	36	30	24	21	18	14

Estimated Cumulative Pct. With Event:

A:		16.1	32.2	37.8	41.7	44.3	48.3	51.3	52.6	53.9	55.2	57.0	57.4
P:		17.9	32.3	41.0	45.4	47.2	48.9	49.8	52.0	54.2	55.5	56.3	58.1

Note: Tests are stratified by disease severity.

fig_t2discharge_home File created=11/17/22 Data cutoff=11/08/22

Status	Aviptadil (n= 231) No.	Aviptadil (n= 231) Pct	Placebo (n= 230) No.	Placebo (n= 230) Pct.	DRR[a] (A/P)	95% CI	P-value
At home	132	57.1	133	57.8	0.97	0.77, 1.23	0.81
Censored	14	6.1	15	6.5			
Died[b]	85	36.8	82	35.7			
1st day home[c] median (95% CI)	47 (30, 78)		52 (24, 73)				

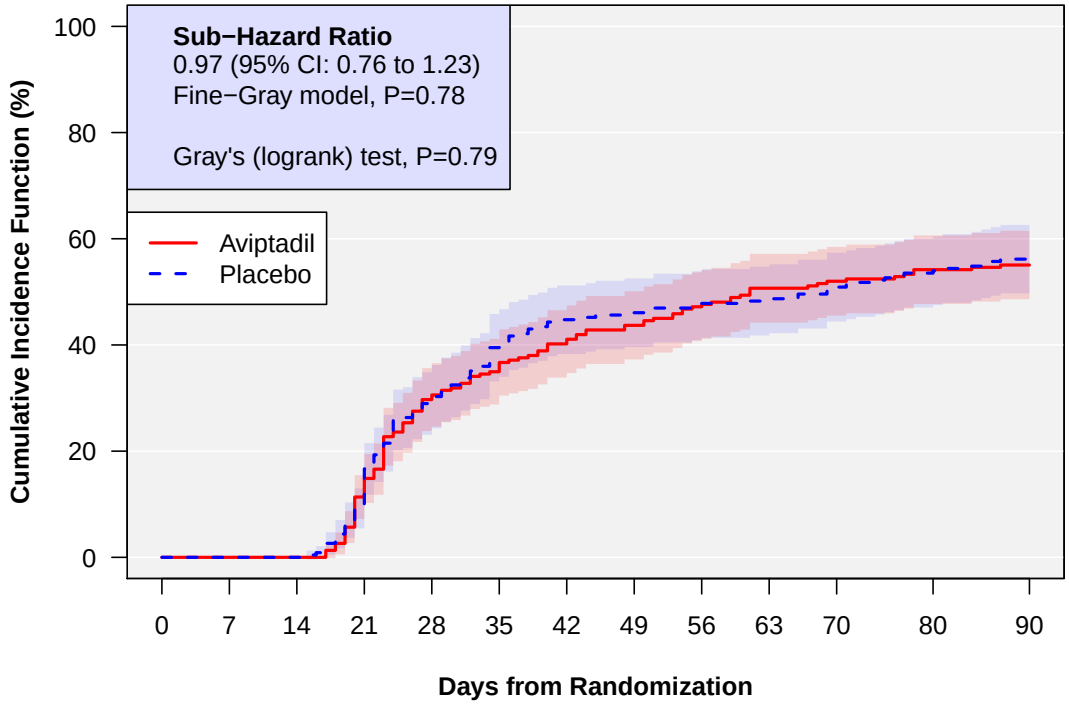
[a] Discharge rate ratio (A vs P) for time to first discharge from the index hospitalization and return home using the Fine-Gray method for considering death as a competing risk; stratified by disease severity (severe or critical). DRR > 1 indicates benefit to the Aviptadil group.

[b] Death before first return home considered a competing risk.

[c] Modified Kaplan-Meier estimate where follow-up for participants who died prior to return home was carried forward to the administrative censoring date (cut date for this current report).

Program Name =mitt vip t2dischargehome Create date=17-NOV-2022 Cut date=08-NOV-2022

Figure S9: Time to Discharge Home for 14 Consecutive Days (Sustained Recovery): Aviptadil Comparison



Number at Risk:

A:	231	215	193	148	93	71	57	47	37	28	25	19	17
P:	230	215	199	153	98	65	50	43	40	36	30	24	18

Estimated Cumulative Pct. With Event:

A:	0.0	0.0	14.9	30.6	36.7	41.1	43.7	47.6	50.7	52.0	54.2	55.1
P:	0.0	0.0	16.7	30.3	40.4	44.8	46.1	47.8	48.7	50.9	54.0	56.2

Note: Tests are stratified by disease severity.

fig_t2susrecovery File created=11/17/22 Data cutoff=11/08/22

	Aviptadil (n= 231)		Placebo (n= 230)				
Status	**No.**	**Pct**	**No.**	**Pct.**	**RRR[a] (A/P)**	**95% CI**	**P-value**
Sustained recovery (home 14+ days)	126	54.5	128	55.7	0.97	0.76, 1.23	0.78
Censored	19	8.2	20	8.7			
Died[b]	86	37.2	82	35.7			
Days recovered[c] median (95% CI)	61 (48, .)		69 (39, .)				

[a] Recovery rate ratio (Aviptadil vs Placebo) for first time at home for 14 consecutive days" using the Fine-Gray method for considering death before recovery as a competing risk; stratified by disease severity (severe or critical). RRR > 1 indicates benefit to Group Aviptadil.

[b] Death before sustained recovery considered a competing risk.

[c] Modified Kaplan-Meier estimate where follow-up for participants who died prior to sustained recovery was carried forward to the administrative censoring date (cut date for this current report).

Program Name =mitt vip t2susrecovery Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S24: Ordinal Outcome with 3 Categories - Recovered; Alive, Not Recovered; Dead at Day 90: Aviptadil Comparison

Category at Day 90	Aviptadil (n= 225) Pts.	Aviptadil (n= 225) Pct.	Placebo (n= 225) Pts.	Placebo (n= 225) Pct.	OR* (A/P)	95% CI*	P-value
1: Recovered (at home and off oxygen ≥ 1 days)	116	51.6	98	43.6	1.17	0.82, 1.66	0.38
2: Alive, but not recovered	23	10.2	44	19.6			
3: Died	86	38.2	83	36.9			
P-value for Proportional Odds Assumption:							
test from partial prop. odds. model, with unequal slopes across outcome categories, but equal slopes across stratification covariates							0.006

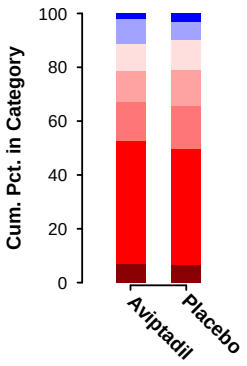
*Odds ratios from logistic regresion model, stratified by disease severity.
Restricted to participants who have reached Day 90 administrative follow-up and are classifiable into one of the 6 categories of the primary ordinal outcome.

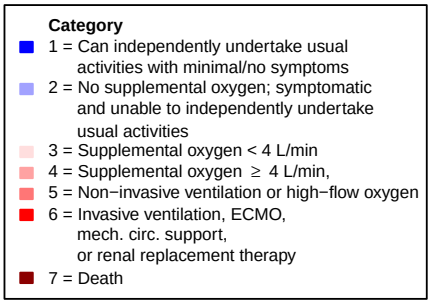
Program Name =mitt vip ordprim3cat Create date=17-NOV-2022 Cut date=08-NOV-2022

Figure S10: ACTIV-3/TICO 7-Category Pulmonary Ordinal Outcome at Days 7, 14, and 28: Aviptadil Comparison

A. Pulmonary Ordinal Outcome on Day 7

Category		Aviptadil N	Aviptadil %	Placebo N	Placebo %
Better	1	5	2.2	7	3.1
	2	21	9.2	16	7.0
	3	23	10.0	25	10.9
	4	26	11.4	31	13.5
	5	34	14.8	37	16.2
Worse	6	104	45.4	98	42.8
	7	16	7.0	15	6.6
Total		229		229	

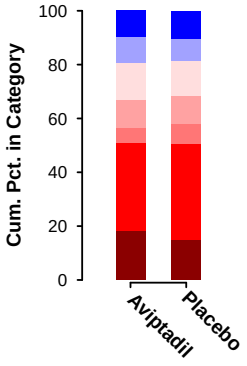


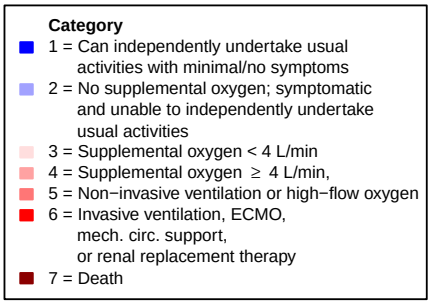


Summary OR (Aviptadil/Placebo):
0.93 (95% CI: 0.67 to 1.31); P=0.69

B. Pulmonary Ordinal Outcome on Day 14

Category		Aviptadil N	Aviptadil %	Placebo N	Placebo %
Better	1	22	9.7	24	10.6
	2	22	9.7	18	8.0
	3	31	13.7	30	13.3
	4	24	10.6	23	10.2
	5	12	5.3	17	7.5
Worse	6	74	32.7	81	35.8
	7	41	18.1	33	14.6
Total		226		226	

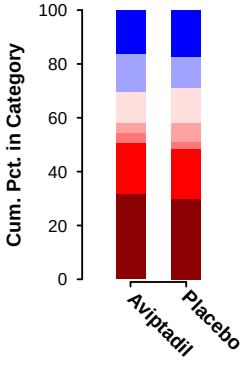


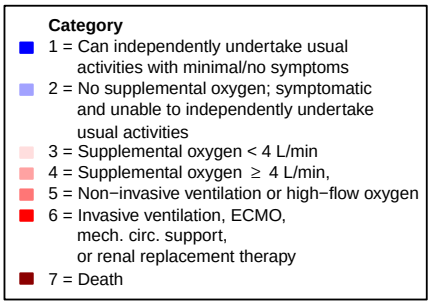


Summary OR (Aviptadil/Placebo):
0.97 (95% CI: 0.70 to 1.35); P=0.85

C. Pulmonary Ordinal Outcome on Day 28

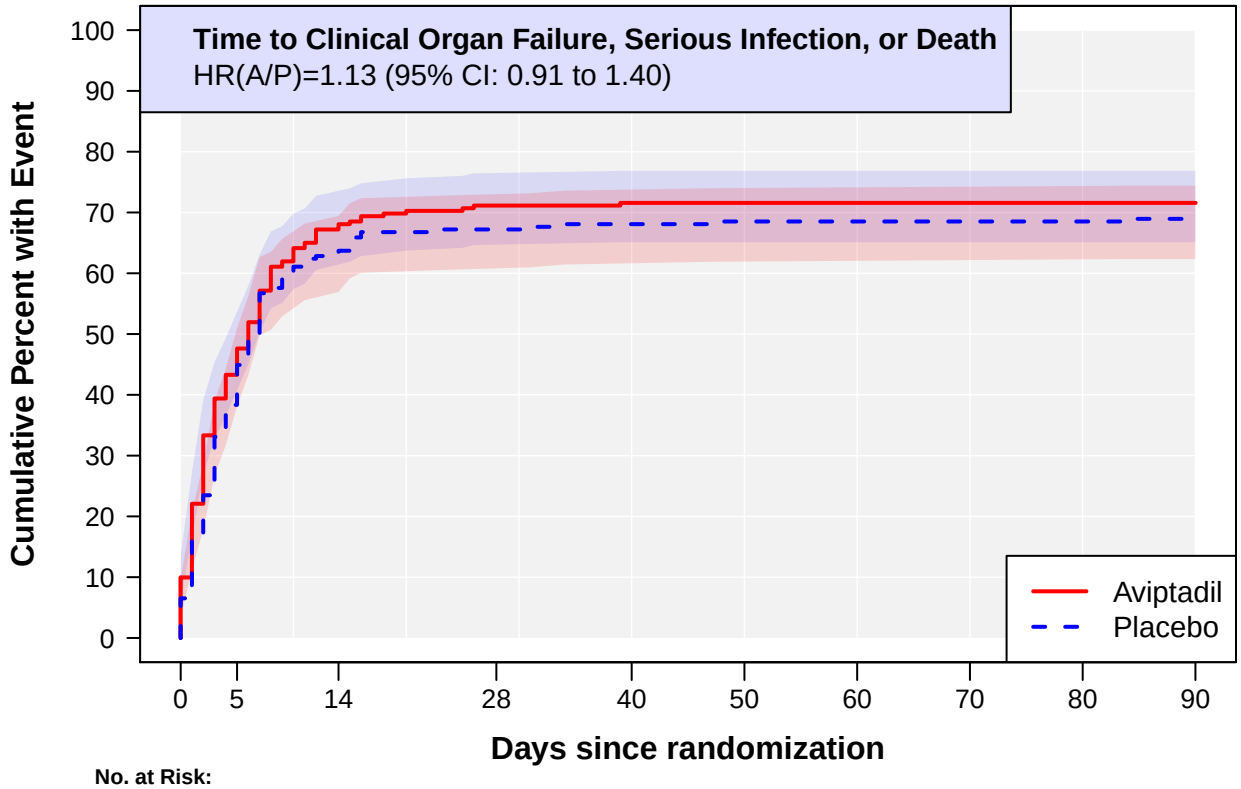
Category		Aviptadil N	Aviptadil %	Placebo N	Placebo %
Better	1	36	16.4	39	17.6
	2	31	14.2	25	11.3
	3	25	11.4	29	13.1
	4	8	3.7	16	7.2
	5	8	3.7	5	2.3
Worse	6	42	19.2	41	18.6
	7	69	31.5	66	29.9
Total		219		221	





Summary OR (Aviptadil/Placebo):
0.95 (95% CI: 0.68 to 1.32); P=0.75

Figure S11: Time to Clinical Organ Failure, Serious Infection, or Death Through Day 90: Aviptadil Comparison



No. at Risk:

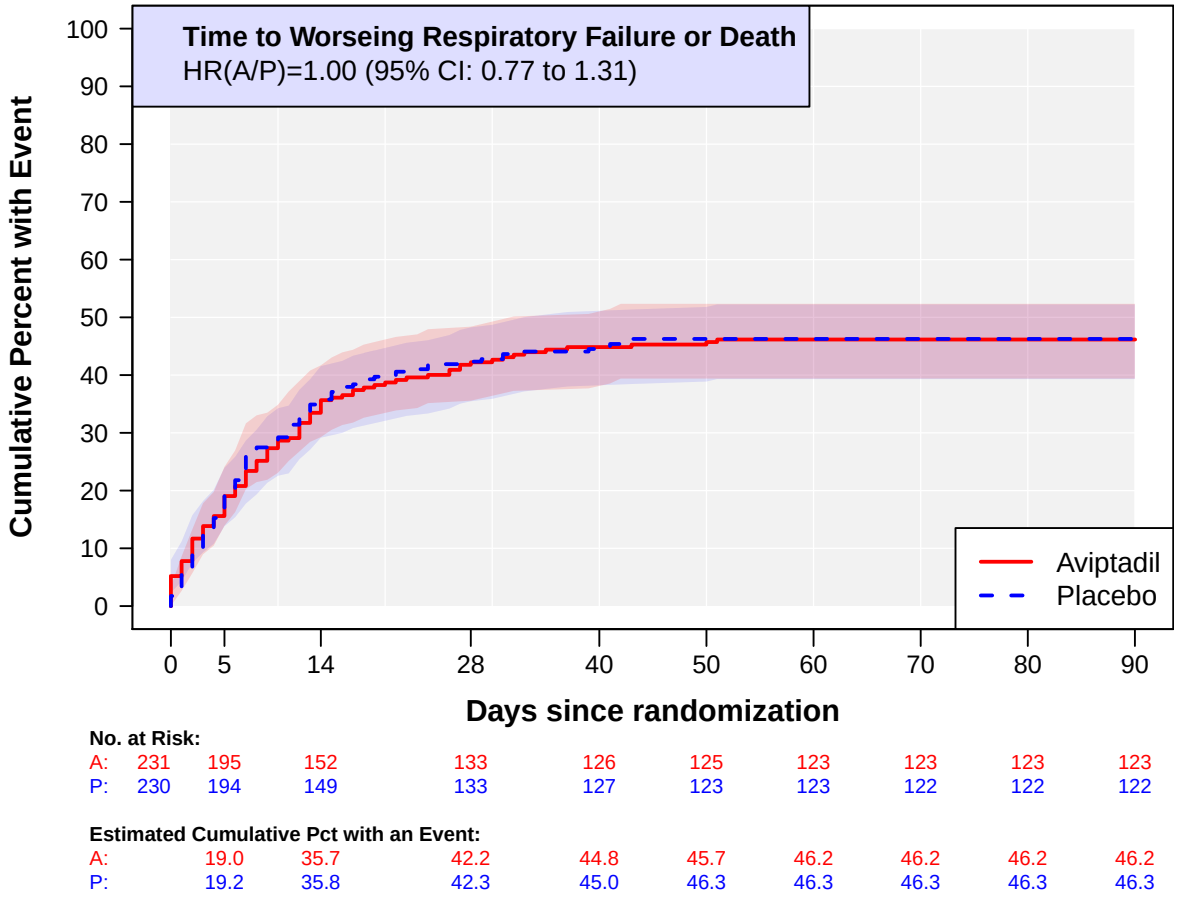
A:	231	131	75	66	65	65	65	65	65	65
P:	230	141	85	75	73	72	72	72	72	71

Estimated Cumulative Pct with an Event:

A:	47.6	68.1	71.1	71.6	71.6	71.6	71.6	71.6	71.6
P:	44.9	63.7	67.2	68.1	68.5	68.5	68.5	68.5	69.0

vip_fig_t2psesedth.pdf File created=11/17/22 Data cutoff=11/08/22

Figure S12: Time to Worsening Respiratory Failure or Death Through Day 90: Aviptadil Comparison



No. at Risk:

A:	231	195	152	133	126	125	123	123	123	123
P:	230	194	149	133	127	123	123	122	122	122

Estimated Cumulative Pct with an Event:

A:	19.0	35.7	42.2	44.8	45.7	46.2	46.2	46.2	46.2
P:	19.2	35.8	42.3	45.0	46.3	46.3	46.3	46.3	46.3

vip_fig_t2resp_fail.pdf File created=11/17/22 Data cutoff=11/08/22

Status at Entry	Progression through Day 90	Aviptadil (n= 231) N. in Grp	Aviptadil (n= 231) N. w/Event	Aviptadil (n= 231) Pct.	Placebo (n= 230) N. in Grp	Placebo (n= 230) N. w/Event	Placebo (n= 230) Pct.
HFNC/NIV	IMV	136	54	39.7	135	56	41.5
	ECMO		3	2.2		7	5.2
	IMV or ECMO		54	39.7		56	41.5
	IMV, ECMO, or Death		63	46.3		65	48.1
IMV	ECMO	93	4	4.3	92	5	5.4
	ECMO or Death		41	44.1		40	43.5
ECMO	Death	2	2	100.0	3	1	33.3
Overall	**IMV or ECMO***	**229**	**58**	**25.3**	**227**	**61**	**26.9**
	IMV, ECMO, or Death	**231**	**106**	**45.9**	**230**	**106**	**46.1**
*HR** [95% CI] (Aviptadil/Placebo) worsening respiratory failure (IMV or ECMO) or death*						*1.00 [0.77 - 1.31]*	
*p-value**						*0.98*	

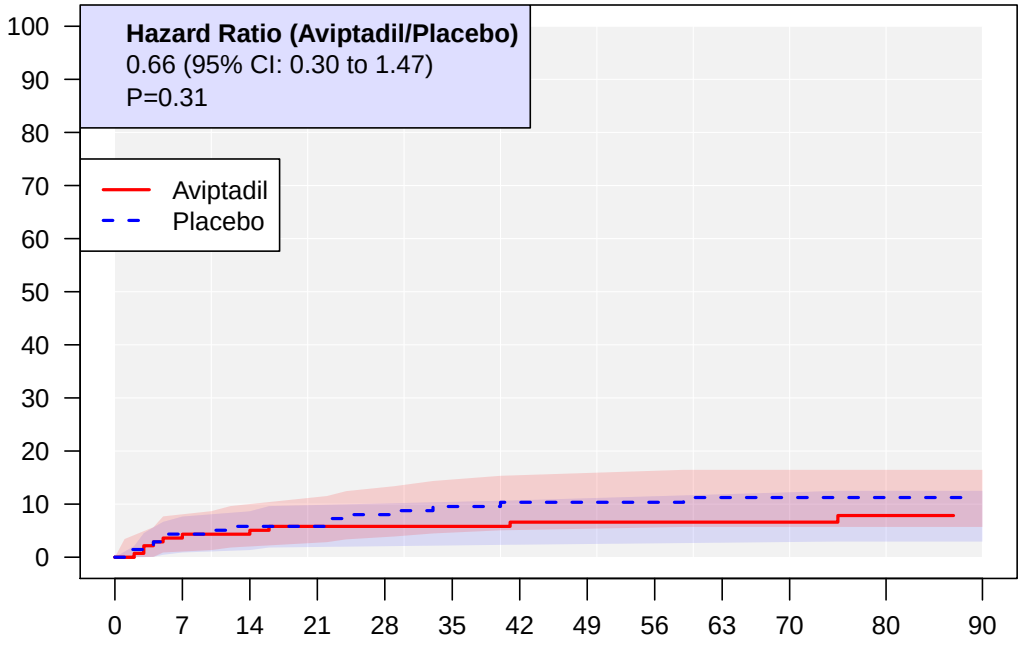
HFNC=High-flow nasal canula device, NIV=non-invasive ventilation, IMV=invasive mechanical ventilation, ECMO=extracorporal membrane oxygenation

*Risk set excludes participants on ECMO at entry.

**Hazard ratio from Cox regression model with 1 indicator for treatment group, stratified by disease severity.

Program Name =mitt vip psese_resp_fail Create date=17-NOV-2022 Cut date=08-NOV-2022

Figure S13: Time to Hospital Readmission or Death After Initial Discharge: Aviptadil Comparison



No. at Risk:

Aviptadil:	139	133	130	126	124	122	117	111	104	97	86	55
Placebo:	138	131	129	128	123	115	110	105	101	96	84	59

Estimated Cumulative Pct with an Event:

Aviptadil:	4.3	5.1	5.8	5.8	5.8	6.6	6.6	6.6	6.6	6.6	7.8
Placebo:	4.3	5.8	5.8	8.0	9.6	10.3	10.3	10.3	11.2	11.2	11.2

vip_fig_t2readmit.pdf File created=11/17/22 Data cutoff=11/08/22

Time to Hospital Readmission or Death, After Initial Discharge

	Aviptadil (n= 139)		Placebo (n= 138)				
'	No. Evt	Pct	No. Evt	Pct.	HR[a] (A/P)	95% CI	P-value
Readmitted	9	6.5	13	9.4			
Died	2	1.4	2	1.4			
Readmitted or Died	10	7.2	15	10.9	0.66	0.30, 1.47	0.31

[a]Hazard ratio (A vs P) for time to hospital readmission or death from a Cox proportional hazards regression model stratified by disease severity. HR < 1 indicates benefit to the Aviptadil group.

Program Name =mitt vip t2readmit Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S25: Infusion Reactions by Grade Cut-Off, Pooled Across Days 0-2: Aviptadil Comparison

	Aviptadil (n= 231)				Placebo (n= 230)			
Days 0-2 Infusion Reaction*	**Grade ≥ 1 N (%)**	**Grade ≥ 2 N (%)**	**Grade ≥ 3 N (%)**	**Grade ≥ 4 N (%)**	**Grade ≥ 1 N (%)**	**Grade ≥ 2 N (%)**	**Grade ≥ 3 N (%)**	**Grade ≥ 4 N (%)**
Altered per. of reality	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Angioedema	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anaphylaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bradycardia	15 (6)	4 (2)	2 (1)	1 (0)	18 (8)	10 (4)	3 (1)	0 (0)
Bronchospasm	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Chills	1 (0)	0 (0)	0 (0)	0 (0)	5 (2)	2 (1)	0 (0)	0 (0)
Confusion	2 (1)	1 (0)	0 (0)	0 (0)	3 (1)	1 (0)	0 (0)	0 (0)
Diaphoresis	4 (2)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	92 (40)	62 (27)	5 (2)	0 (0)	26 (11)	8 (3)	2 (1)	0 (0)
Diarrhea-discontinued	7 (3)	6 (3)	1 (0)	0 (0)	1 (0)	1 (0)	1 (0)	0 (0)
Dizziness	2 (1)	1 (0)	0 (0)	0 (0)	3 (1)	1 (0)	0 (0)	0 (0)
Facial flushing	34 (15)	4 (2)	0 (0)	0 (0)	14 (6)	1 (0)	0 (0)	0 (0)
Fever	24 (10)	13 (6)	7 (3)	1 (0)	13 (6)	9 (4)	6 (3)	1 (0)
Headache	14 (6)	5 (2)	1 (0)	0 (0)	6 (3)	3 (1)	0 (0)	0 (0)
Hypertension	27 (12)	17 (7)	8 (3)	1 (0)	30 (13)	22 (10)	9 (4)	0 (0)
Hypotension	135 (58)	84 (36)	46 (20)	8 (3)	95 (41)	56 (24)	28 (12)	6 (3)
Hypoxia	11 (5)	8 (3)	5 (2)	3 (1)	8 (3)	8 (3)	8 (3)	5 (2)
Itching	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Mental status changes	2 (1)	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Myalgia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea	7 (3)	4 (2)	0 (0)	0 (0)	6 (3)	4 (2)	0 (0)	0 (0)
Rash - non urticarial	5 (2)	1 (0)	1 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
Shortness of breath	2 (1)	0 (0)	0 (0)	0 (0)	3 (1)	2 (1)	1 (0)	1 (0)
Tachycardia	22 (10)	8 (3)	3 (1)	0 (0)	11 (5)	7 (3)	3 (1)	0 (0)
Throat irritation/tightening	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urticaria/hives	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	1 (0)	0 (0)	0 (0)
Wheezing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other reaction	30 (13)	22 (10)	12 (5)	9 (4)	26 (11)	18 (8)	10 (4)	2 (1)
Any of above	200 (87)	142 (61)	71 (31)	18 (8)	132 (57)	87 (38)	51 (22)	14 (6)
p-value**	<0.001	<0.001	0.032	0.47				

* Collected via checklist during and within 2 hours following the completion of administration of the blinded study medication. A participant with multiple *other* reactions is counted once according to highest grade of *other reaction* recorded.

** CMH p-value for aviptadil vs placebo difference in incidence of any infusion reaction in the indicated grade category stratified by disease severity (severe vs. critical). Only shown if at least 5 events occured

Program Name =Day3 infa_reactions_grd Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S26: Frequent Infusion Reactions, Comparing Treatment Groups by Type by Grade Cut-Off, Pooled Across Days 0-2: Aviptadil Comparison

	Aviptadil (n= 231)				Placebo (n= 230)			
Days 0-2 Infusion Reaction*	**Grade ≥ 1 N (%)**	**Grade ≥ 2 N (%)**	**Grade ≥ 3 N (%)**	**Grade ≥ 4 N (%)**	**Grade ≥ 1 N (%)**	**Grade ≥ 2 N (%)**	**Grade ≥ 3 N (%)**	**Grade ≥ 4 N (%)**
Bradycardia	15 (6)	4 (2)	2 (1)	1 (0)	18 (8)	10 (4)	3 (1)	0 (0)
p-value**	0.58	0.10	0.65					
Diarrhea	92 (40)	62 (27)	5 (2)	0 (0)	26 (11)	8 (3)	2 (1)	0 (0)
p-value**	<0.001	<0.001	0.26					
Facial flushing	34 (15)	4 (2)	0 (0)	0 (0)	14 (6)	1 (0)	0 (0)	0 (0)
p-value**	0.002	0.18						
Fever	24 (10)	13 (6)	7 (3)	1 (0)	13 (6)	9 (4)	6 (3)	1 (0)
p-value**	0.054	0.37	0.78					
Headache	14 (6)	5 (2)	1 (0)	0 (0)	6 (3)	3 (1)	0 (0)	0 (0)
p-value**	0.07	0.48						
Hypertension	27 (12)	17 (7)	8 (3)	1 (0)	30 (13)	22 (10)	9 (4)	0 (0)
p-value**	0.66	0.40	0.80					
Hypotension	135 (58)	84 (36)	46 (20)	8 (3)	95 (41)	56 (24)	28 (12)	6 (3)
p-value**	<0.001	0.003	0.021	0.59				
Hypoxia	11 (5)	8 (3)	5 (2)	3 (1)	8 (3)	8 (3)	8 (3)	5 (2)
p-value**	0.49	0.99	0.40	0.47				
Nausea	7 (3)	4 (2)	0 (0)	0 (0)	6 (3)	4 (2)	0 (0)	0 (0)
p-value**	0.79	0.99						
Tachycardia	22 (10)	8 (3)	3 (1)	0 (0)	11 (5)	7 (3)	3 (1)	0 (0)
p-value**	0.049	0.80	1.00					
Other reaction	30 (13)	22 (10)	12 (5)	9 (4)	26 (11)	18 (8)	10 (4)	2 (1)
p-value**	0.58	0.52	0.67	0.034				

* Collected via checklist during and within 2 hours following the completion of administration of the blinded study medication. A participant with multiple *other* reactions is counted once according to highest grade of *other reaction* recorded.

** CMH p-value for aviptadil vs placebo difference in incidence of any infusion reaction in the indicated grade category, stratified by disease severity (severe vs. critical). Only shown if at least 5 events occured

Program Name =Day3 infa_reactions_grd Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S27: Infusion Modifications Due To AEs, Pooled Across Days 0-2: Aviptadil Comparison

	Aviptadil (n= 231)					Placebo (n= 230)				
		Action Taken Due to AE*					Action Taken Due to AE*			
Days 0-2 Adverse Event**	Pts w/AE N (%)*	None N	RateR. N	Paused N	Disc. N	Pts w/AE N (%)*	None N	RateR. N	Paused N	Disc. N
Altered per. of reality	0 (0)	0	0	0	0	1 (0)	1	0	0	0
Angioedema	0 (0)	0	0	0	0	0 (0)	0	0	0	0
Anaphylaxis	0 (0)	0	0	0	0	0 (0)	0	0	0	0
Bradycardia	15 (6)	14	0	0	1	18 (8)	16	0	2	0
Bronchospasm	0 (0)	0	0	0	0	0 (0)	0	0	0	0
Chills	1 (0)	1	0	0	0	5 (2)	5	0	0	0
Confusion	2 (1)	2	0	0	0	3 (1)	3	0	0	0
Diaphoresis	4 (2)	3	0	1	0	1 (0)	1	0	0	0
Diarrhea	92 (40)	80	1	4	7	26 (11)	22	0	3	1
Dizziness	2 (1)	1	0	1	0	3 (1)	3	0	0	0
Facial flushing	34 (15)	28	1	5	0	14 (6)	14	0	0	0
Fever	24 (10)	24	0	0	0	13 (6)	12	0	1	0
Headache	14 (6)	11	0	3	0	6 (3)	6	0	0	0
Hypertension	27 (12)	25	0	2	0	30 (13)	29	0	1	0
Hypotension	135 (58)	83	0	37	15	95 (41)	65	0	21	9
Hypoxia	11 (5)	10	0	0	1	8 (3)	6	0	0	2
Itching	0 (0)	0	0	0	0	1 (0)	1	0	0	0
Mental status changes	2 (1)	2	0	0	0	1 (0)	1	0	0	0
Myalgia	0 (0)	0	0	0	0	0 (0)	0	0	0	0
Nausea	7 (3)	5	0	1	1	6 (3)	6	0	0	0
Rash - non urticarial	5 (2)	4	0	0	1	2 (1)	2	0	0	0
Shortness of breath	2 (1)	2	0	0	0	3 (1)	3	0	0	0
Tachycardia	22 (10)	20	0	2	0	11 (5)	7	0	4	0
Throat irr./tightng	1 (0)	0	0	1	0	0 (0)	0	0	0	0
Urticaria/hives	0 (0)	0	0	0	0	2 (1)	2	0	0	0
Vomiting	0 (0)	0	0	0	0	2 (1)	2	0	0	0
Wheezing	0 (0)	0	0	0	0	0 (0)	0	0	0	0
Other reaction	30 (13)	21	1	6	2	26 (11)	19	0	3	4
Any of above	200 (87)	123	1	52	24	132 (57)	91	0	28	13

* Mutually exclusive, ranked by severity of action - discontinued, paused, rate reduced, none.

** Collected via checklist during and within 2 hours following the completion of administration of the blinded study medication. A participant many have multiple *other* reactions, action taken is report based on any of the other reactions.

Program Name =Day3 infa_reactions_rxaction_ranked Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S28: Infusion Reactions by Grade, Pooled Across Days 0-2: Aviptadil Comparison

	Aviptadil (n= 231)				Placebo (n= 230)			
Days 0-2 Infusion Reaction*	**Grade 1 N (%)**	**Grade 2 N (%)**	**Grade 3 N (%)**	**Grade 4 N (%)**	**Grade 1 N (%)**	**Grade 2 N (%)**	**Grade 3 N (%)**	**Grade 4 N (%)**
Altered per. of reality	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Angioedema	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anaphylaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bradycardia	11 (5)	2 (1)	1 (0)	1 (0)	8 (3)	7 (3)	3 (1)	0 (0)
Bronchospasm	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Chills	1 (0)	0 (0)	0 (0)	0 (0)	3 (1)	2 (1)	0 (0)	0 (0)
Confusion	1 (0)	1 (0)	0 (0)	0 (0)	2 (1)	1 (0)	0 (0)	0 (0)
Diaphoresis	4 (2)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	30 (13)	57 (25)	5 (2)	0 (0)	18 (8)	6 (3)	2 (1)	0 (0)
Diarrhea-discontinued	1 (0)	5 (2)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Dizziness	1 (0)	1 (0)	0 (0)	0 (0)	2 (1)	1 (0)	0 (0)	0 (0)
Facial flushing	30 (13)	4 (2)	0 (0)	0 (0)	13 (6)	1 (0)	0 (0)	0 (0)
Fever	11 (5)	6 (3)	6 (3)	1 (0)	4 (2)	3 (1)	5 (2)	1 (0)
Headache	9 (4)	4 (2)	1 (0)	0 (0)	3 (1)	3 (1)	0 (0)	0 (0)
Hypertension	10 (4)	9 (4)	7 (3)	1 (0)	8 (3)	13 (6)	9 (4)	0 (0)
Hypotension	51 (22)	38 (16)	38 (16)	8 (3)	39 (17)	28 (12)	22 (10)	6 (3)
Hypoxia	3 (1)	3 (1)	2 (1)	3 (1)	0 (0)	0 (0)	3 (1)	5 (2)
Itching	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Mental status changes	1 (0)	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Myalgia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea	3 (1)	4 (2)	0 (0)	0 (0)	2 (1)	4 (2)	0 (0)	0 (0)
Rash - non urticarial	4 (2)	0 (0)	1 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
Shortness of breath	2 (1)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	1 (0)
Tachycardia	14 (6)	5 (2)	3 (1)	0 (0)	4 (2)	4 (2)	3 (1)	0 (0)
Throat irritation/tightening	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urticaria/hives	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)
Wheezing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other reaction	8 (3)	10 (4)	3 (1)	9 (4)	8 (3)	8 (3)	8 (3)	2 (1)
Any of above	136 (59)	111 (48)	63 (27)	18 (8)	86 (37)	63 (27)	43 (19)	14 (6)

* Collected via checklist during and within 2 hours following the completion of administration of the blinded study medication. A participant with multiple *other* reactions is counted once according to highest grade of *other reaction* recorded.

Program Name =Day3 infa_reactions Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S29: Infusion Reactions by Grade, Day 0: Aviptadil Comparison

	Aviptadil (n= 229)				Placebo (n= 229)			
Day 0 Infusion Reaction*	**Grade 1 N (%)**	**Grade 2 N (%)**	**Grade 3 N (%)**	**Grade 4 N (%)**	**Grade 1 N (%)**	**Grade 2 N (%)**	**Grade 3 N (%)**	**Grade 4 N (%)**
Altered per. of reality	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Angioedema	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anaphylaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bradycardia	6 (3)	2 (1)	0 (0)	1 (0)	3 (1)	4 (2)	1 (0)	0 (0)
Bronchospasm	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Chills	1 (0)	0 (0)	0 (0)	0 (0)	2 (1)	1 (0)	0 (0)	0 (0)
Confusion	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Diaphoresis	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	8 (3)	13 (6)	1 (0)	0 (0)	7 (3)	2 (1)	0 (0)	0 (0)
Diarrhea-discontinued	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dizziness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)
Facial flushing	5 (2)	1 (0)	0 (0)	0 (0)	7 (3)	0 (0)	0 (0)	0 (0)
Fever	2 (1)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	2 (1)	1 (0)
Headache	1 (0)	2 (1)	1 (0)	0 (0)	1 (0)	2 (1)	0 (0)	0 (0)
Hypertension	3 (1)	3 (1)	4 (2)	0 (0)	4 (2)	6 (3)	2 (1)	0 (0)
Hypotension	26 (11)	15 (7)	14 (6)	4 (2)	17 (7)	16 (7)	12 (5)	5 (2)
Hypoxia	2 (1)	2 (1)	1 (0)	1 (0)	0 (0)	0 (0)	1 (0)	2 (1)
Itching	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Mental status changes	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Myalgia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)
Rash - non urticarial	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Shortness of breath	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tachycardia	3 (1)	0 (0)	1 (0)	0 (0)	2 (1)	1 (0)	0 (0)	0 (0)
Throat irritation/tightening	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urticaria/hives	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Wheezing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other reaction	2 (1)	2 (1)	3 (1)	2 (1)	2 (1)	2 (1)	4 (2)	1 (0)
Any of above	56 (24)	34 (15)	23 (10)	6 (3)	40 (17)	33 (14)	20 (9)	8 (3)

* Collected via checklist during and within 2 hours following the completion of administration of the blinded study medication. A participant with multiple *other* reactions is counted once according to highest grade of *other reaction* recorded.

Program Name =Day0 infa_reactions Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S30: Infusion Reactions by Grade, Day 1: Aviptadil Comparison

	Aviptadil (n= 228)				Placebo (n= 223)			
Day 1 Infusion Reaction*	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Altered per. of reality	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Angioedema	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anaphylaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bradycardia	5 (2)	0 (0)	0 (0)	0 (0)	5 (2)	4 (2)	1 (0)	0 (0)
Bronchospasm	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Chills	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)
Confusion	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diaphoresis	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	21 (9)	30 (13)	1 (0)	0 (0)	9 (4)	2 (1)	1 (0)	0 (0)
Diarrhea-discontinued	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Dizziness	1 (0)	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Facial flushing	20 (9)	2 (1)	0 (0)	0 (0)	5 (2)	1 (0)	0 (0)	0 (0)
Fever	4 (2)	4 (2)	3 (1)	1 (0)	1 (0)	3 (1)	0 (0)	1 (0)
Headache	5 (2)	1 (0)	0 (0)	0 (0)	4 (2)	1 (0)	0 (0)	0 (0)
Hypertension	6 (3)	5 (2)	3 (1)	0 (0)	5 (2)	4 (2)	3 (1)	0 (0)
Hypotension	36 (16)	19 (8)	22 (10)	3 (1)	28 (13)	6 (3)	8 (4)	3 (1)
Hypoxia	0 (0)	1 (0)	0 (0)	2 (1)	0 (0)	0 (0)	1 (0)	3 (1)
Itching	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mental status changes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Myalgia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea	2 (1)	3 (1)	0 (0)	0 (0)	2 (1)	1 (0)	0 (0)	0 (0)
Rash - non urticarial	2 (1)	0 (0)	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Shortness of breath	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Tachycardia	5 (2)	2 (1)	2 (1)	0 (0)	1 (0)	2 (1)	2 (1)	0 (0)
Throat irritation/tightening	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urticaria/hives	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)
Wheezing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other reaction	5 (2)	7 (3)	1 (0)	5 (2)	3 (1)	4 (2)	2 (1)	2 (1)
Any of above	83 (36)	62 (27)	30 (13)	9 (4)	54 (24)	23 (10)	17 (8)	9 (4)

* Collected via checklist during and within 2 hours following the completion of administration of the blinded study medication. A participant with multiple *other* reactions is counted once according to highest grade of *other reaction* recorded.

Program Name =Day1 infa_reactions Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S31: Infusion Reactions by Grade, Day 2: Aviptadil Comparison

	Aviptadil (n= 211)				Placebo (n= 212)			
Day 2 Infusion Reaction*	**Grade 1 N (%)**	**Grade 2 N (%)**	**Grade 3 N (%)**	**Grade 4 N (%)**	**Grade 1 N (%)**	**Grade 2 N (%)**	**Grade 3 N (%)**	**Grade 4 N (%)**
Altered per. of reality	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Angioedema	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anaphylaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bradycardia	2 (1)	0 (0)	1 (0)	0 (0)	1 (0)	1 (0)	1 (0)	0 (0)
Bronchospasm	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Chills	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Confusion	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)
Diaphoresis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	21 (10)	36 (17)	5 (2)	0 (0)	10 (5)	2 (1)	1 (0)	0 (0)
Diarrhea-discontinued	1 (0)	3 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dizziness	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Facial flushing	18 (9)	2 (1)	0 (0)	0 (0)	6 (3)	1 (0)	0 (0)	0 (0)
Fever	6 (3)	3 (1)	2 (1)	0 (0)	3 (1)	1 (0)	3 (1)	0 (0)
Headache	3 (1)	1 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
Hypertension	8 (4)	3 (1)	0 (0)	1 (0)	5 (2)	4 (2)	4 (2)	0 (0)
Hypotension	35 (17)	23 (11)	19 (9)	3 (1)	13 (6)	14 (7)	4 (2)	1 (0)
Hypoxia	2 (1)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)
Itching	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mental status changes	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Myalgia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea	1 (0)	1 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)
Rash - non urticarial	2 (1)	0 (0)	1 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
Shortness of breath	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)
Tachycardia	8 (4)	3 (1)	0 (0)	0 (0)	2 (1)	1 (0)	2 (1)	0 (0)
Throat irritation/tightening	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urticaria/hives	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Wheezing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other reaction	4 (2)	7 (3)	2 (1)	2 (1)	5 (2)	4 (2)	2 (1)	0 (0)
Any of above	79 (37)	65 (31)	30 (14)	6 (3)	39 (18)	29 (14)	15 (7)	4 (2)

* Collected via checklist during and within 2 hours following the completion of administration of the blinded study medication. A participant with multiple *other* reactions is counted once according to highest grade of *other reaction* recorded.

Program Name =Day2 infa_reactions Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S32: Peri-Infusion Hypotension Summary, Days 0-2: Aviptadil Comparison

	Aviptadil	Placebo	
No. with at least 1 infusion	*231*	*230*	
	N (%) or Mean (SD)	**N (%) or Mean (SD)**	**P-value*** **
Peri-Infusion* Hypotension Adverse Events			
Highest grade hypotension AE			
No hypotension AE on Days 0-2	96 (41.6)	135 (58.7)	<0.001
≥ Grade 1	135 (58.4)	95 (41.3)	<0.001
≥ Grade 2	84 (36.4)	56 (24.3)	0.005
≥ Grade 3	46 (19.9)	28 (12.2)	0.024
≥ Grade 4	8 (3.5)	6 (2.6)	0.59
Peri-Infusion* Blood Pressure			
Within-day MAP change, pre- vs peri infusion			
MAP decrease > 20 mmHg	156 (67.5)	102 (44.3)	<0.001
Lowest peri-infusion MAP, mean (SD) mmHg	67 (9)	71 (10)	
Incidence of MAP < 65 mmHg peri-infusion	90 (39.0)	64 (27.8)	0.011
Pct. of all peri-infusion MAPs < 65 mmHg, mean (SD) of the percents	4.5 (8.1)	2.4 (5.0)	<0.001
Infusion Modification for Hypotension			
Not infused ≥ 1 day due to hypotension/vasopressors	3 (1.3)	2 (0.9)	
Infusion modification for hypotension	52 (22.5)	30 (13.0)	0.008
Highest infusion modification for hypotension on Days 0-2			
Rate decreased but not paused	0 (0.0)	0 (0.0)	
Paused but not discontinued	37 (16.0)	21 (9.1)	
Discontinued for the day	15 (6.5)	9 (3.9)	
Peri-Infusion* Vasopressor Use			
New peri-infusion vasopressor use on any day, those not on vasopressors pre-infusion Day 0 (N_A= 195 N_P= 194)	43 (22.1)	29 (14.9)	0.07
New or increased peri-infusion vasopressor use any day, those on vasopressors pre-infusion Day 0 (N_A= 36 N_P= 36)	28 (77.8)	25 (69.4)	0.43
Max peri-infusion vasopressor rate increase from pre- to peri-infusion, mean (SD) µg/kg/min NE**	0.03 (0.08)	0.02 (0.09)	
Vasopressor rate at 2 hrs post infusion higher than pre-infusion on any day	47 (20.3)	28 (12.2)	0.018
For those with rate increase (pre- vs 2h post), largest increase on Days 0-2, mean (SD) µg/kg/min NE	0.09 (0.17)	0.07 (0.16)	
Pre-infusion vasopressor rate ever increased by > 0.03 µg/kg/min NE peri-infusion**	50 (21.6)	31 (13.5)	0.021
Peak peri-infusion vasopressor rate ever >0.1 µg/kg/min NE	24 (10.4)	14 (6.1)	
Peri-Infusion* IV Fluid Use Due to Hypotension Adverse Event			
Received IV fluid/colloid (≥ 500ml) peri-infusion	27 (11.7)	16 (7.0)	0.08
Received IV fluid/colloid (≥ 2000ml) peri-infusion	1 (0.4)	1 (0.4)	
If received, max volume recd, mean (SD) mL	745 (388)	703 (407)	

*'Peri-infusion' refers to the time immediately after infusion starts up to the 2-hour post infusion assessment (hour 14 for a 12 hour infusion). Routine BP recordings reported on the CRF every 2 hours from hour 2 to 14.

**Being off vasopressors pre-infusion treated as norepinephrine equivalent (NE) dose of 0 µg/kg/min, for calculations. If the peri-infusion vasopressor dose is lower than the daily pre-infusion value for a participant the 'max increase' is set to 0.

***P-values presented if sufficient sample size. Unadjusted comparisons.

Table S33: Grade 3 or 4 AEs, SAEs, Organ Failure, Serious Infections, or Death through Day 5: Aviptadil Comparison

Events through Day 5	Aviptadil (n= 231) Pts.	Aviptadil (n= 231) Pct.	Placebo (n= 230) Pts.	Placebo (n= 230) Pct.	OR* (A/P)	95% CI*	P-value*	P-value**
Composite								
Death	13	5.6	11	4.8	1.19	0.52, 2.71	0.68	0.68
Death, SAE, or Clinical Organ Failure/ Serious Infection	109	47.2	105	45.7	1.07	0.73, 1.56	0.73	0.73
Death, SAE, Clinical Organ Failure/ Serious Infection, or Grade 4 AE***	111	48.1	109	47.4	1.03	0.71, 1.50	0.88	0.88
Death, SAE, Clinical Organ Failure/ Serious Infection, or Grade 3 or 4 AE* **	**146**	**63.2**	**129**	**56.1**	**1.40**	**0.94, 2.08**	**0.10**	**0.10**
Components								
Death	13	5.6	11	4.8				
SAE	8	3.5	5	2.2				
Clinical Organ Failure/Serious Infection	108	46.8	100	43.5				
Grade 4 AE***	39	16.9	48	20.9				
Grade 3 or 4 AE***	118	51.1	101	43.9				

* Logistic regression model, with 1 indicator for treatment group stratified by disease severity (severe vs critical).
** CMH test stratified by disease severity (critical vs. severe) , shown if at least 5 events
*** Includes AEs reported at any time after the first infusion started, during and after completion of the infusions.
Note, summary excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.
Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip day5safety_no_diarr Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S34: SAEs Through Day 5, by SOC: Aviptadil Comparison

SAEs/UPs* through Day 5	Aviptadil (n= 231)		Placebo (n= 230)		P-value**
	Pts	Pct.	Pts	Pct.	
MedDRA System Organ Class					
Blood and lymphatic system	0	0.0	0	0.0	
Cardiac	2	0.9	2	0.9	
Congenital, familial, genetic	0	0.0	0	0.0	
Ear and labyrinth	0	0.0	0	0.0	
Endocrine	0	0.0	0	0.0	
Eye	0	0.0	0	0.0	
Gastrointestinal	2	0.9	1	0.4	
General and administration site	0	0.0	0	0.0	
Hepatobiliary	0	0.0	0	0.0	
Immune system	0	0.0	0	0.0	
Infections and infestations	0	0.0	0	0.0	
Injury, poisoning, procedural complications	1	0.4	0	0.0	
Investigations	0	0.0	0	0.0	
Metabolism and nutrition	0	0.0	0	0.0	
Musculoskeletal and connective tissue	0	0.0	0	0.0	
Neoplasms benign, malignant, unspecified	0	0.0	0	0.0	
Nervous system	0	0.0	1	0.4	
Pregnancy, puerperium, perinatal	0	0.0	0	0.0	
Product issues	0	0.0	0	0.0	
Psychiatric	0	0.0	0	0.0	
Renal and urinary	0	0.0	0	0.0	
Reproductive and breast	0	0.0	0	0.0	
Respiratory, thoracic, mediastinal	1	0.4	0	0.0	
Skin and subcutaneous tissue	0	0.0	0	0.0	
Social circumstances	0	0.0	0	0.0	
Surgical and medical procedures	0	0.0	0	0.0	
Vascular	2	0.9	1	0.4	
Code pending	0	0.0	0	0.0	
Any of the above	**8**	**3.5**	**5**	**2.2**	**0.40**
Any of the above (stratified p-value)**					**0.40**

* Events in this table are limited to those reported on the SAE form. Per section 10.2.3 of the protocol, end organ dysfunction and serious infections were defined as 'protocol-specified exempt serious events'.Those events were reported during follow-up but not reported on SAE forms unless considered related to the study agent. End organ dysunction and serious infections are summarized separately.

** Unstratified CMH test, shown if at least 5 events

*** CMH test stratified by disease severity (critical vs. severe) , shown if at least 5 events

Program Name =mitt vip sae_day5 Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S35: Organ Failure and Serious Infections Through Day 5, by Type: Aviptadil Comparison

Clinical Organ Failure/Serious Infection through Day 5	Aviptadil (n= 231) N in Grp	Aviptadil (n= 231) N. Pts w/Event	Aviptadil (n= 231) Pct.	Placebo (n= 230) N in Grp	Placebo (n= 230) N. Pts w/Event	Placebo (n= 230) Pct.	P-value*
Event							
1. Myocardial infarction	231	4	1.7	230	0	0.0	
2. Congestive heart failure III/IV	231	1	0.4	230	2	0.9	
3. Hypotension, w/vasop	231	58	25.1	230	48	20.9	0.28
4. Myocarditis	231	0	0.0	230	0	0.0	
5. Pericarditis	231	0	0.0	230	0	0.0	
6. Atrial tachyarrhythmias	231	13	5.6	230	10	4.3	0.53
7. Ventricular tachyarrhythmias	231	7	3.0	230	5	2.2	0.56
8. Bleeding	231	1	0.4	230	2	0.9	
9. DIC	231	0	0.0	230	0	0.0	
10. Thromboembolic events	231	18	7.8	230	16	7.0	0.73
11. Hepatic decompensation	231	8	3.5	230	2	0.9	0.056
12. Intercurrent disease, non SARS-CoV-2	231	33	14.3	230	38	16.5	0.51
13. Delirium	231	16	6.9	230	10	4.3	0.23
14. Cerebrovascular event	231	0	0.0	230	2	0.9	
15. Encephalitis	231	1	0.4	230	1	0.4	
16. Meningitis	231	0	0.0	230	0	0.0	
17. Myelitis	231	0	0.0	230	0	0.0	
18. Transient ischemic event	231	0	0.0	230	0	0.0	
19. New requirement for RRT**	213	15	7.0	223	9	4.0	0.17
20. Worseing respiratory failure	229	38	16.6	227	34	15.0	0.64
New requirement for IMV**	136	36	26.5	135	31	23.0	0.50
New requirement for ECMO**	229	2	0.9	227	3	1.3	0.65
Any of the above	**231**	**108**	**46.8**	**230**	**100**	**43.5**	**0.48**
Any of the above, stratified p-value* **							**0.46**
Any PSESE or death	**231**	**109**	**47.2**	**230**	**103**	**44.8**	**0.61**
Any PSESE or death stratified p-value* **							**0.59**

* p-value from unstratified CMH test, shown if at least 5 events

**Participants requiring RRT, IMV, or ECMO at baseline are excluded from the risk set for incident RRT, IMV or ECMO, respectively.

*** p-value from CMH test stratified by disease severity (critical vs. severe) , shown if at least 5 events

RRT=renal replacement therapy, IMV=invasive mechanical ventilation, ECMO=extracorporal membrane oxygenation

Program Name =mitt vip psese_day5 Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S36: Incident Grade 3 and 4 AEs Through Day 5, by MedDRA System Organ Class: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 5	Aviptadil (n= 231) Pts	Aviptadil (n= 231) Pct.	Placebo (n= 230) Pts	Placebo (n= 230) Pct.	P-value*
MedDRA System Organ Class					
Blood and lymphatic system	1	0.4	1	0.4	
Cardiac	15	6.5	19	8.3	0.47
Congenital, familial, genetic	0	0.0	0	0.0	
Ear and labyrinth	0	0.0	0	0.0	
Endocrine	0	0.0	0	0.0	
Eye	0	0.0	0	0.0	
Gastrointestinal	11	4.8	6	2.6	0.22
General and administration site	13	5.6	19	8.3	0.27
Hepatobiliary	0	0.0	1	0.4	
Immune system	0	0.0	0	0.0	
Infections and infestations	22	9.5	18	7.8	0.52
Injury, poisoning, procedural complications	0	0.0	1	0.4	
Investigations	0	0.0	0	0.0	
Metabolism and nutrition	11	4.8	10	4.3	0.83
Musculoskeletal and connective tissue	0	0.0	0	0.0	
Neoplasms benign, malignant, unspecified	0	0.0	0	0.0	
Nervous system	4	1.7	5	2.2	0.73
Pregnancy, puerperium, perinatal	0	0.0	0	0.0	
Product issues	0	0.0	0	0.0	
Psychiatric	4	1.7	5	2.2	0.73
Renal and urinary	15	6.5	12	5.2	0.56
Reproductive and breast	0	0.0	0	0.0	
Respiratory, thoracic, mediastinal	25	10.8	28	12.2	0.65
Skin and subcutaneous tissue	2	0.9	0	0.0	
Social circumstances	0	0.0	0	0.0	
Surgical and medical procedures	1	0.4	1	0.4	
Vascular	79	34.2	66	28.7	0.20
Code pending	0	0.0	0	0.0	
Any of the above	**118**	**51.1**	**101**	**43.9**	**0.12**
Any of the above (stratified p-value)**					**0.11**

* Unstratified CMH test, shown if at least 5 events

**CMH test stratified by disease severity (critical vs. severe) , shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day5_soc Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S37: Incident Grade 3 and 4 AEs Through Day 5, by Cardiac SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 5	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Cardiac SOC, by MedDRA Preferred Term					
Acute myocardial infarction	4	1.7	0	0.0	
Atrial fibrillation	3	1.3	4	1.7	0.70
Bradycardia	4	1.7	6	2.6	0.52
Cardiac arrest	0	0.0	2	0.9	
Cardiac failure	0	0.0	1	0.4	
Cardiogenic shock	1	0.4	1	0.4	
Encephalopathy	0	0.0	1	0.4	
Hypotension	1	0.4	0	0.0	
Pulseless electrical activity	1	0.4	1	0.4	
Right ventricular failure	1	0.4	1	0.4	
Sinus tachycardia	1	0.4	1	0.4	
Supraventricular tachycardia	0	0.0	2	0.9	
Tachycardia	3	1.3	5	2.2	0.47
Ventricular extrasystoles	0	0.0	1	0.4	
Ventricular tachycardia	0	0.0	1	0.4	
Any of the above	**15**	**6.5**	**19**	**8.3**	**0.47**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day5_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S38: Incident Grade 3 and 4 AEs Through Day 5, by Gastrointestinal SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 5	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Gastrointestinal SOC, by MedDRA Preferred Term					
Abdominal distension	1	0.4	0	0.0	
Diarrhoea	4	1.7	3	1.3	0.71
Diverticular perforation	1	0.4	0	0.0	
Dysphagia	0	0.0	1	0.4	
Haematochezia	1	0.4	0	0.0	
Hyperglycaemia	1	0.4	0	0.0	
Ileus	0	0.0	1	0.4	
Intestinal ischaemia	0	0.0	1	0.4	
Nausea	0	0.0	1	0.4	
Pancreatitis	1	0.4	0	0.0	
Rectal haemorrhage	1	0.4	0	0.0	
Vomiting	1	0.4	0	0.0	
Any of the above	**11**	**4.8**	**6**	**2.6**	**0.22**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day5_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S39: Incident Grade 3 and 4 AEs Through Day 5, by General/Administration Site: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 5	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
General and Administration Site SOC, by MedDRA Preferred Term					
Hypothermia	0	0.0	1	0.4	
Pyrexia	13	5.6	18	7.8	0.35
Any of the above	**13**	**5.6**	**19**	**8.3**	**0.27**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day5_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S40: Incident Grade 3 and 4 AEs Through Day 5, by Infections/Infestations SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 5	Aviptadil (n= 231) Pts	Aviptadil (n= 231) Pct.	Placebo (n= 230) Pts	Placebo (n= 230) Pct.	P-value*
Infections and Infestations SOC, by MedDRA Preferred Term					
Bacteraemia	1	0.4	0	0.0	
COVID-19 pneumonia	0	0.0	2	0.9	
Cytomegalovirus infection reactivation	1	0.4	0	0.0	
Enterobacter pneumonia	0	0.0	1	0.4	
Enterococcal bacteraemia	1	0.4	0	0.0	
Haemophilus bacteraemia	1	0.4	0	0.0	
Infectious pleural effusion	1	0.4	0	0.0	
Pneumonia	3	1.3	0	0.0	
Pneumonia bacterial	4	1.7	1	0.4	0.18
Pneumonia haemophilus	1	0.4	1	0.4	
Pneumonia klebsiella	0	0.0	1	0.4	
Pneumonia pseudomonal	2	0.9	1	0.4	
Pneumonia staphylococcal	3	1.3	4	1.7	0.70
Respiratory tract infection fungal	0	0.0	1	0.4	
Sepsis	2	0.9	3	1.3	0.65
Septic shock	4	1.7	6	2.6	0.52
Sinusitis bacterial	0	0.0	1	0.4	
Staphylococcal bacteraemia	0	0.0	2	0.9	
Staphylococcal infection	1	0.4	0	0.0	
Urinary tract infection bacterial	0	0.0	1	0.4	
Urinary tract infection staphylococcal	1	0.4	0	0.0	
Any of the above	**22**	**9.5**	**18**	**7.8**	**0.52**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day5_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S41: Incident Grade 3 and 4 AEs Through Day 5, by Metabolism SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 5	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Metabolism and Nutrition SOC, by MedDRA Preferred Term					
Acidosis	2	0.9	2	0.9	
Acute kidney injury	1	0.4	0	0.0	
Hyperglycaemia	6	2.6	3	1.3	0.32
Hyperkalaemia	0	0.0	1	0.4	
Hypertriglyceridaemia	0	0.0	1	0.4	
Hypocalcaemia	0	0.0	1	0.4	
Hypoglycaemia	1	0.4	0	0.0	
Hypomagnesaemia	0	0.0	1	0.4	
Metabolic acidosis	1	0.4	0	0.0	
Metabolic alkalosis	0	0.0	1	0.4	
Respiratory acidosis	1	0.4	0	0.0	
Type 2 diabetes mellitus	2	0.9	0	0.0	
Any of the above	**11**	**4.8**	**10**	**4.3**	**0.83**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day5_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S42: Incident Grade 3 and 4 AEs Through Day 5, by Nervous System SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 5	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Nervous System SOC, by MedDRA Preferred Term					
Encephalopathy	2	0.9	0	0.0	
Haemorrhagic stroke	0	0.0	1	0.4	
Headache	1	0.4	1	0.4	
Metabolic encephalopathy	1	0.4	1	0.4	
Seizure	0	0.0	1	0.4	
Any of the above	**4**	**1.7**	**4**	**1.7**	**1.00**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day5_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S43: Incident Grade 3 and 4 AEs Through Day 5, by Psychiatric SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 5	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Psychiatric SOC, by MedDRA Preferred Term					
Agitation	1	0.4	2	0.9	
Delirium	3	1.3	2	0.9	0.66
Intensive care unit delirium	0	0.0	1	0.4	
Any of the above	**4**	**1.7**	**5**	**2.2**	**0.73**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day5_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S44: Incident Grade 3 and 4 AEs Through Day 5, by Renal and Urinary SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 5	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Renal and Urinary SOC, by MedDRA Preferred Term					
Acute kidney injury	12	5.2	9	3.9	0.51
Oliguria	1	0.4	0	0.0	
Renal failure	1	0.4	2	0.9	
Renal impairment	0	0.0	1	0.4	
Renal injury	0	0.0	1	0.4	
Urinary retention	1	0.4	0	0.0	
Any of the above	**15**	**6.5**	**12**	**5.2**	**0.56**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day5_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S45: Incident Grade 3 and 4 AEs Through Day 5, by Respiratory, Throacic, Mediastinal SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 5	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Respiratory, Thoracic, Mediastinal SOC, by MedDRA Preferred Term					
Acute respiratory distress syndrome	2	0.9	2	0.9	
Acute respiratory failure	4	1.7	2	0.9	0.41
Dyspnoea	2	0.9	6	2.6	0.15
Epistaxis	1	0.4	0	0.0	
Hypercapnia	1	0.4	0	0.0	
Hypoxia	7	3.0	10	4.3	0.45
Pleural effusion	1	0.4	0	0.0	
Pneumomediastinum	4	1.7	0	0.0	
Pneumothorax	3	1.3	1	0.4	
Pulmonary embolism	3	1.3	1	0.4	
Pulmonary oedema	0	0.0	1	0.4	
Respiratory acidosis	3	1.3	0	0.0	
Respiratory alkalosis	1	0.4	0	0.0	
Respiratory distress	0	0.0	1	0.4	
Respiratory failure	4	1.7	9	3.9	0.16
Tachypnoea	0	0.0	1	0.4	
Any of the above	**25**	**10.8**	**28**	**12.2**	**0.65**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day5_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S46: Incident Grade 3 and 4 AEs Through Day 5, by Vascular SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 5	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Vascular SOC, by MedDRA Preferred Term					
Deep vein thrombosis	5	2.2	7	3.0	0.55
Distributive shock	1	0.4	0	0.0	
Hypertension	15	6.5	15	6.5	0.99
Hypotension	64	27.7	53	23.0	0.25
Shock	0	0.0	3	1.3	
Thrombosis	0	0.0	1	0.4	
Any of the above	**79**	**34.2**	**66**	**28.7**	**0.20**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day5_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

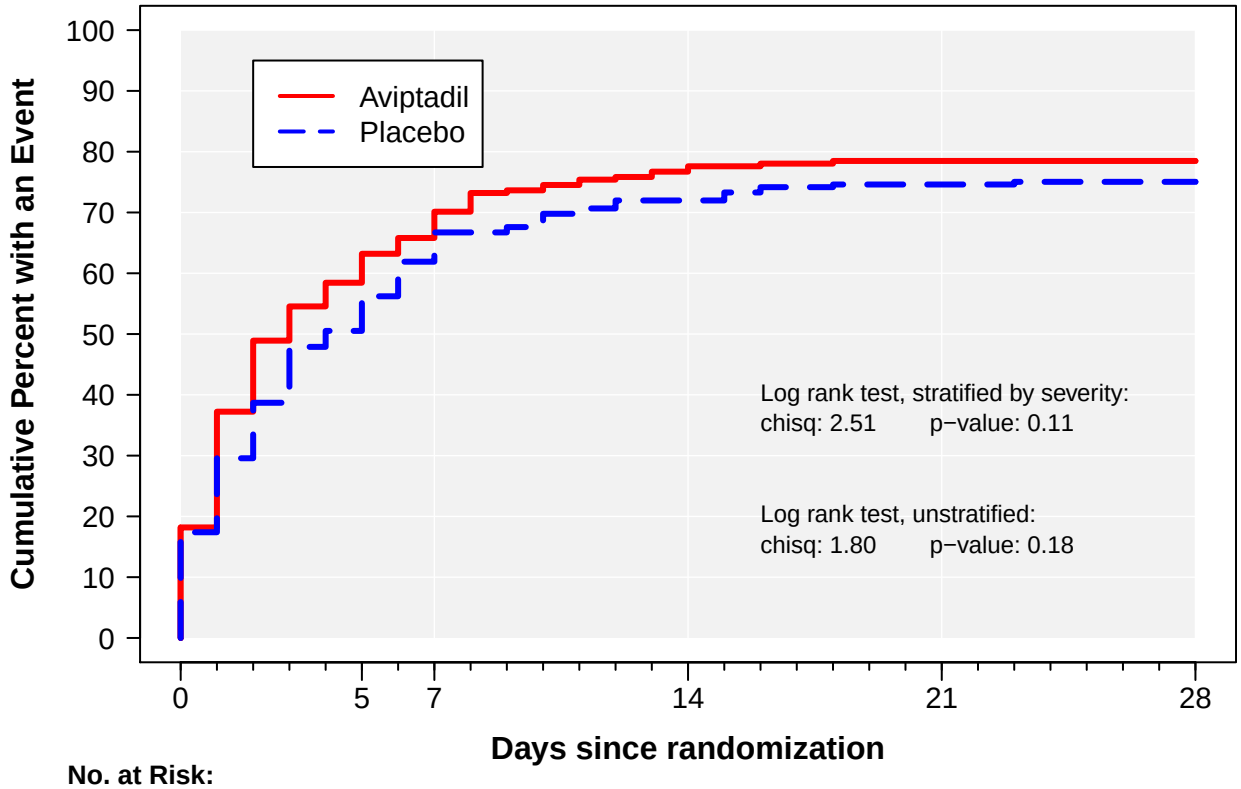
Table S47: Grade 3 or 4 AEs, SAEs, Organ Failure, Serious Infections, or Death Through Day 28: Aviptadil Comparison

Events through Day 28	Aviptadil (n= 231)		Placebo (n= 230)		HR* (A/P)	95% CI*	P-value*	P-value**
	Pts.	Pct.	Pts.	Pct.				
Composite								
Death	69	29.9	66	28.7	1.05	0.75, 1.47	0.77	0.78
Death, SAE, or Clinical Organ Failure/ Serious Infection	164	71.0	156	67.8	1.12	0.90, 1.39	0.32	0.44
Death, SAE, Clinical Organ Failure/ Serious Infection, or Grade 4 AE***	164	71.0	158	68.7	1.09	0.87, 1.35	0.46	0.57
Death, SAE, Clinical Organ Failure/ Serious Infection, or Grade 3 or 4 AE* **	**181**	**78.4**	**172**	**74.8**	**1.17**	**0.95, 1.44**	**0.15**	**0.34**
Components								
Death	69	29.9	66	28.7				
SAE	19	8.2	19	8.3				
Clinical Organ Failure/Serious Infection	155	67.1	146	63.5				
Grade 4 AE***	78	33.8	90	39.1				
Grade 3 or 4 AE***	150	64.9	145	63.0				

* Cox PH regression model, with 1 indicator for treatment group stratified by disease severity (severe vs critical).
** CMH test stratified by disease severity (severe vs critical).
*** Includes AEs reported at any time after the first infusion started, during and after completion of the infusions.
Note, summary excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.
Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip day28safetydata_no_diarr Create date=17-NOV-2022 Cut date=08-NOV-2022

Figure S14: Time to Grade 3 or 4 AE, SAE, Clinical Organ Failure, Serious Infection, or Death Through Day 28: Aviptadil Comparison: Aviptadil Comparison



No. at Risk:

A:	231	96	79	53	49	49
P:	230	113	87	64	58	57

Estimated Cumulative Pct with an Event:

A:	63.2	70.1	77.6	78.5	78.5
P:	56.2	66.7	72.0	74.6	75.0

vip_fig_day28safetydata_no_diarr.pdf File created=11/17/22 Data cutoff=11/08/22

Table S48: SAEs Through Day 28, by SOC: Aviptadil Comparison

SAEs/UPs* through Day 28	Aviptadil (n= 231) N. Pts w/Event	Aviptadil (n= 231) Pct.	Placebo (n= 230) N. Pts w/Event	Placebo (n= 230) Pct.	P-value**	P-value***
MedDRA System Organ Class						
Blood and lymphatic system	0	0.0	1	0.4		
Cardiac	5	2.2	3	1.3	0.48	0.48
Congenital, familial, genetic	0	0.0	0	0.0		
Ear and labyrinth	0	0.0	0	0.0		
Endocrine	0	0.0	0	0.0		
Eye	0	0.0	0	0.0		
Gastrointestinal	3	1.3	2	0.9	0.66	0.66
General and administration site	0	0.0	0	0.0		
Hepatobiliary	0	0.0	0	0.0		
Immune system	0	0.0	0	0.0		
Infections and infestations	1	0.4	0	0.0		
Injury, poisoning, procedural complications	2	0.9	0	0.0		
Investigations	0	0.0	0	0.0		
Metabolism and nutrition	0	0.0	1	0.4		
Musculoskeletal and connective tissue	0	0.0	0	0.0		
Neoplasms benign, malignant, unspecified	0	0.0	0	0.0		
Nervous system	0	0.0	1	0.4		
Pregnancy, puerperium, perinatal	0	0.0	0	0.0		
Product issues	0	0.0	0	0.0		
Psychiatric	0	0.0	1	0.4		
Renal and urinary	0	0.0	0	0.0		
Reproductive and breast	0	0.0	0	0.0		
Respiratory, thoracic, mediastinal	6	2.6	10	4.3	0.32	0.31
Skin and subcutaneous tissue	0	0.0	0	0.0		
Social circumstances	0	0.0	0	0.0		
Surgical and medical procedures	0	0.0	0	0.0		
Vascular	2	0.9	1	0.4		
Code pending	0	0.0	0	0.0		
Any of the above	**19**	**8.2**	**19**	**8.3**	**0.98**	**0.99**
Any of the above (stratified p-value)					**0.98**	**0.99**

* Events in this table are limited to those reported on the SAE form. Per section 10.2.3 of the protocol, end organ dysfunction and serious infections were defined as 'protocol-specified exempt serious events'. Those events were reported during follow-up but not reported on SAE forms unless considered related to the study agent. End organ dysunction and serious infections are summarized separately.

** P-value using Fine-Gray model with death as competing risk, unstratified test. Shown if at least 5 events.

*** Unstratified CMH test, shown if at least 5 events.

Program Name =mitt vip sae_day28 Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S49: Organ Failure and Serious Infections Through Day 28, by Type: Aviptadil Comparison

Clinical Organ Failure or Serious Infections through Day 28	Aviptadil (n= 231)			Placebo (n= 230)				
	N in Grp	N. Pts w/Event	Pct.	N in Grp	N. Pts w/Event	Pct.	P-value*	P-value**
Event								
1. Myocardial infarction	231	6	2.6	230	1	0.4	0.09	0.058
2. Congestive heart failure III/IV	231	2	0.9	230	4	1.7	0.42	0.41
3. Hypotension, w/vasop	231	84	36.4	230	90	39.1	0.74	0.54
4. Myocarditis	231	0	0.0	230	0	0.0		
5. Pericarditis	231	1	0.4	230	0	0.0		
6. Atrial tachyarrhythmias	231	30	13.0	230	22	9.6	0.26	0.25
7. Ventricular tachyarrhythmias	231	15	6.5	230	13	5.7	0.70	0.71
8. Bleeding	231	7	3.0	230	7	3.0	0.99	0.99
9. DIC	231	1	0.4	230	2	0.9		
10. Thromboembolic events	231	33	14.3	230	41	17.8	0.34	0.30
11. Hepatic decompensation	231	16	6.9	230	7	3.0	0.059	0.056
12. Intercurrent disease, non SARS-CoV-2	231	73	31.6	230	73	31.7	0.96	0.97
13. Delirium	231	30	13.0	230	24	10.4	0.38	0.39
14. Cerebrovascular event	231	1	0.4	230	5	2.2	0.14	0.10
15. Encephalitis	231	3	1.3	230	4	1.7	0.70	0.70
16. Meningitis	231	0	0.0	230	0	0.0		
17. Myelitis	231	1	0.4	230	0	0.0		
18. Transient ischemic event	231	0	0.0	230	0	0.0		
19. New requirement for RRT***	213	35	16.4	223	35	15.7	0.75	0.83
20. Worseing respiratory failure	229	58	25.3	227	61	26.9	0.81	0.71
New requirement for IMV***	136	54	39.7	135	56	41.5	0.91	0.77
New requirement for ECMO***	229	7	3.1	227	11	4.8	0.34	0.33
Any of the above	**231**	**155**	**67.1**	**230**	**146**	**63.5**	**0.26**	**0.41**
Any of the above (stratified p-value)							**0.28**	**0.39**
Any PSESE or death	**231**	**164**	**71.0**	**230**	**154**	**67.0**	**0.28**	**0.35**
Any PSESE or death stratified p-value							**0.23**	**0.32**

* P-value using Fine-Gray model with death as competing risk, unstratified test. Shown if at least 5 events. P-value for composite of any PSESE or death from Cox model.

** Unstratified CMH test, shown if at least 5 events.

***Participants requiring RRT, IMV, or ECMO at baseline are excluded from the risk set for incident RRT, IMV or ECMO, respectively.

RRT=renal replacement therapy, IMV=invasive mechanical ventilation, ECMO=extracorporal membrane oxygenation

Program Name =mitt vip psese_day28 Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S50: Incident Grade 3 and 4 AEs Through Day 28, by MedDRA System Organ Class

Grade 3/4 (Infusion/Non-Infusion) Events through Day 28	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
MedDRA System Organ Class					
Blood and lymphatic system	9	3.9	10	4.3	0.81
Cardiac	28	12.1	35	15.2	0.33
Congenital, familial, genetic	0	0.0	0	0.0	
Ear and labyrinth	0	0.0	0	0.0	
Endocrine	0	0.0	0	0.0	
Eye	1	0.4	0	0.0	
Gastrointestinal	22	9.5	15	6.5	0.24
General and administration site	22	9.5	28	12.2	0.36
Hepatobiliary	2	0.9	2	0.9	
Immune system	2	0.9	2	0.9	
Infections and infestations	45	19.5	44	19.1	0.92
Injury, poisoning, procedural complications	2	0.9	1	0.4	
Investigations	0	0.0	2	0.9	
Metabolism and nutrition	14	6.1	13	5.7	0.85
Musculoskeletal and connective tissue	0	0.0	2	0.9	
Neoplasms benign, malignant, unspecified	0	0.0	0	0.0	
Nervous system	13	5.6	13	5.7	0.99
Pregnancy, puerperium, perinatal	0	0.0	0	0.0	
Product issues	0	0.0	0	0.0	
Psychiatric	5	2.2	6	2.6	0.75
Renal and urinary	22	9.5	31	13.5	0.18
Reproductive and breast	0	0.0	0	0.0	
Respiratory, thoracic, mediastinal	44	19.0	47	20.4	0.71
Skin and subcutaneous tissue	2	0.9	2	0.9	
Social circumstances	0	0.0	0	0.0	
Surgical and medical procedures	2	0.9	1	0.4	
Vascular	120	51.9	111	48.3	0.43
Code pending	0	0.0	0	0.0	
Any of the above	**150**	**64.9**	**145**	**63.0**	**0.67**
Any of the above (stratified p-value)**					**0.65**

* Unstratified CMH test, shown if at least 5 events

**CMH test stratified by disease severity (critical vs. severe) , shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day28_soc Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S51: Incident Grade 3 and 4 AEs Through Day 28, by Blood/Lymphatic System SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 28	Aviptadil (n= 231) Pts	Aviptadil (n= 231) Pct.	Placebo (n= 230) Pts	Placebo (n= 230) Pct.	P-value*
Blood and Lymphatic System SOC, by MedDRA Preferred Term					
Anaemia	6	2.6	4	1.7	0.53
Blood loss anaemia	1	0.4	2	0.9	
Coagulopathy	1	0.4	0	0.0	
Disseminated intravascular coagulation	0	0.0	2	0.9	
Heparin-induced thrombocytopenia	0	0.0	1	0.4	
Leukocytosis	1	0.4	0	0.0	
Neutropenia	0	0.0	1	0.4	
Thrombocytopenia	0	0.0	2	0.9	
Any of the above	**9**	**3.9**	**10**	**4.3**	**0.81**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day28_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S52: Incident Grade 3 and 4 AEs Through Day 28, by Cardiac SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 28	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Cardiac SOC, by MedDRA Preferred Term					
Acute myocardial infarction	4	1.7	0	0.0	
Acute right ventricular failure	0	0.0	1	0.4	
Arrhythmia	0	0.0	1	0.4	
Arrhythmia supraventricular	1	0.4	0	0.0	
Atrial fibrillation	5	2.2	12	5.2	0.08
Bradycardia	5	2.2	9	3.9	0.27
Cardiac arrest	4	1.7	3	1.3	0.71
Cardiac failure	0	0.0	1	0.4	
Cardiac failure acute	0	0.0	1	0.4	
Cardiogenic shock	1	0.4	2	0.9	
Encephalopathy	0	0.0	1	0.4	
Hypotension	1	0.4	0	0.0	
Myocardial infarction	1	0.4	0	0.0	
Pulseless electrical activity	2	0.9	1	0.4	
Right ventricular failure	1	0.4	1	0.4	
Sinus tachycardia	1	0.4	1	0.4	
Supraventricular extrasystoles	1	0.4	0	0.0	
Supraventricular tachycardia	1	0.4	3	1.3	
Tachycardia	5	2.2	7	3.0	0.55
Ventricular arrhythmia	1	0.4	0	0.0	
Ventricular extrasystoles	0	0.0	1	0.4	
Ventricular tachycardia	0	0.0	4	1.7	
Any of the above	**28**	**12.1**	**35**	**15.2**	**0.33**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day28_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S53: Incident Grade 3 and 4 AEs Through Day 28, by Gastrointestinal SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 28	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Gastrointestinal SOC, by MedDRA Preferred Term					
Abdominal distension	1	0.4	0	0.0	
Diarrhoea	7	3.0	5	2.2	0.56
Diverticular perforation	1	0.4	0	0.0	
Dysphagia	1	0.4	3	1.3	
Gastrointestinal haemorrhage	4	1.7	0	0.0	
Haematochezia	2	0.9	0	0.0	
Hyperglycaemia	1	0.4	0	0.0	
Ileus	1	0.4	1	0.4	
Intestinal ischaemia	0	0.0	2	0.9	
Melaena	0	0.0	1	0.4	
Nausea	0	0.0	1	0.4	
Pancreatitis	1	0.4	0	0.0	
Peptic ulcer	1	0.4	0	0.0	
Rectal haemorrhage	1	0.4	2	0.9	
Retroperitoneal haematoma	2	0.9	0	0.0	
Retroperitoneal haemorrhage	0	0.0	1	0.4	
Vomiting	1	0.4	1	0.4	
Any of the above	**22**	**9.5**	**15**	**6.5**	**0.24**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day28_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S54: Incident Grade 3 and 4 AEs Through Day 28, by General/Administration Site SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 28	Aviptadil (n= 231) Pts	Aviptadil (n= 231) Pct.	Placebo (n= 230) Pts	Placebo (n= 230) Pct.	P-value*
General and Administration Site SOC, by MedDRA Preferred Term					
Chills	0	0.0	1	0.4	
Complication associated with device	0	0.0	1	0.4	
Fatigue	1	0.4	0	0.0	
Hypothermia	0	0.0	1	0.4	
Oedema	1	0.4	0	0.0	
Pyrexia	19	8.2	25	10.9	0.33
Systemic inflammatory response syndrome	1	0.4	0	0.0	
Any of the above	**22**	**9.5**	**28**	**12.2**	**0.36**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day28_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S55: Incident Grade 3 and 4 AEs Through Day 28, by Infections/Infestations SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 28	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Infections and Infestations SOC, by MedDRA Preferred Term					
Abdominal abscess	1	0.4	0	0.0	
Bacteraemia	2	0.9	0	0.0	
Bronchopulmonary aspergillosis	0	0.0	1	0.4	
COVID-19 pneumonia	0	0.0	2	0.9	
Candida infection	0	0.0	1	0.4	
Clostridium difficile colitis	1	0.4	0	0.0	
Clostridium difficile infection	1	0.4	0	0.0	
Cytomegalovirus infection	1	0.4	0	0.0	
Cytomegalovirus infection reactivation	1	0.4	0	0.0	
Enterobacter pneumonia	0	0.0	1	0.4	
Enterococcal bacteraemia	1	0.4	1	0.4	
Escherichia urinary tract infection	1	0.4	1	0.4	
Fungaemia	1	0.4	1	0.4	
Fungal infection	0	0.0	1	0.4	
Haemophilus bacteraemia	1	0.4	0	0.0	
Helicobacter infection	0	0.0	1	0.4	
Infectious pleural effusion	1	0.4	0	0.0	
Klebsiella sepsis	0	0.0	1	0.4	
Parotitis	0	0.0	1	0.4	
Pneumonia	8	3.5	7	3.0	0.80
Pneumonia aspiration	1	0.4	0	0.0	
Pneumonia bacterial	6	2.6	4	1.7	0.53
Pneumonia haemophilus	1	0.4	1	0.4	
Pneumonia klebsiella	1	0.4	3	1.3	
Pneumonia pseudomonal	3	1.3	3	1.3	1.00
Pneumonia staphylococcal	5	2.2	7	3.0	0.55
Respiratory tract infection fungal	0	0.0	1	0.4	
Sepsis	5	2.2	5	2.2	0.99
Septic shock	12	5.2	14	6.1	0.68
Sinusitis bacterial	0	0.0	1	0.4	
Staphylococcal bacteraemia	2	0.9	4	1.7	0.41
Staphylococcal infection	2	0.9	0	0.0	
Staphylococcal sepsis	2	0.9	2	0.9	
Streptococcal bacteraemia	1	0.4	0	0.0	
Upper respiratory tract infection	1	0.4	0	0.0	
Urinary tract infection	1	0.4	1	0.4	
Urinary tract infection bacterial	0	0.0	2	0.9	
Urinary tract infection enterococcal	0	0.0	1	0.4	
Urinary tract infection fungal	1	0.4	1	0.4	
Urinary tract infection staphylococcal	1	0.4	0	0.0	
Viral sepsis	1	0.4	0	0.0	
Any of the above	**45**	**19.5**	**44**	**19.1**	**0.92**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day28_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S56: Incident Grade 3 and 4 AEs Through Day 28, by Metabolism SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 28	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Metabolism and Nutrition SOC, by MedDRA Preferred Term					
Acidosis	3	1.3	2	0.9	0.66
Acute kidney injury	1	0.4	0	0.0	
Hyperglycaemia	7	3.0	3	1.3	0.20
Hyperkalaemia	1	0.4	2	0.9	
Hypernatraemia	0	0.0	2	0.9	
Hypertriglyceridaemia	1	0.4	1	0.4	
Hypocalcaemia	0	0.0	1	0.4	
Hypoglycaemia	1	0.4	0	0.0	
Hypomagnesaemia	0	0.0	1	0.4	
Metabolic acidosis	4	1.7	2	0.9	0.41
Metabolic alkalosis	0	0.0	1	0.4	
Respiratory acidosis	1	0.4	0	0.0	
Type 2 diabetes mellitus	2	0.9	1	0.4	
Any of the above	**14**	**6.1**	**13**	**5.7**	**0.85**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day28_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S57: Incident Grade 3 and 4 AEs Through Day 28, by Nervous System SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 28	Aviptadil (n= 231) Pts	Aviptadil (n= 231) Pct.	Placebo (n= 230) Pts	Placebo (n= 230) Pct.	P-value*
Nervous System SOC, by MedDRA Preferred Term					
Areflexia	0	0.0	1	0.4	
Cerebellar stroke	0	0.0	1	0.4	
Encephalopathy	5	2.2	3	1.3	0.48
Haemorrhagic stroke	0	0.0	1	0.4	
Headache	1	0.4	1	0.4	
Intensive care unit acquired weakness	0	0.0	2	0.9	
Metabolic encephalopathy	4	1.7	2	0.9	0.41
Polyneuropathy	1	0.4	0	0.0	
Seizure	0	0.0	2	0.9	
Toxic encephalopathy	2	0.9	0	0.0	
Any of the above	**13**	**5.6**	**12**	**5.2**	**0.85**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day28_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S58: Incident Grade 3 and 4 AEs Through Day 28, by Psychiatric SOC

Grade 3/4 (Infusion/Non-Infusion) Events through Day 28	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Psychiatric SOC, by MedDRA Preferred Term					
Agitation	2	0.9	2	0.9	
Anxiety	1	0.4	0	0.0	
Delirium	3	1.3	2	0.9	0.66
Intensive care unit delirium	0	0.0	1	0.4	
Suicidal ideation	0	0.0	1	0.4	
Any of the above	**5**	**2.2**	**6**	**2.6**	**0.75**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day28_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S59: Incident Grade 3 and 4 AEs Through Day 28, by Renal and Urinary SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 28	Aviptadil (n= 231) Pts	Aviptadil (n= 231) Pct.	Placebo (n= 230) Pts	Placebo (n= 230) Pct.	P-value*
Renal and Urinary SOC, by MedDRA Preferred Term					
Acute kidney injury	16	6.9	22	9.6	0.30
Anuria	1	0.4	0	0.0	
Azotaemia	1	0.4	0	0.0	
Haematuria	0	0.0	1	0.4	
Oliguria	1	0.4	0	0.0	
Renal failure	2	0.9	6	2.6	0.15
Renal impairment	0	0.0	2	0.9	
Renal injury	0	0.0	2	0.9	
Renal tubular dysfunction	1	0.4	0	0.0	
Urinary retention	1	0.4	0	0.0	
Any of the above	**22**	**9.5**	**31**	**13.5**	**0.18**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day28_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S60: Incident Grade 3 and 4 AEs Through Day 28, by Respiratory, Throacic, Mediastinal SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 28	Aviptadil (n= 231) Pts	Aviptadil (n= 231) Pct.	Placebo (n= 230) Pts	Placebo (n= 230) Pct.	P-value*
Respiratory, Thoracic, Mediastinal SOC, by MedDRA Preferred Term					
Acute respiratory distress syndrome	3	1.3	4	1.7	0.70
Acute respiratory failure	5	2.2	4	1.7	0.74
Bronchopleural fistula	1	0.4	0	0.0	
Cough	0	0.0	1	0.4	
Dyspnoea	4	1.7	6	2.6	0.52
Epistaxis	1	0.4	0	0.0	
Hypercapnia	1	0.4	0	0.0	
Hypoxia	8	3.5	11	4.8	0.48
Organising pneumonia	1	0.4	0	0.0	
Pleural effusion	2	0.9	0	0.0	
Pneumomediastinum	5	2.2	2	0.9	0.26
Pneumothorax	9	3.9	5	2.2	0.28
Pulmonary alveolar haemorrhage	0	0.0	1	0.4	
Pulmonary embolism	6	2.6	3	1.3	0.32
Pulmonary hypertension	1	0.4	1	0.4	
Pulmonary oedema	0	0.0	1	0.4	
Respiratory acidosis	4	1.7	2	0.9	0.41
Respiratory alkalosis	1	0.4	0	0.0	
Respiratory arrest	1	0.4	0	0.0	
Respiratory distress	0	0.0	3	1.3	
Respiratory failure	12	5.2	14	6.1	0.68
Tachypnoea	0	0.0	1	0.4	
Any of the above	**44**	**19.0**	**47**	**20.4**	**0.71**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day28_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S61: Incident Grade 3 and 4 AEs Through Day 28, by Vascular SOC: Aviptadil Comparison

Grade 3/4 (Infusion/Non-Infusion) Events through Day 28	Aviptadil (n= 231)		Placebo (n= 230)		
	Pts	Pct.	Pts	Pct.	P-value*
Vascular SOC, by MedDRA Preferred Term					
Deep vein thrombosis	9	3.9	16	7.0	0.15
Distributive shock	2	0.9	0	0.0	
Hypertension	26	11.3	21	9.1	0.45
Hypotension	105	45.5	100	43.5	0.67
Peripheral arterial occlusive disease	0	0.0	1	0.4	
Peripheral artery thrombosis	0	0.0	1	0.4	
Peripheral ischaemia	1	0.4	0	0.0	
Shock	1	0.4	6	2.6	0.056
Shock haemorrhagic	0	0.0	1	0.4	
Thrombosis	0	0.0	1	0.4	
Venous thrombosis	1	0.4	0	0.0	
Any of the above	**120**	**51.9**	**111**	**48.3**	**0.43**

* Unstratified CMH test, shown if at least 5 events

Report excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Per protocol, infusion-related diarrhea events excluded unless event led to discontinuation of the blinded agent.

Program Name =mitt vip grd34plus_day28_pt Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S62: SAEs, Organ Failure, Serious Infections, or Death Through Day 90: Aviptadil Comparison

Events through Day 90	Aviptadil (n= 231) Pts.	Aviptadil (n= 231) Pct.	Placebo (n= 230) Pts.	Placebo (n= 230) Pct.	HR* (A/P)	95% CI*	P-value*	P-value**
Composite								
Death	86	37.2	83	36.1	1.04	0.77, 1.41	0.78	0.80
Death or SAE	94	40.7	91	39.6	1.05	0.79, 1.40	0.75	0.80
Death or Clinical Organ Failure/ Serious Infection	165	71.4	158	68.7	1.13	0.90, 1.40	0.29	0.50
Death, SAE, or Clinical Organ Failure/Serious Infection	**166**	**71.9**	**160**	**69.6**	**1.11**	**0.89, 1.38**	**0.36**	**0.52**
Components								
SAE	25	10.8	23	10.0				
Clinical Organ Failure/ Serious Infection	156	67.5	150	65.2				

* Cox PH regression model, with 1 indicator for treatment group stratified by disease severity (severe vs critical).
** CMH test stratified by disease severity (severe vs critical).

Program Name =mitt vip safetyfulldata_day90 Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S63: SAEs Through Day 90, by SOC: Aviptadil Comparison

SAEs/UPs through Day 90	Aviptadil (n= 231) N. Pts w/Event	Aviptadil (n= 231) Pct.	Placebo (n= 230) N. Pts w/Event	Placebo (n= 230) Pct.	P-value**	P-value***
MedDRA System Organ Class						
Blood and lymphatic system	0	0.0	1	0.4		
Cardiac	8	3.5	4	1.7	0.25	0.25
Congenital, familial, genetic	0	0.0	0	0.0		
Ear and labyrinth	0	0.0	0	0.0		
Endocrine	0	0.0	0	0.0		
Eye	0	0.0	0	0.0		
Gastrointestinal	3	1.3	2	0.9	0.66	0.66
General and administration site	0	0.0	0	0.0		
Hepatobiliary	0	0.0	0	0.0		
Immune system	0	0.0	0	0.0		
Infections and infestations	1	0.4	1	0.4		
Injury, poisoning, procedural complications	2	0.9	0	0.0		
Investigations	0	0.0	1	0.4		
Metabolism and nutrition	0	0.0	1	0.4		
Musculoskeletal and connective tissue	0	0.0	0	0.0		
Neoplasms benign, malignant, unspecified	0	0.0	0	0.0		
Nervous system	0	0.0	2	0.9		
Pregnancy, puerperium, perinatal	0	0.0	0	0.0		
Product issues	0	0.0	0	0.0		
Psychiatric	0	0.0	2	0.9		
Renal and urinary	0	0.0	0	0.0		
Reproductive and breast	0	0.0	0	0.0		
Respiratory, thoracic, mediastinal	8	3.5	11	4.8	0.48	0.48
Skin and subcutaneous tissue	1	0.4	0	0.0		
Social circumstances	0	0.0	0	0.0		
Surgical and medical procedures	0	0.0	0	0.0		
Vascular	2	0.9	1	0.4		
Code pending	0	0.0	0	0.0		
Any of the above	**25**	**10.8**	**23**	**10.0**	**0.76**	**0.77**
Any of the above (stratified p-value)					**0.76**	**0.77**

* Events in this table are limited to those reported on the SAE form. Per section 10.2.3 of the protocol, end organ dysfunction and serious infections were defined as 'protocol-specified exempt serious events'. Those events were reported during follow-up but not reported on SAE forms unless considered related to the study agent. End organ dysunction and serious infections are summarized separately.

Table S64: Organ Failure and Serious Infections Through Day 90, by Type: Aviptadil Comparison

Clinical Organ Failure or Serious Infections through Day 90	Aviptadil (n= 231)			Placebo (n= 230)				
	N in Grp	N. Pts w/Event	Pct.	N in Grp	N. Pts w/Event	Pct.	P-value*	P-value**
Event								
1. Myocardial infarction	231	8	3.5	230	1	0.4	0.048	0.019
2. Congestive heart failure III/IV	231	2	0.9	230	7	3.0	0.12	0.09
3. Hypotension, w/vasop	231	87	37.7	230	90	39.1	0.92	0.75
4. Myocarditis	231	0	0.0	230	0	0.0		
5. Pericarditis	231	1	0.4	230	0	0.0		
6. Atrial tachyarrhythmias	231	33	14.3	230	22	9.6	0.13	0.12
7. Ventricular tachyarrhythmias	231	16	6.9	230	14	6.1	0.70	0.72
8. Bleeding	231	9	3.9	230	12	5.2	0.50	0.50
9. DIC	231	1	0.4	230	2	0.9		
10. Thromboembolic events	231	35	15.2	230	46	20.0	0.21	0.17
11. Hepatic decompensation	231	16	6.9	230	9	3.9	0.15	0.15
12. Intercurrent disease, non SARS-CoV-2	231	76	32.9	230	78	33.9	0.83	0.82
13. Delirium	231	35	15.2	230	29	12.6	0.41	0.43
14. Cerebrovascular event	231	2	0.9	230	6	2.6	0.17	0.15
15. Encephalitis	231	3	1.3	230	4	1.7	0.70	0.70
16. Meningitis	231	0	0.0	230	0	0.0		
17. Myelitis	231	1	0.4	230	0	0.0		
18. Transient ischemic event	231	0	0.0	230	0	0.0		
19. New requirement for RRT***	213	40	18.8	223	36	16.1	0.43	0.47
20. Worseing respiratory failure	229	58	25.3	227	61	26.9	0.81	0.71
New requirement for IMV***	136	54	39.7	135	56	41.5	0.91	0.77
New requirement for ECMO***	229	7	3.1	227	12	5.3	0.25	0.23
Any of the above	**231**	**156**	**67.5**	**230**	**150**	**65.2**	**0.34**	**0.60**
Any of the above (stratified p-value)							**0.28**	**0.58**
Any PSESE or death	**231**	**165**	**71.4**	**230**	**158**	**68.7**	**0.36**	**0.52**
Any PSESE or death stratified p-value							**0.29**	**0.50**

* P-value using Fine-Gray model with death as competing risk, unstratified test. Shown if at least 5 events. P-value for composite of any PSESE or death from Cox model.

** Unstratified CMH test, shown if at least 5 events.

*** Participants requiring RRT, IMV, or ECMO at baseline are excluded from the risk set for incident RRT, IMV or ECMO, respectively.

RRT=renal replacement therapy, IMV=invasive mechanical ventilation, ECMO=extracorporal membrane oxygenation

Program Name =mitt vip psese_day90 Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S65: Cardiovascular Events Through Day 90, by Type: Aviptadil Comparison

Cardiac Event	Aviptadil (n= 231)		Placebo (n= 230)					
	Pts.	Pct.	Pts.	Pct.	P-value*	P-value**	P-value***	P-value****
Through Day 5								
Myocardial infarction	4	1.7	0	0.0				
Cerebrovascular event	0	0.0	2	0.9				
Transient ischemic event	0	0.0	0	0.0				
Thromboembolic event, any below	18	7.8	16	7.0	0.73	0.73		
Deep vein thrombosis (DVT)	16	6.9	12	5.2	0.44	0.44		
Pulmonary embolism	4	1.7	3	1.3	0.71	0.71		
Arterial thrombosis	0	0.0	0	0.0				
Death due to any of above	0	0.0	2	0.9				
Any cardiac event or cardiac-related death	**22**	**9.5**	**18**	**7.8**	**0.52**	**0.51**		
Through Day 28								
Myocardial infarction	6	2.6	1	0.4	0.058	0.058	0.10	0.10
Cerebrovascular event	1	0.4	5	2.2	0.10	0.10	0.14	0.14
Transient ischemic event	0	0.0	0	0.0				
Thromboembolic event, any below	33	14.3	41	17.8	0.30	0.30	0.33	0.36
Deep vein thrombosis (DVT)	27	11.7	33	14.3	0.40	0.40	0.43	0.45
Pulmonary embolism	8	3.5	5	2.2	0.40	0.40	0.41	0.41
Arterial thrombosis	1	0.4	2	0.9				
Death due to any of above	0	0.0	3	1.3				
Any cardiac event or cardiac-related death	**40**	**17.3**	**44**	**19.1**	**0.61**	**0.61**	**0.71**	**0.74**
Through Day 90								
Myocardial infarction	8	3.5	1	0.4	0.019	0.019	0.049	0.049
Cerebrovascular event	2	0.9	6	2.6	0.15	0.15	0.17	0.17
Transient ischemic event	0	0.0	0	0.0				
Thromboembolic event, any below	35	15.2	46	20.0	0.17	0.17	0.20	0.22
Deep vein thrombosis (DVT)	29	12.6	36	15.7	0.34	0.34	0.37	0.39
Pulmonary embolism	8	3.5	7	3.0	0.80	0.80	0.80	0.80
Arterial thrombosis	1	0.4	2	0.9				
Death due to any of above	0	0.0	4	1.7				
Any cardiac event or cardiac-related death	**45**	**19.5**	**50**	**21.7**	**0.55**	**0.55**	**0.67**	**0.68**

P-values only shown if at least 5 events in the respective row.

* Unstratified CMH test, shown if at least 5 events

** Stratified CMH test by disease severity (severe vs critical)

*** P-value from unstratified Fine-Gray model for each non-fatal event component with death as competing risk. P-value from unstratified Cox regression model for death and the composite of any cardiac event or death due to a cardiac event.

**** P-value from stratified Fine-Gray model for each non-fatal event component with non-cardiac death as competing risk. P-value from Cox regression models for death and the composite of any cardiac event or death due to a cardiac event.

Program Name =mitt vip cardiac_events_all Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S66: Incident Grade 3/4 Laboratory Abnormalities, Through Day 5: Aviptadil Comparison

	Aviptadil (n= 230)			Placebo (n= 229)			
	Grade 3*	Grade 4*	Grade 3/4	Grade 3*	Grade 4*	Grade 3/4	
Laboratory Measure	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**P-value***
Sodium (low)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	
Sodium (high)	2 (0.9)	0 (0.0)	2 (0.9)	6 (2.6)	0 (0.0)	6 (2.6)	0.15
Potassium (low)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Potassium (high)	3 (1.3)	0 (0.0)	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Bicarbonate/CO_2 (low)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Creatinine (high)	16 (7.0)	6 (2.6)	20 (8.7)	11 (4.8)	2 (0.9)	13 (5.7)	0.21
Total bilirubin (high)	4 (1.8)	0 (0.0)	4 (1.8)	5 (2.2)	0 (0.0)	5 (2.2)	0.74
AST/SGOT (high)	12 (5.3)	6 (2.7)	16 (7.1)	10 (4.5)	4 (1.8)	12 (5.4)	0.45
ALT/SGPT (high)	14 (6.2)	4 (1.8)	15 (6.7)	4 (1.8)	3 (1.3)	6 (2.7)	0.047
White blood cell count (low)	0 (0.0)	5 (2.2)	5 (2.2)	0 (0.0)	10 (4.4)	10 (4.4)	0.19
Hemoglobin (low)	19 (8.3)	0 (0.0)	19 (8.3)	11 (4.8)	1 (0.4)	11 (4.8)	0.13
Platelets (low)	3 (1.3)	1 (0.4)	4 (1.7)	0 (0.0)	2 (0.9)	2 (0.9)	0.41
Neutrophils (low)	1 (0.4)	5 (2.2)	6 (2.7)	1 (0.5)	6 (2.7)	7 (3.2)	0.75
Lymphocytes (low)	16 (7.2)	30 (13.5)	43 (19.3)	28 (12.7)	37 (16.7)	57 (25.8)	0.10
INR, from PT (high)	3 (1.4)	2 (0.9)	4 (1.9)	2 (0.9)	1 (0.5)	3 (1.4)	0.70
Any of the above	67 (29.1)	48 (20.9)	96 (41.7)	59 (25.8)	53 (23.1)	92 (40.2)	0.73
Any of the above (stratified p-value)* **							**0.74**

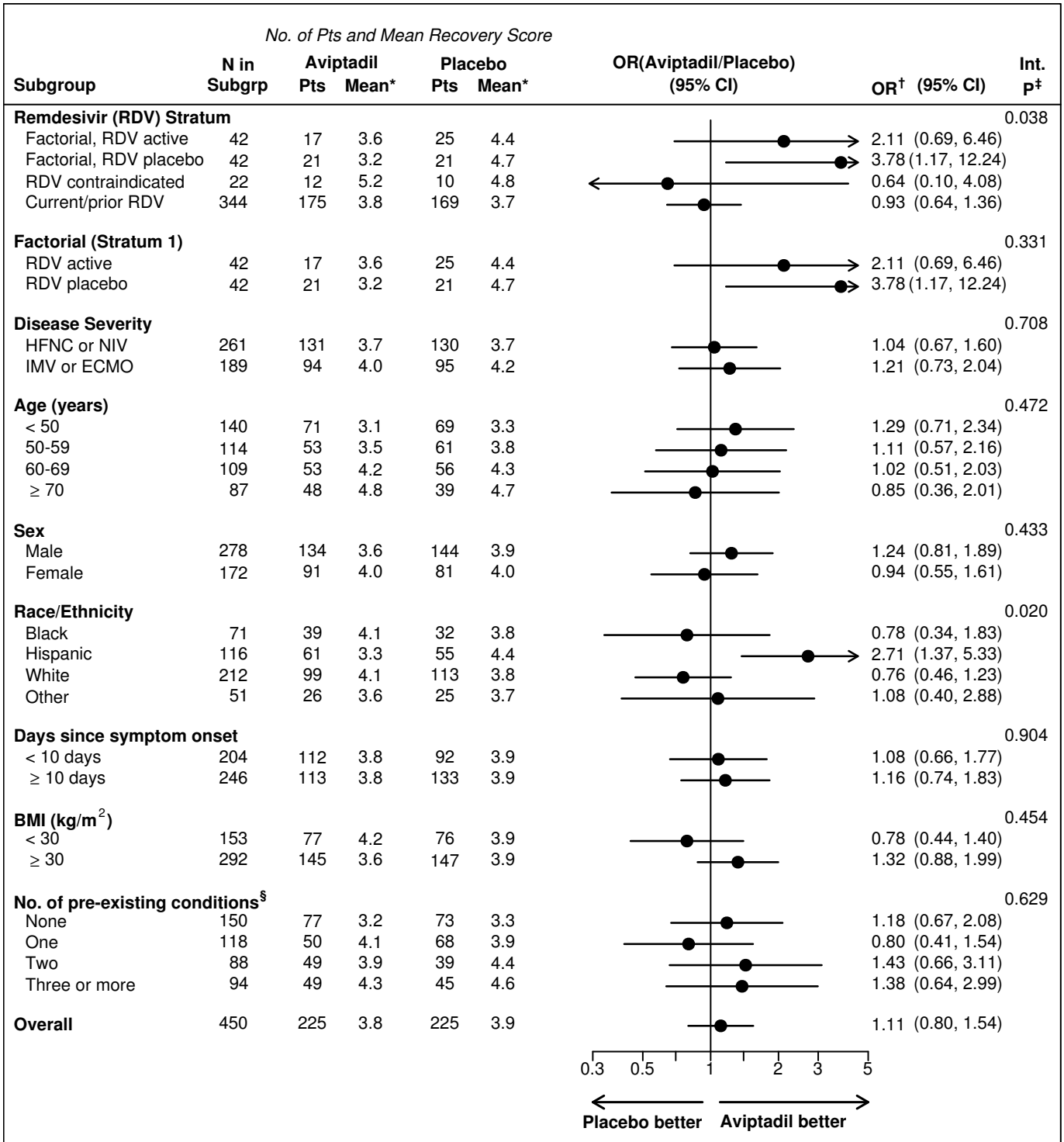
* New or increase in grade from baseline. Grading based on DAIDS Toxicity Table, Corrected Version 2.1, July 2017. ULN/LLN for grading based on MGH Laboratory Handbook, accessed 28-May-2021.

** CMH p-value for treatment group difference in incidence of a grade 3 or 4 toxicity; unstratified. Shown if at least 5 participants with toxicity.

*** CMH p-value stratified by disease severity (critical vs. severe) , shown if at least 5 events

Program Name =mitt vip inc_grd34_labs Create date=17-NOV-2022 Cut date=08-NOV-2022

Figure S15: Subgroup Analyses for Recovery at Day 90 (Primary Efficacy Outcome, Ordinal: Aviptadil Comparison)



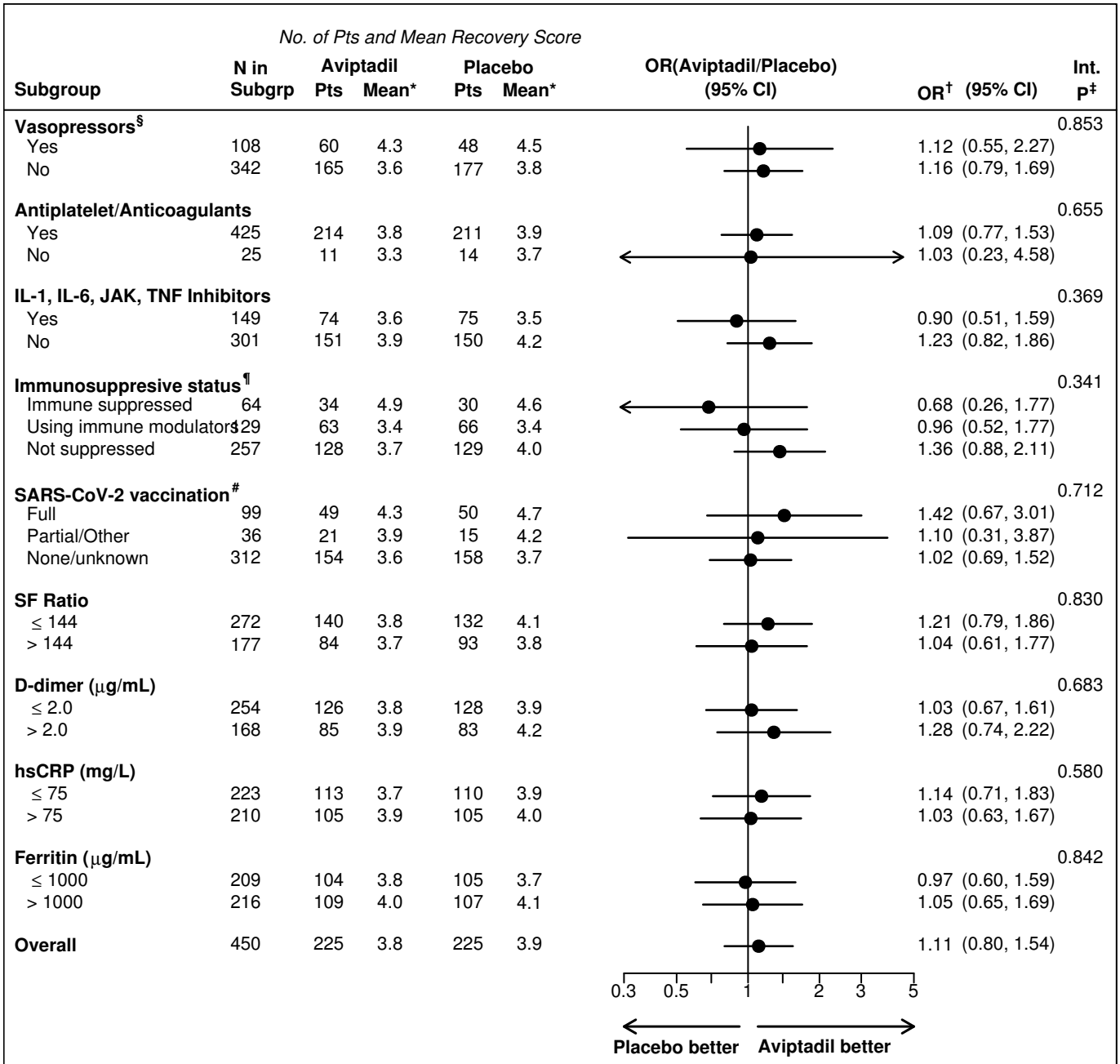
* Mean of the ordinal Recovery score at Day 90, lower is better.

† Odds ratio (OR) of being in a better category of the ordinal recovery outcome at Day 90 in the aviptadil group compared with placebo. ORs and 95% CIs were estimated using logistic ordinal regression models, adjusted for disease severity at study entry.

‡ P-value for interaction between treatment group indicator and subgroup variable. Age, days since symptom onset, and BMI were included as continuous variables. Not adjusted for multiple comparisons.

§ Out of 11 conditions collected as prior medical history, see baseline table in the Supplementary Appendix.

Figure S15: Subgroup Analyses for Recovery at Day 90 (Primary Efficacy Outcome, Ordinal): Aviptadil Comparison Continued



* Mean of the ordinal Recovery score at Day 90, lower is better.

† Odds ratio (OR) of being in a better category of the ordinal recovery outcome at Day 90 in the aviptadil group compared with placebo. ORs and 95% CIs were estimated using logistic ordinal regression models, adjusted for disease severity at study entry.

‡ P-value for interaction between treatment group indicator and subgroup variable. SF ratio, $\log_2$ D-dimer, $\log_2$ hsCRP, and $\log_2$ ferritin were included as continuous variables. Not adjusted for multiple comparisons.

§ On vasopressors at baseline or required vasopressors during hospitalization before randomization.

¶ Immune suppressed = using antirejection medication, biologic medicine for autoimmune disease or cancer (excluding IL-1, IL-6, JAK or TNF inhibitors) or HIV/other immunosuppressived condition; immune modulators = using IL-1, IL-6, JAK or TNF inhibitors, but not in immuno-suppressed category.

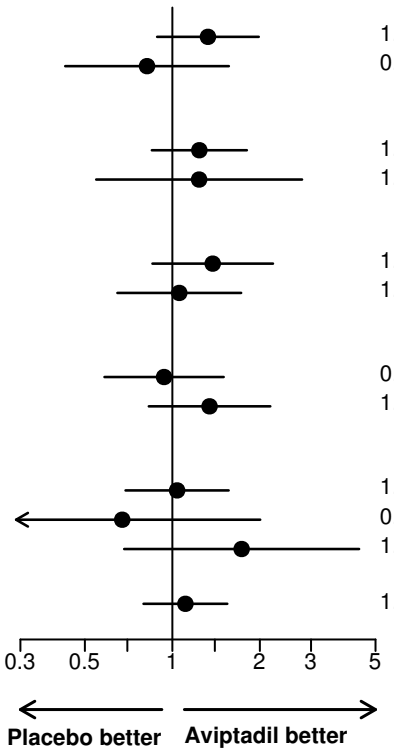
\# Full = 14 days or more after primary series (2 of 2 mRNA or 1 J&J); Partial/Other= <14 days since vaccination or only 1 dose of 2 or 1-2 doses but unknown dates.

vip_fig_subgroups_ordprim.pdf File created=17-NOV-2022 Data cutoff=08-NOV-2022

Figure S15: Subgroup Analyses for Recovery at Day 90 (Primary Efficacy Outcome, Ordinal): Aviptadil Comparison Continued

No. of Pts and Mean Recovery Score

Subgroup	N in Subgrp	Aviptadil Pts	Aviptadil Mean*	Placebo Pts	Placebo Mean*	OR(Aviptadil/Placebo) (95% CI)	OR† (95% CI)	Int. P‡
GenScript Antibody (nAb)								0.201
Positive	305	152	3.5	153	3.8		1.33 (0.89, 1.98)	
Negative	130	64	4.5	66	4.4		0.82 (0.43, 1.56)	
Biorad Antibody (Anti-N Ab)								0.967
Positive	346	167	3.6	179	3.8		1.24 (0.85, 1.80)	
Negative	89	49	4.6	40	4.9		1.24 (0.55, 2.79)	
Quanterix Antigen (pg/mL)								0.926
≤ 1294	218	109	3.3	109	3.6		1.38 (0.85, 2.22)	
> 1294	217	107	4.3	110	4.4		1.06 (0.65, 1.72)	
Nasal Swab Viral Load§ (copies/mL)								0.813
≤ 23733	219	116	3.5	103	3.4		0.94 (0.58, 1.50)	
> 23733	223	104	4.1	119	4.4		1.34 (0.83, 2.17)	
SARS-CoV-2 Variant¶								0.373
Delta	298	152	3.9	146	3.9		1.04 (0.69, 1.56)	
Omicron	49	24	4.8	25	4.6		0.67 (0.23, 2.01)	
Other#	59	27	3.0	32	3.6		1.73 (0.68, 4.39)	
Overall	450	225	3.8	225	3.9		1.11 (0.80, 1.54)	



* Mean of the ordinal Recovery score at Day 90, lower is better.

† Odds ratio (OR) of being in a better category of the ordinal recovery outcome at Day 90 in the aviptadil group compared with placebo. ORs and 95% CIs were estimated using logistic ordinal regression models, adjusted for disease severity at study entry.

‡ P-value for interaction between treatment group indicator and subgroup variable. Log_{10} -transformed Quanterix antigen and log_{10} nasal swab viral load were included as continuous variables. Not adjusted for multiple comparisons.

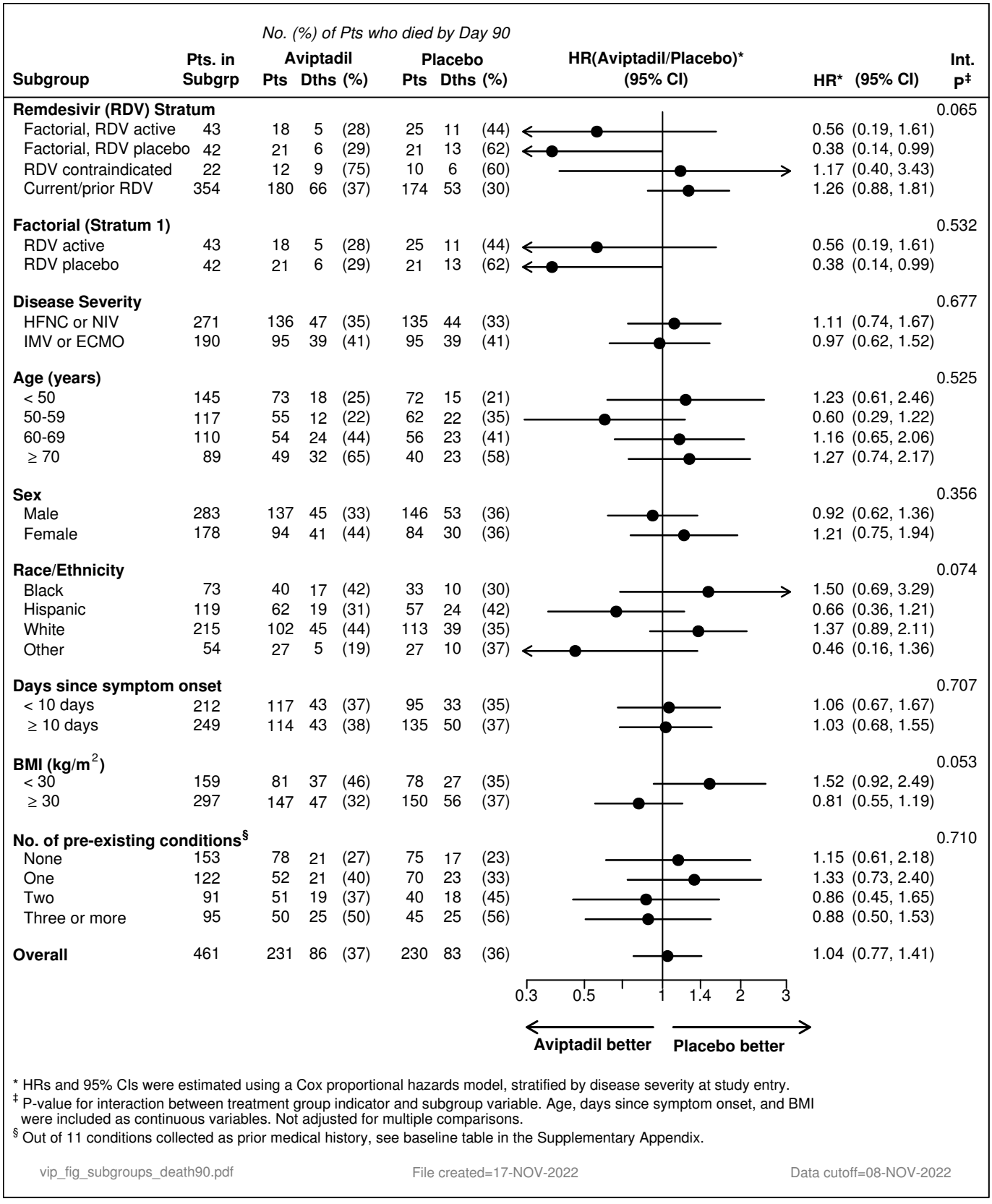
§ Of those with a positive quantitative result.

¶ Of those with positive nucleocapsid PCR.

Most participants with Other variants enrolled prior to June 15, 2021.

vip_fig_subgroups_ordprim.pdf File created=17-NOV-2022 Data cutoff=08-NOV-2022

Figure S16: Subgroup Analyses for Time to Death Through Day 90: Aviptadil Comparison



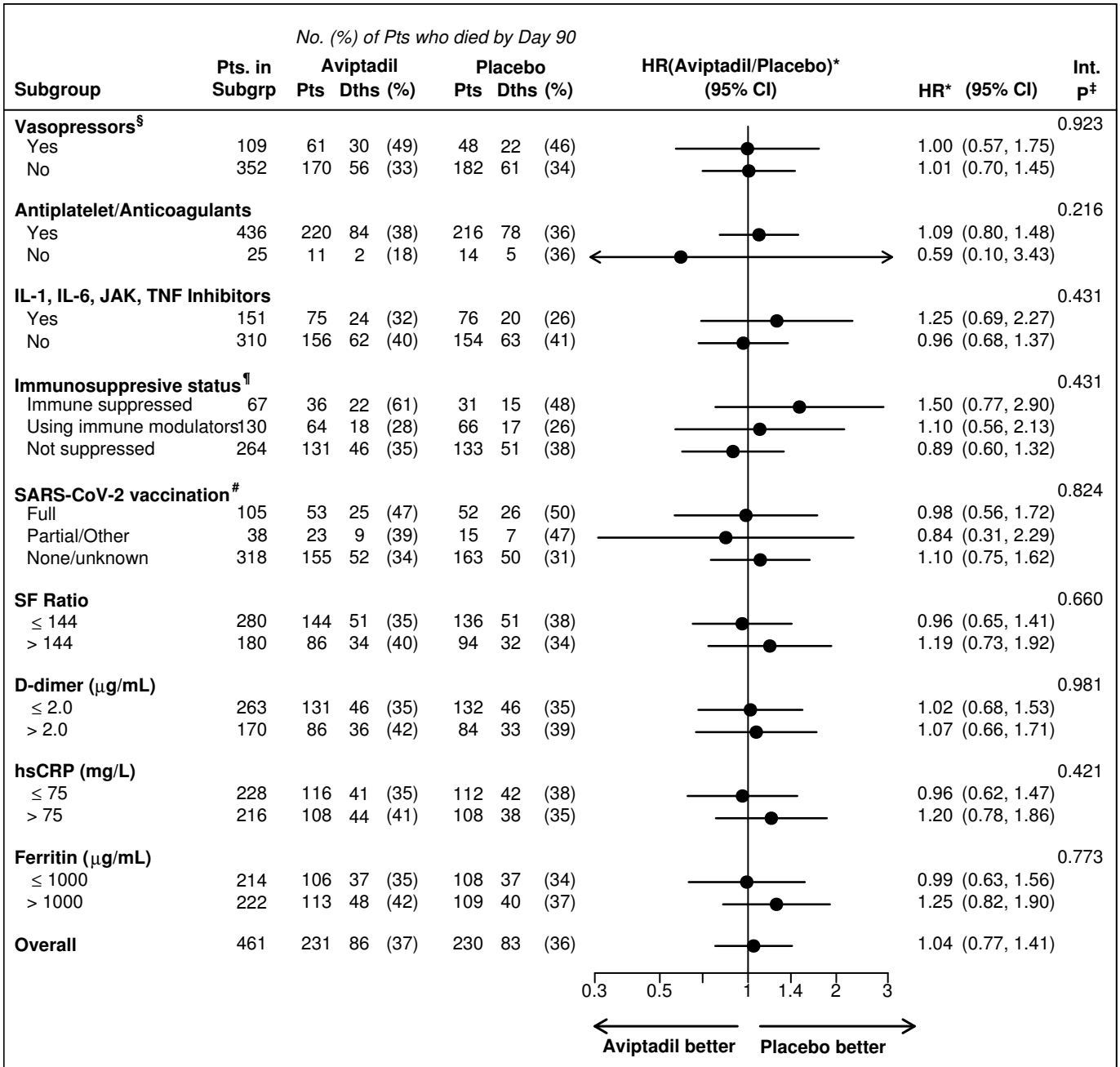
* HRs and 95% CIs were estimated using a Cox proportional hazards model, stratified by disease severity at study entry.

‡ P-value for interaction between treatment group indicator and subgroup variable. Age, days since symptom onset, and BMI were included as continuous variables. Not adjusted for multiple comparisons.

§ Out of 11 conditions collected as prior medical history, see baseline table in the Supplementary Appendix.

vip_fig_subgroups_death90.pdf File created=17-NOV-2022 Data cutoff=08-NOV-2022

Figure S16: Subgroup Analyses for Time to Death Through Day 90, : Aviptadil Comparison Continued



* HRs and 95% CIs were estimated using a Cox proportional hazards model, stratified by disease severity at study entry.

‡ P-value for interaction between treatment group indicator and subgroup variable. SF ratio, $\log_2$ D-dimer, $\log_2$ hsCRP, and $\log_2$ ferritin were included as continuous variables. Not adjusted for multiple comparisons.

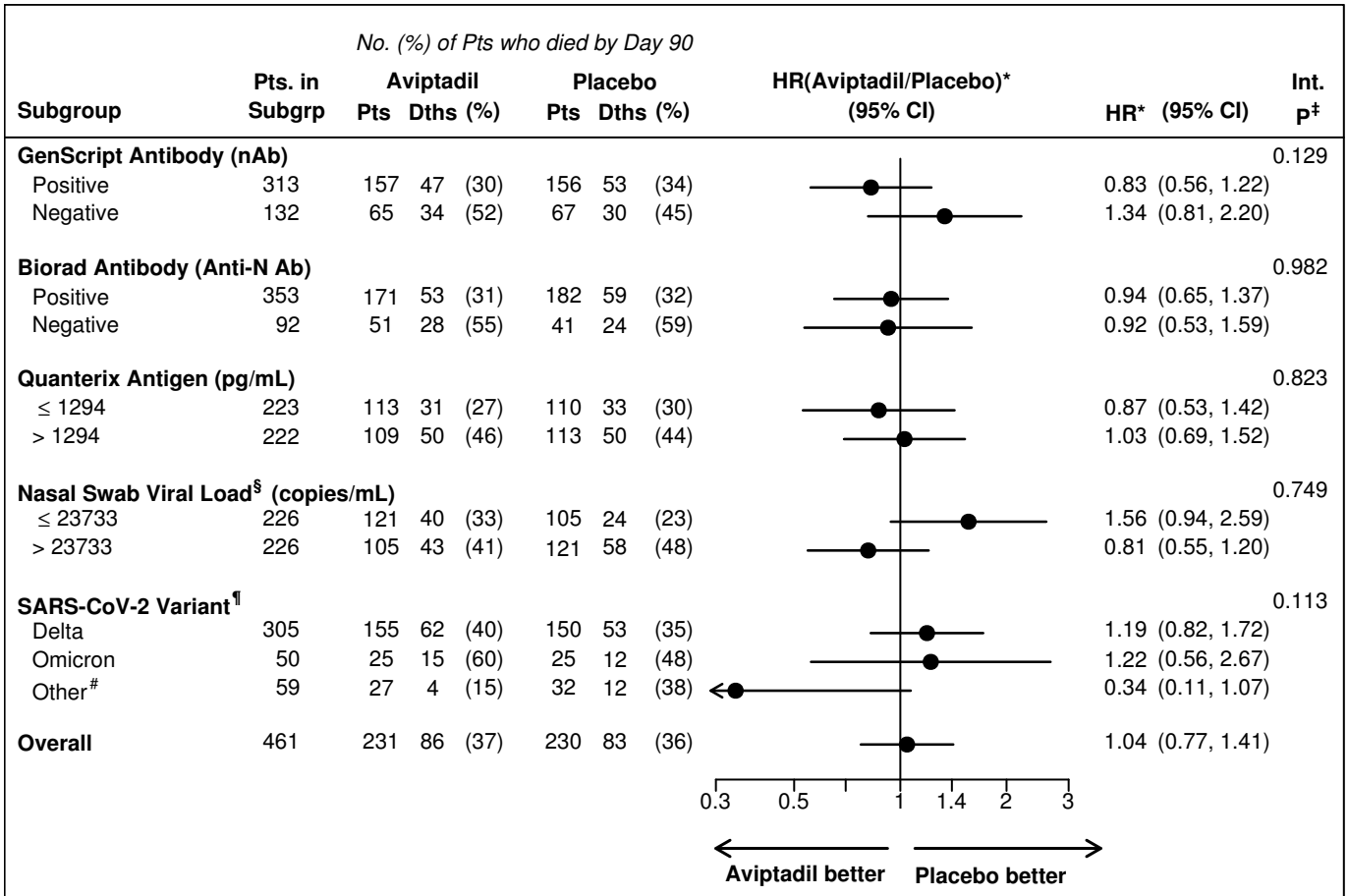
§ On vasopressors at baseline or required vasopressors during hospitalization before randomization.

¶ Immune suppressed = using antirejection medication, biologic medicine for autoimmune disease or cancer (excluding IL-1, IL-6, JAK or TNF inhibitors) or HIV/other immunosuppressived condition; immune modulators = using IL-1, IL-6, JAK or TNF inhibitors, but not in immunosuppressed category.

Full = 14 days or more after primary series (2 of 2 mRNA or 1 J&J); Partial/Other= <14 days since vaccination or only 1 dose of 2 or 1-2 doses but unknown dates.

vip_fig_subgroups_death90.pdf File created=17-NOV-2022 Data cutoff=08-NOV-2022

Figure S16: Subgroup Analyses for Time to Death Through Day 90, : Aviptadil Comparison Continued



* HRs and 95% CIs were estimated using a Cox proportional hazards model, stratified by disease severity at study entry.

‡ P-value for interaction between treatment group indicator and subgroup variable. Log_{10} -transformed Quanterix antigen and log_{10} nasal swab viral load were included as continuous variables. Not adjusted for multiple comparisons.

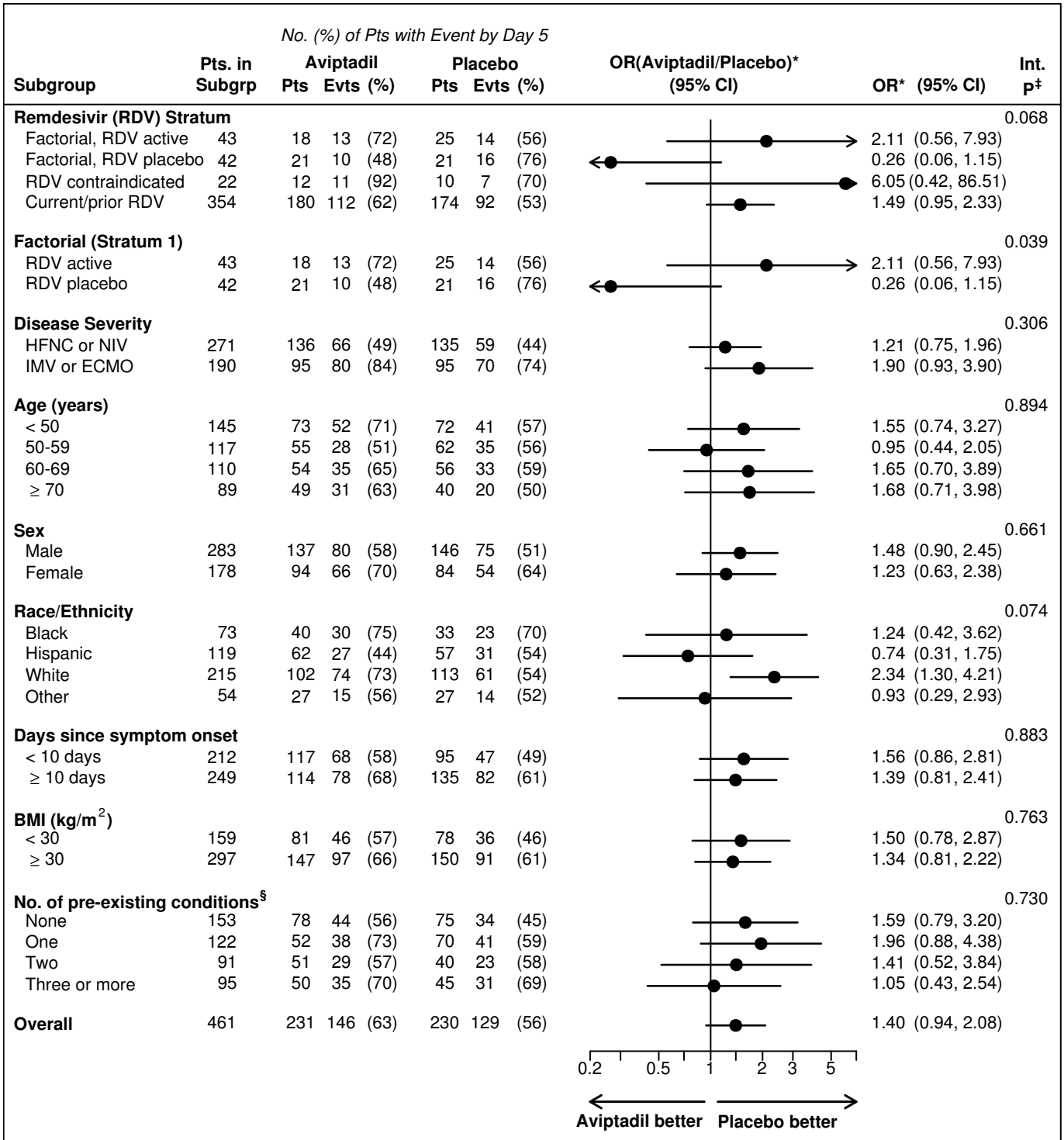
§ Of those with a positive quantitative result.

¶ Of those with positive nucleocapsid PCR.

Most participants with Other variants enrolled prior to June 15, 2021.

vip_fig_subgroups_death90.pdf File created=17-NOV-2022 Data cutoff=08-NOV-2022

Figure S17: Subgroup Analyses for the Composite Safety Outcome on Day 5: Aviptadil Comparison



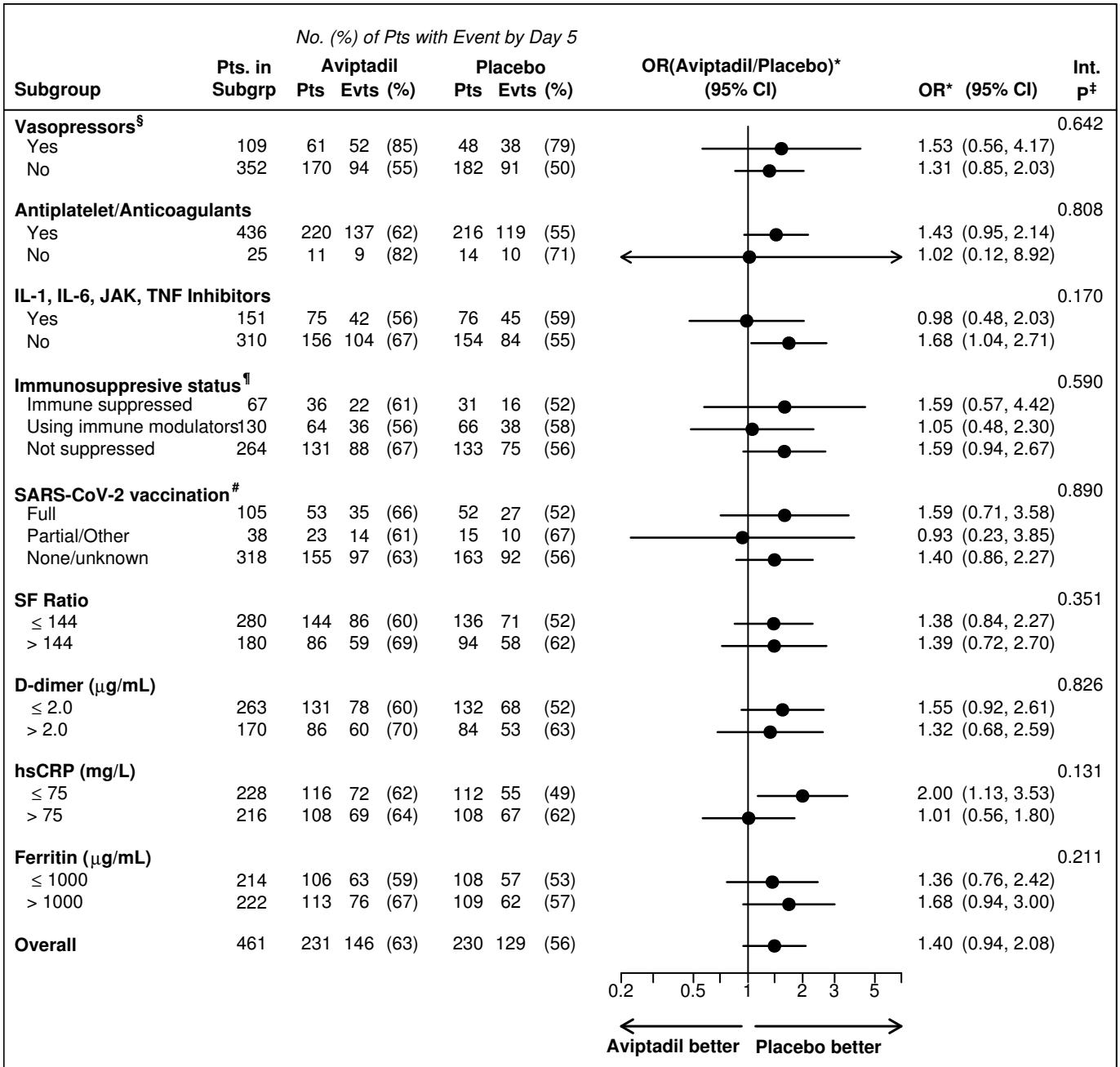
* ORs and 95% CIs were estimated using logistic regression models, adjusted for disease severity at study entry.

‡ P-value for interaction between treatment group indicator and subgroup variable. Age, days since symptom onset, and BMI were included as continuous variables. Not adjusted for multiple comparisons.

§ Out of 11 conditions collected as prior medical history, see baseline table in the Supplementary Appendix.

vip_fig_subgroups_day5safety.pdf File created=17-NOV-2022 Data cutoff=08-NOV-2022

Figure S17: Subgroup Analyses for the Composite Safety Outcome on Day 5: Aviptadil Comparison Continued



* ORs and 95% CIs were estimated using logistic regression models, adjusted for disease severity at study entry.

‡ P-value for interaction between treatment group indicator and subgroup variable. SF ratio, $\log_2$ D-dimer, $\log_2$ hsCRP, and $\log_2$ ferritin were included as continuous variables. Not adjusted for multiple comparisons.

§ On vasopressors at baseline or required vasopressors during hospitalization before randomization.

¶ Immune suppressed = using antirejection medication, biologic medicine for autoimmune disease or cancer (excluding IL-1, IL-6, JAK or TNF inhibitors) or HIV/other immunosuppressived condition; immune modulators = using IL-1, IL-6, JAK or TNF inhibitors, but not in immunosuppressed category.

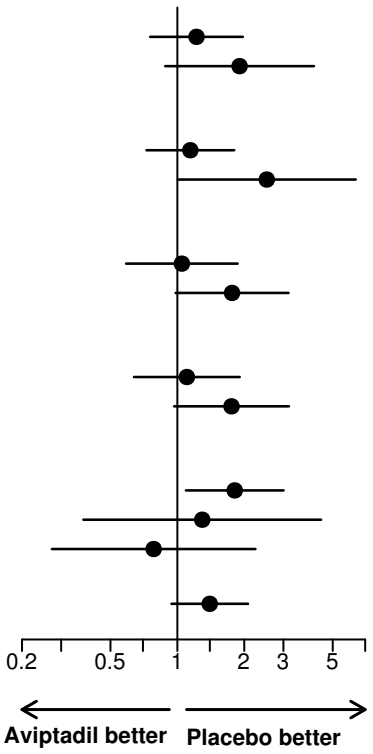
Full = 14 days or more after primary series (2 of 2 mRNA or 1 J&J); Partial/Other= <14 days since vaccination or only 1 dose of 2 or 1-2 doses but unknown dates.

vip_fig_subgroups_day5safety.pdf File created=17-NOV-2022 Data cutoff=08-NOV-2022

Figure S17: Subgroup Analyses for the Composite Safety Outcome on Day 5: Aviptadil Comparison Continued

No. (%) of Pts with Event by Day 5

Subgroup	Pts. in Subgrp	Aviptadil Pts	Aviptadil Evts	Aviptadil (%)	Placebo Pts	Placebo Evts	Placebo (%)	OR* (95% CI)	Int. P‡
GenScript Antibody (nAb)									0.368
Positive	313	157	99	(63)	156	88	(56)	1.22 (0.75, 1.97)	
Negative	132	65	42	(65)	67	38	(57)	1.91 (0.88, 4.12)	
Biorad Antibody (Anti-N Ab)									0.122
Positive	353	171	103	(60)	182	103	(57)	1.14 (0.73, 1.80)	
Negative	92	51	38	(75)	41	23	(56)	2.52 (1.00, 6.35)	
Quanterix Antigen (pg/mL)									0.354
≤ 1294	223	113	65	(58)	110	58	(53)	1.05 (0.59, 1.87)	
> 1294	222	109	76	(70)	113	68	(60)	1.76 (0.98, 3.16)	
Nasal Swab Viral Load§ (copies/mL)									0.208
≤ 23733	226	121	68	(56)	105	55	(52)	1.10 (0.64, 1.91)	
> 23733	226	105	75	(71)	121	73	(60)	1.75 (0.97, 3.18)	
SARS-CoV-2 Variant¶									0.483
Delta	305	155	107	(69)	150	84	(56)	1.81 (1.09, 3.00)	
Omicron	50	25	17	(68)	25	15	(60)	1.29 (0.38, 4.43)	
Other#	59	27	12	(44)	32	17	(53)	0.78 (0.27, 2.25)	
Overall	461	231	146	(63)	230	129	(56)	1.40 (0.94, 2.08)	



* ORs and 95% CIs were estimated using logistic regression models, adjusted for disease severity at study entry.

‡ P-value for interaction between treatment group indicator and subgroup variable. Log_{10} -transformed Quanterix antigen and log_{10} nasal swab viral load were included as continuous variables. Not adjusted for multiple comparisons.

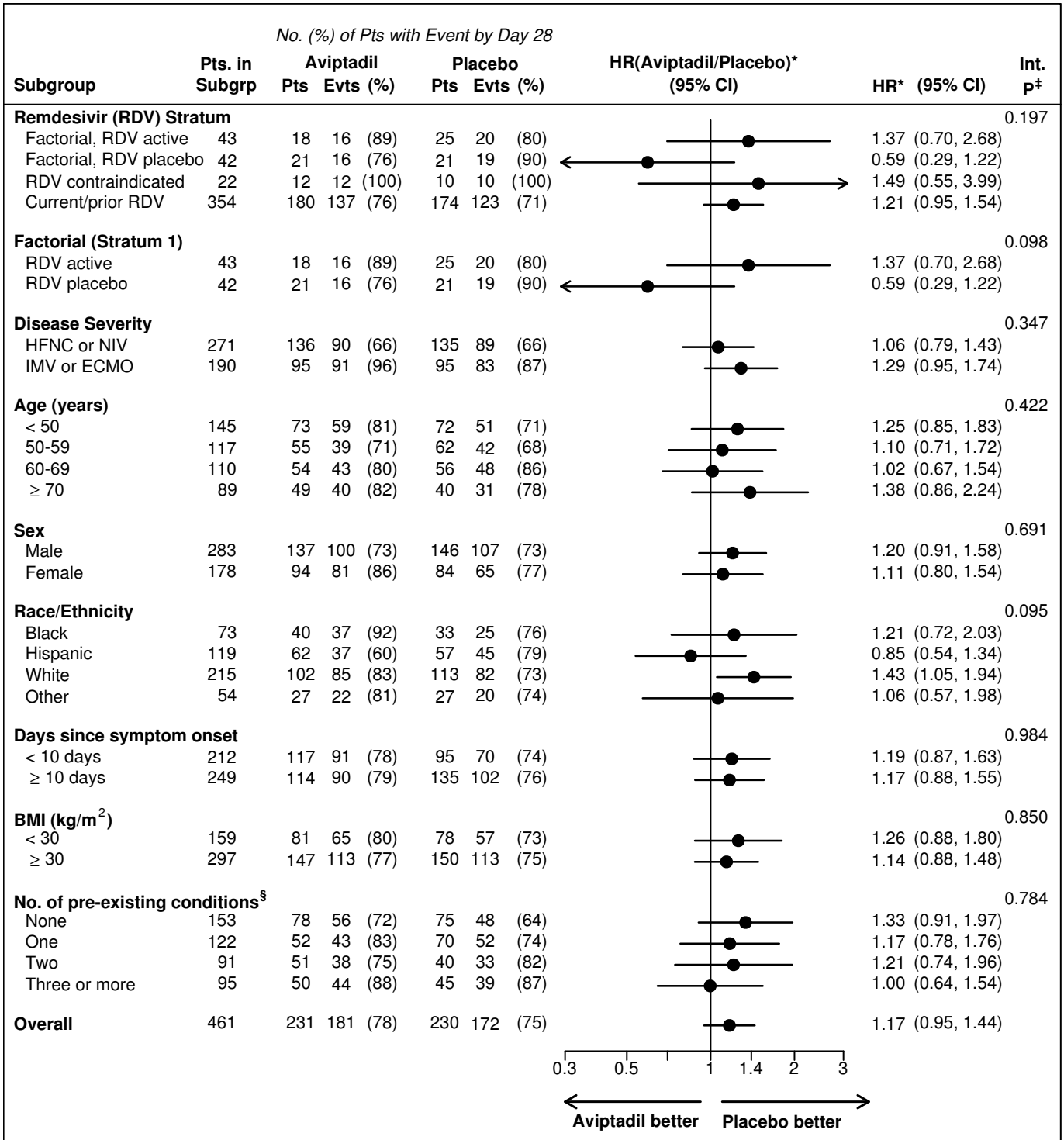
§ Of those with a positive quantitative result.

¶ Of those with positive nucleocapsid PCR.

Most participants with Other variants enrolled prior to June 15, 2021.

vip_fig_subgroups_day5safety.pdf File created=17-NOV-2022 Data cutoff=08-NOV-2022

Figure S18: Subgroup Analyses for the Composite Safety Outcome on Day 28: Aviptadil Comparison



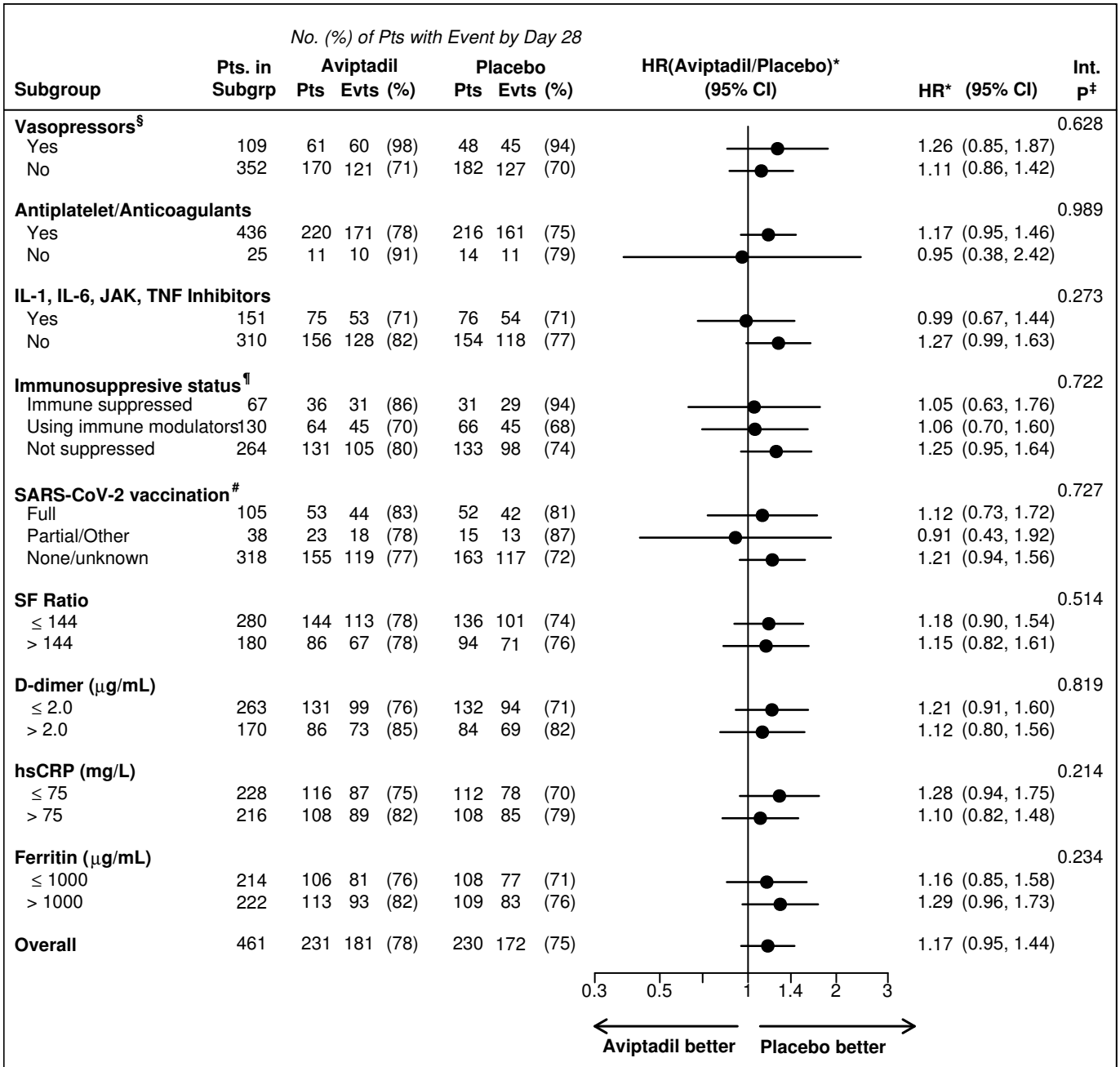
* HRs and 95% CIs were estimated using a Cox proportional hazards model, stratified by disease severity at study entry.

‡ P-value for interaction between treatment group indicator and subgroup variable. Age, days since symptom onset, and BMI were included as continuous variables. Not adjusted for multiple comparisons.

§ Out of 11 conditions collected as prior medical history, see baseline table in the Supplementary Appendix.

vip_fig_subgroups_day28safety.pdf File created=17-NOV-2022 Data cutoff=08-NOV-2022

Figure S18: Subgroup Analyses for the Composite Safety Outcome on Day 28: Aviptadil Comparison Continued



* HRs and 95% CIs were estimated using a Cox proportional hazards model, stratified by disease severity at study entry.

‡ P-value for interaction between treatment group indicator and subgroup variable. SF ratio, $\log_2$ D-dimer, $\log_2$ hsCRP, and $\log_2$ ferritin were included as continuous variables. Not adjusted for multiple comparisons.

§ On vasopressors at baseline or required vasopressors during hospitalization before randomization.

¶ Immune suppressed = using antirejection medication, biologic medicine for autoimmune disease or cancer (excluding IL-1, IL-6, JAK or TNF inhibitors) or HIV/other immunosuppressived condition; immune modulators = using IL-1, IL-6, JAK or TNF inhibitors, but not in immunosuppressed category.

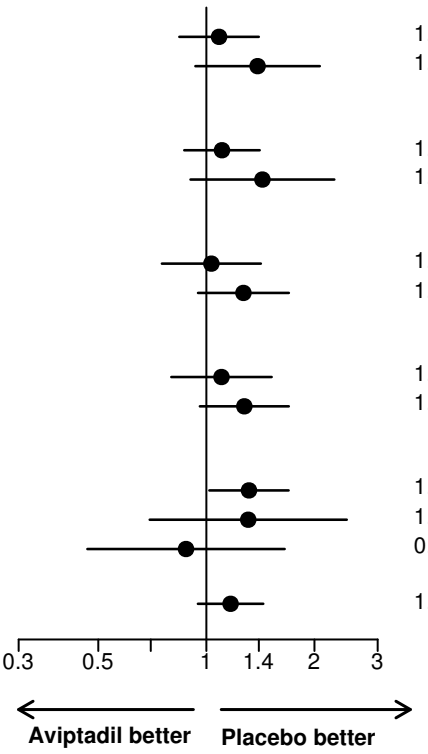
Full = 14 days or more after primary series (2 of 2 mRNA or 1 J&J); Partial/Other= <14 days since vaccination or only 1 dose of 2 or 1-2 doses but unknown dates.

vip_fig_subgroups_day28safety.pdf File created=17-NOV-2022 Data cutoff=08-NOV-2022

Figure S18: Subgroup Analyses for the Composite Safety Outcome on Day 28: Aviptadil Comparison Continued

No. (%) of Pts with Event by Day 28

Subgroup	Pts. in Subgrp	Aviptadil Pts	Aviptadil Evts	Aviptadil (%)	Placebo Pts	Placebo Evts	Placebo (%)	HR* (95% CI)	Int. P‡
GenScript Antibody (nAb)									0.302
Positive	313	157	124	(79)	156	116	(74)	1.08 (0.84, 1.40)	
Negative	132	65	52	(80)	67	53	(79)	1.39 (0.93, 2.07)	
Biorad Antibody (Anti-N Ab)									0.499
Positive	353	171	131	(77)	182	133	(73)	1.11 (0.87, 1.41)	
Negative	92	51	45	(88)	41	36	(88)	1.43 (0.90, 2.27)	
Quanterix Antigen (pg/mL)									0.526
≤ 1294	223	113	82	(73)	110	74	(67)	1.03 (0.75, 1.42)	
> 1294	222	109	94	(86)	113	95	(84)	1.27 (0.95, 1.70)	
Nasal Swab Viral Load§ (copies/mL)									0.535
≤ 23733	226	121	83	(69)	105	68	(65)	1.10 (0.80, 1.52)	
> 23733	226	105	94	(90)	121	102	(84)	1.28 (0.96, 1.70)	
SARS-CoV-2 Variant¶									0.431
Delta	305	155	130	(84)	150	114	(76)	1.31 (1.02, 1.69)	
Omicron	50	25	20	(80)	25	19	(76)	1.31 (0.70, 2.46)	
Other#	59	27	17	(63)	32	23	(72)	0.88 (0.47, 1.65)	
Overall	461	231	181	(78)	230	172	(75)	1.17 (0.95, 1.44)	



* HRs and 95% CIs were estimated using a Cox proportional hazards model, stratified by disease severity at study entry.

‡ P-value for interaction between treatment group indicator and subgroup variable. Log_{10} -transformed Quanterix antigen and $\log_{10}$ nasal swab viral load were included as continuous variables. Not adjusted for multiple comparisons.

§ Of those with a positive quantitative result.

¶ Of those with positive nucleocapsid PCR.

Most participants with Other variants enrolled prior to June 15, 2021.

vip_fig_subgroups_day28safety.pdf File created=17-NOV-2022 Data cutoff=08-NOV-2022

Table S67: Cumulative Percent Who Died by Baseline Oxygen Requirement: Aviptadil Comparison

	Aviptadil (n= 231)			Placebo (n= 230)		
Death Cut Point	**N in Grp**	**No. Dths**	**% Dths***	**N in Grp**	**No. Dths**	**% Dths***
Through Day 5	**231**	**13**	**5.6**	**230**	**11**	**4.8**
High-flow nasal cannula (HFNC) oxygen device	127	7	5.5	118	3	2.6
Non-invasive ventilation (NIV)	9	2	22.2	17	0	0.0
Invasive mechanical ventilation (IMV)	93	4	4.3	92	8	8.7
Extracorporeal membrane oxygenation (ECMO)	2	0	0.0	3	0	0.0
Through Day 28	**231**	**69**	**30.1**	**230**	**66**	**28.8**
High-flow nasal cannula (HFNC) oxygen device	127	33	26.3	118	30	25.6
Non-invasive ventilation (NIV)	9	6	66.7	17	6	35.3
Invasive mechanical ventilation (IMV)	93	30	32.3	92	30	32.6
Extracorporeal membrane oxygenation (ECMO)	2	0	0.0	3	0	0.0
Through Day 90	**231**	**86**	**37.5**	**230**	**83**	**36.2**
High-flow nasal cannula (HFNC) oxygen device	127	41	32.7	118	38	32.5
Non-invasive ventilation (NIV)	9	6	66.7	17	6	35.3
Invasive mechanical ventilation (IMV)	93	37	39.8	92	38	41.3
Extracorporeal membrane oxygenation (ECMO)	2	2	100.0	3	1	33.3
Through Day 180	**231**	**90**	**39.3**	**230**	**86**	**37.6**
High-flow nasal cannula (HFNC) oxygen device	127	45	36.2	118	41	35.1
Non-invasive ventilation (NIV)	9	6	66.7	17	6	35.3
Invasive mechanical ventilation (IMV)	93	37	39.8	92	38	41.3
Extracorporeal membrane oxygenation (ECMO)	2	2	100.0	3	1	33.3

*Kaplan-Meier estimate for the cumulative percent who died by the given day.

Program Name =mitt fig_subgroups_death_o2stat Create date=17-NOV-2022 Cut date=08-NOV-2022

7 Supplementary Tables and Figures: Follow-up for the Remdesivir Comparison

Below is a summary of the tables and figures in the supplement related to follow-up, including efficacy and safety for participants in the remdesivir comparison. The tables and figures included in the supplement are shown in the order that they are referred to in the main text.

Table S68. **Overview table** - this table provides a summary of the major efficacy and safety outcomes that are presented in tables and figures in the rest of this section.

Figure S19. 6-category primary ordinal outcome at day 90 - category percentages at Day 90 for the remdesivir and placebo groups are shown. The summary odds ratio (OR) was estimated with the use of a proportional odds model that was stratified by disease severity at entry. An OR > 1.0 favors remdesivir. The OR for being in a better category at day 90 for the remdesivir vs. placebo groups was 0.98 (95% CI: 0.45, 2.11). This outcome was estimated from 86 participants with known status on Day 90.

Figure S20. Time to death – this figure presents Kaplan-Meier estimates of cumulative mortality through Day 180 for the remdesivir and placebo groups. The cumulative incidences of death through Day 90 were 38.6% and 46.5% in the remdesivir and placebo groups, respectively. By Day 180, these percentages were 43.7% and 48.8%. The hazard ratios (HRs) through Days 90 and 180 estimated with a proportional hazards regression model stratified by disease severity at entry were 0.74 (95% CI: 0.39-1.42) and 0.81 (95% CI: 0.43-1.50), respectively.

Figure S21. Time to discharge – this figure and the two which follow describe 3 ways for defining recovery. The subhazard ratio (sHR) for time to discharge was 1.06 (95% CI: 0.61-1.83). Cumulative incidence after 90 days was 54.5% for remdesivir and 53.5% for placebo.

Figure S22. Time to discharge home –the sub-hazard ratio (sHR) for time to discharge home (ignoring oxygen requirement after discharge) was 1.00 (95% CI: 0.56-1.77).

Figure S23. Time to discharge home for at least 14 days – the sub-hazard ratio (sHR) for time to discharge home for at least 14 cumulative days (an endpoint referred to as sustained recovery in other trials) was 1.00 (95% CI: 0.56-1.77).

Table S69. 3-category ordinal outcome at day 90 - a 3-category ordinal outcome was also defined at day 90. This ordinal outcome combines the first 3 categories (discharged home and off supplemental oxygen) into a single category and combines the two categories for surviving participants who have not been discharged home off supplemental oxygen in a single category. The OR for this ordinal outcome was 1.01

(95% CI: 0.46-2.24). The p-value corresponding to the test for the proportional odds assumption was 0.08.

Figure S24. 7-category pulmonary ordinal outcome on day 7, 14 and 28 – an ordinal outcome used in other COVID-19 trials is summarized. This ordinal outcome takes into account oxygen requirements and ranges from "can independently undertake usual activities with minimal/no symptoms" to "death". ORs and 95% CIs for a more favorable outcome response on remdesivir versus placebo on day 7, 14 and 28 are 1.04 (95%CI: 0.47-2.27), 0.79 (95% CI: 0.37-1.69), and 1.06 (95%CI: 0.49-2.29), respectively.

Figure S25. Time to clinical organ failure, serious infection or death – The hazard ratio (HR) (remdesivir versus placebo) for the composite outcome of clinical organ failure, serious infection, or death through Day 90 was 1.02 (95% CI 0.63-1.67). A HR > 1.0 indicates a more favorable result for placebo.

Figure S26. Time to respiratory worsening or death - the HR (remdesivir versus placebo) for respiratory worsening or death through Day 90 was 0.92 (95% CI 0.50-1.69). Through day 90 respiratory failure was experienced by 48% of participants assigned remdesivir and 51% among those assigned placebo.

Figure S27. Time to rehospitalization or death after initial discharge– Among participants who were discharged, 24 in the remdesivir group and 23 in the placebo group, the cumulative incidence of rehospitalization or death through study day 90 was 8.3% for remdesivir and 8.7% for placebo.

Tables S70. Infusion reactions by treatment group – infusion reactions reported on a checklist on the 10 days the infusion of remdesivir or placebo was to be given are summarized over all 10 days on which the infusion was given in Table S70. For participants who reported the same reaction on more than one day, the one with highest severity grade is counted.

Table S71. Composite safety outcome through day 5 – Table S69 summarizes the day 5 composite safety outcome. The OR (remdesivir versus placebo) for the composite of grade 3 or 4 adverse events, SAEs, end organ failure, serious infections or death was 0.89 (95% CI: 0.37-2.14). End organ dysfunction and serious infections and grade 3 or 4 adverse events accounted for most of the events.

Table S72 and Figure S28. Composite safety outcome through day 28 – Table S72 summarizes the day 28 composite safety outcome. The HR (remdesivir versus placebo) for the composite of grade 3 or 4 adverse events, SAEs, organ failure, serious infections or death was 1.04 (95% CI: 0.64-1.67). Figure S28 gives the Kaplan-Meier plot for time to the day 28 composite safety outcome.

Tables S73-S75. Composite safety outcome through day 90 - Table S73 summarizes the day 90 composite safety outcome, and Tables S74-S75 provide additional details on the components of the day 90 composite safety outcome. The HR (remdesivir versus placebo) for the composite of SAEs, end organ failure, serious infections or death was 1.06 (95% CI 0.65, 1.71).

MedDRA SOCs for the 11 serious events reported on SAE forms through day 90 (9 on remdesivir and 2 on placebo) are summarized in Table S74. Respiratory failure was the most common event (5 on remdesivir and 2 on placebo). These events were considered related to the study treatment.

End organ failure and serious infections through day 90 are summarized in Table S75. Thirty-two (73%) participants randomized to remdesivir and 30 (70%) randomized to placebo experienced at least one of the events shown. The most common events were hypotension requiring a vasopressor, thromboembolic events, non-SARS-CoV-2 intercurrent disease, delirium, a new requirement for renal replacement treatment, and respiratory failure.

Table S68: Summary of Major Efficacy and Safety Outcomes: Remdesivir Comparison

	Remdesivir (n=44)	Placebo (n=43)		
Primary Outcome at Day 90	**No. with Event (%)**	**No. with Event (%)**	**Odds Ratio for Remdesivir/Placebo (95% CI)**	**p value**
6-category primary ordinal outcome at Day 90[a,b]			0.98 (0.45, 2.11)	0.96
Other Efficacy Outcomes Through Day 90	**No. with Event (Estimated Cumulative % in Group)**	**No. with Event (Estimated Cumulative % in Group**	**Hazard Ratio or Sub-Hazard Ratio for Remdesivir/Placebo (95% CI)**	**p value**
Death[c]	17 (38.6)	20 (46.5)	0.74 (0.39, 1.42)	0.37
Discharged[d]	24 (54.5)	23 (53.5)	1.06 (0.61, 1.83)	0.85
Discharged home[d]	22 (50.0)	22 (51.2)	1.00 (0.56, 1.77)	0.99
Discharged home for 14 consecutive days (sustained recovery)[d]	22 (50.0)	22 (51.2)	1.00 (0.56, 1.77)	0.99
Death, end-organ failure or serious infection[c]	34 (77.3)	32 (74.4)	1.02 (0.63, 1.67)	0.93
Worsening respiratory failure or death[c]	21 (47.7)	22 (51.2)	0.92 (0.50, 1.69)	0.79
Hospital readmission or death, after initial discharge[c,e]	2 (8.3)	2 (8.7)	0.99 (0.14, 7.12)	>0.99
Through Day 180				
Death[d]	19 (43.7)	21 (48.8)	0.81 (0.43, 1.50)	0.50
Safety Outcome Through Day 5	**No. with Event (%)**	**No. with Event (%)**	**Odds Ratio for Remdesivir/Placebo (95% CI)**	**p value**
Composite safety outcome of SAE, Grade 3/4 AE, Organ Failure/Serious Infection, or Death[f]	25 (56.8)	25 (58.1)	0.89 (0.37, 2.14)	0.80
Death	1 (2.3)	4 (9.3)	--	--
Safety Outcome Through Day 28	**No. with Event (%)**	**No. with Event (%)**	**Hazard Ratio for Remdesivir/Placebo (95% CI)**	**p value**
Composite safety outcome of SAE, Grade 3/4 AE, Organ Failure/Serious Infection, or Death[c]	36 (81.8)	34 (79.1)	1.04 (0.64, 1.67)	0.88
Death[c]	13 (29.5)	16 (37.2)	0.70 (0.34, 1.46)	0.34

OR: Odds ratio; sHR=sub-hazard ratio; HR=hazard ratio.

[a] Category 1: At home and off oxygen ≥ 77 days (best)
Category 2: At home and off oxygen 49-76 days
Category 3: At home and off oxygen 1-48 days
Category 4: Discharged, but not at home, or at home requiring supplemental oxygen
Category 5: Hospitalized or receiving hospice care
Category 6: Died (worst)

[b] Summary odds ratio for being in a better category, remdesivir vs. placebo. Proportional odds regression model with 1 indicator for treatment group stratified by disease severity. Computed for the 86 participants with known status on Day 90; 1 participant in the remdesivir group with unknown status was excluded from this analysis.

[c] Hazard ratio for time to first event, remdesivir vs. placebo. Cox proportional hazards regression model with 1 indicator for treatment group stratified by disease severity.

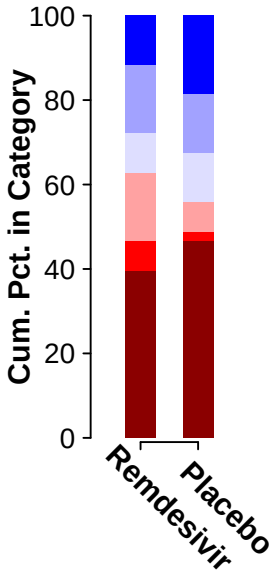
[d] Sub-hazard ratio for time to first event, remdesivir vs. placebo. Fine-Gray model considering death a competing risk with 1 indicator for treatment group stratified by disease severity.

[e] Among participants who were discharged from the index hospital. Time=0 is the date of discharge.

[f] Odds ratio for experiencing the event, remdesivir vs. placebo. Logistic regression model with 1 indicator for treatment group stratified by disease severity.

Figure S19: Primary 6-Category Ordinal Outcome at Day 90: Remdesivir Comparison

Category		Remdesivir N	Remdesivir %	Placebo N	Placebo %
Better	1	5	11.6	8	18.6
	2	7	16.3	6	14.0
	3	4	9.3	5	11.6
	4	7	16.3	3	7.0
	5	3	7.0	1	2.3
Worse	6	17	39.5	20	46.5
Total		43		43	



Category
1 = At home and off oxygen ≥ 77 days,
2 = At home and off oxygen 49−76 days,
3 = At home and off oxygen 1−48 days,
4 = Not hospitalized AND either at home on oxygen OR not at home
5 = Hospitalized for medical care OR in hospice care,
6 = Death

OR(Remdesivir/Placebo):
Unstratified:
0.96 (95% CI: 0.45 to 2.08) P=0.92
Stratified by severity:
0.98 (95% CI: 0.45 to 2.11) P=0.96

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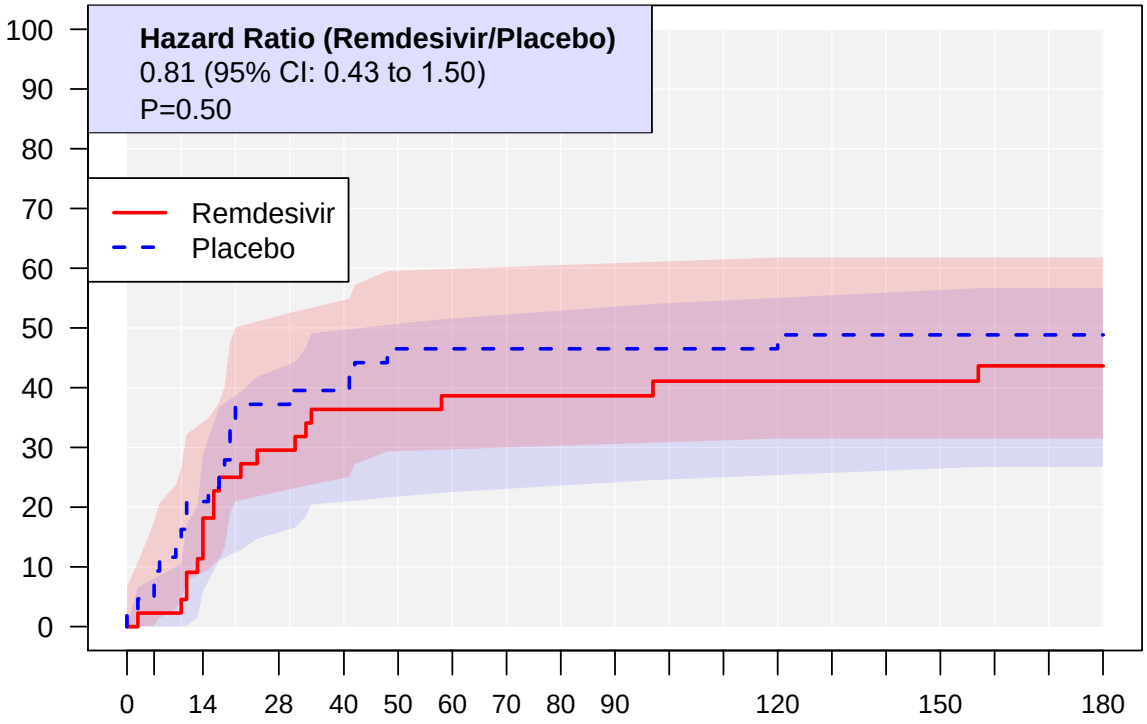
Figure S20: Time to Death through Day 180: Remdesivir Comparison



No. at Risk:

R:	44	43	39	31	28	27	27	23	23	17
P:	43	41	34	27	26	23	23	23	22	16

Estimated Cumulative Pct with an Event:

R:	2.3	18.2	29.5	36.4	38.6	38.6	41.1	41.1	43.7
P:	9.3	20.9	37.2	39.5	46.5	46.5	48.8	48.8	48.8

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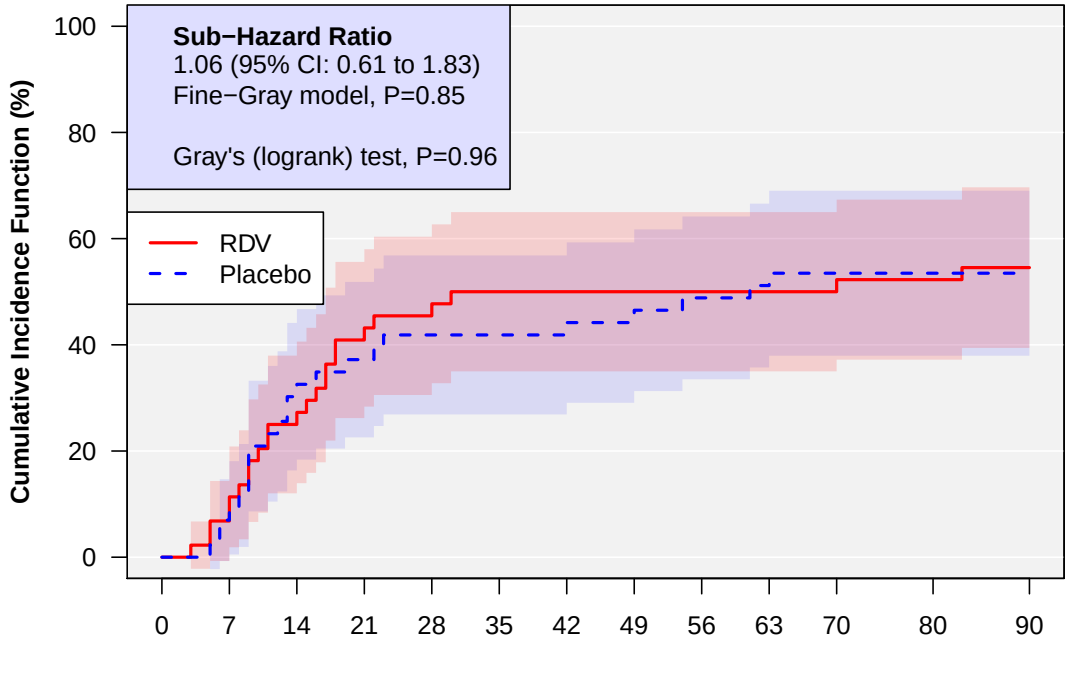
Figure S21: Time to Hospital Discharge: Remdesivir Comparison



Number at Risk:

R:	44	40	28	15	11	6	6	6	6	5	5	4	3
P:	43	35	21	11	9	8	8	5	3	2	1	1	1

Estimated Cumulative Pct. With Event:

R:		11.4	27.3	43.2	47.7	50.0	50.0	50.0	50.0	50.0	52.3	52.3	54.5
P:		9.3	32.6	37.2	41.9	41.9	44.2	46.5	48.8	53.5	53.5	53.5	53.5

Note: Tests are stratified by disease severity.

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	RDV (n= 44)		Placebo (n= 43)				
Status	**No.**	**Pct**	**No.**	**Pct.**	**DRR[a] (R/P)**	**95% CI**	**P-value**
Discharged	24	54.5	23	53.5	1.06	0.61, 1.83	0.85
Censored	3	6.8	1	2.3			
Died[b]	17	38.6	19	44.2			
Days to discharge[c] median (95% CI)	50 (17, .)		61 (16, .)				

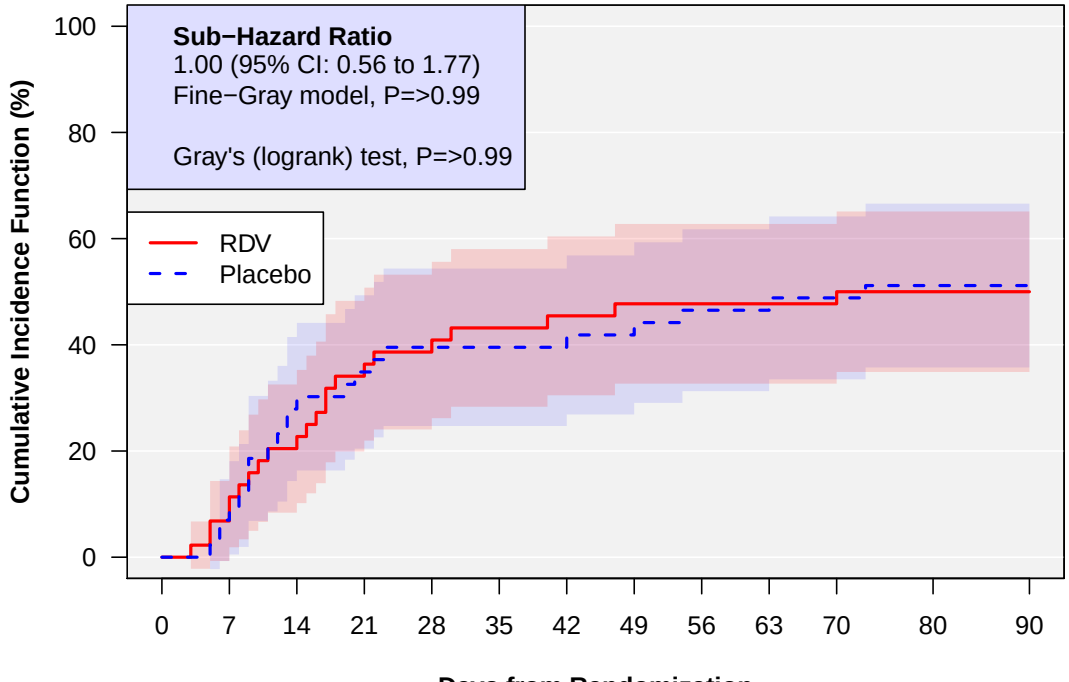
[a] Discharge rate ratio (R vs P) for time to discharge from the index hospitalization using the Fine-Gray method for considering death as a competing risk; stratified by disease severity (severe or critical). DRR > 1 indicates benefit to the RDV group.

[b] Death before discharge from hospital considered a competing risk.

[c] Modified Kaplan-Meier estimate where follow-up for participants who died prior to discharge was carried forward to the administrative censoring date (cut date for this current report).

Program Name =mitt rdv t2discharge90 Create date=17-NOV-2022 Cut date=08-NOV-2022

Figure S22: Time to Hospital Discharge and First Return Home: Remdesivir Comparison



Number at Risk:

R:	44	40	30	18	14	9	8	7	7	6	6	5	5
P:	43	35	22	12	10	9	9	6	4	4	3	2	2

Estimated Cumulative Pct. With Event:

R:		11.4	22.7	36.4	40.9	43.2	45.5	47.7	47.7	47.7	50.0	50.0	50.0
P:		9.3	30.2	34.9	39.5	39.5	41.9	44.2	46.5	48.8	48.8	51.2	51.2

Note: Tests are stratified by disease severity.

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Status	RDV (n= 44) No.	RDV (n= 44) Pct	Placebo (n= 43) No.	Placebo (n= 43) Pct.	DRR[a] (R/P)	95% CI	P-value
At home	22	50.0	22	51.2	1.00	0.56, 1.77	0.99
Censored	5	11.4	2	4.7			
Died[b]	17	38.6	19	44.2			
1st day home[c] median (95% CI)	. (18, .)		73 (20, .)				

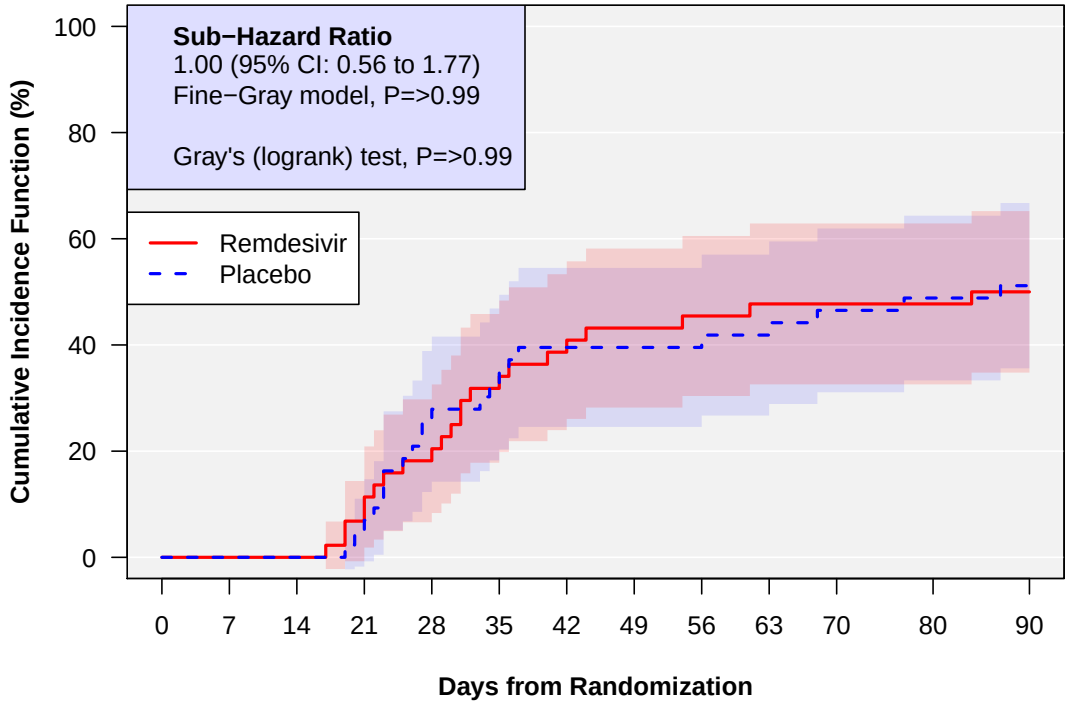
[a] Discharge rate ratio (R vs P) for time to first discharge from the index hospitalization and return home using the Fine-Gray method for considering death as a competing risk; stratified by disease severity (severe or critical). DRR > 1 indicates benefit to the RDV group.

[b] Death before first return home considered a competing risk.

[c] Modified Kaplan-Meier estimate where follow-up for participants who died prior to return home was carried forward to the administrative censoring date (cut date for this current report).

Program Name =mitt rdv t2dischargehome Create date=17-NOV-2022 Cut date=08-NOV-2022

Figure S23: Time to Discharge Home for 14 Consecutive Days (Sustained Recovery): Remdesivir Comparison



Number at Risk:

R:	44	43	39	30	23	14	11	9	8	6	6	6	5
P:	43	38	34	25	16	12	9	7	7	6	4	3	2

Estimated Cumulative Pct. With Event:

R:	0.0	0.0	11.4	20.5	34.1	40.9	43.2	45.5	47.7	47.7	47.7	50.0
P:	0.0	0.0	7.0	27.9	34.9	39.5	39.5	41.9	44.2	46.5	48.8	51.2

Note: Tests are stratified by disease severity.

fig_t2susrecovery File created=11/17/22 Data cutoff=11/08/22

Status	RDV (n= 44) No.	RDV (n= 44) Pct	Placebo (n= 43) No.	Placebo (n= 43) Pct.	RRR[a] (R/P)	95% CI	P-value
Sustained recovery (home 14+ days)	22	50.0	22	51.2	1.00	0.56, 1.77	0.99
Censored	5	11.4	2	4.7			
Died[b]	17	38.6	19	44.2			
Days recovered[c] median (95% CI)	. (35, .)		87 (35, .)				

[a] Recovery rate ratio (RDV vs Placebo) for first time at home for 14 consecutive days" using the Fine-Gray method for considering death before recovery as a competing risk; stratified by disease severity (severe or critical). RRR > 1 indicates benefit to Group RDV.

[b] Death before sustained recovery considered a competing risk.

[c] Modified Kaplan-Meier estimate where follow-up for participants who died prior to sustained recovery was carried forward to the administrative censoring date (cut date for this current report).

Program Name =mitt rdv t2susrecovery Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S69: Ordinal Outcome with 3 Categories - Recovered; Alive, Not Recovered; Dead at Day 90: Remdesivir Comparison

Category at Day 90	RDV (n= 43) Pts.	RDV (n= 43) Pct.	Placebo (n= 43) Pts.	Placebo (n= 43) Pct.	OR* (R/P)	95% CI*	P-value
1: Recovered (at home and off oxygen ≥ 1 days)	16	37.2	19	44.2	1.01	0.46, 2.24	0.98
2: Alive, but not recovered	10	23.3	4	9.3			
3: Died	17	39.5	20	46.5			
P-value for Proportional Odds Assumption:							
test from partial prop. odds. model, with unequal slopes across outcome categories, but equal slopes across stratification covariates							0.08

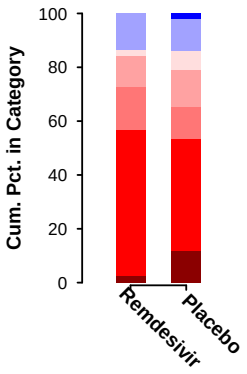
*Odds ratios from logistic regresion model, stratified by disease severity.
Restricted to participants who have reached Day 90 administrative follow-up and are classifiable into one of the 6 categories of the primary ordinal outcome.

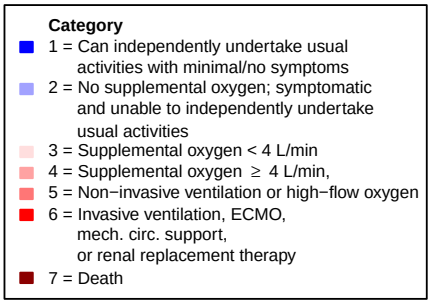
Program Name =mitt rdv ordprim3cat Create date=17-NOV-2022 Cut date=08-NOV-2022

Figure S24: ACTIV-3/TICO 7-Category Pulmonary Ordinal Outcome at Days 7, 14, and 28: Remdesivir Comparison

A. Pulmonary Ordinal Outcome on Day 7

		Remdesivir		Placebo	
Category		N	%	N	%
Better	1	0	0.0	1	2.3
	2	6	13.6	5	11.6
	3	1	2.3	3	7.0
	4	5	11.4	6	14.0
	5	7	15.9	5	11.6
Worse	6	24	54.5	18	41.9
	7	1	2.3	5	11.6
Total		44		43	

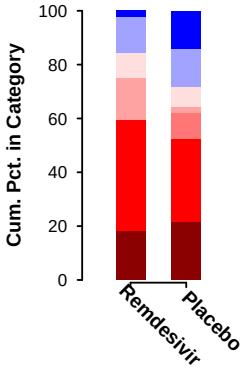


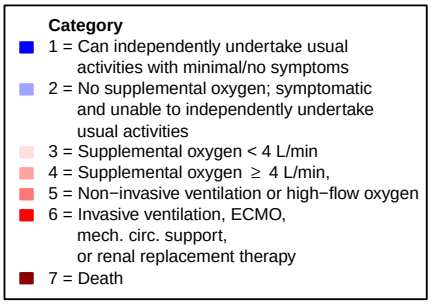


Summary OR (Remdesivir/Placebo):
1.04 (95% CI: 0.47 to 2.27); P=0.93
Test stratified by disease severity.

B. Pulmonary Ordinal Outcome on Day 14

		Remdesivir		Placebo	
Category		N	%	N	%
Better	1	1	2.3	6	14.3
	2	6	13.6	6	14.3
	3	4	9.1	3	7.1
	4	7	15.9	1	2.4
	5	0	0.0	4	9.5
Worse	6	18	40.9	13	31.0
	7	8	18.2	9	21.4
Total		44		42	

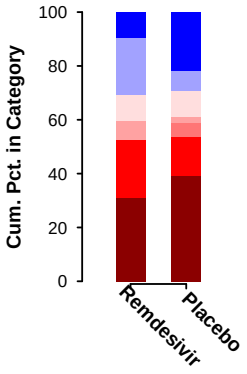


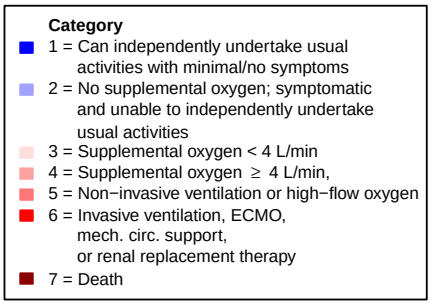


Summary OR (Remdesivir/Placebo):
0.79 (95% CI: 0.37 to 1.69); P=0.54
Test stratified by disease severity.

C. Pulmonary Ordinal Outcome on Day 28

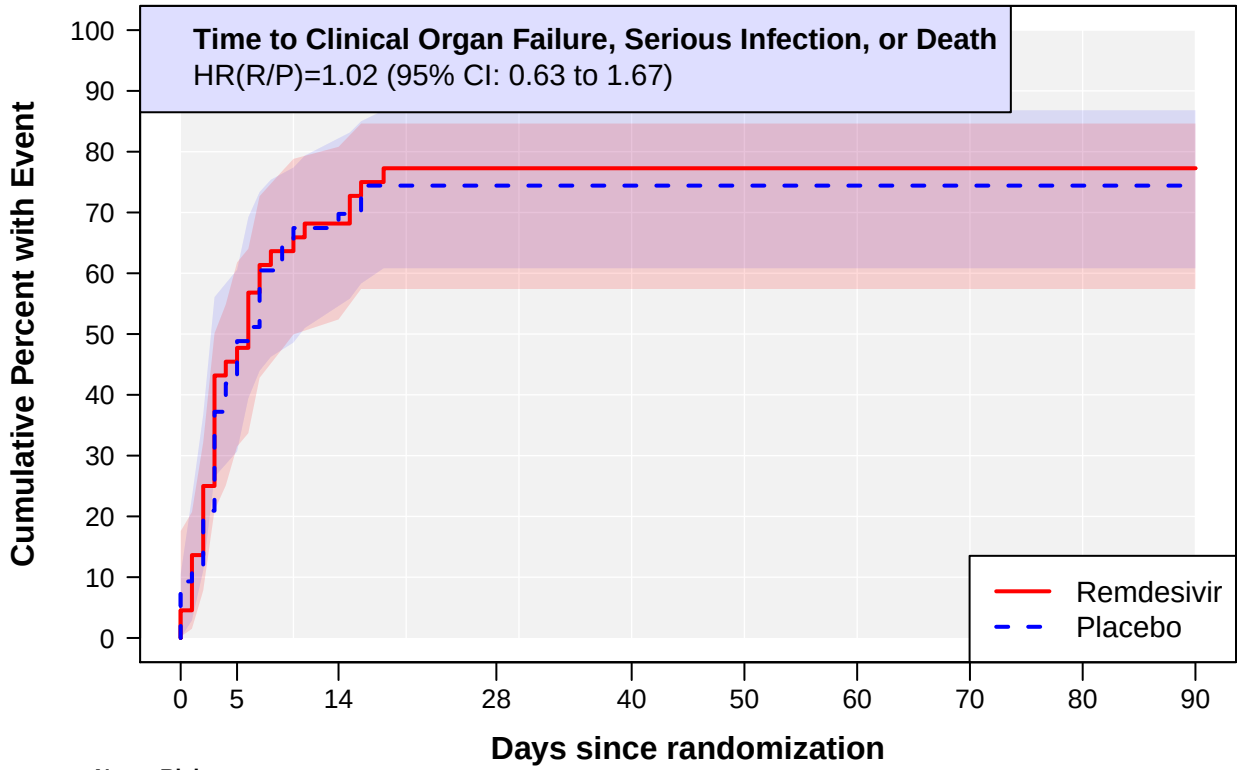
		Remdesivir		Placebo	
Category		N	%	N	%
Better	1	4	9.5	9	22.0
	2	9	21.4	3	7.3
	3	4	9.5	4	9.8
	4	3	7.1	1	2.4
	5	0	0.0	2	4.9
Worse	6	9	21.4	6	14.6
	7	13	31.0	16	39.0
Total		42		41	





Summary OR (Remdesivir/Placebo):
1.06 (95% CI: 0.49 to 2.29); P=0.88
Test stratified by disease severity.

Figure S25: Time to Clinical Organ Failure, Serious Infection, or Death Through Day 90: Remdesivir Comparison



No. at Risk:

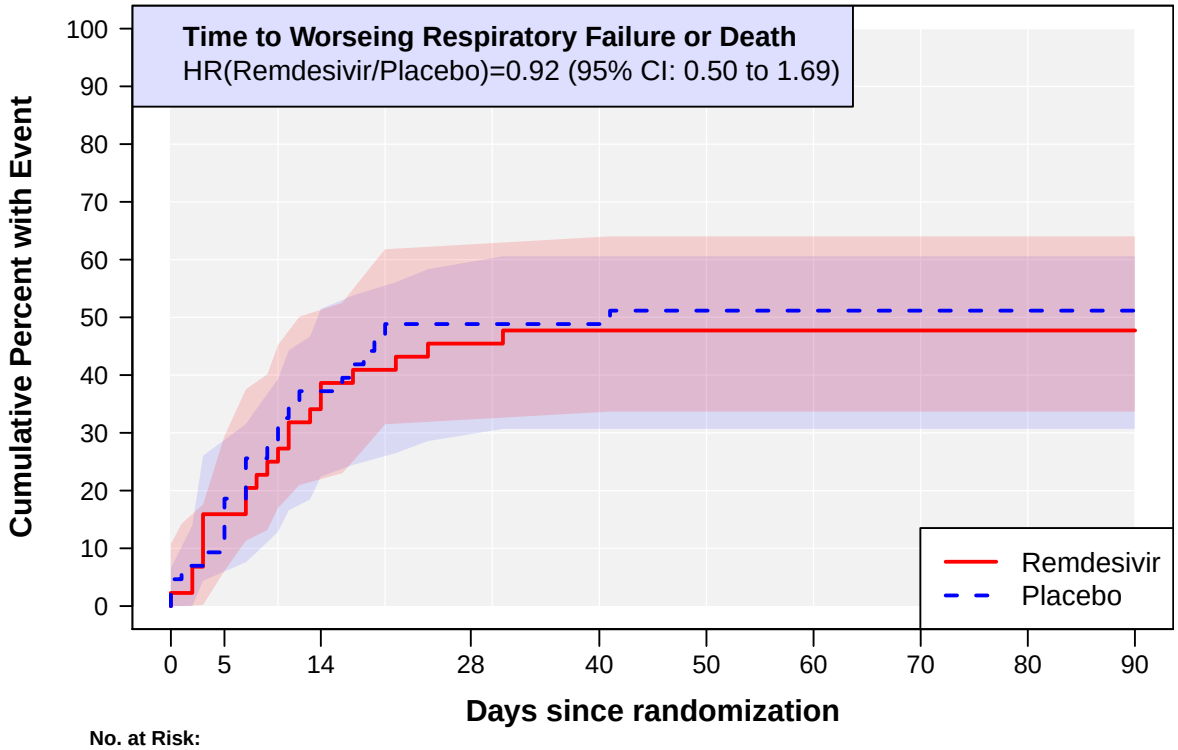
R:	44	24	14	10	10	10	10	10	10	10
P:	43	25	14	11	11	11	11	11	11	11

Estimated Cumulative Pct with an Event:

R:	47.7	68.2	77.3	77.3	77.3	77.3	77.3	77.3	77.3
P:	48.8	69.8	74.4	74.4	74.4	74.4	74.4	74.4	74.4

rdv_fig_t2psesedth.pdf File created=11/17/22 Data cutoff=11/08/22

Figure S26: Time to Worsening Respiratory Failure or Death Through Day 90: Remdesivir Comparison



No. at Risk:

R:	44	37	29	24	23	23	23	23	23	23
P:	43	39	27	22	22	21	21	21	21	21

Estimated Cumulative Pct with an Event:

R:		15.9	38.6	45.5	47.7	47.7	47.7	47.7	47.7	47.7
P:		18.6	37.2	48.8	48.8	51.2	51.2	51.2	51.2	51.2

rdv_fig_t2resp_fail.pdf File created=11/17/22 Data cutoff=11/08/22

Status at Entry	Progression through Day 90	Remdesivir (n= 44) N. in Grp	Remdesivir (n= 44) N. w/Event	Remdesivir (n= 44) Pct.	Placebo (n= 43) N. in Grp	Placebo (n= 43) N. w/Event	Placebo (n= 43) Pct.
HFNC/NIV	IMV	19	10	52.6	21	10	47.6
	ECMO		1	5.3		1	4.8
	IMV or ECMO		10	52.6		10	47.6
	IMV, ECMO, or Death		11	57.9		11	52.4
IMV	ECMO	23	0	0.0	22	1	4.5
	ECMO or Death		9	39.1		11	50.0
ECMO	Death	2	1	50.0			
Overall	**IMV or ECMO***	**42**	**10**	**23.8**	**43**	**11**	**25.6**
	IMV, ECMO, or Death	**44**	**21**	**47.7**	**43**	**22**	**51.2**
*HR** [95% CI] (Remdesivir/Placebo) worsening respiratory failure (IMV or ECMO) or death*						*0.92 [0.50 - 1.69]*	
*p-value**						*0.79*	

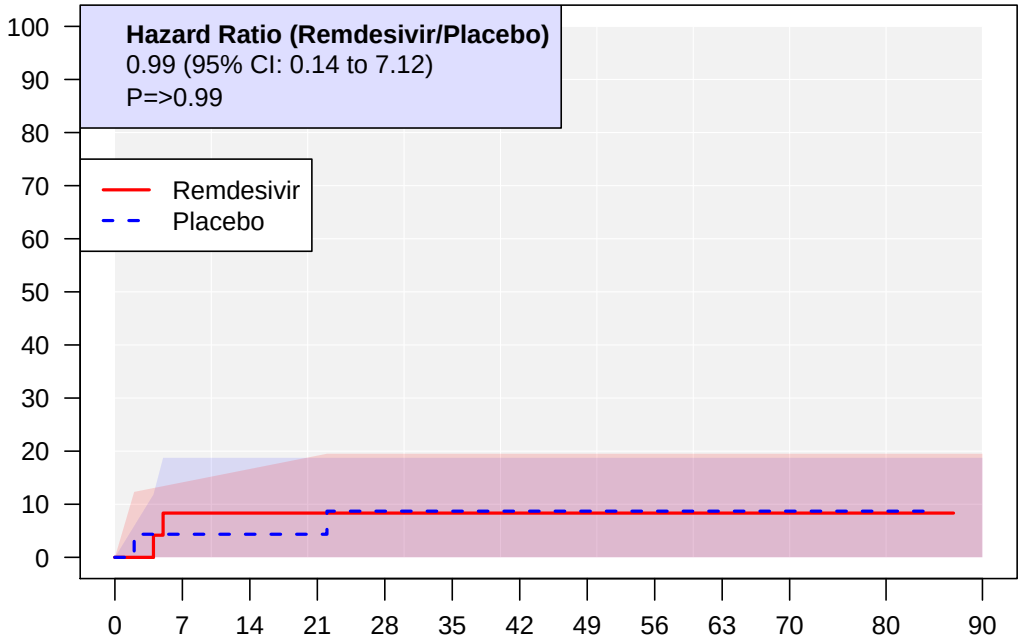
HFNC=High-flow nasal canula device, NIV=non-invasive ventilation, IMV=invasive mechanical ventilation, ECMO=extracorporal membrane oxygenation

*Risk set excludes participants on ECMO at entry.

**Hazard ratio from Cox regression model with 1 indicator for treatment group, stratified by disease severity.

Program Name =mitt rdv psese_resp_fail Create date=17-NOV-2022 Cut date=08-NOV-2022

Figure S27: Time to Hospital Readmission or Death After Initial Discharge: Remdesivir Comparison



No. at Risk:

Remdesivir:	24	22	21	20	20	20	20	20	20	18	16	8
Placebo:	23	22	22	22	20	19	17	16	16	16	14	8

Estimated Cumulative Pct with an Event:

Remdesivir:	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3
Placebo:	4.3	4.3	4.3	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7

rdv_fig_t2readmit.pdf File created=11/17/22 Data cutoff=11/08/22

Time to Hospital Readmission or Death, After Initial Discharge

'	RDV (n= 24)		Placebo (n= 23)				
	No. Evt	Pct	No. Evt	Pct.	HR[a] (R/P)	95% CI	P-value
Readmitted	2	8.3	1	4.3			
Died	0	0.0	1	4.3			
Readmitted or Died	2	8.3	2	8.7	0.99	0.14, 7.12	>0.99

[a]Hazard ratio (R vs P) for time to hospital readmission or death from a Cox proportional hazards regression model stratified by disease severity. HR < 1 indicates benefit to the RDV group.

Program Name =mitt rdv t2readmit Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S70: Infusion Reactions by Grade, Pooled Across Days 0-9: Remdesivir Comparison

	Remdesivir (no. infused= 44)				Placebo (no. infused= 43)			
Days 0-9 Infusion Reaction*	**Grade 1 N (%)**	**Grade 2 N (%)**	**Grade 3 N (%)**	**Grade 4 N (%)**	**Grade 1 N (%)**	**Grade 2 N (%)**	**Grade 3 N (%)**	**Grade 4 N (%)**
Altered per. of reality	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Angioedema	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anaphylaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bradycardia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Bronchospasm	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Chills	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Confusion	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diaphoresis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dizziness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Facial flushing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fever	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)
Headache	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Hypertension	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)
Hypotension	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	2 (5)	0 (0)	0 (0)
Hypoxia	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Itching	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mental status changes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Myalgia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Rash - non urticarial	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Shortness of breath	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tachycardia	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Throat irritation/tightening	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urticaria/hives	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Wheezing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other reaction	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Any of above	0 (0)	3 (7)	2 (5)	1 (2)	1 (2)	4 (9)	1 (2)	0 (0)

* Collected via checklist during and within 2 hours following the completion of administration of the blinded study medication. A participant with multiple *other* reactions is counted once according to highest grade of *other reaction* recorded.

Program Name =Day10 infr_reactions Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S71: Grade 3 or 4 AEs, SAEs, Organ Failure, Serious Infections, or Death through Day 5: Remdesivir Comparison

Events through Day 5	Remdesivir (n= 44) Pts.	Remdesivir (n= 44) Pct.	Placebo (n= 43) Pts.	Placebo (n= 43) Pct.	OR* (R/P)	95% CI*	P-value*	P-value**
Composite								
Death	1	2.3	4	9.3	0.21	0.02, 1.97	0.17	0.14
Death, SAE, or Clinical Organ Failure/ Serious Infection	21	47.7	21	48.8	0.91	0.39, 2.15	0.83	0.83
Death, SAE, Clinical Organ Failure/ Serious Infection, or Grade 4 AE***	21	47.7	22	51.2	0.82	0.35, 1.95	0.65	0.66
Death, SAE, Clinical Organ Failure/ Serious Infection, or Grade 3 or 4 AE* **	**25**	**56.8**	**25**	**58.1**	**0.89**	**0.37, 2.14**	**0.80**	**0.80**
Components								
Death	1	2.3	4	9.3				
SAE	1	2.3	0	0.0				
Clinical Organ Failure/Serious Infection	20	45.5	20	46.5				
Grade 4 AE***	7	15.9	9	20.9				
Grade 3 or 4 AE***	20	45.5	21	48.8				

* Logistic regression model, with 1 indicator for treatment group stratified by disease severity (severe vs critical).
** CMH test stratified by disease severity (critical vs. severe) , shown if at least 5 events
*** Includes AEs reported at any time after the first infusion started, during and after completion of the infusions.
Note, summary excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Program Name =mitt rdv rdv_day5safety Create date=17-NOV-2022 Cut date=08-NOV-2022

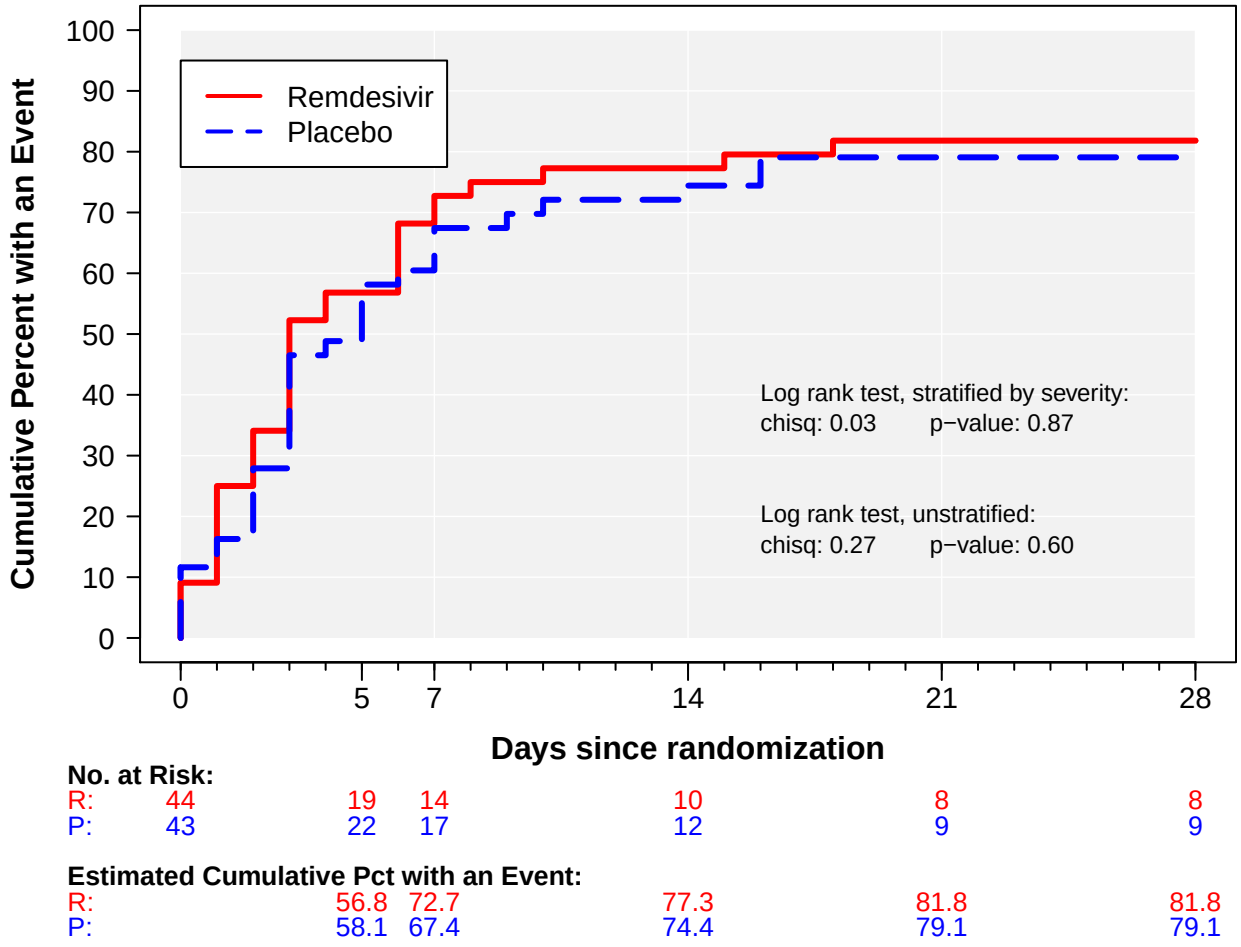
Table S72: Grade 3 or 4 AEs, SAEs, Organ Failure, Serious Infections, or Death Through Day 28: Remdesivir Comparison

Events through Day 28	Remdesivir (n= 44)		Placebo (n= 43)		HR* (R/P)	95% CI*	P-value*	P-value**
	Pts.	Pct.	Pts.	Pct.				
Composite								
Death	13	29.5	16	37.2	0.70	0.34, 1.46	0.34	0.40
Death, SAE, or Clinical Organ Failure/ Serious Infection	34	77.3	32	74.4	1.02	0.63, 1.66	0.93	0.81
Death, SAE, Clinical Organ Failure/ Serious Infection, or Grade 4 AE***	34	77.3	33	76.7	0.97	0.60, 1.57	0.90	0.98
Death, SAE, Clinical Organ Failure/ Serious Infection, or Grade 3 or 4 AE* **	**36**	**81.8**	**34**	**79.1**	**1.04**	**0.64, 1.67**	**0.88**	**0.80**
Components								
Death	13	29.5	16	37.2				
SAE	6	13.6	2	4.7				
Clinical Organ Failure/Serious Infection	32	72.7	30	69.8				
Grade 4 AE***	19	43.2	17	39.5				
Grade 3 or 4 AE***	27	61.4	29	67.4				

* Cox PH regression model, with 1 indicator for treatment group stratified by disease severity (severe vs critical).
** CMH test stratified by disease severity (severe vs critical).
*** Includes AEs reported at any time after the first infusion started, during and after completion of the infusions.
Note, summary excludes grade 3 or 4 AEs that were reported only on Day 0 pre-infusion but not thereafter.

Program Name =mitt rdv rdv_day28safetydata Create date=17-NOV-2022 Cut date=08-NOV-2022

Figure S28: Time to Grade 3 or 4 AE, SAE, Clinical Organ Failure, Serious Infection, or Death Through Day 28: Remdesivir Comparison



No. at Risk:

R:	44	19	14	10	8	8
P:	43	22	17	12	9	9

Estimated Cumulative Pct with an Event:

R:	56.8	72.7	77.3	81.8	81.8
P:	58.1	67.4	74.4	79.1	79.1

rdv_fig_day28safetydata.pdf File created=11/17/22 Data cutoff=11/08/22

Table S73: SAEs, Organ Failure, Serious Infections, or Death Through Day 90: Remdesivir Comparison

Events through Day 90	Remdesivir (n= 44) Pts.	Remdesivir (n= 44) Pct.	Placebo (n= 43) Pts.	Placebo (n= 43) Pct.	HR* (R/P)	95% CI*	P-value*	P-value**
Composite								
Death	17	38.6	20	46.5	0.74	0.39, 1.42	0.37	0.45
Death or SAE	22	50.0	20	46.5	1.05	0.57, 1.92	0.88	0.73
Death or Clinical Organ Failure/ Serious Infection	34	77.3	32	74.4	1.02	0.63, 1.66	0.93	0.81
Death, SAE, or Clinical Organ Failure/Serious Infection	**35**	**79.5**	**32**	**74.4**	**1.06**	**0.65, 1.71**	**0.82**	**0.76**
Components								
SAE	9	20.5	2	4.7				
Clinical Organ Failure/ Serious Infection	32	72.7	30	69.8				

* Cox PH regression model, with 1 indicator for treatment group stratified by disease severity (severe vs critical).

** CMH test stratified by disease severity (severe vs critical).

Program Name =mitt rdv safetyfulldata_day90 Create date=17-NOV-2022 Cut date=08-NOV-2022

Table S74: SAEs Through Day 90, by SOC: Remdesivir Comparison

SAEs through Day 90	Remdesivir (n= 44) N. Pts w/Event	Remdesivir (n= 44) Pct.	Placebo (n= 43) N. Pts w/Event	Placebo (n= 43) Pct.	P-value*	P-value**
MedDRA System Organ Class						
Blood and lymphatic system	0	0.0	0	0.0		
Cardiac	0	0.0	0	0.0		
Congenital, familial, genetic	0	0.0	0	0.0		
Ear and labyrinth	0	0.0	0	0.0		
Endocrine	0	0.0	0	0.0		
Eye	0	0.0	0	0.0		
Gastrointestinal	0	0.0	0	0.0		
General and administration site	0	0.0	0	0.0		
Hepatobiliary	0	0.0	0	0.0		
Immune system	0	0.0	0	0.0		
Infections and infestations	1	2.3	0	0.0		
Injury, poisoning, procedural complications	0	0.0	0	0.0		
Investigations	1	2.3	0	0.0		
Metabolism and nutrition	0	0.0	0	0.0		
Musculoskeletal and connective tissue	0	0.0	0	0.0		
Neoplasms benign, malignant, unspecified	0	0.0	0	0.0		
Nervous system	0	0.0	0	0.0		
Pregnancy, puerperium, perinatal	0	0.0	0	0.0		
Product issues	0	0.0	0	0.0		
Psychiatric	1	2.3	0	0.0		
Renal and urinary	0	0.0	0	0.0		
Reproductive and breast	0	0.0	0	0.0		
Respiratory, thoracic, mediastinal	5	11.4	2	4.7	0.29	0.25
Skin and subcutaneous tissue	1	2.3	0	0.0		
Social circumstances	0	0.0	0	0.0		
Surgical and medical procedures	0	0.0	0	0.0		
Vascular	1	2.3	0	0.0		
Code pending	0	0.0	0	0.0		
Any of the above	**9**	**20.5**	**2**	**4.7**	**0.050**	**0.027**
Any of the above (stratified p-value)					**0.039**	**0.019**

*P-value using Fine-Gray model with death as competing risk, unstratified test. Shown if at least 5 events.
**Unstratified CMH test, shown if at least 5 events.

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Table S75: Organ Failure and Serious Infections Through Day 90, by Type: Remdesivir Comparison

Clinical Organ Failure or Serious Infections through Day 90	Remdesivir (n= 44)			Placebo (n= 43)				
	N in Grp	N. Pts w/Event	Pct.	N in Grp	N. Pts w/Event	Pct.	P-value*	P-value**
Event								
1. Myocardial infarction	44	0	0.0	43	2	4.7		
2. Congestive heart failure III/IV	44	1	2.3	43	0	0.0		
3. Hypotension, w/vasop	44	18	40.9	43	21	48.8	0.48	0.46
4. Myocarditis	44	0	0.0	43	0	0.0		
5. Pericarditis	44	0	0.0	43	0	0.0		
6. Atrial tachyarrhythmias	44	4	9.1	43	3	7.0	0.72	0.72
7. Ventricular tachyarrhythmias	44	2	4.5	43	4	9.3	0.38	0.38
8. Bleeding	44	2	4.5	43	2	4.7		
9. DIC	44	0	0.0	43	1	2.3		
10. Thromboembolic events	44	9	20.5	43	10	23.3	0.78	0.75
11. Hepatic decompensation	44	4	9.1	43	2	4.7	0.45	0.42
12. Intercurrent disease, non SARS-CoV-2	44	17	38.6	43	16	37.2	0.88	0.89
13. Delirium	44	8	18.2	43	2	4.7	0.07	0.049
14. Cerebrovascular event	44	1	2.3	43	1	2.3		
15. Encephalitis	44	1	2.3	43	0	0.0		
16. Meningitis	44	0	0.0	43	0	0.0		
17. Myelitis	44	0	0.0	43	0	0.0		
18. Transient ischemic event	44	0	0.0	43	0	0.0		
19. New requirement for RRT***	42	10	23.8	42	5	11.9	0.16	0.16
20. Worseing respiratory failure	42	10	23.8	43	11	25.6	0.91	0.85
New requirement for IMV***	19	10	52.6	21	10	47.6	1.00	0.75
New requirement for ECMO***	42	1	2.4	43	2	4.7		
Any of the above	**44**	**32**	**72.7**	**43**	**30**	**69.8**	**0.73**	**0.76**
Any of the above (stratified p-value)							**0.87**	**0.79**
Any PSESE or death	**44**	**34**	**77.3**	**43**	**32**	**74.4**	**0.77**	**0.76**
Any PSESE or death stratified p-value							**0.93**	**0.81**

* P-value using Fine-Gray model with death as competing risk, unstratified test. Shown if at least 5 events. P-value for composite of any PSESE or death from Cox model.

** Unstratified CMH test, shown if at least 5 events.

*** Participants requiring RRT, IMV, or ECMO at baseline are excluded from the risk set for incident RRT, IMV or ECMO, respectively.

RRT=renal replacement therapy, IMV=invasive mechanical ventilation, ECMO=extracorporal membrane oxygenation

Program Name =mitt rdv psese_day90 Create date=17-NOV-2022 Cut date=08-NOV-2022

8 Protocol

The TESICO protocol had three versions. In this section are the original protocol (V1.0), final protocol(V3.0), and itemized changes between the versions.

Original - Version 1.0

- TESICO master protocol, V1.0 15 March 2021, corrected 01 April 2021
- Aviptadil Appendix H1, V1.0 15 March 2021, corrected 01 April 2021
- Remdesivir Appendix H2, V1.0 15 March 2021, corrected 01 April 2021

Final - Version 3.0

- TESICO master protocol, V3.0 08 March 2022
- Aviptadil Appendix H1, V3.0 08 March 2022
- Remdesivir Appendix H2 did not change from V1.0

Changes Between Versions

- Version 1.0 to Version 2.0
- Version 2.0 to Version 3.0

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

Short Title: *Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO)*

INSIGHT Protocol Number: 015 / ACTIV-3b

Version: 1.0, 15 March 2021

(corrections made 01 April 2021)

Funded by the USG COVID-19 Therapeutics Response through National Heart, Lung, and Blood Institute (NHLBI) and National Institute for Allergy and Infectious Disease (NIAID), National Institutes of Health (NIH),

sponsored by NIAID,

and carried out by a collaboration of

International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

Prevention and Early Treatment of Acute Lung Injury (PETAL) Network

Cardiothoracic Surgical Trials Network (CTSN)

Department of Veterans Affairs, USA

INSIGHT consists of the University of Minnesota (INSIGHT Statistical and Data Management Center (SDMC) in collaboration with six International Coordinating Centers (ICCs)

-Centre of Excellence for Health, Immunity and Infection (CHIP), Rigshospitalet, University of Copenhagen - Copenhagen, Denmark

-Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL) - London, United Kingdom

-The Kirby Institute, University of New South Wales - Sydney, Australia

-The Institute for Clinical Research at the Veterans Affairs Medical Center - Washington, D.C., United States of America (US)

-Department of Veterans Affairs, USA

-Division of Clinical Research, NIAID, USA

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1 Protocol Summary

DESIGN

TESICO (Therapeutics for Severely Ill Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of investigational agents aimed at improving outcomes for patients with acute respiratory failure related to COVID-19. The focus in this master protocol, a sister protocol to the TICO master protocol, is on patients with critical respiratory failure (i.e., those receiving high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or ECMO to treat acute hypoxemic respiratory failure caused by SARS-CoV-2 pneumonia).

Trials within this protocol will be adaptive, randomized, blinded and initially placebo-controlled. Participants will receive standard of care (SOC) treatment as part of this protocol. If an investigational agent shows superiority over placebo, SOC for the study of future investigational agents may be modified accordingly.

The international trials within this protocol will be conducted in up to several hundred clinical sites. Participating sites are affiliated with networks funded by the United States National Institutes of Health (NIH) and the US Department of Veterans Affairs.

The protocol is for a phase III randomized, blinded, controlled platform trial that allows investigational agents to be added and dropped during the course of the study for efficient testing of new agents against control within the same trial infrastructure. When more than one agent is being tested concurrently, participants may be randomly allocated across agents (as well as between the agent and its placebo) so the same control group can be shared, when feasible. In some situations, a factorial design may be used to study multiple agents.

The primary endpoint is a 6-category ordinal outcome that assesses the recovery status of the patient at Day 90. The categories of the ordinal outcome, from best to worst, start with 3 categories of “recovery” defined by the number of days alive at home and not on new supplemental oxygen, followed by 3 categories for “not recovered” defined as a) discharged but not to home or at home but still requiring continued new supplemental oxygen, b) hospitalized or receiving hospice care, and c) death at day 90. The definition of home will be operationalized as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this protocol.

DURATION

Participants will be followed for 90 days following randomization for the primary endpoint and most secondary endpoints. Selected secondary endpoints will be measured at 180 days.

SAMPLE SIZE

This Phase III trial is planned to provide 80% power to detect an odds ratio of 1.5 for improvement in recovery status at Day 90 for an investigational agent versus placebo with use of the ordinal outcome. The planned sample size is 640 participants (320 per group) for each investigational agent / placebo. Sample size may be re-estimated before enrollment is complete based on an assessment of whether the pooled proportions of the outcome are still

consistent with adequate power for the hypothesized difference measured by the odds ratio.

POPULATION — All participants enrolled will include inpatient adults (≥18 years) who have documented SARS-CoV-2 infection within 14 days of enrollment and are receiving high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO at enrollment, in whom the current respiratory failure is thought to be due to SARS-CoV-2 infection and in whom respiratory support was initiated within 4 days prior to randomization.

STRATIFICATION — Randomization will be stratified by study site pharmacy and by receipt of invasive mechanical ventilation or ECMO at enrollment. Other agent-specific stratification factors may be considered.

REGIMEN — Investigational agents suitable for testing in the inpatient setting will be prioritized based on in vitro data, preclinical data, phase I pharmacokinetic and safety data, and clinical data from completed and ongoing trials. In some cases, a vanguard cohort/initial pilot phase may be incorporated into the trial.

MONITORING — An independent DSMB will review interim safety and efficacy data at least monthly. Pre-specified guidelines will be established to recommend early stopping of the trial for evidence of harm or substantial efficacy. The DSMB may recommend discontinuation of an investigational agent if the risks are judged to outweigh the benefits.

2 Introduction

2.1 Study rationale

COVID-19 is a respiratory disease caused by a novel coronavirus (SARS-CoV-2). While most cases are mild or asymptomatic, progressive disease can result in hospitalization, requirement for mechanical ventilation, and substantial morbidity and mortality.[1] While the most common mode of disease progression is progressive respiratory failure following the development of pneumonia, other severe complications including thrombosis and ischemia are increasingly recognized.[2,3] Patients with respiratory failure, which in COVID-19 is likely best termed Acute Respiratory Distress Syndrome (ARDS), have extremely high morbidity and mortality. Novel treatments for these patients are an urgent clinical and public health need. (We use the term ARDS interchangeably with acute respiratory failure in this master protocol.)

Several clinical trials utilizing novel drugs and repurposing older agents have been implemented to investigate the treatment of adults hospitalized with severe or critical COVID-19 (see section 2.2.6). Standard-of-care is hence rapidly evolving (see Appendix I for current recommendations).

2.2 Background

2.2.1 SARS-CoV-2 Infection and Coronavirus Disease 19 (COVID-19)

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. A novel coronavirus was rapidly identified by sequencing and named SARS-CoV-2, and the illness caused by infection with SARS-CoV-2 has been named COVID-19.[4] While SARS-CoV-2 mostly causes a mild respiratory illness, some individuals, particularly those who are elderly[5,6] and have comorbidities,[7] may progress to severe disease requiring hospitalization, mechanical ventilation in intensive care units, and death. As of 5 October 2020, less than seven months following the declaration of a pandemic on 11 March 2020 by the World Health Organization (WHO), there have been more than 35 million cases diagnosed and more than 1 million deaths worldwide.[1] Over 300,000 cases continue to be reported daily.[5]

2.2.2 Natural history of COVID-19

SARS-CoV-2 has a median incubation period of 4 days (interquartile range [IQR] 2-7 days)[8] and the mean serial interval defined as the time duration between a primary case-patient (infector) having symptom onset and a secondary case-patient (infectee) having symptom onset for COVID-19 was calculated as 3.96 (95% confidence interval [CI] 3.53–4.39) days.[9] COVID-19 illness is predominantly a respiratory disease typified by upper respiratory symptoms in mild cases and pneumonia and ARDS in advanced disease. Initial symptoms typically involve the upper respiratory tract with cough, sore throat and malaise. Fever is present in approximately 44-98% of cases. Notably, persons with COVID-19 often experience loss of smell and taste.[10]

Complications of COVID-19 illness include cytopenias (lymphopenia, thrombocytopenia and anemia), and acute cardiac events (elevated troponin, changes on electrocardiogram), vasopressor-dependent shock, acute kidney injury and dialysis-dependent renal failure, liver impairment, and neurological events including acute cerebrovascular events, impaired consciousness, muscle injury and thrombotic events.

In most patients (approximately 80%) symptoms resolve without the need for intervention within five to seven days of symptom onset up to a maximum of 14 days. However,

approximately 20% of patients show signs of clinical disease progression, most notably pneumonia, around day 3 to 8 following symptom onset. Other manifestations of disease progression include thrombotic episodes including stroke and myocardial infarction (MI). This resembles the documented 6-8 fold excess risk of thrombosis when patients are infected with influenza virus.[11]

A proportion of those who progress then further deteriorate, including with the development of ARDS around 1-5 days after onset of respiratory symptoms.[6,12-14] Acute kidney injury necessitating dialysis and failure of other organs may also occur at this severe stage of disease.

Of the nearly 1,099 persons described in the Wuhan cohort, 16% had severe disease at presentation; 67 persons (6%) reached a composite primary endpoint of intensive care admission, mechanical ventilation or death.[9,15] As described below, outcomes for those requiring mechanical ventilation and with other manifestations of end-organ failure are poor, and treatments for such patients are critically needed.

In this protocol, we aim to enroll patients hospitalized for medical management of COVID-19, with acute respiratory failure, defined as the use of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or ECMO (extracorporeal membrane oxygenation).

2.2.3 Hospitalization of people with COVID-19

Countries and jurisdictions differ in the clinical management of COVID-19 patients. Early in the epidemic, faced with small numbers of infected persons, some resource-rich countries such as Singapore elected to admit all persons with COVID-19 regardless of symptom severity to facilitate strict isolation. Admission for reasons of public health or quarantine, rather than medical management, continues to be a requirement in some countries, notably in Asia. Elsewhere, it is more common for those with mild illness to be advised to self-isolate at home, while only those severely unwell are admitted for medical management.

Mortality rates for those who develop end-organ failure requiring intensive support, including those admitted to ICU, differ widely. Among 1,591 ICU patients from Lombardy, the region in Italy hardest hit by COVID-19, 88% required mechanical ventilation and 11% noninvasive ventilation.[14] The ICU mortality rate was 26%. Of 1,043 patients with available data, 709 (68%) had at least 1 comorbidity, 509 (49%) had hypertension, and 21% had cardiovascular disease. Younger patients (≤63 years) compared to older patients, had lower ICU mortality and higher rates of discharge from ICU. The median length of stay in the ICU was 9 days, though 58% remained in ICU at time of report.[16] In the United Kingdom, of the 4,078 COVID-19 patients admitted into critical care with reported outcomes, 50.7% died in ICU; those requiring advanced respiratory support and renal support had worse outcomes.[15] More recent mortality estimates among patients with COVID-19-associated ARDS range from 30–45%. These mortality estimates underline the importance of testing and implementing new effective treatments for these critically ill patients.

2.2.4 Viral kinetics of SARS-CoV-2 infection

Viral kinetic studies have demonstrated extensive SARS-CoV-2 viral replication in the pharynx just before and early after symptom onset.[17] Viral ribonucleic acid (RNA) shedding

from the pharynx gradually wanes as symptoms resolve, but viral RNA is still detectable weeks after symptom resolution.[18-20] Median duration of viral shedding was 20 days in survivors (longest 37 days), but SARS-CoV-2 was detectable until death in non-survivors.[7] Whether this is viable virus with the potential for continued transmission remains uncertain. RNAemia has been reported especially in more severe disease but is relatively rare among outpatients.[21-23] Viral detection in sputum is higher and outlasts pharyngeal swabs in those with pneumonia.[24] Persons with asymptomatic disease clear their virus faster than symptomatic individuals.[25]

The contribution of ongoing viral replication to disease progression in the most severe stage of COVID-19 (i.e., on ventilator or ECMO) is unclear, but one study reported that SARS-CoV2 viral loads were higher on admission and throughout the hospital course in patients who died,[26] a finding that matches well with evidence for impaired type-1 interferon responses with more severe COVID-19 illness.[27] SARS-CoV-2 viral RNA is also present in blood in large numbers of critically ill patients, with higher viral loads in blood among non-survivors than among survivors.[23] Distribution of virus in the body of severely ill patients is heterogeneous in both space and time, and even patients who die of COVID-19 ARDS may have high viral load in lung, especially in the first two weeks.[28]

2.2.5 COVID-19 ARDS, attributes and treatments

Notwithstanding the observed high viral loads, and progression of viral shedding from the upper to lower respiratory tract in those with progressive disease, the humoral immune response to SARS-CoV-2 appears variable and may be impaired.[29]

SARS-CoV-2 infection may also induce significant changes in elements of the cellular immune response. As the disease process progresses, the peripheral lymphocyte count typically declines. The depletion of peripheral lymphocytes likely reflects translocation to the pulmonary tissue. The extent that this influx is exclusively helpful to the host, or possibly may contribute adversely to disease severity is currently unclear. In severe cases this decline in CD4+ and CD8+ lymphocytes is also associated with an increase in activated CD4+ and CD8+ subsets, increases in key proinflammatory cytokines including interleukin 6 (IL-6), and increases in natural killer (NK) cells.[30,31] Trials assessing the use of various immunomodulatory agents with the aim of dampening this migration and systemic inflammation are underway, and may help to clarify this question.[32,33]

In addition, cohorts of patients with ARDS before COVID-19 (a physiology that is likely highly relevant to patients with COVID-19-associated ARDS) identify risks of ventilator-associated injury, immune depletion and associated risk of secondary infection, encephalopathy and delirium, dysfunctional repair mechanisms, oxidative stress, NETosis, surfactant dysfunction, impairment in GM-CSF and macrophage function, mitochondropathy, dysregulated microvascular thrombosis and shunting, myocardial suppression, and multiple other insults, which together contribute to the high morbidity and mortality in ARDS. One recent study provided detailed information on COVID-19 ARDS[34] and a recent review considers features of classical ARDS and selected issues related to COVID-19 ARDS.[35]

Phenotypic variability of ARDS is also well described in multiple cohorts, especially with sorting into inflammatory and pauci-inflammatory phenotypes.[36] While COVID-19 has a single underlying cause (SARS-CoV-2 infection), phenotypic variability has also been observed in COVID-19.[34,35,37] The relevance of such subtypes to possibly heterogenous treatment effects is as yet unknown.

Standard supportive care for ARDS from COVID-19 including lung protective ventilation, prone positioning and fluid conservative care is still the most important approach to reducing mortality and morbidity when COVID-19 patients develop ARDS.[35,38] The addition of dexamethasone for treatment of patients who are mechanically ventilated was effective in reducing mortality in the large pragmatic UK RECOVERY trial,[39] although several outstanding issues relate to glucocorticoids for severe COVID-19.[40]

2.2.6 Current treatment strategies for COVID-19

Hundreds of clinical trials have been completed or are underway to study the safety and efficacy of treatments for COVID-19. Treatments being studied include direct anti-viral treatments, including repurposed drugs found in vitro to have activity against SARS-CoV-2; immune modulators especially in patients with advanced disease; drugs to reduce inflammation, including corticosteroids, and modifiers of other pathophysiological pathways implicated in disease progression, including potentially anticoagulants and anti-platelet agents.

As results of randomized trials for these and other treatments become available and treatment guidelines are updated, standard of care (SOC) for hospitalized patients with COVID-19 will change. This may influence the background treatment recommended (or required) by this protocol and/or second line or supportive care treatments recommended by the protocol. To accommodate this fast-moving field Appendix I (which outlines the SOC to be recommended in addition to investigational agent or matched placebo) will be regularly updated.

Of note, whereas evidence supports use of the interventions outlined in Appendix I, the most optimal approach to applying these interventions remains uncertain, and is the subject of ongoing comparative effectiveness trials.

2.3 Investigational Agents

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) has formed an overarching “trial oversight committee (TOC)” for both ACTIV-2 (a parallel study assessing COVID-19 therapeutics in outpatients) and ACTIV-3 (the TICO master protocol and this paired TESICO master protocol). The TOC (and the agent selection committee) will select agents for study in the three protocols. Members of the protocol team (non-voting) and NIH are members of this committee. This committee reviews data for investigational agents and considers a number of factors relevant to the likely efficacy and safety of candidates for inclusion in the relevant protocols.

It is possible that several agents from different sources will be combined at some point in the conduct of this master protocol – but not initially. It is also possible that one agent will be identified as effective and then incorporated as SOC (providing there is good safety data and adequate supply of the agent).

Information on dosing, administration, supply and distribution, matching placebo, and any special considerations as far as inclusion/exclusion criteria and safety monitoring for each investigational agent studied as part of this protocol is outlined in an appendix (see Appendix H), including known benefits and risk, justification for dosing, and administration. The appendix will also include whether any aspects of study procedures outlined in this master protocol will need to be deviated from. The informed consent will describe any risks associated with the investigational agents.

In some cases, especially where additional data about safety and feasibility are desired, a vanguard cohort/pilot phase may be incorporated into a trial of a given investigational agent. Details of such vanguard cohorts—including design features, additional safety monitoring, and sample size—will be specified in the agent-specific appendix.

3 Risk/Benefit Assessment

3.1 Known Potential Risks

Potential risks of participating in this trial are those associated with the product, and these are described in an agent-specific appendix and in the sample informed consent. Other risks include having blood drawn, intravenous (IV) catheterization, and breach of confidentiality. Given the significant disease-related risks faced by this target population, there is felt to be a favorable risk/benefit profile, and significant risk acceptability.

3.1.1 Risks of Drawing Blood and IV Catheterization

Drawing blood may cause transient discomfort and, rarely, fainting. Fainting is usually transient and managed by having the participant lie down and elevate his/her legs. Bruising at the blood collection sites may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. IV catheterization may cause insertion site pain, phlebitis, hematoma formation, and infusate extravasation; less frequent but significant complications include bloodstream and local infections. The use of aseptic (sterile) technique will make infection at the site of blood draw or at catheterization less likely.

3.1.2 Risks due to Study Treatments

Infusions of investigational agents likely to be used in this protocol are generally well-tolerated, except in rare cases of existing allergy to the products infused. However, each agent may have associated risks, which will be specified in the relevant agent-specific appendix.

3.1.3 Risks to Privacy

Participants will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the participant's PHI. All source records including electronic data will be stored in secured systems in accordance with institutional policies and government regulations.

All study data that leave the site (including any electronic transmission of data) will be identified only by a coded number that is linked to a participant through a code key maintained at the clinical site. Names or readily identifying information will not be released. Electronic files will be password protected.

Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publication from this trial will not use information that will identify study participants. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the study monitor, other authorized representatives of the institutional review board (IRB), NIH, and applicable regulatory agencies (e.g. FDA).

3.2 Known Potential Benefits

While the trial is conducted to test the hypothesis that each investigational agent will improve participant status on an ordinal recovery outcome assessed at 90 days, the agents studied may or may not achieve these outcomes in any individual who participates in this trial. However, there is an anticipated benefit to society from a patient's participation in this trial, due to insights that will be gained about the investigational agent(s) under study as well as the natural history of the disease. While there may not be benefits for an individual, there will be benefits to society if a safe, efficacious therapeutic agent can be identified during this global COVID-19 outbreak.

4 Outcomes

This section describes the key outcome measures used in this phase III protocol.

4.1 Primary and Secondary Outcomes to Evaluate Efficacy and Safety

The primary endpoint is an ordinal outcome that assesses participant recovery status at Day 90. The primary ordinal endpoint is referred to as ***recovery***. The outcome includes 6 categories, consisting of 3 ranked categories of the number of days alive, at home, and not receiving new supplemental oxygen ***at Day 90*** (77 or more consecutive days, 49–76 days, or 1–48 days) as well as an additional 3 categories for patients who are not recovered at Day 90: (1) discharged from the hospital but either not yet home, or home but receiving new supplemental oxygen, (2) still hospitalized or receiving hospice care, or (3) dead.

Consistent with the TICO protocol (NCT04501978), *home* is defined as the level of residence or facility where the participant was residing prior to onset of COVID-19 leading to the hospital admission that led to enrollment in this protocol. Residence or facility groupings to define home are: 1) **Independent/community dwelling** with or without help, including house, apartment, undomiciled/homeless, shelter, or hotel; 2) **Residential care facility** (e.g., assisted living facility, group home, other non-medical institutional setting); 3) **Other healthcare facility** (e.g., skilled nursing facility, acute rehab facility); and 4) **Long-term acute care hospital** (hospital aimed at providing intensive, longer term acute care services, often for more than 28 days). Lower (less intensive) level of residence or facility will also be considered as home. By definition, "home" cannot be a "short-term acute care" facility. Participants previously residing in a "long-term acute care" hospital recover when they return to the same or lower level of care.

Since some patients will be receiving supplemental oxygen before their COVID-19 illness, we define new supplemental oxygen as any supplemental oxygen in participants who were not receiving supplemental oxygen before their COVID-19 illness or an increase in supplemental oxygen above pre-COVID-19 baseline among patients who were receiving supplemental oxygen before their COVID-19.

The "last-off" method for assessing recovery will be used, as has been customary in the use of similar ordinal endpoints in ARDS trials for decades. According to the "last-off" method, periods of recovery that are followed by hospital re-admission, change from home to a higher level of care, or receipt of new supplemental oxygen will *not be counted* toward the number of days of recovery. In other words, only days between the last time the patient entered a recovered state (returned home, free of new supplemental oxygen), and Day 90 are counted as days of recovery. The categories of the primary endpoint are displayed in Table 1.

Table 1 Categories of the primary endpoint

Category	Status at 90 days
1 (Best)	At home and off oxygen. No. of consecutive days at Day 90 ≥ 77
2	49-76
3	1-48
4	Not hospitalized AND either at home on oxygen OR not at home
5	Hospitalized for medical care OR in hospice care
6 (Worst)	Dead

Participants residing in a facility solely for public health or quarantine purposes will be considered as residing in the lowest level of required residence had these public health measures not been instated. If such patients are receiving new supplemental oxygen, they will not be classified as recovered.

4.1.1 Rationale for primary outcome

The primary ordinal endpoint, recovery, was selected given the high mortality in COVID-19 ARDS and the expectation that agents may have effects on both mortality and time to recovery among survivors. The common use of new supplemental oxygen after discharge (as high as 40% of discharged patients among ARDS patients in prior cohorts) and frequent rehospitalizations also motivated the structure of this endpoint.

The primary outcome is intended to identify relevant efficacy among investigational agents using an endpoint that is patient-centered, clinically relevant, and appropriately efficient.

Whereas mortality may be the most important ultimate outcome, the sample size to detect a plausible treatment effect for such an outcome would be much larger than outlined in this protocol. It was determined that use of a mortality-only endpoint would unduly increase the amount of time and resources necessary to make a determination of efficacy and was thus not feasible in current pandemic circumstances. Importantly, mortality was not considered to be the only relevant measure of efficacy in COVID-19—among survivors, the duration of recovery at Day 90, which also reflects length of hospitalization, is also an important benchmark. This position is consistent with decades of work in ARDS trials. Notably, while data specific to COVID-19 have not yet been generated, in general ARDS populations, a longer time to recovery has been associated with worse long-term outcomes, making recovery evaluated at Day 90 an important patient-centered endpoint.[41-44]

The primary outcome is assessed at 90 days of follow-up, which is longer than for other trials of investigational agents for COVID-19, which have typically been 28 days. The longer follow-up will allow better ascertainment of recovery from the longer-term consequences of the underlying disease, and hence the efficacy of the investigational agent. This is likely to be particularly true for the TESICO target population, who are critically ill. Based on data from COVID-19 observational cohorts and ARDS trials before the pandemic, it is also projected that excess mortality will be observed between Day 28 and Day 90. A single category of death at Day 90 is used for the worst category of the primary endpoint instead of time to death given the 90 day follow-up period. Time to death is a secondary endpoint.

4.1.2 Secondary outcomes

In addition to the primary endpoint, several secondary efficacy endpoints will be assessed. These endpoints will be assessed for all participants enrolled.

1. All-cause mortality through Day 90, dichotomous as well as time to death

2. (a) Composite endpoint that considers the number of days at home off oxygen and the time to death as well as the other categories of the primary ordinal outcome; (b) a dichotomous composite endpoint of alive and free of respiratory support at Day 90; (c) a three-category ordinal endpoint, measured at Day 90, that includes alive and free of respiratory support, alive and not free of respiratory support, and dead.

3. Time from randomization to recovery defined as alive, at home, and off oxygen (treating death as a competing risk).

4. Days alive outside of a short-term acute care hospital up to Day 90 (among survivors), using the “last off” method

5. Clinical organ failure or serious infections defined by development of any one or more of the following clinical events through Day 28 (see PIM for criteria for what constitutes each of these conditions; such conditions that existed at baseline are not counted):

    a. Cardiac and vascular dysfunction:
        1. Myocardial infarction
        2. Myocarditis or pericarditis
        3. Congestive heart failure: new onset NYHA class III or IV, or worsening to class III or IV
        4. Hypotension requiring institution of vasopressor therapy
        5. Atrial or ventricular tachyarrhythmias

    b. Renal dysfunction:
        1. New requirement for renal replacement therapy

    c. Hepatic dysfunction:
        1. Hepatic decompensation

    d. Neurological dysfunction
        1. Acute delirium
        2. Cerebrovascular event (stroke, cerebrovascular accident [CVA])
        3. Transient ischemic events (i.e., CVA symptomatology resolving <24 hrs)
        4. Encephalitis, meningitis or myelitis

    e. Haematological dysfunction:
        1. Disseminated intravascular coagulation
        2. New arterial or venous thromboembolic events, including pulmonary embolism and deep vein thrombosis
        3. Major bleeding events (>2 units of blood within 24 hours, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding).

f. Serious infection:
   1. Intercurrent, at least probable, documented serious disease caused by an infection *other than* SARS-CoV2, requiring antimicrobial administration and care within an acute-care hospital.

6. A composite of death, clinical organ failure or serious infections (see above) through Day 90.

7. Outcomes assessed in other treatment trials of COVID-19 for hospitalized participants in order to facilitate meta analyses and facilitate generation of norms, including an ordinal scale measuring the degree of oxygen support through Day 14, time to discharge from the initial hospitalization, and binary outcomes defined by worsening based on the worst 3 categories of the primary ordinal recovery outcome at day 90.

8. A composite of cardiovascular events (outcomes listed above in items 5a1, 5d2 and 5d3) and thromboembolic events (item 5e2) through Day 90.

9. Safety and tolerability as measured by
   a. A composite safety outcome of grade 3 and 4 clinical adverse events, SAEs, PSESEs (see 10.2.3), or death through Day 5 (*primary safety endpoint*) and through Day 28 (secondary safety endpoint)
   b. Infusion-related reactions of any severity
   c. Percentage of participants for whom the infusion was interrupted or stopped prior to completion for any reason and separately for an adverse event
   d. A composite of hospital readmissions or death through 90 days.

4.1.3 Rationale for secondary outcomes

The main secondary outcomes for the TESICO trial are constituents of the primary outcome (mortality, time to death, number of days home off oxygen) or closely related to them (days alive outside of the hospital. In addition, given the evolving information about the effects of COVID-19 outside of the lungs, measuring organ failure is important to understand the full range of COVID-19. Given that secondary infections are common among ARDS patients, including those with ARDS from COVID-19, measuring and monitoring secondary infections is also important to understanding the full scope of the effect of a COVID-19 therapeutic agent. In addition, the importance of understanding COVID-19 epidemiology (and supporting potential meta-analyses) across the range of therapeutic trials mandates collection of outcomes relevant to the calculation of endpoints from other trials. The rationale for the safety outcomes collected is presented in Section 10. If a specific secondary outcome is to be added for a given investigational agent, that additional outcome will be specified in the corresponding Appendix H.

5 Objectives

5.1 Primary Objective

The primary objective of this protocol is to determine whether investigational agents are safe and superior to control (initially and primarily placebo) when given with SOC for the

primary endpoint of recovery (based on a 6-category ordinal outcome) evaluated at 90 days after randomization.

SOC may be modified (updated based on data from this or other trials) during the course of evaluating different investigational agents with this master protocol. SOC may also be studied in this master protocol along with investigational agents if data from trials indicate that efficacy is uncertain for this target population of patients with COVID-19 ARDS.

5.2 Secondary Objectives

Three key secondary objectives are to compare each investigational agent with control for time to mortality (censored at 90 days), a composite endpoint that considers the number of days at home off new supplemental oxygen and the time to death as well as the other categories of the primary ordinal outcome, and time to recovery defined as alive, at home, and off new supplemental oxygen.

Other secondary objectives are to compare each investigational agent with control for the secondary outcomes listed in section 4.

In addition, the primary ordinal endpoint of recovery will be evaluated for subgroups defined by the following characteristics measured at enrollment:

- Receipt of invasive mechanical ventilation or ECMO
- Age
- Biological sex
- Race/ethnicity
- Type of residence/facility (home)
- Body mass index (BMI)
- History of chronic conditions (cardiovascular disease, diabetes, asthma, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, hepatic impairment, or cancer)
- Geographic location
- Duration of symptoms prior to enrollment
- Concomitant treatments (including other randomized treatments) at enrollment
- SARS-CoV-2 vaccination status at baseline
- Disease progression risk score (defined using pooled treatment groups with the following baseline predictors of the primary outcome (recovery evaluated at 90 days): age, biological sex, duration of symptoms, receipt of invasive mechanical ventilation or ECMO, and presence of chronic health conditions.

6 Study Design

TESICO (Therapeutics for Severely Ill Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of multiple investigational agents for COVID-19 ARDS. Master protocols can be a more efficient approach to the evaluation of multiple experimental interventions for a single disease such as COVID-19 in a continuous manner.

The trial described in this master protocol is a phase III randomized, blinded, controlled platform trial that allows investigational agents to be added and dropped during the study for efficient testing of new agents against placebo within the same trial infrastructure. When more than one agent is being tested concurrently, participants will be randomized across agents, as well as to agent/control. This general approach will allow rapid testing of multiple

agents as the pooling of controls across agents requires fewer patients to be randomized to the matched control arm of each agent. However, this will only occur when feasible and when multiple agents are available to be tested at the same time. If an investigational agent shows superiority over placebo + SOC as initially defined, SOC for future investigational treatment evaluations will be modified accordingly.

In some cases, more than one dose of an investigational agent will be studied. For such agents, specific details of the dose selection will be outlined in the relevant Appendix H.

6.1 Randomization and Stratification

Patients will be equally allocated to each investigational agent + SOC or to placebo + SOC. For example, for a study of a single investigational agent, participants will be randomized in a 1:1 ratio to the investigational agent + SOC or to placebo + SOC. If a participant is eligible for two investigational agents, the allocation will be 1:1:1 to investigational agent A + SOC, agent B + SOC, or placebo + SOC. Because the two investigational agents (A and B) may require different placebos (for example, when infusion volumes or route of administration differ), the 1:1:1 allocation ratio will be achieved through a two-step randomization procedure: in *step 1*, the participant is randomized 2:1 to "active" versus "placebo"; in *step 2*, the participant is randomized 1:1 to A versus B. With k agents, this can be viewed as an initial k:1 allocation to "active" versus "placebo", followed by a second, even allocation to one of the available agents (for example, if a participant was allocated to "placebo" in step 1, then the step 2 allocation will be 1:1 to "agent-specific placebo for A" versus "agent-specific placebo for B"). Sites will be informed of the specific investigational agent/placebo (e.g., A or B) to which the participant was randomized (see section 6.2) but not whether the patient is receiving active agent versus placebo. For the analysis, the concurrent agent-specific placebo groups will be pooled, resulting in a 1:1 allocation ratio for comparing each investigational agent versus the (pooled) placebo group.

If investigational agents are added or dropped, the allocation ratio to active versus placebo will be appropriately modified, and overall sample size will be recalculated as appropriate.

Randomization will be stratified by study site pharmacy (several clinical sites may share one study site pharmacy) and receipt of invasive mechanical ventilation or ECMO at entry. Within each randomization stratum, mass-weighted urn randomization[45] will be used to generate the active and placebo assignments. This will ensure throughout the trial placebo allocation near the intended ratio while also ensuring near equal numbers of active and matched placebo assignments to each agent.

If more than one investigational agent is being compared with placebo and they have different contraindications, consideration will be given to allowing participants to enter with randomization to each agent versus placebo separately as well as randomization to both agents. If the number of participants expected to have a contraindication is small, they will be excluded from the trial rather than establishing a separate randomization mechanism. Comparisons will be of each investigational treatment against its control arm. The control arm consists of all participants who were "at risk" for being randomized to the investigational agent but were randomized to a control group instead. This concept is relevant when the randomization includes investigational agents with different eligibility criteria or introduction into the platform trial at different time points. Formal randomization includes a matched placebo group for each agent, and the placebo groups will be pooled

across agents, but only participants who (1) were eligible for the investigational agent under consideration, and (2) were randomized contemporaneously and at participating sites will be included in the control group for a given agent.

The default randomization allocation to agent (or its placebo) for which a participant is eligible is as outlined above. However, in some circumstances this allocation ratio may be changed by the (blinded) protocol leadership based on an overall assessment of how the master protocol framework is able to produce relevant and novel findings most effectively. In addition, some agents may undergo factorial randomization with other agents. Such details will be specified in the relevant agent-specific appendix.

6.2 Blinding

Investigational agents or placebo (as necessary) will be prepared by a pharmacist who is not blinded to the treatment assignment. All other study staff, including those at sites, and those in roles spanning multiple sites or spanning the protocol as a whole, will be blinded unless otherwise specified herein.

For investigational agents infused, blinding of the participant and clinical staff may be achieved by placing a colored sleeve over the infusion bags used for investigational agents and placebos. Placebo will consist of an isotonic crystalloid, referred to as an isotonic saline solution.

When more than one investigational agent is available for randomization, the clinical staff will be informed to which investigational agent/placebo the participant was randomly assigned for infusion, but they will remain blinded to whether the random assignment was to the active investigational agent or matching placebo.

If the blind is broken, whether by accident, or for safety reasons, this will be recorded, and the protocol chair will be notified of the event. In that situation, every attempt will be made to minimize the number of people unblinded. Specific unblinding procedures and instructions are found in the PIM.

6.3 Sample size assumptions

All sample size calculations are aimed at pairwise comparisons between a given investigational agent and its control arm. The following assumptions were made in estimating the required sample size for this phase III trial.

a. The primary analysis will be intention to treat.
b. A proportional odds model will be used to compare recovery at Day 90 for the investigational agent and placebo.
c. Patients will be assigned the worst category that applies at Day 90.
d. The “last-off” method (for return to home and liberation from new supplemental oxygen) is used to calculate days of recovery among those who are recovered on Day 90.
e. Approximately 80% of patients will enter the trial on high-flow nasal oxygen, while approximately 20% will enter with non-invasive or invasive mechanical ventilation or ECMO. Control-group event rates for these patients are based on findings from ACTT-1, the Intermountain Prospective COVID Registry (IPOC), ISARIC, and other data sources. This includes estimates of the percentage of patients in each category of respiratory support (i.e., high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO) at baseline.[46]

f. Most patients will be discharged in the first month after randomization; based on ACTT-1 and PETAL Network data, we estimate 25% will be discharged to their home and stay home for 14 days by day 28 following randomization; half of these patients will be discharged to their home on oxygen; and most will receive oxygen for 3-4 weeks. Thus, the category 1 percentage is approximately 12% considering re-initiation of home oxygen and re-hospitalization.
g. Categories 2 and 3 are wider and also consider home oxygen re-initiation and re-hospitalization.
h. Three categories of time at home off oxygen were considered because an intervention that shortened time on new supplemental oxygen and also decreased mortality was considered clinically relevant.
i. Based on data from PETAL Network and Intermountain Healthcare, 33% of participants will die by Day 90. A single category is used for death at Day 90 instead of time of death given the target population and planned follow-up.
j. At Day 90 < 10% of patients will be in the hospital; and about 10% will be on oxygen or not at home.
k. With type 1 error of 0.05 (2-sided) and 80% power to detect the OR of 1.5, sample size is 602. This is increased to 640 (320 in each group) to allow for a small percentage of patients who withdraw consent or are lost to follow-up before Day 90.

The estimated control and treatment arm distribution of endpoint categories used to calculate sample size and power is displayed in Table 2.

Table 2 Estimated Distribution of Endpoint Categories Used for Power Calculation

Category	Status at 90 days	Investigational Agent (%)	Control (%)
1	At home and off oxygen. No. consecutive days at Day 90 ≥ 77	17.0	12.0
2	49-76	27.7	23.0
3	1-48	17.2	17.0
4	Not hospitalized AND either at home on oxygen OR not at home	9.1	10.0
5	Hospitalized for medical care OR in hospice care	4.3	5.0
6	Dead	24.7	33.0
	Total	100.0	100.0

Sample size may be re-estimated before enrollment is complete to determine whether the pooled proportions are still consistent with 80% power to detect an OR 1.5.

6.4 Schedule of Assessments

Participants will be randomized and start therapy on Day 0. The primary endpoint and most secondary endpoints will be measured through Day 90. After Day 90 results are completed, data will be unblinded to allow expeditious reporting of primary results. In addition, all

participants randomized will be followed through 180 days following randomization for collection of study data (Appendix B and section 9.1 for details).

6.5 Approach to Intercurrent Therapies and Clinical Trial Co-enrollment

In general, the study will take a pragmatic approach to the use of intercurrent, concomitant medications. Sponsor and/or protocol leadership may, based upon convincing new evidence, act in the interest of participant protection, and in avoidance of confounding, to exclude/disallow use of any specific concomitant therapy found to be reasonably contraindicated for a well-defined portion of the study population (see Appendix I). Such a determination may be made, communicated, and implemented by a Protocol Clarification Memo until it is reasonable to amend the protocol for other reasons.

Coenrollment in other trials will only be allowed where a coenrolling trial has been approved by trial leadership for coenrollment.

The protocol leadership will use the following principles to judge the appropriateness of a trial for which co-enrolment will be allowed.

1. Trials involving interventions that are contraindicated in combination with a TESICO investigational agent are not permitted (see Appendix H for details of possible contraindications for each investigational agent).

2. Study procedures of the co-enrolling trial must not impose an undue burden on research participants or research staff when viewed within the context of TESICO study procedures. For example, volume of blood drawn for research purposes must not be excessive when added to the volume drawn for study procedures.

3. With the exception of TICO, participation in the TESICO trial will be treated as the principal trial for the study participant, and study procedures for TESICO will be prioritized.

4. With the exception of TICO, the trial must be open-label (non-blinded) in order to facilitate interim and final analyses of data for this trial, including treatment interactions, and the attribution of causality of serious adverse events and unanticipated problems (see section 10.1.5.) Alternatively the coenrolling trial may agree to confidentially break blind (DSMB to DSMB) to allow for proper assessment, and to facilitate assignment of attribution (causality) of serious adverse events and unanticipated problems within the respective trial.

The planned analyses are by intention to treat. All participants will be compared throughout follow-up, irrespective of use of concomitant treatments or coenrollment in other trials. Concomitant treatments will be recorded at baseline, daily through Day 7, and on Days 14 (which will reference Days 8–14), and 28.

7 Study Population

Pragmatic classifications of COVID-19 severity, largely based on an early WHO scale or variants, have been widely adopted in clinical trials. These scales generally specify the degree of respiratory impairment as determined by the location of care and the degree of organ support.[47] The target population of TESICO are patients with SARS-CoV-2 pulmonary involvement severe enough to cause acute hypoxemic respiratory failure that is treated with high flow nasal oxygen or mechanical ventilation (whether invasive or

noninvasive). The TESICO target population is thus a subset of "critical COVID-19," as it is focused on hypoxemic respiratory failure due to COVID-19 pneumonia as the critical organ failure. The TESICO target population is also a subset of COVID-19 respiratory failure, since it is restricted to those with hypoxemia who are receiving advanced respiratory support. Based on unpublished data from a national and a regional cohort of hospitalized patients with COVID-19 pneumonia suggesting that >90–95% of patients in this target population would meet the Berlin consensus statement[48] oxygenation and radiographic criteria for ARDS, we at times use the term ARDS interchangeably with COVID-19-associated critical respiratory failure to describe our target population in this protocol. We anticipate that the members of the target population so defined will benefit from the investigational agents, as the vast majority will have bilateral pulmonary infiltrates from lung inflammation and injury due to life-threatening SARS-CoV-2 infection. (To facilitate inferences about generalizability and subsequent meta-analyses, we will record and report chest radiograph results and SF ratios to allow alignment with the Berlin definition and newly proposed modifications[49] at the conclusion of the trial.)

In the context of this understanding of COVID-19-associated critical respiratory failure, COVID-19 participants with ARDS will be enrolled at clinical trial sites globally. The estimated time from screening (Day -1 or Day 0) to end of study for an individual participant is 90 days for the primary endpoint and 6 months for some secondary endpoints.

Patient eligibility must be confirmed by study personnel named on the delegation log.

Protocol inclusion and exclusion criteria are intentionally straightforward and are NOT subject to exception for even minor deviations, e.g., by Study Medical Officers or by the Sponsor Medical Monitor.

7.1 Inclusion Criteria

1. Age ≥ 18 years;

2. Informed consent by the patient or the patient's legally-authorized representative (LAR)*;

3. Requiring admission for inpatient hospital acute medical care for clinical manifestations of COVID-19, per the responsible investigator, and NOT for purely public health or quarantine purposes.

4. Current respiratory failure (i.e., receipt of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO used to treat acute hypoxemic respiratory failure).

5. SARS-CoV-2 infection, documented by a nucleic acid test (NAT) or equivalent testing with most recent test within 14 days prior to randomization. (For non-NAT tests, only those deemed to have equivalent specificity to NAT by the protocol team will be allowed. A central list of allowed non-NAT tests will be maintained.)

6. Respiratory failure is believed to be due to SARS-CoV-2 pneumonia.

***Continuing consent**
Participants for whom consent was initially obtained from a LAR, but who subsequently regain decision-making capacity while in hospital will be approached for consent for continuing participation, including continuance of data acquisition.

7.2 Exclusion Criteria

1. Known allergy to investigational agent or vehicle
2. More than 4 days since initiation of support for respiratory failure (i.e., receipt of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or ECMO used to treat acute hypoxemic respiratory failure).
3. Chronic/home mechanical ventilation (invasive or non-invasive) for chronic lung or neuromuscular disease (non-invasive ventilation used solely for sleep-disordered breathing is not an exclusion).
4. Moribund patient (i.e., not expected to survive 24 hours)
5. Active use of "comfort care" or other hospice-equivalent standard of care
6. Expected inability to participate in study procedures;
7. In the opinion of the responsible investigator, any condition for which, participation would not be in the best interest of the participant or that could limit protocol-specified assessments;
8. Previous enrollment in TESICO

Exclusions that may be specifically appropriate for an investigational agent studied are referenced in the relevant appendix (H) for the investigational agent. The contraindications for use of components of SOC are outlined in Appendix I and in the PIM.

7.3 Costs to Participants

There is no cost to participants for the research tests, procedures/evaluations and study product while taking part in this trial. Procedures and treatment for clinical care including costs associated with hospital stay may be billed to the participant, participant's insurance or third party.

8 Study Product

Investigational agents and SOC treatment to be used are described in Appendices H and I, respectively.

9 Study Assessments and Procedures

9.1 Screening/Baseline and Follow-up Assessments

Data collection at each visit is outlined below and summarized in Appendix B. Day 0 refers to the day on which randomization occurs and on which the investigational agent/placebo is first administered. Screening and randomization can be done in the same session. The term "baseline" refers to data that are collected prior to randomization.

9.1.1 Screening/Baseline Assessments

After obtaining informed consent, the following assessments are performed within 24 hours prior to randomization to confirm eligibility and to collect baseline data:

- Documentation of laboratory diagnosis of SARS-CoV-2 infection in the appropriate timeframe

- A focused medical history, including the following information:
    - Demographics including age, gender, and type residence or facility prior to current illness (i.e. “home”)
    - Day of onset of COVID-19 signs and symptoms
    - History of chronic and current medical conditions, including targeted conditions for outcome analysis
    - Targeted concomitant medications and SARS-CoV-2 vaccine receipt or trial participation

- A focused physical examination including vital signs (at least heart rate, systolic and diastolic blood pressure, respiratory rate, temperature, and oxygen saturation), height and weight, baseline degree of oxygen supplementation/respiratory support

- Blood draw for local laboratory evaluations:
    - White blood cell count
    - Hemoglobin
    - Platelets
    - Lymphocyte and neutrophil counts
    - Ferritin
    - C-reactive protein
    - Basic metabolic panel
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)
    - Total bilirubin
    - INR
    - D-DIMER

- Plasma and serum specimens for future related research (four 1.0 mL aliquots of serum and four 1.0 mL aliquots of plasma). Two 9 mL tubes, one SST and one EDTA, of blood (18 mL total) will be drawn in order obtain 8 aliquots.
- A mid-turbinate nasal swab for SARS-CoV-2
- Among those who provide consent for host genetics, whole blood will be collected and stored for RNA (one 2.5mL PAXgene tube) and DNA (one 9mL EDTA tube to produce six 1-mL aliquots) extraction
- Contact details (phone, e-mail or other types of contact) for the participant and at least two close relatives/friends, to ensure reliable data collection during follow-up in the trial.
- Urine or serum pregnancy test in women of childbearing potential who do not already have evidence of pregnancy

In some cases, it may not be possible to draw blood for local laboratory assessments and storage prior to the time of randomization. In these cases, the blood draw can be performed after the time of randomization but before the infusion of the blinded investigational agent/placebo.

The overall eligibility of the patient for the study will be assessed once all screening information is available. The screening process can be suspended prior to completion of the assessment at any time if exclusions are identified by the study team.

Participants who qualify will be randomized within 24 hours of consent and given the infusion of the blinded investigational agent/placebo. Immediately prior to randomization,

receipt of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO by the participant should be verified.

On days of study drug administration before and during study drug administration:

- Adverse events of any grade severity present prior to the infusion (Day 0 only)
- Start and stop times of the infusion of the investigational agent/placebo
- Doses of study drug
- Infusion-related reactions to the investigational agent/placebo
- New adverse events of any grade severity during and up to 2 hours after the infusion
- On Days 0, 1, and 2, a blood draw for local laboratory evaluations

The details of monitoring during and immediately after the infusion will be specified in the agent-specific appendices. Participants who experience AEs during or immediately after the infusion should be followed closely until the resolution of the AE.

9.1.2 Follow-up Assessments

Participants will be followed through 180 days following randomization for collection of study data (Appendix B). Relevant clinical data will be collected on Days 0–7, 14, 28, 42, 60, 75, 90, and 180. These data will include discharge status, and interim changes in medical history (targeted to components of primary and secondary endpoints). Concomitant medications will be collected on Days 0-7, Day 14 (retrospectively for Days 8-14), and on Day 28, clinical (i.e., not limited to a laboratory abnormality) incident AEs of grade 3 and 4 severity through Day 28, and hospitalization readmissions and deaths through 180 days.

Components necessary to determine the ordinal WHO/NIH ordinal outcome and the TICO Pulmonary endpoint will be collected to allow the computation of the ordinal outcome for every day through Day 14 and on Day 28. On Days 14 and 28 AEs of any grade severity will also be collected.

At Day 3 for all participants still hospitalized and Day 5 for those still in the ICU or equivalent, plasma and serum specimens for central testing for SARS-CoV-2 antibody determination and storage (four 1.0 mL aliquots of serum and four 1.0 mL aliquots of plasma) will be obtained for future related research. Two 9 mL tubes, SST and EDTA, of blood (18 mL total) will be drawn in order obtain the 8 aliquots.

At Day 3, among those participants who provided consent for host genetics, a whole blood specimen for RNA extraction will be collected (sufficient for one 2.5 mL PAXgene tube).

At the time of discharge, the residence/place of living to which the participant was discharged and whether it was the type of residence (i.e. “home”) occupied at the time of onset of COVID-19 symptoms will be ascertained. All changes in this status (e.g., re-admission to another hospital or an intermediate care facility) will be collected at approximately 2-week intervals, starting with the day 14 visit, to determine the time of return “home” and time of liberation from new supplemental oxygen (as well as readmissions or resumption of new supplemental oxygen). Entry into hospice care will also be collected.

For visits on Days 7, 14, 42, 60, 75, 90, and 180, contact with the participant for study data collection may be performed by telephone. However, other information will be gathered, as outlined in Appendix B. At Day 90 and Day 180, the EQ-5D-5L will be administered by telephone. Safety data collection and reporting are described further in Section 10.

9.1.3 Stored Samples and Future Research

The plasma, mid-turbinate, and serum specimens collected as outlined above will be stored at a central specimen repository in the US. In addition to the specified testing to be done per protocol (collected at baseline and Day 3 for all hospitalized participants and collected at Day 5 among participants still in the ICU on Day 5), the specimens will be available for later use in research concerning COVID-19, SARS-CoV-2, and the impact of the study treatment. The whole blood specimens for RNA and DNA extraction from those participants who provided consent for host genetics will also be stored at the same central specimen repository in the US. Proposed research utilizing these specimens will be reviewed and approved by the study scientific steering committee and overseen by an ethics committee as appropriate. Results of research tests on individual specimens will not be provided to participants or their clinicians. Aggregate research results will be made available.

10 Safety Assessment

The safety monitoring and assessment within this trial reflects attributes of the anticipated investigational agents and the target population.

First, investigational agents studied in this protocol are commonly expected to have short half-lives and low probability of triggering a pathologic process or demonstrating a toxicity that would not manifest during, or shortly after treatment. As a consequence, the mainstay of safety monitoring will be broad safety monitoring through Day 90 plus collection and reporting of serious and/or high-grade events thought to be at least possibly related to the investigational agent for the duration of participation. If agents with longer half-lives or a likelihood of demonstrating effects that may potentially manifest with substantial delay are included, a longer duration of broad safety monitoring will be employed for those agents. Details of such additional safety monitoring will be specified in the corresponding agent-specific Appendix H .

Second, patients with ARDS may each be reasonably anticipated to experience multiple serious adverse events regardless of any study procedures. Therefore, certain reasonably anticipated serious adverse events will be collected as study outcomes (these are termed protocol-specified exempt serious events (PSESEs); see Section 10.2.3), and will be monitored by the DSMB rather than reporting these as adverse events per se.

Safety events and PSESEs will be monitored to ensure real-time participant protection through frequent unblinded DSMB review. The DSMB will review unblinded safety reports on an at least monthly basis.

The safety evaluation of the study intervention includes several components, all of which will be regularly reviewed by the independent DSMB. For this protocol, the term "*study intervention*" refers to the investigational agent or placebo, and to study provided SOC treatment(s).

Infusion-related reactions are only collected for the blinded investigational agent/placebo. All other AEs are collected for the study intervention (either the blinded investigational agent/placebo or study provided SOC treatment).

Events will be reported to regulators and IRBs/ethics committees as appropriate/required.

Adverse events, infusion reactions and unanticipated problems will be regularly reviewed by the DSMB.

The following information will be collected on electronic case report forms, and will be regularly reviewed by the DSMB, to evaluate and help ensure safety:

- Infusion-related reactions during and within 2 hours post-infusion of the investigational agent/placebo.
- Clinical adverse events of grade 3 and 4 through study day 28 (isolated laboratory abnormalities that are not associated with signs or symptoms are not collected).
- Protocol-specified exempt serious events (see section 10.2.3) through Day 90.
- Serious adverse events, including laboratory-only serious events, through Day 90, if they are not being collected as clinical organ failure or serious infections (Item 5 of 4.1.2) or protocol-specified exempt serious events.
- Serious adverse events through Day 180 if they are related to study intervention
- Unanticipated Problems through Day 180
- Deaths through Day 180.
- Hospital readmissions through Day 180.

An overview of safety data collected during the study is given in Table 3.

Table 3 Overview of Safety Data Collection

	During and at least 2 hrs after infusion (all days on which infusion occurs)	Day 0–7	Day 14	Day 28	Day 90
Infusion-related reactions and symptoms of any grade[a]	X				
All grade 3 and 4 clinical AEs (new or increased in severity to Grade 3/4)	X	X	X[b]	X[b]	
Protocol-specified exempt serious events (PSESEs)[c]	Collected through Day 90				
SAEs that are not PSESEs	Collected through Day 90				
Unanticipated problems	Collected through End of Subject Participation (Day 180)				
Hospital admissions and deaths	Collected through End of Subject Participation (Day 180)				
Any SAE related[d] to study intervention	Collected through End of Subject Participation (Day 180)				

[a]This includes reporting of AEs of any grade present on day 0, before the first infusion. This allows assessment of whether a given AE is new after infusion.
[b]Participants will be asked about all new relevant adverse events of Grade 3 or 4 which have occurred since the last data collection, up to that time point. On these visits, AEs of Grade 1 or 2 that are present on the day of the visit will also be collected.
[c]These are explained and defined in section 10.2.3.
[d]Relatedness determined as per protocol rules in section 10.

Definitions and methods of reporting each type of event are given below.

10.1 Definitions

10.1.1 Adverse Event (AE)

An AE is any untoward or unfavourable medical occurrence in a study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with their participation in research, whether or not considered related to the research. If a diagnosis is clinically evident (or subsequently determined), the diagnosis, rather than the individual signs and symptoms or lab abnormalities, will be recorded as the AE.

In Appendix H details are outlined for each investigational agent under study of the following: specific AEs observed to be possibly associated with the agent in question, and how to monitor for, clinically handle and report such AEs, should they arise.

10.1.2 Criteria for Seriousness

Events are serious if they lead to one of the following outcomes:

- Death
- Life-threatening (i.e., an immediate threat to life)
- Hospitalization or prolongation of hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital abnormalities/birth defects
- Other important medical events that may jeopardize the participant and/or may require intervention to prevent one of the outcomes listed above

10.1.3 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience or outcome that is:

1. Unexpected in terms of nature, severity, or frequency in relation to:
   a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents; and
   b. the characteristics of the population being studied; and
2. Possibly, probably, or definitely related to participation in the research; and
3. Places study participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized per the Investigator's Brochure(s) (IBs).

Furthermore, a UP could be an expected event that occurs at a greater frequency than would be expected based on current knowledge of the disease and treatment under study. The DSMB providing oversight to the study may make such an assessment based on an aggregate analysis of events.

10.1.4 Severity

The investigator will evaluate all AEs with respect to both seriousness (results in outcomes as above) and **severity** (intensity or grade). AEs will be graded for severity according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events* (also known at the DAIDS AE Grading Table; see Appendix D for the URL).

For specific events that are not included in the DAIDS AE Grading Table, the generic scale in Table 4 is to be used:

Table 4 Generic AE Grading Scale

Grade 1	Events causing no or minimal interference with usual social and functional activities, and NOT raising a concern, and NOT requiring a medical intervention/ therapy.
Grade 2	Events causing greater than minimal interference with usual social and functional activities; some assistance may be needed; no or minimal medical intervention/therapy required.
Grade 3	Events causing inability to perform usual social and functional activities; some assistance usually required; medical intervention/therapy required.
Grade 4	Events causing inability to perform basic self-care functions; medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
Grade 5	Events resulting in death

10.1.5 Causality

Causality refers to the likelihood that the event is related to the study intervention. It will be assessed for SAEs and UPs. This assessment will be made for both the blinded investigational agent/placebo and any study-supplied SOC treatment using the following guidelines:

- Reasonable possibility: There is a clear temporal relationship between the study intervention and the event onset, and the event is known to occur with the study intervention or there is a reasonable possibility that the study intervention caused the event.
  NOTE: Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the event.

- No reasonable possibility: There is no evidence suggesting that the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or a more reasonable/likely alternate etiology has been established.

The causality assessment is based on available information at the time of the assessment of the event. The investigator may revise these assessments as additional information becomes available.

10.1.6 Expectedness

Expectedness will be assessed for SAEs using the Reference Safety Information section of the IB(s) for the investigational agent(s) and any study-provided background therapy.

The expectedness assessment is based on available information at the time of the assessment of the event. The investigators and the sponsor may revise these assessments as additional information becomes available.

10.2 Schedule for Reporting of Specific Events

This section describes the schedule for reporting different types of safety outcomes on eCRFs as part of the protocol data collection plan. It is recognized that in the care of study participants, more information may be collected and recorded in the participant's medical record. The information collected in the medical record serves as source documentation of events (e.g., signs, symptoms, diagnoses) considered for reporting on eCRFs as part of protocol data collection.

10.2.1 Infusion-related reactions

Certain infusion-related signs/symptoms will be collected as protocol-specified exempt serious events (see section 10.2.3) and will not be separately reported as adverse events.

Adverse events that are
(a) not protocol-specified exempt serious events, AND
(b) are of grade 3 or 4 (whether new or as an increase in grade), AND
(c) occur during or within 2 hours post infusion
will be reported as adverse events on an eCRF.

10.2.2 Grade 3 and 4 clinical adverse events on days of study drug administration, and Days 0–7, 14, and 28

From Day 0 through Day 28, adverse clinical events reaching Grade 3 or 4 severity level will be reported on an eCRF. For a clinical adverse event that was present at baseline, only those which newly reach Grade 3 or 4 will be reported.

Beginning 2 hours post-infusion of the investigational agent or matched placebo, on Days 0–7, clinical AEs of Grade 3 or 4 that are new or that have increased in grade compared to their pre-infusion level will be reported on eCRFs.

Adverse clinical events reaching Grade 3 or 4 severity level that occur between Days 7 and 28 will be reported on an eCRF at the Day 14, and Day 28 visits. The date the event reached the indicated grade will be collected to permit time-to-event analyses. These reportable AEs should be assessed for SAE/UP reporting on the SAE eCRF or for protocol-specified exempt serious events reporting on the eCRF documenting the hospital course.

On Days 14 and 28, AEs of any grade that are present on the day of the visit will also be collected.

10.2.3 Protocol-specified exempt serious events (PSESEs)

Consistent with FDA guidance on protocol-specified serious adverse events, the TESICO trial will systematically collect certain adverse events that are expected to occur commonly in the target population even in the absence of study interventions. These events, termed protocol-specified exempt serious events (PSESEs), are in general exempted from the usual expedited reporting requirements for SAEs. This approach is taken to avoid creating a 'noisy' safety oversight environment, obscuring genuine safety signals, and imposing potentially unmanageable burdens on clinical/study staff, particularly in a pandemic critical care setting. Even as they are exempted from expedited reporting requirements, PSESEs

will be reviewed regularly (unblinded, by treatment arm) by the DSMB to maintain the integrity of safety monitoring for the trial.

PSESEs will NOT be reported as SAEs, even if they meet one or more of the criteria for seriousness, ***unless considered related to study intervention (blinded investigational agent/ placebo or study-supplied SOC treatment) (see section 10.2.4)***. These events may occur during the initial hospitalization, lead to a re-admission, or occur in a later hospitalization during follow-up.

The following are **protocol-specified exempt serious events.**

- Death
- Stroke
- Meningitis
- Encephalitis
- Myelitis
- Myocardial infarction
- Myocarditis
- Pericarditis
- New onset of worsening of CHF (NYHA class 3 or 4)
- Arterial or deep vein thromboembolic events
- Renal dysfunction treated with renal replacement therapy
- Hepatic decompensation
- Neurologic dysfunction, including acute delirium and transient ischemic events
- Disseminated intravascular coagulation
- Major bleeding events
- Serious infections
- Worsening respiratory failure
- Hypotension treated with vasopressor therapy
- Atrial or ventricular arrhythmias

Consistent with this approach, sites will evaluate a potential adverse event to determine whether it is a PSESE:

- If it is not a PSESE, it will be reported as an adverse event as outlined in section 10 of the protocol.
- If the event is a PSESE, it will be evaluated for relatedness.
    - If it is related to study interventions (either investigational agent or study-supplied SOC therapy), it will be reported as an adverse event.
    - If, however, the event is a PSESE and is not related to study procedures, then the event will be recorded in the PSESE eCRF as a study endpoint and not as an SAE.

As noted earlier in this section, PSESEs are included in the unblinded safety reports reviewed by the DSMB to allow early detection of important imbalances in the distribution of these events between arms in the trial.

10.2.4 Reportable SAEs

Reportable SAEs for this study are:

- Clinical SAEs which are not exempt from expedited reporting per the protocol-specified exempt serious event list and associated rules (10.2.3); and
- Any SAE related to the study intervention

Deaths, life-threatening events, and other SAEs considered potentially *related to the blinded investigational agent/placebo or study-supplied SOC treatment*, that occur from the time of infusion of the study intervention through the Day 180 visit must be recorded by sites on the SAE eCRF **within 24 hours of site awareness**.

Suspected unexpected serious adverse reactions (SUSARs) are reportable SAEs that are assessed as related to a study intervention and are unexpected per the Reference Safety Information of the IB for that intervention. SUSARs are reported from the INSIGHT Safety Office to applicable regulators in an expedited fashion. SUSARs that result in death or are immediately life-threatening are reported to regulators within 7 calendar days of receipt. All other SUSARs are reported to regulators within 15 calendar days. The INSIGHT Safety Office will generate a Safety Report for each SUSAR for distribution to investigators and other parties. Investigators are responsible for submitting Safety Reports to their overseeing IRB/EC per requirements.

SAEs that are not PSESEs and that are not related to the study intervention must be reported on the SAE eCRF within 3 days of site awareness. Such SAEs will be recorded through day 90.

SAEs are followed until the outcome of the SAE is known. If the outcome of an SAE is still unknown at the time of the final follow-up visit, the outcome will be entered in the database as “unknown.”

10.2.5 Unanticipated Problems (UPs)

UPs must be reported via the appropriate eCRF to the INSIGHT Safety Office no later than 7 calendar days after site awareness of the event. Investigators are responsible for submitting UPs that are received from the sponsor to their overseeing IRB/EC. Investigators must also comply with all reporting requirements of their overseeing IRB/EC.

10.2.6 Deaths

All deaths are reported on the eCRF for deaths. Deaths considered **related to the study intervention** (blinded investigational agent/placebo or study-supplied SOC) must **also** be reported as an SAE.

10.2.7 Pregnancy

The investigator will collect pregnancy information on any female participants who are or become pregnant while participating in this study. (Where the agent-specific appendix excludes pregnant women, this applies to participants who become pregnant.)

The participant will be followed to determine the outcome of the pregnancy.

Male participants with partners who become pregnant

If an investigator learns that a male participant’s partner becomes pregnant while the male participant is in this study, the investigator is asked to attempt to obtain information on the pregnancy, including its outcome. Information obtained on the status of the mother and child will be forwarded to the sponsor. Whether such monitoring will be required is outlined in the agent-specific appendix.

10.3 Medical Monitor

A Medical Monitor appointed by the sponsor will be responsible for reviewing all SAEs, making an independent assessment of causality and expectedness, preparing sponsor safety reports, and communicating as needed with the DSMB and the Investigational New Drug (IND) holder through the study safety office or other mechanism mutually agreed to and documented.

10.4 Halting Enrollment for Safety Reasons

The sponsor medical monitor or the DSMB may request that enrollment be halted for safety reasons (e.g., unacceptably high rate of infusion-related reactions or other unanticipated AEs). If the study is temporarily halted or stopped for safety reasons, IRBs/ethics committees will be informed. The IND holder and sponsor, in collaboration with the protocol chair and the DSMB, will determine if it is safe to resume the study. The sponsor will notify the Site Investigators of this decision. The conditions for resumption of the study will be defined in this notification. The Site Investigators will notify their local IRBs/ethics committees of the decision to resume the study.

11 Statistical Analyses and Monitoring Guidelines

This section describes the analysis for primary and secondary outcomes stated in section 4. A more detailed statistical analysis plan (SAP) will be developed as a separate document. The SAP for each investigational agent may be updated by the blinded statisticians prior to unblinding for a specific treatment comparison.

All analyses will be intent to treat with comparisons to concurrent controls as described in section 6.3. It is anticipated that all study site pharmacies serving active sites will be randomizing all agents under study at any given time, but if this is not the case, comparisons will be restricted to the set of controls enrolled at study site pharmacies where the drug was available for randomization. Specifically, the control group for an investigational agent will consist of those participants who could have been randomized to the agent, but were randomized to a control group instead (i.e., randomized to the matched control group of one of the agents included in the randomization). Agents will be compared to controls, but not to each other, unless explicitly specified in the analysis plan.

All analyses will utilize 2-sided tests with a 5% significance level unless otherwise noted.

11.1 Analysis of the Primary Efficacy Endpoint

The primary ordinal outcome—*recovery*—assessed at Day 90 includes 6 ordered categories, best to worst, that assess 4 clinical states. The categories correspond to (1) the number of consecutive days at home off oxygen (3 categories); (2) receiving oxygen at home or living in a location other than home; (3) hospitalized for medical care or in hospice care; and (4) death. The percentage of patients in each category (6 total) will be compared at Day 90. The primary analysis will use a proportional odds model to estimate a summary odds ratio (OR) for being in a better category in the investigational agent group compared with placebo; an OR > 1.0 will reflect a more favorable outcome for patients randomized to the investigational agent vs. placebo.

The proportional odds regression model will include a treatment indicator, indicators for site pharmacy, and an indicator for receipt of mechanical ventilation or ECMO at enrollment.

A test for the proportional odds assumption will be carried out. Even if the proportional odds assumption is violated, the overall summary OR will be the basis for inference in the

primary analysis, given the robustness of proportional odds regression to violation of the proportionality assumption. In order to further characterize the summary OR and any deviations from proportional odds, separate ORs will be estimated for different dichotomized definitions of improvement formulated from the components of the ordinal outcome (e.g., alive versus dead, alive and out of the hospital versus hospitalized or dead, etc.)

11.2 Analyses of Secondary Efficacy Endpoints, Safety Outcomes, and Subgroups

Four key secondary objectives are to compare investigational agent with placebo for the following endpoints

1. Time to death through Day 90.

2. A composite endpoint that considers the number of days at home off oxygen and the time to death as well as the other categories of the primary ordinal recovery outcome.

3. Time to recovery defined as alive, at home, and off new oxygen.

4. Status on a 3-category ordinal outcome that includes (a) alive and respiratory failure free, (b) alive but still in respiratory failure, and (c) dead, assessed at Day 90.

Time to death will be summarized using a log-rank test, stratified by receipt of invasive mechanical ventilation at randomization and study site pharmacy. The hazard ratio (investigational agent vs control) will be estimated using a stratified Cox proportional hazards model, and the proportion of participants who died by fixed time points (for example, Day 28 or Day 90) will be estimated using Kaplan-Meier estimates.

The composite outcome will be summarized with a win ratio statistic that ranks patients by time to death (instead of just survival status at Day 90), hospitalization at Day 90, home on oxygen or at not at home, and duration of time (in days instead of weekly intervals) at home off oxygen. Matching on mechanical ventilation (or ECMO) and a disease progression risk score at entry will be used to estimate the win ratio statistic.

The cumulative incidence functions for recovery taking into account death as a competing risk will be estimated using the Aalen-Johansen method and compared using Gray's test. The recovery rate ratio will be estimated using a Fine-Gray regression model. The comparisons between treatment groups will be stratified by receipt of invasive mechanical ventilation at randomization and by study site pharmacy. Recovery is defined using the last-off method, as described in section 4.

If there is evidence of benefit for an investigational agent versus placebo for the primary ordinal outcome, the comparison of the investigational agent with placebo for these three outcomes will help to inform the interpretation of the treatment effect.

The primary safety outcome is a composite of grade 3 or 4 events, SAEs, PSESEs (see 10.2.3), or death through Day 5, and tests for differences between treatment arms will be conducted with a Cochran Mantel Haenszel test stratified by study site pharmacy and receipt of invasive mechanical ventilation at study entry, comparing the proportion of participants who had experienced any of these events by Day 5. Treatment differences for each of the components of this composite outcome will also be summarized. This composite safety outcome will also be assessed at Day 28. Time to event analysis will also be used to summarize this composite safety outcome. Proportions of participants who

experienced any of these events will be compared using stratified Mantel Haenszel tests and logistic regression. SAEs and grade 3/4 events will be classified by system organ class according to MedDRA®.

Safety analyses also include infusion reactions collected during or within 2 hours after the infusion of the investigational agent or placebo. Proportions of participants who experienced infusion reactions or prematurely terminated infusions will be summarized by study arm, and Mantel Haenszel tests will be used to test for differences across arms.

Several other secondary efficacy outcomes will also be investigated. The models will include an indicator for treatment group, and stratify by study site pharmacy and receipt of invasive mechanical ventilation or ECMO at study entry as appropriate. Time from study entry to discharge from the hospital admission during which randomization took place will be analyzed using the same methods as described above for time to recovery. Readmissions will be summarized using methods for recurrent events (i.e. those who are readmitted will reenter the risk set).

Clinical organ failure is a composite of many different organ-specific events, listed in section 4.1.2, item 5. This outcome will be summarized as part of both safety and efficacy analyses. The incidence of organ failure, serious infection or death through Day 28 will be compared between arms using the log-rank test and Cox proportional hazards models. In addition, specific components (e.g., cardiac and vascular dysfunction, or the composite of cardiovascular outcomes and thromboembolic events described in section 4.1.2, item 10) will be analyzed using time-to-event analyses under competing risks, as described above for the primary analysis. Proportions of participants who experienced organ failure, serious infection or death will be summarized and compared between treatment arms at fixed time points using stratified Mantel Haenszel tests, overall and for specific organ dysfunctions.

The impact of study arm on the primary efficacy (recovery) and safety outcomes (primary composite safety endpoint, composite of grade 3 or 4 events, SAEs, PSESEs, and death through Day 5 and through Day 28, composite of hospital readmissions and death through Day 90) along with mortality will be assessed for subgroups defined by baseline characteristics, including demographics, baseline classification of “home”, duration of symptoms at enrollment, clinical history and presentation, and tests for homogeneity of the treatment effect across subgroups will be carried out. Additionally, subgroup analyses will be conducted for subgroups formed by a disease progression risk score at baseline. The construction of this risk score is described in section 5.2. Subgroup analyses will be interpreted with caution due to limited power and uncontrolled type I error.

11.3 Data Monitoring Guidelines for an Independent DSMB

An independent DSMB will review interim data on a regular basis and use pre-specified guidelines to identify agents with evidence of harm based on a difference in all-cause mortality. The DSMB will also monitor other adverse events and safety signals.

As a guideline, we do not recommend early termination for benefit based on the primary endpoint, which is most reliably estimated at Day 90. In addition, given the relatively short follow-up period of 90 days for this target population, full follow-up for the primary and all secondary endpoints is considered important to evaluate the investigational agents to be studied. An exception to this guideline is if the DSMB believe there is clear and substantial evidence of a mortality benefit for an investigational agent

11.3.1 Monitoring Guidelines for Interim Analyses

Multiple distinctive features of potential therapies for COVID-19-associated ARDS contribute to the monitoring guidelines for interim analyses within the master protocol. (If a specific investigational agent requires an alternative approach to interim monitoring, those details will be specified in the relevant agent-specific appendix.)

First, in many cases, potential agents may be relevant not only to COVID-19-associated ARDS but to other forms of ARDS. As such, even if an agent did not achieve its efficacy endpoint, enrollment to the planned sample size is expected to provide important insights relevant to future investigations in ARDS. These insights may especially pertain to potential effects among subgroups of patients or less common safety events of interest.

Second, the primary endpoint of this trial requires 90 days of follow-up since the final classification of a patient's recovery requires knowledge of their status on Day 90. While this duration of follow-up for the primary endpoint is essential for a patient-centered result at the conclusion of the trial, in the context of the anticipated rapid enrolment of the trial, this endpoint is infeasible to use for stopping boundaries for either efficacy or futility on the basis of conditional power.

Third, enrollment should stop early for any agent that shows clear evidence for increased mortality. A stopping boundary for harm is thus indicated.

Fourth, while it is important to avoid premature stopping for a potentially non-reproducible efficacy signal for the primary endpoint, clear and substantial improvement in mortality may appropriately lead to a DSMB recommendation to stop early for efficacy.

On the basis of these and related factors, the monitoring guidelines for this master protocol will focus on a stopping boundary for harm, a stopping boundary for efficacy based on mortality, and ongoing close monitoring of safety by the DSMB, based on the totality of evidence.

As a guideline to the DSMB for assessment of harm, a Haybittle-Peto boundary using a 2.5 standard deviation (SD) for the first 100 participants enrolled and 2.0 SD afterwards. Harm will be assessed using all-cause mortality, specifically using a hazard ratio from a proportional hazard model for the time to death associated with the investigational agent. As an additional guideline to the DSMB for assessment of efficacy, a Haybittle-Peto boundary using a 3.0 SD threshold will be used after 100 patients have been enrolled and followed for at least 5 days. Efficacy will be assessed using all-cause mortality, specifically using a hazard ratio from a proportional hazard model for the time to death associated with the investigational agent.

12 Protection of Human Subjects and Other Ethical Considerations

12.1 Participating Clinical Sites and Local Review of Protocol and Informed Consent

This study will be conducted by major medical centers participating in INSIGHT and partnering networks, including especially NHLBI networks. It is anticipated that potential participants will be recruited by the site investigators (and/or their delegates, as appropriate) and/or that positive SARS-CoV-2 laboratory testing will be used to enquire about potential enrollment. Information about this study will be disseminated to health care workers at enrolling sites.

Prior to the initiation of the study at each clinical research site, the protocol, informed consent form and any participant information materials will be submitted to and approved by a central/national IRB/EC and/or the site's local IRB/EC as required. Likewise, any future amendments to the study protocol will be submitted and approved by the same IRB(s) or EC(s). After IRB/EC approval, sites must register for this study before screening potential participants, and must register for any protocol amendments. Protocol registration procedures are described in the PIM.

12.2 Ethical Conduct of the Study

The study will be conducted according to the Declaration of Helsinki in its current version; the requirements of Good Clinical Practice (GCP) as defined in Guidelines, EU Clinical Trials Directive (2001/20/EC), and EU GCP Directive (2005/28/EC); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines; Human Subject Protection and Data Protection Acts; the US Office for Human Research Protections (OHRP); or with the local law and regulation, whichever affords greater protection of human subjects.

12.3 Informed Consent of Study Participants

Informed consent must be obtained (see sample in Appendix A) prior to conducting any study-related procedures. Many of the patients approached for participation in this research protocol will often have limitations of decision-making abilities due to their critical illness. Hence, some patients will not be able to provide informed consent. For patients who are incapacitated, informed consent may be obtained from a legally-authorized representative (LAR). Because the investigational agents are intended to treat critical illness and the impairment of decisional capacity is intrinsic to the critical illness, the use of LARs for consent is appropriate for this trial. The use of consent from LARs will follow applicable legislation (e.g., in the United States, 45 CFR 46.116 and 45 CFR 46 102 (i)). Capacity will be assessed according to local standards and policies. Local standards and policies will also determine who is legally authorized to consent for an individual who is incapacitated. Should the individual regain capacity during the study, their direct reconsent should be obtained at the earliest feasible opportunity.

Electronic consent may be used when a validated and secure electronic system is in place to do so, if in compliance with national legislation and approved by the responsible IRB/EC. Other methods of obtaining documentation of consent may be used when site staff are unable to be in direct contact with a potential participant or a legally-authorized representative due to infection-control restrictions. No matter how the participant's consent is obtained and documented, it is expected that consent will be preceded by research staff providing an explanation of the research and an opportunity for the participant (or their LAR) to have questions answered. Sites should follow all available local or national guidance on suitable methods for obtaining documentation of participant (or their LAR) consent.

12.4 Confidentiality of Study Participants

The confidentiality of all study participants will be protected in accordance with GCP guidelines and national regulations.

12.5 Regulatory Oversight

Sites in the US will conduct this trial under the terms of the IND and will adhere to FDA regulations found in 21 CFR 312, Subpart D. Sites in countries other than the US will not conduct the trial under the IND. As stated in Section 12.2 above, all sites will conduct the

trial in accordance with the requirements of GCP as codified in their local law and regulation, under the oversight of their institution and competent regulatory authority.

As part of fulfilling GCP and FDA requirements for adequate trial monitoring, multiple modalities will be employed. The objectives of trial monitoring are to ensure that participant rights and safety are protected, to assure the integrity and accuracy of key trial data, and to verify that the study has been conducted in accord with GCP standards and applicable regulations.

A specific risk-based protocol monitoring plan will be developed. The plan will include strategies for central monitoring of accumulating data and will take into account site-level quality control procedures. On-site monitoring visits for targeted source document verification and review of regulatory and study pharmacy files will be conducted when possible, but these tasks will most likely need to be handled remotely during the pandemic. The monitoring plan will outline the frequency of this aspect of monitoring based on such factors as study enrollment, data collection status and regulatory obligations.

Appendix A

Sample Informed Consent form ***Short Title: Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO)***

Sponsored by: The University of Minnesota (UMN)/National Institute of Allergy and Infectious Diseases (NIAID)

Funded by: The National Heart, Lung, and Blood Institute (NHLBI) and National Institute of Allergy and Infectious Diseases (NIAID), US National Institutes of Health (NIH)

Full Title of the Study: **A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Severely Ill Patients with COVID-19**

CONSENT FOR PARTICIPATING IN AN NIH-FUNDED RESEARCH STUDY

SITE INVESTIGATOR: _____ **PHONE:** _____

ALL SITE INSTRUCTION THAT IS INCLUDED IN A TEXT BOX SHOULD BE REMOVED FROM THE SITE'S INFORMED CONSENT FOR PARTICIPANTS

US Office for Human Research Protections (OHRP) Requirements to be read by the sites:

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB/EC REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB/EC WITH A COPY OF THIS SAMPLE LANGUAGE ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBs/ECs ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OR SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB/EC, AND NOTED IN THE IRB/EC MINUTES. JUSTIFICATION AND IRB/EC APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO THE INTERNATIONAL COORDINATING CENTER OR COLLABORATING NETWORK. SPONSOR-APPROVED CHANGES IN THE PROTOCOL MUST BE APPROVED BY THE LOCAL IRB/EC BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB/EC MAY OTHERWISE ADDITIONALLY REQUIRE.

PID: _____

Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO) Master Protocol
Version 1.0, 15 March 2021 (corrections made 01 April 2021)

Key information:

We are asking you to join a research study about COVID-19. It is your choice whether or not you want to join. This form gives you information about the study that will help you make your choice. You can discuss this information with your doctor or family or anyone else you would like before you make your choice. Your choice will not affect the care you are getting for COVID-19.

What is the research question we are trying to answer?

We are studying two treatments for COVID-19. We are asking you to join the study because you are in the hospital with COVID-19 and have significant trouble with your breathing.

First, we are studying an experimental medicine, aviptadil (also called VIP), supplied by NeuroRx. We are trying to find out if giving this experimental medicine can help sick people in the hospital with COVID-19 have fewer bad effects from the disease, and if it may possibly help them get better and go home faster. We are also trying to see if it is safe.

This experimental medicine is a man-made version of a naturally occurring hormone in the body. It may decrease COVID-19 virus levels, inflammation, and blood clotting, and help protect the lung against injury. We think this experimental medicine may possibly help patients with COVID-19, and we think it will be safe, but we are not sure and so we are doing this study.

Second, we are studying a drug called remdesivir (also called Veklury) supplied by Gilead. Remdesivir is approved in the United States for the treatment for COVID-19 in people who are in the hospital. We are trying to find out if remdesivir helps patients with your level of COVID-19 illness get better and go home faster. Remdesivir may decrease COVID-19 virus levels and lung injury. Currently we do not know if remdesivir will help people with your level of COVID-19 illness which is why we are doing this study.

What do you have to do if you decide to be in the study?

The study staff at your hospital will check to see if there is any reason you should not be in the study. They will check your medical history. They will look at tests commonly done for your condition. They will also check to see if you are able to get both of the drugs we are studying or just one of the drugs. For example, if you are pregnant you will not be able to receive the aviptadil or matching placebo (inactive salt solution) but you will be able to receive the remdesivir or matching placebo.

If you agree to be in the study, and you are able to get both treatments, we will assign you to one of four study groups. This will be done by random chance -- like flipping a coin. You will have an equal chance of getting either the active drug or placebo (salt solution) for both drugs.

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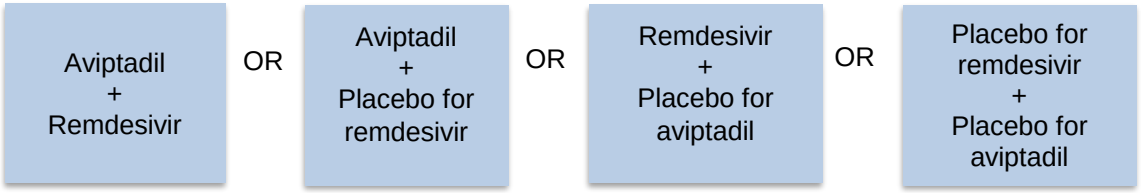
You will be assigned to one of the following 4 groups:



Your doctor will NOT decide and will not know which of these four options you will get. The study staff will also not know which option you will get.

If you agree to be in the study, and you are ONLY able to get Aviptadil we will assign you to one of two study groups. This will be done by random chance -- like flipping a coin.

If you agree to be in the study, and you are ONLY able to get remdesivir we will assign you to one of two study groups. This will be done by random chance -- like flipping a coin.

Aviptadil: You will receive the Aviptadil study product (either the experimental medicine or the matching placebo) for three consecutive days starting on the day you join the study (study Day 0). You will get it by an intravenous (IV) drip through a tube in your vein. This is called an infusion. The infusion will take about 12 hours on each day that it is given.

Aviptadil is the only thing you may be given that is experimental. It is NOT approved for use in people with COVID-19 by the United States Food and Drug Administration (FDA) or any other regulatory body in the world. It is approved in some countries outside the US for another condition but is given in a different way. Its use in the United States is strictly limited to research.

Remdesivir: You will receive the remdesivir study product (either the active medicine or matching placebo) once per day for up to 10 days. You will also get this by an IV drip through a tube in your vein, which will generally take 1-2 hours. Remdesivir is approved in the United States for the treatment of COVID-19 in people who are in the hospital. It's not known whether it works in people with more severe COVID-19.

Other treatments: As part of the study you may also get a drug called a steroid for up to 10 days while you are in the hospital, as care for your COVID-19, unless your doctor thinks the steroid would not be safe for you to take. Steroids have been shown in prior studies to help people survive COVID-19. Steroids are available for other diseases in the United States, so your doctor will be using it "off-label," which means that while there is not formal

PID: _____

FDA approval for this use, your doctors think it is reasonable. It is likely that you would receive steroid medicine even if you were not in the study.

Any other medications or treatments you will be given will be what you would usually receive in this hospital for your condition. There may be some additional procedures or testing done for study purposes. We will describe these below.

You will be in the study for 180 days. We will check on your health every day while you are in the hospital, and regularly after you leave the hospital.

We will swab your nose to see how much of the virus that causes COVID-19 is present. We will take blood samples from you to better understand the body's response to the infection. Some of the blood may be used in future studies.

To be in the remdesivir/placebo part of the study, you will need to agree to not have sex that could make you or a partner pregnant for seven days after you finish the remdesivir or placebo infusion. This may involve not having sex at all (abstinence), or you may use effective contraception (hormonal contraception or barrier methods with spermicide) to avoid pregnancy. Methods like rhythm, sympto-thermal or withdrawal are not effective for the purpose of the study. You can ask the study team about this if you have questions or concerns.

If you are pregnant, you cannot be in the aviptadil/placebo part of the study. You can still be in the remdesivir/placebo part of the study.

If you become pregnant during the study, please let your study team know as soon as possible. We will ask to follow you until your pregnancy is over, to see if there were any problems that may have been caused by any of the study treatments.

PID: _____

We will need to do the following things with you, and gather detailed information at these times:

Study Timepoint	What will happen & what we will check
Up to 1 day before you get study product	• Informed consent (this document) • Check to see how you are feeling • Your medical history • Whether you are taking certain medicines • A swab of your nose for virus detection • Blood tests to check your health (9 mL, about ½ tablespoon) • Blood for future research (18 mL, about 1 tablespoon) • Collection of urine or blood for a pregnancy test • Contact information like telephone numbers and addresses for you and at least two close relatives or friends
Day 0, Day 1, Day 2	• Infusion of study product (the experimental medicine or else placebo) if able to get this drug • Infusion of remdesivir study product (active drug or placebo) if able to get this drug (you may get this treatment for up to 10 days) • Blood tests to check your health (9 mL, about ½ tablespoon), unless your treatment team has already performed those tests
Day 3, Day 5	• How you are feeling • Blood for future research (18 mL, about a tablespoon) – at Day 5 this will only be done if you are still in the ICU • If you're not in the hospital, we will not draw your blood and the visit may take place by phone
Day 2, Day 4, Day 5, Day 7, Day 14, Day 42, Day 60, Day 75	• How you are feeling (Days 2, 4, 7, 14, 60) • Update on return to home (Days 14, 42, 60, 75) • On Days 0-7 and 14, also whether you have taken certain medicines These "visits" may take place by phone.
Day 28, Day 90, and Day 180	• How you are feeling • On Day 28, also whether you have taken certain medicines • On day 90 and 180 only: we will ask you additional questions about your health These "visits" will take place by phone.

We may need to get some information from your medical record.

- By signing this consent, you agree to let us get information for this study from your medical record.

PID: _____

- By signing this consent, you are giving us permission to contact other hospitals or medical facilities if you are admitted there during the time you are in the study. We will contact them to be sure we know how you are doing.
- We will ask you to give us information about other people we can contact if we are not able to reach you after you leave the hospital, so we can find out how you are doing.

PID: _____

We will send the information we collect to the University of Minnesota (UMN) in the US where it will be stored and analyzed. In this information, only a code number, your year of birth, and a 3-letter code that the study staff chooses identifies you.

The study staff here at this site are responsible for keeping your identifying information safe from anyone who should not see it.

We will send the blood samples to a laboratory in the US for storage. We will keep them for as long as we have the funding and space to do so, which we expect to be many years. There is more information below about how we will use these samples.

Why would you want to be in the study?

If you get study drug, it is possible it may help you get better, or that you may get home faster, but we do not know that.

It is important to remember that some people in this study will get inactive placebo and will not get study drug.

By being in this study, you will help doctors learn more about how to treat COVID-19 in people in the hospital. Because so many people are getting hospitalized with COVID-19, this could help others. There may be a large health impact if a treatment proves to be safe and is shown to be effective.

Why would you NOT want to be in the study?

Since only some people in this study will get study drug, you may not receive it. Even if you do get study drug, it may not be useful, or it may have harmful side effects, so being in the study would not be of any direct help to you.

What are the risks or side effects of the study treatments?

All treatments have risks and may cause side effects. These may happen to you from the study treatment.

You may have an allergic reaction, including hives, trouble breathing, or other allergic responses. Allergic reactions like these are likely to be rare, but may be severe or life-threatening.

You will be monitored very closely while you are being given the infusion of the study product (aviptadil or placebo) and for at least 2 hours after the infusion is finished. We will give you prompt medical care if needed to treat any side effects from the infusion.

There are discomforts and risks associated with blood draws. You will have these things done while you are in the hospital even if you are not in the study. These discomforts and risks are no different from what you would experience if they were performed as part of your regular hospital care for COVID-19.

PID: _____

What are the risks or side effects of Aviptadil?

One effect of aviptadil is that it relaxes smooth muscle such as in your lungs, blood vessels, and intestines. Relaxing this type of muscle opens up your airways so it is easier to breathe and get oxygen into your body.

The most common side effect of aviptadil infusion is decreased blood pressure. In early studies of very ill patients with lung injury, about 1 in 5 people (20%) had lower blood pressure during the infusion of aviptadil. The decrease was usually small and went away within 10 minutes of stopping the infusion.

Facial flushing is common with aviptadil and is not dangerous. It is caused by relaxation of the blood vessels in the skin and goes away when the infusion is stopped.

Increases in heart rate are common and usually not dangerous. The increase in heart rate is mostly due to blood vessel relaxation.

Some people getting aviptadil have had mild to moderate diarrhea. The diarrhea goes away when the infusion is stopped.

What are the risks or side effects of Remdesivir?

The most common side effects of remdesivir included abnormal liver function test results, abnormal blood clotting test results, constipation, diarrhea, nausea, vomiting, decreased appetite, and headache. The abnormal liver function tests lasted longer than a few days in some people but went back to normal within a few weeks or less.

Remdesivir might affect the way that other medications are processed by your body. They might stay in your body longer, or shorter, at higher or lower levels. At the time this document was written, one person in another study had an increase in the level of a medication in their blood that was considered by study doctors to be at least possibly related to having taken remdesivir. There did not appear to be any harm from this temporary change. You can ask the study team more about this if you are concerned.

Some people may have some side effects after the infusion of remdesivir. Other people may have no side effects.

What are the risks and benefits of taking steroids?

Steroids may cause your sodium (salt) and glucose (sugar) levels to rise in your blood. You may feel anxious while taking steroids. You may be given steroids to treat your COVID-19 even if you do not join this study.

What if you are pregnant or breastfeeding?

PID: _____

If you are pregnant or breastfeeding, you can still join this study, although you cannot participate in the aviptadil portion of the study. However, we do not have any information about how either aviptadil or remdesivir may affect your baby. The risks to a pregnant woman or an unborn baby might be serious. Please take this into account as you make your decision about whether to join this study.

Additional information:

Here is some additional information about the study that may help you make your choice about whether you want to be in the study.

The NIH, an agency of the US Federal government, is paying for this study.

We are required to comply with all rules and regulations for human research as well as the laws of each country where the study is taking place.

This study is taking place in several countries. We expect to enroll about 800 people around the world.

You do not have to join this research study if you do not want to. If you choose to join the study, you can stop at any time. If you choose not to join or to stop, the medical care you are getting now will not change.

If we get any new information that might change whether you want to join or stay in the study, we will tell you right away.

If you do not want to be in this study, you will still get the usual care to treat COVID-19. However, you cannot get Aviptadil because it is experimental.

What are the costs to you?

We will give you the study treatment at no cost. We will pay for all clinic visits, lab work, and other tests that are part of this study.

THE NEXT PARAGRAPH IS FOR UNITED STATES SITES ONLY. SITES IN OTHER COUNTRIES SHOULD DELETE THE NEXT PARAGRAPH.

You, your insurance company, or some other third-party payer must pay for all other medicines and hospital costs.

SITES OUTSIDE THE UNITED STATES: Please replace the paragraph above with language appropriate for your location

PID: _____

Will you be paid to be in the study?

We will compensate you for your time and inconvenience participating in the study. *[Specific details to be completed by site.]*

What if you are hurt as part of this study?

If you are hurt because of being in this study, *[insert the name of the hospital/clinic]* will treat your injury right away. You or your insurance will have to pay for this treatment. The study cannot pay you or pay for any care for study-related injuries or for your illness.

If the above is not true for your site, i.e., if trial insurance covers such cost, please replace the above with appropriate language.

What happens to the blood samples?

We will send the blood samples to a central laboratory in the United States. You and your doctor will **not** get the results of any tests done on these samples. We will not sell your samples and they will not be used for research aimed at making money (commercial research). The laboratory where the samples are stored will not have any information that could identify you.

The blood samples will measure how many COVID-19 antibodies are in your blood. This will tell us how your immune system responded to your COVID-19.

Any blood samples that are left over after these tests will be stored at the central laboratory for as long as we are able to keep them. We hope to use these in the future to answer other questions about COVID-19, the virus that causes it, and how people respond to treatment. You and your doctor will **not** get any results from these tests.

You can withdraw your consent for us to keep these specimens at any time. Let your study team know if you do not want the study to keep your specimens anymore, and every effort will be made to destroy all of your specimens that are still at the central laboratory.

How do we protect your privacy?

We will take every reasonable step to keep your health information private and to keep anyone from misusing it.

Your information (data) and samples will not be identified by name, or in any other way, in anything published about this study.

PID: _____

We will do everything we can to keep your personal information private, but we cannot guarantee that nobody will get it. We may have to release your personal information if required by law.

These people may see your medical and research information:

- the ***[insert the name of the hospital/clinic]*** ethics committee (institutional review board [IRB]);
- the sponsor, the group paying for the research (US NIH), other study research staff and study monitors
- US and other participating countries' health regulatory agencies, including the US FDA.

They are committed to protecting your privacy.

As the research staff at *[inset the name of the hospital/clinic]*, we are required to make sure that people not involved with this study cannot see your research and medical information. We will keep your research files in a safe place and will handle your personal information very carefully.

Your study data are sent electronically to the UMN in the US through a secure system. By signing this consent, you agree to having your data sent to UMN. No information that could directly identify you is sent to UMN. This is called "pseudonymized data." Access to the data at UMN is limited through security measures, and no data breach or unauthorized access has ever occurred in this system. After the study is over, the data will be stored securely for the period required by law.

Your study data will be shared with the US National Institutes of Health (which is paying for this study), and with regulators that oversee the study, including the US FDA, as required by law. Your study data will also be shared with the drug company that provides the study medicine to help them develop the drug.

UMN may share your data and specimens with other people who study COVID-19. UMN will remove any information that could possibly be used to identify you before sharing. This is called "anonymizing the data." We will not ask you for additional consent for this sharing. UMN will only share data and specimens for research projects that are approved by the group that is conducting this study.

This study has a Certificate of Confidentiality from the US Federal Government. This means that UMN cannot share any data it has about you with national, state, or local civil, criminal, administrative, legislative, or other authorities unless you specifically allow us to share it.

A description of this clinical trial will be available at http://www.ClinicalTrials.gov, and on the EudraCT website (https://eudract.ema.europa.eu/). These websites will not include your name or any other direct identifiers such as your contact information. These

PID: _____

websites will include a summary of the results of this research once the study has been completed. You can search either website at any time.

[Note for US sites: The following brief HIPAA authorization is provided. Your site-specific consent should be modified to reflect the HIPAA authorization language requirements at your site.]

To do this research, we will collect and use your personal data, as described above and in any HIPAA Authorization Form we have given you. Please tell us whether you agree to have us collect and use your personal data by placing your initials in front of your selection.

____**Yes**, I agree to the collection and processing of my personal data.

____**No**, I do not agree to the collection and processing of my personal data.

It is your choice whether you allow us to collect and use your data. However, you will not be able to be in this study if we cannot collect and use your data.

[The following section (up to "What if you have problems or questions?") is for countries subject to the GDPR or similar legislation requiring this information. It should only be included in consents for sites subject to such legislation. It will vary from place to place whether it must be in this consent document, a separate consent document, or an information sheet that does not require signature. The amount of information provided may be reduced to meet the requirements of a particular country (e.g., not all countries/ECs require an enumeration of all of a data subject's rights).]

What are your rights regarding your data?

The UMN is a public research university, and this study is funded primarily by a grant from the US Federal government. UMN and the study funding source require the sponsor (UMN) to follow regulations and policies that are meant to protect your privacy. UMN is also required to comply with the General Data Protection Regulation (GDPR), because it processes data obtained from people in Europe.

There is no specific independent supervisory authority overseeing the processing of data in the US. Any complaint you might have about the use of your data would be made to your national data protection authority.

The GDPR gives you additional rights which we would like to inform you about below.

Right to Information: You have the right to know what data about you is being processed. You can also get a free copy of this data provided.

Right to Correction: You have the right to correct any information about you which is incorrect or had become incorrect.

Right to Erasure/Anonymization: The sponsor is required under both EU and US law to retain data from research studies like this one for many years. However, you have the right to request that your personal data be completely anonymized. This is done by destroying the information at your study center that links your identity to the pseudonymized data held by the sponsor. This means that no one would ever be able to link the data held by the sponsor to you personally.

Right to Restriction of processing: Under certain conditions, you have the right to demand processing restrictions, i.e. the data may then only be stored, not processed. You must apply for this. Please contact your study physician or the data protection officer of the study center if you want to do so. This right may be limited if the restriction would affect the reliability of the study results.

Right to Data portability: You have the right to receive the personal data that you have provided to the study center. This will allow you to request that this information be transmitted either to you or, where technically possible, to another agency designated by you.

Right to Contradiction: You have the right to object at any time to any specific decision or action taken to process your personal data. This right is limited for data that have already been processed and may be limited if your objection would affect the reliability of the study results.

Right to Withdrawal of this consent: You may withdraw your consent at any time with effect for future data collection. This withdrawal may be in an informal or verbal communication to your investigator. If you withdraw your consent this will not affect the lawfulness of the data processing that has been or will be done with data collected until you withdraw consent. Data already collected will be anonymized.

If you would like to use one of these rights, please first contact the person responsible for the data collection at your study center:

Person responsible for data collection at the study center:
Name:
Address:
Phone:
Email

For concerns about data processing and compliance with data protection requirements you can also contact the data protection officer responsible for the study center:

Data protection officer responsible for the study center:
Name:

PID: _____

Address:
Phone:
Email

In addition, you have the right to lodge a complaint with the competent authority if you believe that the processing of personal data concerning you is contrary to the GDPR:

Data protection authority responsible for the study center:
Name:
Address:
Phone:
Email

What if you have problems or questions?

If you ever have questions about this study, or about the storage or use of your data or samples, or if you are hurt by being in the study, contact:

- *[name of the investigator or other study staff]*
- *[telephone number of the above]*

If you have questions about your rights as a research participant, you can call:

- *[name or title of person on the ethics committee (IRB) or other organization appropriate for the site]*
- *[telephone number of the above]*

PID: _____

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE TESICO STUDY

I have read the consent or have had it explained to me. I believe that I understand the information. By signing this consent, I am stating that I want to join this study. I understand that I do not waive any of my legal rights as a study participant by signing this consent. I understand that I will receive a copy of the signed and dated consent.

If you agree to be in this study, please sign below.

_____ Date: _____

Signature of participant

_____

Printed name of participant

_____ Date: _____

Signature of investigator/designee

_____

Printed name of investigator/designee

FOR ADULTS NOT CAPABLE of GIVING CONSENT

_____ Date: _____

Signature of Legally Authorized Representative (LAR)

_____

Printed name of LAR

PID: _____

_____

Relationship of LAR to Participant

(Indicate why the LAR is authorized to act as a surrogate health care decision-maker under state or applicable local law)

Witness to Consent Interview

On the date given next to my signature, I witnessed the consent interview for the research study named above in this document. I attest that the information in this consent form was explained to the subject, and the subject indicated that his/her questions and concerns were adequately addressed.

_____ Date: _____

Signature of witness

_____

Printed name of witness

NOTE: This consent form, with the original signatures, MUST be retained on file by the Investigator of Record. A copy of the signed and dated consent must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

If no-touch / electronic consent is used, the participant must be provided with a copy of the consent in a manner appropriate to the method used to obtain it. A record of the act of consent must also be appropriately retained in the participant's medical record.

Additional Consent for Genetic Testing on Stored Specimens

WHY IS GENETIC TESTING BEING DONE? The study team would like your permission to collect a small amount of your blood and store them for researchers who will do genetic testing (testing on your genes) and other related tests in the future. These tests will help us understand how the genetic makeup of people affects the COVID-19 virus and how it makes people sick.

Any future research done on the blood collected for this study will be related to the COVID-19 virus for which you are being studied in ***this trial.***

WHAT WILL HAPPEN DURING GENETIC TESTING?

If you agree to take part in this study, three blood specimens will be collected along with other blood being drawn for the study, approximately 15 mL (about 1 tablespoon) in total. The blood will be taken with other laboratory test samples so you will not get an extra needle stick.

HOW WILL YOUR BLOOD BE USED? Your blood will be used to learn more about the health problems that may be caused by COVID-19. This may include tests to better understand why some people have more severe complications (get sicker) than others and why medicines to prevent or treat these infections might work better in some people than in others.

Researchers involved with this blood collection project do not know yet exactly which tests will be done.

You and your study doctor or nurse will not get any results from the tests done on your blood collected for this genomics study. These tests will only be used for research and may not apply to your medical care.

Your blood sample collected for this study will:

- Become the property of INSIGHT.
- Not be sold or used to make commercial products.
- Not be tested for any specific research study unless the plan for using your blood is approved - based on scientific and ethical considerations - by the INSIGHT Scientific Steering Committee, the U.S. National Institutes of Health (NIH), and a special committee (an Institutional Review Board or Ethics Committee) at the researcher's institution.

HOW WILL YOUR PRIVACY AND THE CONFIDENTIALITY OF YOUR INFORMATION BE PROTECTED?

Every reasonable step will be taken to protect your privacy and the confidentiality of your health information and to prevent misuse of this information, and to make sure your blood sample is handled with care at the storage facility. For example, your research

PID: _____

records will be identified only by a code. Your blood sample and results of any genetic testing will be identified by a second code. Only a few statisticians (persons who analyze the study results) associated with the INSIGHT studies will have access to both codes in order to analyze the test results. These statisticians will not have access to any information that can identify you.

Researchers will write reports, including information they learn from future tests on your blood. These reports will be shared with participating research sites. These findings will also be submitted for publication in scientific or medical journals. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

However your records may be seen by:

- Institutional Review Boards (IRBs) or Ethic Committees (ECs) who review the study to make sure it is ethically acceptable
- Agencies of the U.S. government that fund or oversee this research, for example, the U.S. National Institutes of Health (NIH) or the U.S. Office for Human Research Protections (OHRP)
- Research staff and study monitors, and their designees.

Staff at ***[insert the name of the site]*** will handle your personal information very carefully. They are required to make sure that people not involved with this study do not have access to your research and medical records.

[For U.S. Sites Only]

In addition to these efforts to keep your information confidential, the INSIGHT Genomics study is covered by a *Certificate of Confidentiality* from the U.S. Department of Health and Human Services. This certificate means that researchers cannot be forced to give information collected as part of this study to people who are not involved with the study, for example, the court system. However, this certificate has limited protection rights. You should know that it does not stop the doctor in charge of this study from taking appropriate steps to prevent serious harm to yourself or others. Federal and state laws also help protect research participants and others who have genetic testing done.

[For International Sites Only]

Efforts will be made to keep your personal information confidential, but we cannot guarantee complete confidentiality. Your personal information may be released if required by law. Any publication of this study will not use your name or identify you personally.

HOW LONG WILL YOUR BLOOD BE KEPT?

PID: _____

Your blood specimen will be stored as long as funding is available for storage and testing.

[Alternative to Previous Paragraph for International Sites Only]

Your blood specimen will be stored safely and securely at a special facility called a specimen repository. The repository may be located in the United States. This facility follows strict procedures so that only approved researchers can use the stored specimen for future testing. The employees at this facility who will store and track your blood specimen will not have information that identifies you by name.

Risks: There are few risks involved with your participation in this study. Having your blood drawn may result in a little pain and slight bruising where the needle goes into your skin. You may also feel lightheaded, bleed, develop a small blood clot where the needle goes into your skin, or faint. Very rarely, your skin may get infected. Another small but unlikely risk is the possibility of others finding out about your participation in this study.

Benefits: You will not receive any direct benefit from your samples. Information obtained from the tests may provide useful information, to help other patients, about the causes, risks, and prevention of the COVID-19 virus.

WHAT IF YOU DON'T WANT YOUR BLOOD FOR GENETIC TESTING STORED ANY LONGER? If you sign the consent that your blood can be stored for research to be done at a later date you can change your mind at any time. If you change your mind, you must write a letter to ***[insert the name of the principal investigator*]** at the ***[insert the name and address of the site]*** to let them know that you do not want your blood specimen collected for this study used for future research. A sample letter will be given to you as a guide to help you express your request in writing.

When ***[insert the name of the principal investigator]*** receives your letter, the research staff will contact you to come to the clinic to verify your decision by signing and dating this original informed consent form. A second copy of this consent will be given to you as proof that we received your request. If we do not hear from you within 30 days after getting your letter to withdraw from this study, we will send your request to the storage facility.

If you decide to withdraw consent for this study, your blood sample, including any parts separated from the sample, will not be used. Every effort will be made to destroy your blood sample and any parts separated from it. If some testing has already been done on your blood sample, the results from this testing will remain as part of this research. The research staff at the ***[insert the name of the site]*** will notify you of the date your blood specimen and any of its parts were destroyed.

Costs or compensation of study: There will be no costs to you or compensation.

PID: _____

Consent: Please ***initial*** yes or no and ***sign your name***, indicating you have freely given your answers and consent:

- My blood samples may be stored for future genetic research in COVID-19 or other serious illness: **Yes** ____ **No** ____

_____ _____

Signature (subject or surrogate) Date

_____ _____

Signature of Person Obtaining Consent Printed Name and Title of Person

PID: _____

Appendix B Schedule of Assessments

	Screen or Day 0	**Day 0**	**Study Day**													
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**180**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+ 10**	**± 14**
ELIGIBILITY & BASELINE DATA																
Informed consent	X															
Baseline medical and social history	X															
Baseline concomitant medications	X															
Symptom-directed physical exam by the clinical team (includes vital signs)	X															
Nasal swab for virus detection and review SARS-CoV-2 test results	X															
Baseline study labs (CBC with differential, ferritin, CRP, BMP, INR, D-DIMER, AST, ALT, bilirubin)[2]	X															
Research sample storage (includes DNA and RNA at baseline among patients who consent to genetics)	X															
Urine pregnancy test or other documentation of pregnancy status	X															
STUDY INTERVENTION																
Randomization		X														

	Screen or Day 0	**Day 0**	**Study Day**													
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**180**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+ 10**	**± 14**
Study Drug/Placebo Administration[3]		X	X	X												
Assess infusion completion and adverse reactions[3]		X	X	X												
STUDY PROCEDURES																
Post-randomization concomitant medications		X	X	X	X	X	X	X	X	X[4]	X					
On-study labs (BMP, CBC with differential, INR, D-DIMER, AST, ALT, bilirubin)[2,5]		X	X	X												
Clinical labs (BMP, CBC with differential, INR, D-DIMER, AST, ALT, bilirubin)[5,6]					X		X[7]									
Research sample storage (includes RNA at day 3 among patients who consent to genetics)[4]					X		X[7]									
Vital signs[5]	X	X	X	X			X			X						
Hospitalization status					X		X		X	X	X	X	X	X	X	X
Changes in residence/facility										X	X	X	X	X	X	
Interim medical history									X	X	X	X	X	X	X[8]	X[8]
Oxygen support (for WHO/NIH/TICO ordinal outcome)	X	X	X	X	X	X	X	X	X	X[4]						

	Screen or Day 0	Day 0	Study Day													
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**180**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+10**	**±14**
Clinical AEs of grade 3 and 4 severity		X	X	X	X	X	X	X	X	X	X					
Clinical AEs of any grade on day indicated										X	X					
SAEs and PSESEs		Report through 90 days														
SAEs related to study interventions		Report as they occur														
Unanticipated problems		Report as they occur														
Deaths and readmissions		Report as they occur														
Hospitalization Summary		Report upon hospital discharge														

[1] Screening must be performed within 24 hours of randomization.
[2] These laboratory evaluations will only be performed as study procedures if they are unavailable clinically on that study day
[3] Duration of study drug administration may vary by investigational agent; the sample provided here is for 3 successive days. Where the duration of study drug administration varies from this schedule, the duration will be specified in the relevant agent-specific Appendix H .
[4] The Day 14 visit will record values for Days 8–14.
[5] These will be not be collected after hospital discharge.
[6] These laboratory assessments will only include clinically available results
[7] The Day-5 draw will occur only among patients who remain in the intensive care unit (ICU) or equivalent.
[8] Includes telephone administration of the Euro-QOL-5D-5L instrument.

Appendix C TESICO / ACTIV-3b protocol team

To oversee the implementation of this master protocol, a protocol team will be formed and include:

- Protocol co-chair(s)
- NIAID, Division of Clinical Research representatives
- NHLBI Program Officers
- INSIGHT University of Minnesota representatives
- INSIGHT International Coordinating Center representatives
- Representatives from collaborating trials networks, including PETAL, CTSN, and VA
- Representatives from collaborating laboratory representatives
- Representatives from collaborating manufacturers of investigational agents
- Representatives from site investigators
- Study biostatisticians
- Community representative(s)

A core team consisting of the co-chair(s), ICC leaders, NIH representatives, study statisticians, representatives from collaborating trials networks, and other representatives and the INSIGHT PI will also regularly convene to review study progress and address study conduct and administrative issues that arise.

Appendix D REFERENCES ON THE INSIGHT WEBSITE

The INSIGHT website (**www.insight-trials.org**) will maintain updated links to the following documents referenced in the INSIGHT 014 protocol and to other information pertinent to the study:

- DAIDS toxicity table: (https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables)

- INSIGHT Publications and Presentations Policy (http://insight.ccbr.umn.edu/resources/P&P_policy.pdf)

- Centers for Disease Control and Prevention (CDC) and European Centre for Disease Prevention and Control (ECDC) guidance on how to handle infection control measures (https://www.cdc.gov/sars/guidance/i-infection/healthcare.html and https://www.ecdc.europa.eu/en/publications-data/infection-prevention-and-control-and-preparedness-covid-19-healthcare-settings).

- Treatment guidelines, incl from NIH and WHO (https://www.covid19treatmentguidelines.nih.gov/, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/, https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation and https://www.ersnet.org/covid-19-guidelines-and-recommendations-directory)

Appendix E LIST OF ACRONYMS

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ACTT	Adaptive COVID-19 Treatment Trial
AE	adverse event
ARDS	acute respiratory distress syndrome
CDC	Centers for Disease Control and Prevention (US)
CHF	Congestive heart failure
CI	confidence interval
COVID-19	Coronavirus-Induced Disease 2019
CTSN	Cardiothoracic Surgical Trials Network
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
EU	European Union
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HR	hazard ratio
ICC	International Coordinating Center
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Institutional Ethics Committee
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IQR	interquartile range
IRB	Institutional Review Board
IV	intravenous

LAR	Legal Authorized Representative
MI	Myocardial infarction
mL	milliliter
NAT	Nucleic acid test (to identify genomic material; some uses amplification)
NHLBI	National Heart, Lung, and Blood Institute, NIH (US)
NIAID	National Institute of Allergy and Infectious Diseases, NIH (US)
NIH	National Institutes of Health (US)
NIHSS	National Institutes of Health Stroke Scale/Score
nMAb	Neutralizing Monoclonal Antibodies
OHRP	Office for Human Research Protections (US)
OR	odds ratio
PCR	polymerase chain reaction
PETAL	Prevention and Early Treatment of Acute Lung Injury Network
PHI	personal health information
PIM	Protocol Instruction Manual
RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TOC	trial oversight committee
UMN	University of Minnesota
UP	Unanticipated problem
US	United States of America
VA	Veterans Administration
WHO	World Health Organization

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Appendix H Investigational Agent.

This appendix will include the following information for each investigational agent studied. The rationale for studying the agent and the description and administration of the agent. Also, as appropriate, specific AEs observed to be possibly associated with the agent in question, and how to monitor for, clinically handle and report such AEs, should they arise. Changes in endpoint, SOC, inclusion and/or exclusion criteria, sample size estimation and approach to interim analyses and data analyses will also be included if appropriate for the investigation of the agent in question relative to what is stated in the master protocol. Finally, the text will also clarify whether the manufacturer of the investigational agent plans to pursue licensure in the countries where the trial will occur, should the investigational agent be demonstrated in the trial to have overall benefit.

Introduction/Rationale for studying the agent

  - Potential risks and benefits of agent
  - Motivation for agent selection with consideration of results from trials of other agents
- Agent-specific eligibility criteria
- Description of investigational agent
  - Administration and duration
  - Formulation and preparation
  - Supply, distribution, and accountability
  - Contraindicated medications
  - Precautionary medications
- Clinical and laboratory evaluations in addition to master protocol
  - Timing
  - Special instructions
- Clinical management issues
  - Infusion-related reactions
  - Hypersensitivity
- Pregnancy and breast-feeding considerations
- Criteria for discontinuation of infusion
- References

Appendix I Standard of Care

I1. Overview

Currently, the only licensed treatment for COVID-19 is remdesivir, but the *registration trials for remdesivir were too small to demonstrate efficacy in patients with critical illness from COVID-19.* Considering the number of randomized trials being conducted to study treatments for COVID-19, it is likely that other effective treatments will be identified during performance of this master protocol.

When treatments for COVID-19 are demonstrated to have safety and efficacy, those treatments should be considered in designing new studies. Depending on the scientific question, an experimental treatment will be coupled with or compared to a known effective treatment. When such known effective treatments are incorporated into both arms, they are called "background therapy" or standard of care (SOC). In this case, the scientific question addressed is whether a new treatment added to an already effective treatment is superior to the established effective treatment alone.

SOC may include general supportive care appropriate to the participant's clinical status, and specific therapeutic agents, and measures to reduce risk of SARS-CoV-2 transmission to the participant and health care givers.

As stated in section 5.1, the objective of this protocol is to evaluate investigational agents - aimed at treating patients with critical illness from SARS-CoV-2 infection - for safety and efficacy compared to placebo control, when all eligible participants receive background therapy that is considered effective. Consistent with precedent, we refer to background therapy as standard of care (SOC). All participants will receive an investigational agent + SOC vs. placebo + SOC.

Below, principles for defining SOC are provided, and recommendations and guidance on SOC are given. Whether an individual SOC treatment is provided by the trial or not is based on multiple factors, including clinical and scientific considerations. In some cases, the decision to administer an SOC treatment is left entirely to the research participant's primary medical team.

I2. Guiding principles for inclusion of measures as part of SOC

The SOC will be regularly updated based on review of the scientific literature and updated authoritative treatment guidelines on this topic. The standard for including one or more measures as SOC, includes a careful review of the existing literature and current guidelines (see Appendix D). As for therapeutic agents, those having been shown to be clinically effective in properly powered Phase III or Phase IV trials (i.e., high quality/level 1 evidence) and with a reasonable safety profile will be considered by the protocol team for inclusion, if recommended by at least one major treatment guideline. This evaluation may also lead to a statement that one or more agents are either not recommended or should not be used as part of SOC. As knowledge will likely continue to accumulate rapidly, the protocol leadership team may occasionally decide to include or exclude an intervention as part of SOC before it is recommended in at least one major treatment guideline. In such cases, the relevant literature that lead to the determination will be cited.

The use of a given SOC intervention may apply to all or to a subgroup of the participants in the master protocol based on available evidence – the subgroup may be defined based on severity of disease, a clinical or laboratory defined feature, or a clinically or laboratory defined contraindication for using the SOC treatment. An SOC agent may be mandated for participants (required for protocol entry); mandated where not contraindicated (participants may enter if that SOC is unsuitable, and not receive that SOC); or recommended subject to clinical discretion. SOC may be protocol-supplied where mandated.

The master protocol acknowledges that there may be local variation in the clinical availability of one or more agents chosen to be part of mandated protocol-supplied SOC from site to site. While acknowledging risks of inadvertent coercion, the importance of the scientific question (how candidate agents perform against the background of the current SOC treatments) is a crucial, high-priority question. There is no possible way to answer the question of efficacy against the background of an already proven effective agent without providing the agent – if not readily available - within the trial.

I3. Current SOC in the master protocol:

I3.1 Remdesivir

Although remdesivir is licensed for use in the United States and is SOC for most hospitalized patients with COVID-19, the key registration trials[50] included insufficient patients in this subgroup to provide strong evidence in favor of remdesivir for critically ill patients. It is anticipated that this master protocol may include a placebo-controlled investigation of remdesivir, possibly in a factorial design, in this patient population. Thus remdesivir is not considered SOC presently for this protocol: the protocol does not recommend routine initiation of remdesivir in this patient population (except potentially as an investigational agent). For patients who have already initiated remdesivir by the time of enrollment, this protocol makes no recommendation regarding whether to continue or discontinue remdesivir as part of background therapy. (For patients enrolling in a remdesivir randomization, see the remdesivir appendix for further guidance on receipt of remdesivir prior to randomization.)

I3.2 Dexamethasone and Other Corticosteroids

Based on the findings of the RECOVERY trial,[39] a meta-analysis of glucocorticoid trials,[51] and in line with NIH treatment guideline (Appendix D), it is recommended to consider initiation of corticosteroid therapy in participants with COVID-19 who have respiratory failure—the target population of this master protocol. Corticosteroids may increase the probability of reactivating latent infections including herpes viruses and tuberculosis, hyperglycemia, hypernatremia, secondary infections, and may delay clearance of SARS-CoV-2, but the balance of evidence favors glucocorticoid therapy. Treatment with a corticosteroid is recommended for a total of 10 days, using doses outlined in this table.

Corticosteroid name	Daily dose
Dexamethasone	6 mg PO or IV
Prednisone	~40 mg PO
Methylprednisolone	~32 mg IV
Hydrocortisone	~160 mg IV

I3.3 Other Supportive Care

All participants will be given *supportive care* for most complications of severe COVID-19 including: pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization, including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy. Links to details of such care can be found in Appendix D. Supportive care components of SOC include lung-protective ventilation for patients who require invasive mechanical ventilation[52] (high quality evidence) and prone positioning for mechanically ventilated patients with more than moderate ARDS (high quality evidence[53,54]), treatment with anti-bacterial agents for patients believed to have bacterial infection (high quality evidence), guidelines-compliant management of sepsis when it is present (moderate quality evidence).[55] Use or non-use of extra-corporeal life support (ECLS) is not mandated as part of SOC; nor is any specific approach to renal replacement therapy.

Consideration should be given to the use of pharmacological thromboprophylaxis (thrombosis prevention) in line with local clinical guidelines for hospitalized patients as appropriate for an individual participant, in addition to approaches to maintain mobility and minimize other thrombotic risks. Standard approaches to thromboprophylaxis supported by high quality evidence include the use of low molecular weight heparin (for example, enoxaparin 0.5 m/kg daily), which is the preferred agent in some COVID-19 treatment guidelines. However other standard approaches in accordance with local and institutional guidelines and the medical circumstances of an individual participant may also be considered, including the use of low (prophylactic) dose unfractionated heparin (high quality evidence). Specialist advice should be sought for participants with pre-existing prothrombotic states, or who are pregnant.

I3.4 Cautions and Contraindications

It is not recommended to use chloroquine as SOC due to excess harm and no demonstrable benefit. Neither hydroxychloroquine nor chloroquine have documented clinical benefit, and hence are not recommended for use as SOC. Similarly, it is not recommended to use lopinavir/ritonavir as SOC, since there are studies suggesting no clinical benefit.[56,57] These recommendations are consistent with current guidelines by the Infectious Disease Society of America, as included in Appendix D.

I3.5 SARS-CoV-2 Infection Control

Minimum standards of protection to *reduce the risk of SARS-CoV-2 transmission* from trial participants to research personnel, participants in other trials, or patients treated in the same facility can be found in links displayed in Appendix D.

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TESICO Appendix H1: Aviptadil version 1.0, 15MAR2021 (corrections made 01 Apr 2021)

The content of this appendix is confidential and should only be viewed by persons covered by the relevant CDA between NIAID and the collaborating companies.

This appendix provides detailed information pertaining to the study of this investigational agents. If not stated otherwise in this appendix, the text in the TESICO master protocol provides the approach that will be taken to study this agent.

The principal difference of the study of this agent with the master protocol is that it will be studied, in part, using a 2x2 factorial design with remdesivir. Study objectives, randomization and data analyses take this factorialization into account and are described in Appendix H2 for remdesivir.

At the outset of this study, there will not be a shared placebo with another investigational agent.

1. Introduction and rationale for studying aviptadil

Vasoactive Intestinal Peptide (VIP; aviptadil is the generic name for the synthetic peptide) is a 28-amino acid signaling peptide that belongs to the glucagon-secretin superfamily. VIP is an abundant biologically active peptide endogenous in humans as well as in other species. It is produced by neurons in the peripheral and central nervous system, by endocrine cells such as pituitary lactotrophs, cells of the endocrine pancreas as well as T-lymphocytes, and B-lymphocytes. This natural peptide is one of the signal molecules of the neuroendocrine-immune network. VIP is an inhibitory neurotransmitter that binds G-protein coupled receptors named VPAC1 and VPAC2, generally leading to an increase in cAMP in target cells. Originally described in the intestinal tract,[1] it is expressed widely in the body, with multiple functions. The lung is the primary location of binding of VIP, as evidenced by radiolabeled VIP perfusion experiments (within 30 minutes, 45% of all infused VIP is bound in the lung, with minimal binding in other organs[2]). Cells expressing VIP receptors in the lung include vascular and bronchial smooth muscle cells as well as alveolar type 2 cells (ATII).[3] Critically, ATII cells are also a primary target for SARS-CoV2, the virus causing COVID-19.

The effects of aviptadil are pleiotropic, with key effects being (1) antiviral effects, (2) immune modulation, (3) increase in ATII surfactant production, (4) ATII cell protection, (5) smooth muscle relaxation (leading to bronchodilation and vasodilation), (6) decrease in platelet activation.

Antiviral effects. VIP is known to decrease HIV production within monocytes,[4,5] which drove interest in evaluating antiviral properties for SARS-CoV2. In a series of experiments, Temerozo and colleagues established that VIP decreased viral replication within infected Calu-3 cells (an immortalized lung cancer cell line), plus increased monocyte and Calu-3 viability after SARS-CoV2 infection.[6] These experiments also established that VIP treatment decreased the production of inflammatory cytokines within SARS-CoV2-infected monocytes.[6]

Immune modulation. VIP has multiple immune-modulatory effects.[7] In the lung, VIP decreases inflammation through multiple interdependent mechanisms, including inhibition of effector T cells and supplementation of regulatory T cells, with an associated decrease in local cytokines, as observed in sarcoid.[8] In a rat ATII cell model of smoke-associated lung inflammation, VIP decreased inflammation and proteinase activity.[3] Similar pre-clinical data in sepsis demonstrated decreases in TNFa and TGFb with VIP administration.[9-11] In terms of post-inflammatory injury, VIP has been shown to decrease myofibroblast proliferation in cell models.[12]

Surfactant production. In a lung explant model, VIP directly increased phosphatidylcholine production via PKC and C-Fos mechanisms.[13,14] In a similar model, VIP increased surfactant protein A production in ATII cells.[15]

ATII cell protection. VIP prevents apoptosis of ATII cells via multiple mechanisms including Granzyme and Fas-ligand.[16,17] In multiple animal models of ARDS, VIP is protective against acute lung injury.[17-21]

Smooth muscle relaxation. VIP is a non-adrenergic pulmonary and systemic vasodilator that in ex vivo pulmonary artery is substantially more potent at muscle relaxation than prostacyclin.[22] The increases in muscle relaxation are independent of the endothelium. VIP is also a direct bronchodilator based on relaxation of bronchial smooth muscle.[23] In a cat bronchoconstriction model, intravenous (but not inhaled) VIP resulted in significant bronchodilation.[24]

Platelet effects. VIP inhibits pro-inflammatory platelet activation via inhibition of platelet activating factor.[25]

These mechanistic observations in cell and animal models have been corroborated in various human observations in a variety of conditions, including ARDS and COVID-19.

Clinical experience with aviptadil

Non-randomized data in other disease states

Sarcoidosis. Twenty patients with chronic sarcoidosis were treated with nebulized aviptadil, which was associated with increases in regulatory T cells and decreases in macrophage activation.[8] There were no important safety concerns.

Checkpoint inhibitor pneumonitis. Inhaled VIP was used successfully to treat pneumonitis caused by checkpoint inhibitor therapy in a patient with advanced melanoma. The pneumonitis had recurred after an initial course of steroid therapy, and VIP was used in hopes of avoiding a second course of steroids.[26] The patient recovered from the pneumonitis, and no safety concerns were identified.

Pulmonary hypertension. Twenty patients with pulmonary hypertension (PH) of various etiologies received 100mcg of inhaled VIP during right heart catheterization, with an immediate decrease in vascular resistance. Among patients with lung disease as the cause of PH, increases in oxygen saturation were observed.[27] Similar results were observed in a smaller cohort of PH patients.[28] No important safety concerns were identified.

Non-randomized data in ARDS and COVID-19

Currently, there are multiple case reports and case series of patients with either septic ARDS or COVID-19 ARDS who have been treated with intravenous VIP or in whom biological samples have been collected.

In the mid-2000s, Youssef, Said and colleagues treated 8 patients with septic ARDS with VIP. They used 50 pmol/kg/hr in 5 patients, of whom one had hypotension requiring decrease to 25 pmol/kg/hr. The other three patients received 100 pmol/kg/hr, in whom one patient required temporary reduction (to 85 pmol/kg/hr) for hypotension. The target dosing duration was 6 or 12 hours. (An intended increase to 150 pmol/kg/hr was not undertaken because the senior author retired.) All but 2 patients

survived their ARDS.[29] VIP infusion appeared safe and feasible, and mortality appeared to be on the low end for septic ARDS, suggesting possible clinical efficacy.

During the COVID-19 pandemic, Youssef and colleagues studied 21 patients receiving intravenous aviptadil under an expanded access program (EAP). The patients receiving aviptadil were compared to non-randomized concurrent controls who were either admitted by physicians who were not investigators on the VIP trial or in the two weeks before and after this cohort was assembled. Four-week survival in the EAP cohort (primarily but not exclusively patients with immune suppression or undergoing ECMO therapy who were excluded from a concurrent randomized trial) was 90%; 4 of 5 ECMO patients were "successfully decannulated." All patients were treated with glucocorticoids, 18 of 21 patients were treated with tocilizumab, and 6 of 21 were treated with remdesivir before VIP infusion. Hypotension occurred in 5 of 21 (24%) of patients receiving VIP infusion, primarily among those on ECMO and/or receiving vasopressors. In the other 16 patients, blood pressure was stable or improved during aviptadil infusion. Diarrhea was present in 4 of 21 patients; prophylactic or therapeutic loperamide was used in 86% of patients. The survival among the non-randomized concurrent controls was substantially lower, suggesting possible clinical efficacy. Approximately 200 patients have been studied under this EAP at multiple centers in the United States as of December 16, 2020. Reports from the full EAP cohort are pending.

In terms of observational data, Temerozo et al studied 24 patients with severe COVID-19 (i.e., requiring ICU admission), demonstrating significantly higher endogenous VIP levels among survivors than non-survivors.[5] In this observational cohort, no aviptadil was administered.

Randomized data in COVID-19. A randomized controlled trial (NCT04311697) has enrolled 196 patients (2:1 randomization) using the same intravenous dosing schedule as the Phase 1 trial in septic ARDS patients and the COVID-19 EAP experience. Final results from this trial are pending; preliminary results suggested survival of 71–72% at 28 days in both groups with exploratory signals suggesting possible benefit in time to recovery in the largest subgroup, those receiving high-flow nasal cannula at randomization. The DSMB did not identify any important safety concerns during interim monitoring; hypotension has been uncommon and has not generally resulted in changes to aviptadil infusion. Mild-moderate diarrhea occurred in approximately a third of patients.

1.1 Potential risk and benefits from aviptadil

Primary effects of VIP infusion, generally dose dependent, include facial flushing, increase in heart rate, decrease in blood pressure, and diarrhea. Effects on renal function and fluid status are transient and mild, with the possible exception of patients with advanced liver disease.

Facial flushing is common with VIP and is not dangerous. It is generally well tolerated and resolves when the VIP infusion is stopped. It is caused by dilation of cutaneous vasculature.

Increases in heart rate are common and rarely clinically significant. The increase in heart rate primarily reflects changes in cardiac preload and an adrenergic response to decreased afterload.

The primary known risk of intravenous VIP infusion is of decreased blood pressure. The clinician investigators with the most experience with the agent report (personal communication) approximately 25% incidence of hypotension during infusion in ICU patients with shock present before initiation of VIP. These rates are observed in treatment protocols that do not exceed 150 pmol/kg/hr. When present, the decrease in blood pressure appears to be approximately 10% of mean arterial pressure

(e.g., a decrease from 80 mmHg to 72 mmHg). In other settings (generally healthy volunteers at higher doses), a modest decrease in mean arterial pressure in most (but not all) studied populations has been observed. This is generally in the range of 10–15% decrease in MAP. The findings in normal volunteers are presented in Table 1.

Table 1. Hypotensive Effects Observed During VIP Infusion in Phase 1 or Similar Experience

Patient type	Patients infused with VIP	Rate in pmol/kg/hr	Blood pressure change	Study
Stable patients with stable cancer	79	300 pmol bolus (not adjusted for body mass)	7mm Hg nominal decrease (probably not significant)	Virgolini et al[2]
Healthy volunteers	6	400 pmol/kg/hr	MAP decrease by 12%	Frase et al[30]
Healthy volunteers	6	180 pmol/kg/hr	MAP decrease by 15%	Erikkson et al[31]
Healthy volunteers	8	360 pmol/kg/hr	MAP decrease by 5–10%	Unwin et al[32]
Healthy volunteers	4	198 pmol/kg/hr	DBP decrease by 15%/stable SBP	Domschke et al[33]
Healthy volunteers	6	360 pmol/kg/hr	MAP decrease by 7%	Calam et al[34]
Healthy volunteers	22	400 pmol/kg/hr	No change in blood pressure	Krejs et al[35]
Healthy volunteers	2	720 pmol/kg/hr	No change in blood pressure	Unwin et al[36]
Outpatient asthmatics	7	360 pmol/kg/hr	DBP decrease by 10%/stable SBP	Morice et al[37]
Cirrhotic patients	6	360 pmol/kg/hr	BP decrease by 10%	Calam et al[38]
BP: blood pressure; MAP: mean arterial pressure; DBP: diastolic blood pressure; VIP: vasoactive intestinal peptide				

The infusion rates used in this study are substantially lower than those used in healthy volunteers. Relevant to the proposed population for TESICO is the experience with aviptadil administered to patients with ARDS at infusion rates ranging from 50 to 150 pmol/kg/hr. In patients with septic ARDS, approximately 25% of patients encountered some decrease in blood pressure during infusion.[29] In the EAP experience with aviptadil for COVID-19 (unpublished data supplied to investigators by NeuroRX), which included patients on vasopressors, ECMO, CRRT, approximately 25% had hypotension during infusion, while the balance of patients either had stable or increased blood pressure, including several patients who weaned off vasopressors during aviptadil infusion. In the preliminary results of the randomized trial, hypotension was observed in 25.2% of aviptadil patients and 18.5% of placebo patients.

Diarrhea, which can lead to bicarbonate wasting and metabolic acidosis, was observed in 5 healthy volunteers receiving 400 pmol/kg/hr of VIP, reproducing the syndrome of “pancreatic cholera” associated with VIP-producing tumors.[39] Youssef and colleagues report (personal communication)

that the diarrhea observed during infusion rates of 50–150 pmol/kg/hr are easily managed with enteral loperamide.

Hemoconcentration, presumably through diarrhea, has been observed with VIP infusion, primarily manifesting as a modest increase in hematocrit or serum albumin concentration. While urine output may decrease during aviptadil infusion, the glomerular filtration rate (GFR) does not.[34] The hemoconcentration does not persist after discontinuation of aviptadil infusion.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of aviptadil may be found in the Investigator's Brochure(s) (IB) and Participant Information Leaflet.

Given the high morbidity and mortality of COVID-19 ARDS, the short half-life of aviptadil, the close monitoring and early detection of abnormal vital signs present in the settings where the trial will be performed, and the ease of management of expected adverse events in care environments treating critically ill patients, the overall benefit-risk assessment of this study is considered favorable in the clinical settings where the trial will be performed.

1.2 Motivation for agent selection by the ACTIV Agent Selection Committee (ASC) and Trial Oversight Committee (TOC)

The ACTIV Agent Prioritization Committee (APC) Subteam reviewed the NeuroRX agent aviptadil (VIP) and voted in favor of the agent proceeding into ACTIV-3, and the TOC endorsed that recommendation. NeuroRX's aviptadil was supported because it binds to VPAC receptors on the pulmonary Alveolar Type II cell that is a selective target of SARS-CoV-2. The agent has suggested positive effects on lung function and clinical outcomes in small clinical studies of ARDS.

While the reviewers noted the mechanism of action in SARS-CoV-2 infection is not yet well elucidated, some published preclinical tests show a ~50% reduction in viral replication in infected Calu-3 cells, suggesting partial efficacy as an antiviral[5]; however, the agent has shown promising effects in clinical trials against SARS-CoV-2. In addition, the company provided a preprint of in vitro data, which suggests that this compound is efficacious as an antiviral. The Subteam also noted that its target within the host is a good candidate for preventing fluid accumulation and inflammation in the lung, which is a major factor in COVID-19, and the natural endogenous peptide is increased in survivors of severe COVID-19. Aviptadil is available in both IV and nebulized formulations, but the inhaled version may cause some nasal and respiratory epithelium degeneration; thus, the IV formulation is preferred for this trial. At the time of APC review, the Phase 2a trial of 50–150 pmol/kg/hr was close to completion—the company shared promising interim results from that trial.

Based on the positive response to the data presented for the agent, the Subteam discussed which ACTIV trial platform should test it. The agent already has safety data from indications other than COVID-19, which could allow it to proceed to a Phase III trial. The Subteam selected ACTIV-3 for effective testing of the agent, and the agent would fill a void in the more severely ill patients screened for that trial that are not eligible for the neutralizing antibodies currently being tested in the trial.

Finally, the APC Subteam found the manufacturing and scalability strategy for aviptadil sufficient for the full trial and beyond.

Statement regarding plans for licensure: NeuroRx, Inc., has filed IND 149,152 for Intravenous Use of Aviptadil with the FDA and been awarded Fast Track designation. FDA has indicated in writing that

all preclinical data have been submitted that are required for NDA and that an NDA would be accepted based on efficacy as demonstrated in adequately controlled studies. EMA licensure will be sought by Relief Therapeutics AG (Geneva, Switzerland).

1.3 Justification for dose selected

Given temporal constraints imposed by the pandemic, selection of the dose and duration of therapy are based on preliminary observations from multiple sources, which together provide a reasonable basis for the dose and duration selected. Lines of evidence include pre-clinical observations, observations from cell models of SARS-CoV-2 infection, known serum pharmacokinetics, rapid trafficking to and accumulation in the target organ, lung, and an observational human cohort suggesting relevant differences in serum VIP concentrations between survivors and non-survivors.

Half life of VIP. The well-established serum half-life of VIP, due to degradation by serum peptidases, is 1 minute. In dogs, only repeat daily administration for 4 weeks was associated with effects that persisted for more than a few minutes after discontinuation of the infusion. The precise elimination dynamics from lung are not well established, but empirically, the accumulation of aviptadil in lung increases over time. In addition, concentrations in serum slowly increase over the course of a prolonged infusion.

Observations from cell models of SARS-CoV-2 infection. Temerozo and colleagues identified in multiple cell models of SARS-CoV-2 infection that a VIP concentration of approximately 10nM provided maximal anti-viral and cell-protective effects, especially in lung cells (Calu-3 cells) and monocytes. In some additional experiments, concentrations of 1nM demonstrated a relevant effect.[6]

An observational cohort of patients with COVID-19 ARDS. In a complementary observational cohort of 24 patients with severe COVID-19, Temerozo and colleagues demonstrated that VIP levels of 10–12 pg/ml were present among non-survivors (N=13), as opposed to 20 pg/ml among survivors (N=11). While these data are observational and do not provide causal evidence of the effect of ~10 pg/ml change in serum VIP levels, they nevertheless suggest the possibility that increases in VIP levels may be clinically relevant.

Expected blood and/or lung levels achieved with a given infusion. The infusion rates necessary to achieve serum levels have been demonstrated in pre-clinical experiment in dogs. Unverferth and colleagues infused 0.02 and 0.05 mcg/kg/min (360 and 900 pmol/kg/hr, respectively) in 12 dogs. The dogs had a baseline VIP blood level below the level of detection (<50 pg/ml), and the two infusion rates achieve blood levels of 540 pg/ml and 1200 pg/ml, respectively.[40] Extrapolating from these experiments (assuming a consistent relationship between infusion rate and resulting blood concentrations), 50 pmol/kg/hr would be expected to result in 71 pg/ml, and 100 pmol/kg/hr would result in 143 pg/ml in this model. These blood levels are substantially higher than those observed among survivors in the Temerozo cohort and also substantially higher than the difference between survivor and non-survivor VIP levels.

In a 10-hour infusion of 400 pmol/kg/hr of VIP among healthy volunteers, blood VIP levels rose over the course of infusion, achieving 782 pg/ml by the end of the 10-hour infusion.[39] Extrapolating this observed relationship between infusion rate and resulting blood concentrations to a 100 pmol/kg/hr infusion rate, we anticipate a blood level of 195 pg/ml by the 10-hour timepoint.

Following an intravenous dose, aviptadil rapidly distributes into tissue with approximately 45% of the dose distributing to the lungs within 30 minutes of administration.[2] The apparent volume of distribution

following a 300 pmol dose is 135 mL/kg. Therefore, an initial aviptadil plasma concentration is estimated to be 0.03 nM for a 70 kg patient for which 45% of the plasma concentration is anticipated to be distributed into the lungs. Assuming dose-proportionality and drug-tissue accumulation, where dose escalation proportionally increases drug exposure, a 100 pmol/kg/hr aviptadil dose over 12 hours is estimated to achieve pulmonary concentrations within 10 nM for a 70 kg patient. A 150 pmol/kg/hr for 12 hours would with greater confidence achieve 10nM in lung. The 10nM concentration in lung is specific to a cell model of SARS-CoV-2 infection; lower concentrations may be protective. Extrapolation from serum concentrations suggest that rates as low as 50 pmol/kg/hr may have efficacy. The time course of subsequent decreases in lung concentrations is not well established, but the approach of interrupted infusion envisioned in this protocol is thought to represent the optimal balance of risk and benefit on the basis of current information.

Clinical experience. When Said and colleagues selected the range of doses/durations for the initial phase 1 trial in patients with septic ARDS,[29] they did so in the context of the infusion rates that were well tolerated in healthy volunteers (~300–400 pmol/kg/hr) and the awareness that even low infusion rates were associated with substantial increases in plasma VIP levels. That phase 1 trial envisioned dose escalation in small cohorts of patients, from 50 pmol/kg/hr for 6 hours up to 150 pmol/kg/hr for 12 hours. The investigators completed dosing through the 100 pmol/kg/hr for 12 hours (3 patients treated at that infusion rate). According to investigators (personal communication), VIP was infused daily for 3 days in the Phase 1 trial.

The COVID-19 experience to date (~200 patients in a 2:1 randomized trial and another ~200 treated open label under an expanded access program [EAP]) have employed a sequential dose escalation strategy, in which a 12-hour infusion is performed daily for 3 days. The initial dose is 50 pmol/kg/hr, followed on day 2 by 100 pmol/kg/hr and on day 3 by 150 pmol/kg/hr. Treatment is not continued after the patient leaves the ICU. If a patient develops intolerance at a given infusion rate, the infusion period is increased (commonly to 18 hours) without a change in the overall dose administered. These rates have been reasonably well tolerated (personal communication). The EAP experience (compared with non-randomized concurrent controls) suggested the possibility of clinical efficacy; the Phase 2a trial has not yet read out. Unpublished reports (personal communication from Dr. Youssef) from the EAP experience suggest that intolerance may be somewhat higher at the conclusion of the 100 pmol/kg/hr infusion and with the 150 pmol/kg/hr infusion among patients with ARDS and shock.

The maximum infusion rate used to date in COVID-19 (150 pmol/kg/hr) is substantially below the infusion rates used in healthy volunteers (300–400 pmol/kg/hr) which either elicited no hypotension or elicited an average of 10% decrease in mean arterial pressure. The approach taken in the present trial is thus designed to optimize tolerability while achieving adequate blood levels and lung tissue concentrations of aviptadil.

Given this context and background, the vanguard cohort of 40 participants (see below) is planned to evaluate and fine-tune the approach to managing aviptadil infusions and further assess anticipated feasibility/tolerance in the target population.

1.4 Vanguard cohort

In order to assure timely and sufficient evaluation of aviptadil using an optimal approach to managing aviptadil infusion in this target population, a vanguard cohort will be incorporated. It is recognized that prior experience with aviptadil in similar populations appears to be safe and well-tolerated, and that additional insights relevant to the conduct of the present trial can be gleaned from a vanguard cohort. The target population for the vanguard cohort will be identical to the overall trial, with the exception of the requirement that vanguard participants be admitted to an intensive care unit to facilitate more

intensive monitoring. The vanguard cohort will be limited to approximately 10 sites and approximately 40 patients (randomized 1:1 to aviptadil vs. control). The focus in the vanguard cohort will be in understanding the usability and feasibility of infusion management guidelines and making minor adjustments to “fine-tune” the infusion guidelines. Investigators will received blinded adherence reports for receipt of study drug infusion as would be typical of a DSMB open report. Extensive unblinded data will also be provided on a weekly basis to the DSMB, detailing blood pressure, heart rate, vasopressors, fluid administration as well as data on the study drug infusions. These features will be monitored during the infusions and through 2 hours after the conclusion of the infusion.

In order to protect the overall blind and allow inclusion of vanguard participants in the final analytic cohort, investigators will only review (1) interviews with treating clinicians and site investigators regarding the utility and clarity of the infusion management guidelines, (2) blinded aggregate data on adherence with study drug infusion, and (3) recommendations from the DSMB. Standard firewalls between the DSMB and investigators will be maintained during the vanguard cohort.

The vanguard cohort is intended to assess and finetune guidelines for study drug infusion management. It is recognized that the small size of the vanguard cohort will not support conclusive inferences about safety or efficacy and is focused on feasibility and tolerance. If experience with the vanguard cohort reveals that the original infusion management guidelines are infeasible, the infusion management guidelines may undergo modification. If necessary, a second vanguard cohort may be enrolled to allow further assessment of feasibility/tolerance and further finetuning of the approach to management of aviptadil infusion. If a second vanguard cohort is required, the patients in the first vanguard cohort will not be included in the final trial analysis.

In general modifications to infusion management guidelines will not require an enrollment pause or protocol amendment, but will be managed through a protocol clarification memo and revision to the case report forms and PIM. The DSMB will also advise the study team and sponsor on the need for changes (or not) to the informed consent based on the experience in the vanguard cohort.

2. Agent-specific eligibility criteria

2.1 There is no change in inclusion criteria for this agent

2.2 Agent specific exclusion criteria

- *Refractory hypotension*, defined as infusion of vasopressors at or above norepinephrine equivalent of 0.1 mcg/kg/min (or infusion of more than one simultaneous vasopressor) in prior 4 hours to maintain MAP > 65 mmHg OR systolic blood pressure <90 mmHg or MAP < 65 mmHg at time of enrollment (or randomization, if the patient has already been enrolled) confirmed on two consecutive measurements at least 5 minutes apart (if a single measurement meets those criteria, a second measurement is required). Since aviptadil may induce hypotension, as noted above, patients with critical hypotension have a different risk:benefit profile that is less likely to favor aviptadil even where aviptadil is efficacious.
- *Severe diarrhea*, defined as 3 or more liquid bowel movements within the last 24 hours. Since diarrhea is a common side effect of aviptadil, if patients already have severe diarrhea, they may have a different risk:benefit profile that is less likely to favor aviptadil.
- *Current C. difficile infection (CDI)*. CDI generally causes diarrhea, its severity is often gauged in part by the volume of diarrhea, and anti-motility agents that may be used to manage aviptadil-associated diarrhea are contraindicated in CDI. These factors suggest that the risk:benefit ratio in patients with CDI may not be favorable.

- *Pregnancy or current breast-feeding*. Aviptadil was associated with involution of embryos in animal models and may be associated with changes in visceral and/or placental perfusion. It is thus felt not appropriate to infuse aviptadil in pregnant patients or in women who are breastfeeding.
- *End-stage liver disease (ESLD)*, defined as hepatic decompensation in a person with or without cirrhosis, usually associated with ascites (fluid in the peritoneal cavity), jaundice, variceal hemorrhage or hepatic encephalopathy (confusion, change in behavior, forgetfulness). Liver function tests and/or coagulation profile are usually abnormal. An isolated elevation in serum bilirubin does not meet criteria for end-stage liver disease.

3. Description of investigational agent

3.1. Administration and duration
The approach to infusion is based on prior clinical experience with the use of aviptadil. Aviptadil is infused over 12 hours per day for three days. The day 1 infusion rate is 50 pmol/kg/hr, the day 2 infusion rate is 100 pmol/kg/hr, while the day 3 infusion rate is 150 pmol/kg/hr. The primary factors defining intolerance to aviptadil infusion are hypotension or diarrhea. The PIM will include infusion management guidelines to assist clinicians in responding to hypotension or diarrhea among patients receiving aviptadil. The total volume of the infusion (aviptadil vs. saline placebo) is approximately 100ml per day.

3.2. Formulation and preparation
Aviptadil is a sterile drug product that must be formulated by a hospital pharmacist under sterile conditions according to the supplied pharmacy manual. Formulation is in 0.9% sodium chloride, with standard mixing procedures. Standard intravenous bags and tubing are used. Dosing is at 50/100/150 pmol/kg/hr.

3.3 Supply, distribution, and accountability
Procedures for ordering and accepting drug, for maintaining inventory of aviptadil, and for breaking the blind in the event of a medical emergency will be described in the Pharmacy Procedures.

3.4. Contraindicated medications
There are no known contraindicated medications. There is a theoretical consideration about use of nitric oxide or prostanoid therapy, but there is no compelling data to date to suggest that such medication should be restricted. Use of pulmonary vasodilators will thus be tracked with concomitant medications.

3.5. Precautionary medications
The clinical site should have necessary equipment and medications for the management of any infusion reaction. These include capacity to monitor vital signs, ability to infuse and monitor vasopressor agents if necessary, and capacity to manage diarrhea and electrolyte loss. Unrelated to aviptadil but centrally related to COVID-19, sites must be able to manage progression of respiratory failure.

4. Clinical and laboratory evaluations

Clinical and laboratory evaluations will follow the master protocol schedule of assessments.

4.1 Timing of Assessments

All assessments are outlined in the relevant section of the master protocol.

4.2. Pharmacokinetic Assessments

Pharmacokinetic assessments are being performed in a Phase 2 trial performed by NeuroRX.

5. Clinical management issues

All participants should be monitored closely for hypotension and diarrhea and any additional adverse events, with special attention to treatment-emergent adverse events.

5.1. Symptoms and Signs

Symptoms and signs that may occur as part of an infusion reaction, include, but are not limited to, decrease in mean arterial pressure, diarrhea, facial flushing. Infusion-related reactions' severity will be assessed and reported using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected version 2.1.

5.2. Site Needs

The clinical site should have necessary equipment, medications, adequately qualified and experienced staff with appropriate medical cover for the management of any infusion reaction, which may include, but is not limited to, hypotension and diarrhea.

5.3. Management of Infusion Reactions including Discontinuation

Infusion of aviptadil or its placebo will be guided by infusion management guidelines in the context of clinician judgment. If the complete infusion is not administered, all follow-up procedures and reporting outlined in the master protocol should be adhered to as indicated.

6. Agent-specific safety monitoring activities

Safety monitoring for aviptadil is specified in the master protocol, with two modifications. First, two additional components relevant to aviptadil infusion will be added to the composite safety outcome: (1) new or worsening hypotension and (2) worsening respiratory failure. Second, diarrhea will only be included in the composite safety endpoint if it is a serious adverse event or results in decrease or discontinuation of study drug infusion. There is no change to the safety monitoring schedule displayed in Table 3 of the master protocol.

Note that as part of the oversight of this trial, the DSMB will review unblinded safety data weekly during the trial.

Hypotension is defined as low arterial blood pressure/perfusion leading to (1) initiation or increase in vasopressor therapy, (2) administration of an intravenous fluid bolus (≥500 ml of crystalloid solution or equivalent volume of colloid), or (3) modification or discontinuation of study drug infusion. While the master protocol composite safety endpoint includes both hypotension and organ dysfunction by definition, the trial will also separately report hypotension (as defined in this paragraph) associated with organ dysfunction.

Worsening respiratory failure is defined as an increase in the level of respiratory support from high-flow nasal cannula to mechanical ventilation or from non-invasive ventilation to invasive mechanical ventilation. For patients receiving invasive mechanical ventilation at baseline, worsening respiratory failure is defined as receipt of extracorporeal life support.

Diarrhea is common with aviptadil and is generally well managed with loperamide in prior clinical experience. To avoid mistaken inferences regarding safety, diarrhea is not included in the composite safety outcome (as would otherwise be the case for, e.g., diarrhea treated with loperamide, which would generally be classified as a grade 3 adverse event) unless it is an SAE or leads to discontinuation of study drug.

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TESICO Appendix H2: Remdesivir v 1.0 (15MAR2021) (corrections made 01 Apr 2021)

The content of this appendix is confidential and should only be viewed by persons covered by the relevant CDA between NIAID and the collaborating companies.

This appendix provides detailed information pertaining to the study of remdesivir when studied alone and in combination with aviptadil. Although remdesivir is licensed for use in the United States and is standard of care for most hospitalized patients with COVID-19, the key registration trials[1] included insufficient patients in this subgroup to provide strong evidence in favor of remdesivir for critically ill patients. Thus, randomization to remdesivir versus placebo is a key component of this trial.

Remdesivir is not considered standard of care for this protocol: the protocol does not recommend routine initiation of remdesivir in this patient population. For patients who have already initiated remdesivir by the time of enrollment, this protocol makes no recommendation regarding whether to continue or discontinue remdesivir as part of background therapy. The core question being evaluated by this protocol is whether to start (or not to start) remdesivir among patients with ARDS from COVID-19.

Following a description of our rationale for studying remdesivir and description of the study agent, we state the objectives of the factorial study of aviptadil and remdesivir, describe the study design, and provide an overview of the planned analyses.

If not stated otherwise in this appendix, the text in the TESICO master protocol provides the approach that will be taken to study these agents

1. Introduction and rationale for studying remdesivir

Remdesivir is an adenosine nucleotide prodrug with antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Specifically, remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA.

COVID-19 is caused by infection with SARS-CoV-2, which requires viral replication. While such replication initially occurs in the upper respiratory tract, a transition to the lower respiratory tract and other tissues marks disease progression, which may develop into COVID-19 pneumonia. In the most severe stage of the disease, COVID-19 presents as ARDS; at this stage of illness, both ongoing viral replication and dysfunctional immune activation contribute to morbidity and mortality.[2] Importantly, RNA-emia is more prevalent in COVID-19 ARDS than in mild-to-moderate disease; in addition, levels of RNA in blood are prognostic among COVID-19 ARDS patients.[3] These observations suggest the possibility that anti-viral therapies may be of use in patients with COVID-19 ARDS.

In the Adaptive COVID-19 Treatment Trial 1 (ACTT-1) trial, remdesivir administered once daily for up to 10 days reduced time to recovery in hospitalized patients with COVID-19.[4] The rate ratio for recovery was largest in patients receive low flow rates of oxygen at baseline (ordinal category 5, rate ratio for recovery, 1.45; 95% CI, 1.18 to 1.79) and among patients without supplemental oxygen at baseline (ordinal category 4, rate ratio 1.29; 95% CI, 0.91 to 1.83). However, the clinical impact was uncertain for patients receiving baseline high flow oxygen or non-invasive ventilation (ordinal category 6, rate ratio for recovery 1.09; 95% CI, 0.76 to 1.57) and those receiving invasive mechanical ventilation or ECMO (ordinal category 7, rate ratio for recovery 0.98; 95% CI, 0.70 to 1.36). These

subgroup comparisons were underpowered, though, and do not exclude clinically important benefit for patients with COVID-19 ARDS.

In the large, open-label, pragmatic SOLIDARITY trial, no survival benefit was observed with use of remdesivir, although the study design did not allow direct assessment of the effect on time to recovery.[5] In the subgroup of hospitalized patients without COVD-19 ARDS (no mechanical ventilation), the observed mortality favored remdesivir treatment (rate ratio for mortality 0.86; 95% CI 0.67-1.11), consistent with that observed in the ACTT-1, whereas for patients with COVID-19 ARDS (mechanical ventilation required) in the SOLIDARITY trial, the opposite was present (rate ratio for mortality 1.20; 95% CI 0.80-1.80). Given the pragmatic nature of the trial, the lack of blinding, and the requirement for longer hospital stay among treated patients, how best to interpret the SOLIDARITY results is not clear.

Despite the FDA approval for remdesivir, on the basis of the SOLIDARITY trial results, NIH treatment guidelines do not currently recommend remdesivir for patients receive invasive mechanical ventilation/ECMO and provides a weak recommendation (BIII) for remdesivir in combination with dexamethasone in patients receiving high flow oxygen or non-invasive ventilation.[6] The lack of definitive evidence for remdesivir in patients with COVID-19 ARDS provides motivation for this substudy.

1.1 Potential risk and benefits from remdesivir

Anticipated risk is considered low, based on the known mechanism of action and extensive clinical experience with the drug. The most common adverse reactions observed more commonly with treatment with remdesivir than with placebo are nausea, increase in ALT, and increase in AST.

The potential benefits of remdesivir include faster time to recovery, including earlier hospital discharge. There is no current evidence to suggest that remdesivir reduces mortality in hospitalized patients based on data from ACTT-1 and the WHO SOLIDARITY trial.[5]

Remdesivir is currently FDA approved and licensed in the United States for the treatment of hospitalized patients with COVID-19. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of remdesivir may be found in the Package Insert.[5] The overall benefit-risk assessment of this study is considered favorable.

1.2 Justification for dose chosen

Remdesivir will be administered as a 200 mg IV loading dose, followed by a 100 mg once-daily IV maintenance dose while hospitalized up to a 10-day total course. This regimen is the dosing recommended by the FDA (https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf) and evaluated in prior trials.

B2. Agent-specific exclusion criteria

1) Prior receipt of any dose of remdesivir during the present illness
2) GFR < 30 ml/min and not receiving dialysis
3) ALT or AST > 10 times upper limit of normal
4) Unwillingness to commit to avoid sex that may result in pregnancy for at least 7 days after completion of remdesivir vs. placebo

B3. Description of investigational agent

3.1. Administration and duration

The prepared diluted solution should be administered through a separated/dedicated intravenous line and should not be infused simultaneously with other antimicrobials or antibody preparations (e.g., monoclonal antibodies, convalescent plasma, hyperimmune globin). The compatibility of remdesivir injection with IV solutions and medications other than 0.9% sodium chloride is not known. Administer remdesivir via IV infusion over 30 minutes. Slower infusion rates of up to 120 minutes can be considered to potentially prevent signs and symptoms of infusion-related reaction. See the PIM and Pharmacy Procedures for additional details.

The duration of study treatment will be 10 days. The initial loading dose is 200 mg, with all subsequent doses 100 mg. Treatment will be discontinued if the participant is discharged or transferred from the study hospital. In addition, the study treatment may be discontinued after at least 5 days, per discretion of the treating clinician, if the participant is no longer requiring respiratory support (high flow oxygen, noninvasive ventilation or invasive mechanical ventilation).

3.2. Formulation and preparation

Remdesivir is a sterile drug product. Remdesivir for injection, 100 mg, is a preservative-free, white to off-white to yellow, lyophilized solid containing 100 mg of remdesivir that is to be reconstituted with sterile water for injection and diluted into 0.9% saline prior to administration by IV infusion. Once prepared for infusion, remdesivir is colorless. In addition to the active ingredient, remdesivir for injection, 100 mg, contains the following inactive ingredients: sulfobutylether-beta-cyclodextrin (SBECD), water for injection, hydrochloric acid, and sodium hydroxide. Hydrochloric acid and sodium hydroxide are used to adjust the formulation to a pH of 3.0 to 4.0. Remdesivir for injection is supplied as a sterile product in a single-use, 30-mL Type I clear glass vial. Each vial is sealed with a rubber stopper and an aluminum overseal with a red, plastic flip-off cap.

The placebo to match remdesivir for injection, 100 mg, is 0.9% sodium chloride solution, commercially available and prepared locally in the research site pharmacy, as was true for the ACTT-1 trial.

3.3 Supply, distribution, and accountability

Procedures for ordering and accepting drug, for maintaining inventory of remdesivir, and for breaking the blind in the event of a medical emergency will be described in the Pharmacy Procedures.

3.4. Contraindicated medications

1) Hydroxychloroquine or chloroquine for any indication

3.5. Precautionary medications

The clinical site should have necessary equipment and medications for the management of any infusion-related or anaphylactic reaction.

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4. Clinical and laboratory evaluations

4.1 Timing of Assessments

All assessments are outlined in the relevant section of the master protocol.

4.2. Pharmacokinetic Assessments

Relevant pharmacokinetics are outlined in the FDA-approved package insert for remdesivir (Veklury). After a 10-day course of remdesivir, it is anticipated that remdesivir will persist in the body for 5 days after completion of the course of therapy. No pharmacokinetic assessments will occur within this trial.

5. Clinical management issues

All participants should be monitored closely for infusion-related or anaphylactic reactions. eGFR and transaminases should be monitored during use as clinically appropriate, consistent with the Package Insert. Since remdesivir is approved in the United States, has been used extensively in clinical practice, and has a good safety protocol, specific additional monitoring for infusions is not required for this agent.

5.1. Symptoms and Signs

Hypersensitivity, including infusion-related and anaphylactic reactions, has been observed during and following administration of remdesivir, and hence it is required to monitor patients under medical supervision for hypersensitivity reactions during and following administration of remdesivir. This occurs as part of standard clinical practice. Symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates (maximum infusion time ≤120 minutes) can potentially prevent these reactions if there are symptoms of infusion-related hypersensitivity reaction during the current or prior infusion. If a severe infusion-related hypersensitivity reaction occurs, remdesivir will be immediately discontinued and appropriate treatment initiated.

Transaminase elevations have been observed in healthy volunteers and in patients with COVID-19 who received remdesivir; frank hepatic failure has not been observed. Other minor side effects have been observed including constipation, nausea, vomiting, decreased appetite, and headache.

5.2. Site Needs

The clinical site should have necessary equipment, medications, adequately qualified and experienced staff with appropriate medical cover for the management of any infusion-related or anaphylactic reactions.

5.3. Management of Infusion Reactions including Discontinuation

Investigators will use their clinical judgement and standard of care to evaluate and manage all infusion reactions. Severe infusion-related hypersensitivity reaction should result in immediate discontinuation of remdesivir. Discontinuation should be considered if transaminases increase to >10x upper limit of normal or if transaminase elevation is accompanied by signs or symptoms of liver inflammation. If the complete infusion is not administered, all follow-up procedures and reporting outlined in the master protocol should be adhered to as indicated.

5.4. Factorial design features

5.4.1 Rationale for Studying Remdesivir and Aviptadil in a Factorial Study

Remdesivir and aviptadil have complementary mechanisms (pure anti-viral versus immune-modulator and pneumocyte stabilization combined with modest anti-viral effects) and no evidence to suggest an important drug-drug interaction. Notably, remdesivir has been commonly coadministered with aviptadil in the Expanded Access Program (EAP) and Phase 2 clinical experience with aviptadil. In neither experience was an important safety concern related to coadministration identified. Based on

this, we do not anticipate an interaction between aviptadil and remdesivir (i.e., the effect of aviptadil compared to placebo will be similar for those randomized to remdesivir and placebo for remdesivir).

If this assumption about the absence of an interaction is valid, there are substantial efficiencies gained by combining the study of remdesivir and aviptadil in a single 2x2 factorial study where possible.

Certain key assumptions and principles guide the approach to factorial study.

5.4.2 Severability of factors. Some patients will be eligible for aviptadil but not for remdesivir and vice versa. This may include patients with low GFR being ineligible for remdesivir as well as patients who have already received remdesivir. To accommodate such patients, randomization will be carried out in four distinct strata (see Figure 1). Considering the percentage of patients who enroll in each stratum, we estimated that approximately 800 patients will be randomized in order to achieve 640 participants for each of the two primary comparisons.

5.4.3 Primary objectives of the factorial study

- Primary objective 1. To determine whether aviptadil is superior to placebo when given with standard of care for the primary outcome of recovery based on a 6-category ordinal outcome evaluated at 90 days after randomization.
- Primary objective 2. To determine whether remdesivir is superior to placebo when given with standard of care for the primary outcome of recovery based on a 6-category ordinal outcome evaluated at 90 days after randomization.

5.4.4 Randomization

As described in the master protocol, randomization will be stratified by study site pharmacy and receipt of mechanical ventilation at enrollment. Randomization will be further stratified by the strata shown in Figure 1.

Within each stratum, as indicated in the master protocol, mass-weighted urn randomization will be used to prepare randomization schedules. For the 2x2 factorial, patients will be equally allocated to four possible combinations of aviptadil, remdesivir, that the matching placebos for these drugs: 1) aviptadil + remdesivir placebo; 2) aviptadil placebo + remdesivir; 3) aviptadil + remdesivir; and 4) aviptadil placebo + remdesivir placebo. For strata 2 through 4 in Figure 1, treatment will also be equally allocated to either aviptadil or placebo (strata 2 and 4) or to remdesivir or placebo (stratum 3).

5.4.5 Analysis principles

For each primary objective the two treatments will be compared using a proportional odds model for the primary analysis. This analysis will pool results over the four strata shown in Figure 1 and by receipt of mechanical ventilation. Analyses will also be stratified by geographic region instead of site pharmacy to minimize the number strata. The effect of aviptadil and remdesivir, each compared to placebo will be estimated from a single proportional odds model. For example, just considering the strata in Figure 1, the comparison of aviptadil with placebo will be pooled over those assigned remdesivir and those given placebo for remdesivir in stratum 1, over those randomized in stratum 2, and over those randomized in stratum 4. The effect of remdesivir will be similarly estimated pooling

results over those assigned aviptadil and those assigned placebo for aviptadil in stratum 1, and over those randomized in stratum 3.

An interaction test will be carried out for those randomized in stratum 1. In addition, an interaction test will be carried for aviptadil versus placebo for 4 subgroups defined by randomization to remdesivir or placebo in the factorial (2 subgroups in stratum 1), contraindications to remdesivir (stratum 2), and current or previous use of remdesivir (stratum 4). Similar subgroup analyses will be performed for 3 groups for remdesivir versus placebo, e.g., randomization to aviptadil or placebo (2 subgroups in stratum 1) and randomization to remdesivir or placebo only due to contraindication to aviptadil (stratum 3).

Analyses of secondary endpoints and of subgroups will follow the general plan described in the master protocol.

Figure 1

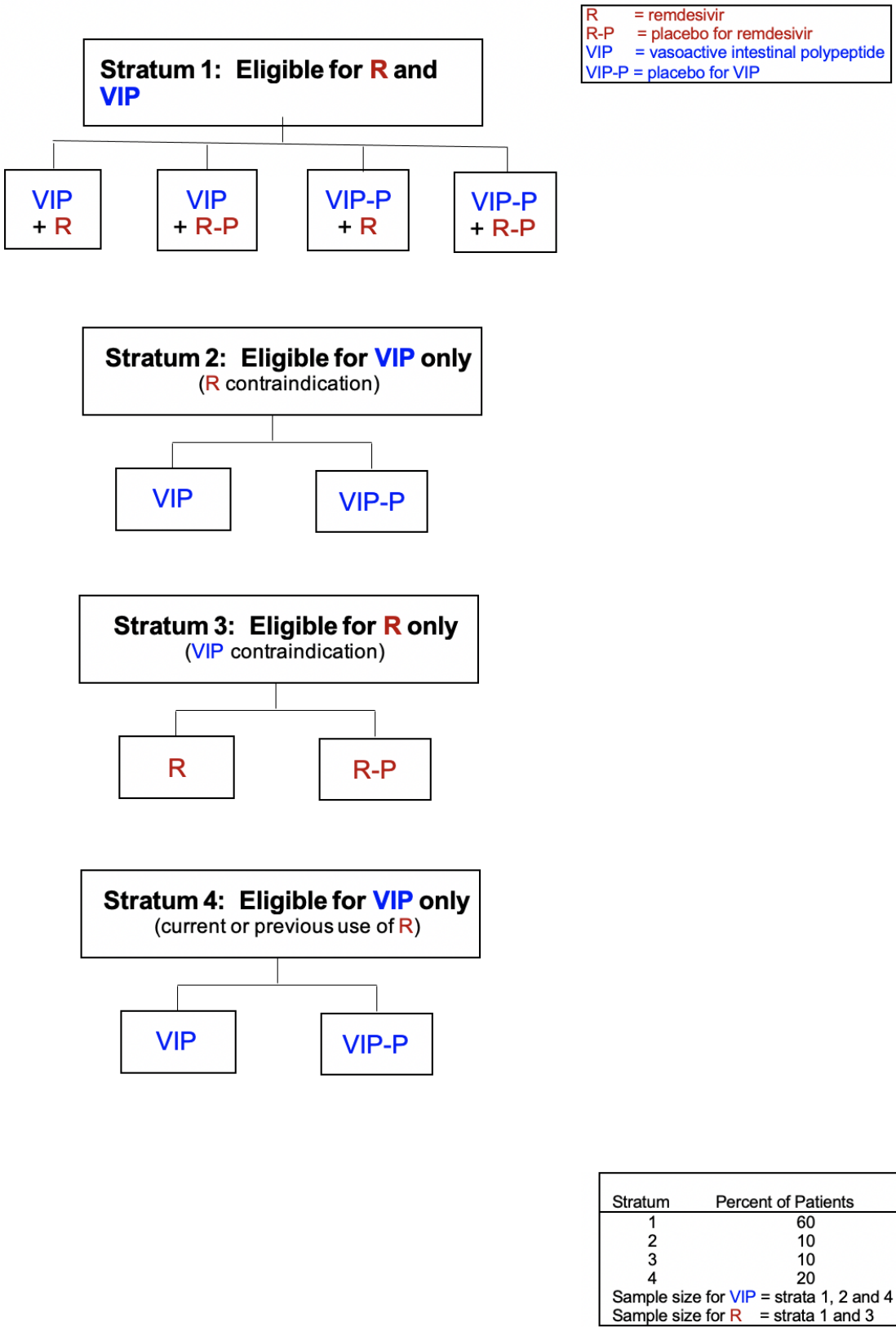

Figure 1. Schematic of approach to factorialization of aviptadil and remdesivir

6. Specific safety-monitoring activities

Because remdesivir is already approved for the treatment of hospitalized patients with COVID-19 and has been administered to very large numbers of patients without significant safety concerns, remdesivir safety monitoring is simpler than for an investigational agent with limited human safety data. Specifically, no additional infusion monitoring beyond standard clinical monitoring will be required during remdesivir infusions. All other safety monitoring will occur as directed by the master protocol.

No additional components will be added to the safety outcome outlined in the master protocol.

The safety monitoring table (Table 1) from the master protocol has been reproduced here with the appropriate modifications relevant to remdesivir. Specifically, the requirement for additional infusion monitoring has been removed.

Table 1 Overview of Safety Data Collection Specific to Remdesivir

	Day 0–7	Day 14	Day 28	Day 90
All grade 3 and 4 clinical AEs (new or increased in severity to Grade 3/4)	X	X[a]	X[a]	
Protocol-specified exempt serious events[b]	Collected through Day 90			
SAEs that are not PSESEs	Collected through Day 90			
Unanticipated problems	Collected through End of Subject Participation (Day 180)			
Hospital admissions and deaths	Collected through End of Subject Participation (Day 180)			
Any SAE related[c] to study intervention	Collected through End of Subject Participation (Day 180)			

[a]Participants will be asked about all new relevant adverse events which have occurred since the last data collection, up to that time point. On these visits, AEs of Grade 1 or 2 that are present on the day of the visit will also be collected.
[b]These are collected on designated forms and consist of events most likely occurring due to the underlying disease. Hence they are study endpoints and will be reviewed by the DSMB regularly, but will be "exempt" from additional collection and reporting as adverse events for safety. See section 10.2.3 of the master protocol for further details
[c]Relatedness determined as per protocol rules in section 10.

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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

Short Title: *Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO)*

INSIGHT Protocol Number: 015 / ACTIV-3b

NCT04843761, EudraCT 2021-001650-56

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-Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL) - London, United Kingdom

-The Kirby Institute, University of New South Wales - Sydney, Australia

-The Institute for Clinical Research at the Veterans Affairs Medical Center - Washington, D.C., United States of America (US)

-Department of Veterans Affairs, USA

-Division of Clinical Research, NIAID, USA

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1 Protocol Summary

DESIGN

TESICO (Therapeutics for Severely Ill Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of investigational agents aimed at improving outcomes for patients with acute respiratory failure related to COVID-19. The focus in this master protocol, a sister protocol to the TICO master protocol, is on patients with critical respiratory failure (i.e., those receiving high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or ECMO to treat acute hypoxemic respiratory failure caused by SARS-CoV-2 pneumonia).

Trials within this protocol will be adaptive, randomized, blinded and initially placebo-controlled. Participants will receive standard of care (SOC) treatment as part of this protocol. If an investigational agent shows superiority over placebo, SOC for the study of future investigational agents may be modified accordingly.

The international trials within this protocol will be conducted in up to several hundred clinical sites. Participating sites are affiliated with networks funded by the United States National Institutes of Health (NIH) and the US Department of Veterans Affairs.

The protocol is for a phase III randomized, blinded, controlled platform trial that allows investigational agents to be added and dropped during the course of the study for efficient testing of new agents against control within the same trial infrastructure. When more than one agent is being tested concurrently, participants may be randomly allocated across agents (as well as between the agent and its placebo) so the same control group can be shared, when feasible. In some situations, a factorial design may be used to study multiple agents.

The primary endpoint is a 6-category ordinal outcome that assesses the recovery status of the patient at Day 90. The categories of the ordinal outcome, from best to worst, start with 3 categories of “recovery” defined by the number of days alive at home and not on new supplemental oxygen, followed by 3 categories for “not recovered” defined as a) discharged but not to home or at home but still requiring continued new supplemental oxygen, b) hospitalized or receiving hospice care, and c) death at day 90. The definition of home will be operationalized as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this protocol.

DURATION

Participants will be followed for 90 days following randomization for the primary endpoint and most secondary endpoints. Selected secondary endpoints will be measured at 180 days.

SAMPLE SIZE

This Phase III trial is planned to provide 80% power to detect an odds ratio of 1.5 for improvement in recovery status at Day 90 for an investigational agent versus placebo with use of the ordinal outcome. The planned sample size is 640 participants (320 per group) for each investigational agent / placebo. Sample size may be re-estimated before enrollment is complete based on an assessment of

whether the pooled proportions of the outcome are still consistent with adequate power for the hypothesized difference measured by the odds ratio.

POPULATION — All participants enrolled will include inpatient adults (≥18 years) who have documented SARS-CoV-2 infection within 14 days of enrollment and are receiving high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO at enrollment, in whom the current respiratory failure is thought to be due to SARS-CoV-2 infection and in whom respiratory support was initiated within 4 days prior to randomization.

STRATIFICATION — Randomization will be stratified by study site pharmacy and by receipt of invasive mechanical ventilation or ECMO at enrollment. Other agent-specific stratification factors may be considered.

REGIMEN — Investigational agents suitable for testing in the inpatient setting will be prioritized based on in vitro data, preclinical data, phase I pharmacokinetic and safety data, and clinical data from completed and ongoing trials. In some cases, a vanguard cohort/initial pilot phase may be incorporated into the trial.

MONITORING — An independent DSMB will review interim safety and efficacy data at least monthly. Pre-specified guidelines will be established to recommend early stopping of the trial for evidence of harm or substantial efficacy. The DSMB may recommend discontinuation of an investigational agent if the risks are judged to outweigh the benefits.

2 Introduction

2.1 Study rationale

COVID-19 is a respiratory disease caused by a novel coronavirus (SARS-CoV-2). While most cases are mild or asymptomatic, progressive disease can result in hospitalization, requirement for mechanical ventilation, and substantial morbidity and mortality.[1] While the most common mode of disease progression is progressive respiratory failure following the development of pneumonia, other severe complications including thrombosis and ischemia are increasingly recognized.[2,3] Patients with respiratory failure, which in COVID-19 is likely best termed Acute Respiratory Distress Syndrome (ARDS), have extremely high morbidity and mortality. Novel treatments for these patients are an urgent clinical and public health need. (We use the term ARDS interchangeably with acute respiratory failure in this master protocol.)

Several clinical trials utilizing novel drugs and repurposing older agents have been implemented to investigate the treatment of adults hospitalized with severe or critical COVID-19 (see section 2.2.6). Standard-of-care is hence rapidly evolving (see Appendix I for current recommendations).

2.2 Background

2.2.1 SARS-CoV-2 Infection and Coronavirus Disease 19 (COVID-19)

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. A novel coronavirus was rapidly identified by sequencing and named SARS-CoV-2, and the illness caused by infection with SARS-CoV-2 has been named COVID-19.[4] While SARS-CoV-2 mostly causes a mild respiratory illness, some individuals, particularly those who are elderly[5,6] and have comorbidities,[7] may progress to severe disease requiring hospitalization, mechanical ventilation in intensive care units, and death. As of 5 October 2020, less than seven months following the declaration of a pandemic on 11 March 2020 by the World Health Organization (WHO), there have been more than 35 million cases diagnosed and more than 1 million deaths worldwide.[1] Over 300,000 cases continue to be reported daily.[5]

2.2.2 Natural history of COVID-19

SARS-CoV-2 has a median incubation period of 4 days (interquartile range [IQR] 2-7 days)[8] and the mean serial interval defined as the time duration between a primary case-patient (infector) having symptom onset and a secondary case-patient (infectee) having symptom onset for COVID-19 was calculated as 3.96 (95% confidence interval [CI] 3.53–4.39) days.[9] COVID-19 illness is predominantly a respiratory disease typified by upper respiratory symptoms in mild cases and pneumonia and ARDS in advanced disease. Initial symptoms typically involve the upper respiratory tract with cough, sore throat and malaise. Fever is present in approximately 44-98% of cases. Notably, persons with COVID-19 often experience loss of smell and taste.[10]

Complications of COVID-19 illness include cytopenias (lymphopenia, thrombocytopenia and anemia), and acute cardiac events (elevated troponin, changes on electrocardiogram), vasopressor-dependent shock, acute kidney injury and dialysis-dependent renal failure, liver

impairment, and neurological events including acute cerebrovascular events, impaired consciousness, muscle injury and thrombotic events.

In most patients (approximately 80%) symptoms resolve without the need for intervention within five to seven days of symptom onset up to a maximum of 14 days. However, approximately 20% of patients show signs of clinical disease progression, most notably pneumonia, around day 3 to 8 following symptom onset. Other manifestations of disease progression include thrombotic episodes including stroke and myocardial infarction (MI). This resembles the documented 6-8 fold excess risk of thrombosis when patients are infected with influenza virus.[11]

A proportion of those who progress then further deteriorate, including with the development of ARDS around 1-5 days after onset of respiratory symptoms.[6,12-14] Acute kidney injury necessitating dialysis and failure of other organs may also occur at this severe stage of disease.

Of the nearly 1,099 persons described in the Wuhan cohort, 16% had severe disease at presentation; 67 persons (6%) reached a composite primary endpoint of intensive care admission, mechanical ventilation or death.[9,15] As described below, outcomes for those requiring mechanical ventilation and with other manifestations of end-organ failure are poor, and treatments for such patients are critically needed.

In this protocol, we aim to enroll patients hospitalized for medical management of COVID-19, with acute respiratory failure, defined as the use of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or ECMO (extracorporeal membrane oxygenation).

2.2.3 Hospitalization of people with COVID-19

Countries and jurisdictions differ in the clinical management of COVID-19 patients. Early in the epidemic, faced with small numbers of infected persons, some resource-rich countries such as Singapore elected to admit all persons with COVID-19 regardless of symptom severity to facilitate strict isolation. Admission for reasons of public health or quarantine, rather than medical management, continues to be a requirement in some countries, notably in Asia. Elsewhere, it is more common for those with mild illness to be advised to self-isolate at home, while only those severely unwell are admitted for medical management.

Mortality rates for those who develop end-organ failure requiring intensive support, including those admitted to ICU, differ widely. Among 1,591 ICU patients from Lombardy, the region in Italy hardest hit by COVID-19, 88% required mechanical ventilation and 11% noninvasive ventilation.[14] The ICU mortality rate was 26%. Of 1,043 patients with available data, 709 (68%) had at least 1 comorbidity, 509 (49%) had hypertension, and 21% had cardiovascular disease. Younger patients (≤63 years) compared to older patients, had lower ICU mortality and higher rates of discharge from ICU. The median length of stay in the ICU was 9 days, though 58% remained in ICU at time of report.[16] In the United Kingdom, of the 4,078 COVID-19 patients admitted into critical care with reported outcomes, 50.7% died in ICU; those requiring advanced respiratory support and renal support had worse outcomes.[15] More recent mortality

estimates among patients with COVID-19-associated ARDS range from 30–45%. These mortality estimates underline the importance of testing and implementing new effective treatments for these critically ill patients.

2.2.4 Viral kinetics of SARS-CoV-2 infection

Viral kinetic studies have demonstrated extensive SARS-CoV-2 viral replication in the pharynx just before and early after symptom onset.[17] Viral ribonucleic acid (RNA) shedding from the pharynx gradually wanes as symptoms resolve, but viral RNA is still detectable weeks after symptom resolution.[18-20] Median duration of viral shedding was 20 days in survivors (longest 37 days), but SARS-CoV-2 was detectable until death in non-survivors.[7] Whether this is viable virus with the potential for continued transmission remains uncertain. RNAemia has been reported especially in more severe disease but is relatively rare among outpatients.[21-23] Viral detection in sputum is higher and outlasts pharyngeal swabs in those with pneumonia.[24] Persons with asymptomatic disease clear their virus faster than symptomatic individuals.[25]

The contribution of ongoing viral replication to disease progression in the most severe stage of COVID-19 (i.e., on ventilator or ECMO) is unclear, but one study reported that SARS-CoV2 viral loads were higher on admission and throughout the hospital course in patients who died,[26] a finding that matches well with evidence for impaired type-1 interferon responses with more severe COVID-19 illness.[27] SARS-CoV-2 viral RNA is also present in blood in large numbers of critically ill patients, with higher viral loads in blood among non-survivors than among survivors.[23] Distribution of virus in the body of severely ill patients is heterogeneous in both space and time, and even patients who die of COVID-19 ARDS may have high viral load in lung, especially in the first two weeks.[28]

2.2.5 COVID-19 ARDS, attributes and treatments

Notwithstanding the observed high viral loads, and progression of viral shedding from the upper to lower respiratory tract in those with progressive disease, the humoral immune response to SARS-CoV-2 appears variable and may be impaired.[29]

SARS-CoV-2 infection may also induce significant changes in elements of the cellular immune response. As the disease process progresses, the peripheral lymphocyte count typically declines. The depletion of peripheral lymphocytes likely reflects translocation to the pulmonary tissue. The extent that this influx is exclusively helpful to the host, or possibly may contribute adversely to disease severity is currently unclear. In severe cases this decline in CD4+ and CD8+ lymphocytes is also associated with an increase in activated CD4+ and CD8+ subsets, increases in key proinflammatory cytokines including interleukin 6 (IL-6), and increases in natural killer (NK) cells.[30,31] Trials assessing the use of various immunomodulatory agents with the aim of dampening this migration and systemic inflammation are underway, and may help to clarify this question.[32,33]

In addition, cohorts of patients with ARDS before COVID-19 (a physiology that is likely highly relevant to patients with COVID-19-associated ARDS) identify risks of ventilator-associated injury, immune depletion and associated risk of secondary infection, encephalopathy and delirium, dysfunctional repair mechanisms, oxidative stress, NETosis, surfactant dysfunction, impairment in GM-CSF and macrophage function, mitochondropathy, dysregulated

microvascular thrombosis and shunting, myocardial suppression, and multiple other insults, which together contribute to the high morbidity and mortality in ARDS. One recent study provided detailed information on COVID-19 ARDS[34] and a recent review considers features of classical ARDS and selected issues related to COVID-19 ARDS.[35]

Phenotypic variability of ARDS is also well described in multiple cohorts, especially with sorting into inflammatory and pauci-inflammatory phenotypes.[36] While COVID-19 has a single underlying cause (SARS-CoV-2 infection), phenotypic variability has also been observed in COVID-19.[34,35,37] The relevance of such subtypes to possibly heterogenous treatment effects is as yet unknown.

Standard supportive care for ARDS from COVID-19 including lung protective ventilation, prone positioning and fluid conservative care is still the most important approach to reducing mortality and morbidity when COVID-19 patients develop ARDS.[35,38] The addition of dexamethasone for treatment of patients who are mechanically ventilated was effective in reducing mortality in the large pragmatic UK RECOVERY trial,[39] although several outstanding issues relate to glucocorticoids for severe COVID-19.[40]

2.2.6 Current treatment strategies for COVID-19

Hundreds of clinical trials have been completed or are underway to study the safety and efficacy of treatments for COVID-19. Treatments being studied include direct anti-viral treatments, including repurposed drugs found in vitro to have activity against SARS-CoV-2; immune modulators especially in patients with advanced disease; drugs to reduce inflammation, including corticosteroids, and modifiers of other pathophysiological pathways implicated in disease progression, including potentially anticoagulants and anti-platelet agents.

As results of randomized trials for these and other treatments become available and treatment guidelines are updated, standard of care (SOC) for hospitalized patients with COVID-19 will change. This may influence the background treatment recommended (or required) by this protocol and/or second line or supportive care treatments recommended by the protocol. To accommodate this fast-moving field Appendix I (which outlines the SOC to be recommended in addition to investigational agent or matched placebo) will be regularly updated.

Of note, whereas evidence supports use of the interventions outlined in Appendix I, the most optimal approach to applying these interventions remains uncertain, and is the subject of ongoing comparative effectiveness trials.

2.3 Investigational Agents

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) has formed an overarching “trial oversight committee (TOC)” for both ACTIV-2 (a parallel study assessing COVID-19 therapeutics in outpatients) and ACTIV-3 (the TICO master protocol and this paired TESICO master protocol). The TOC (and the agent selection committee) will select agents for study in the three protocols. Members of the protocol team (non-voting) and NIH are members of this committee. This committee reviews data for investigational agents and considers a number of factors relevant to the likely efficacy and safety of candidates for inclusion in the relevant protocols.

It is possible that several agents from different sources will be combined at some point in the conduct of this master protocol – but not initially. It is also possible that one agent will be identified as effective and then incorporated as SOC (providing there is good safety data and adequate supply of the agent).

Information on dosing, administration, supply and distribution, matching placebo, and any special considerations as far as inclusion/exclusion criteria and safety monitoring for each investigational agent studied as part of this protocol is outlined in an appendix (see Appendix H), including known benefits and risk, justification for dosing, and administration. The appendix will also include whether any aspects of study procedures outlined in this master protocol will need to be deviated from. The informed consent will describe any risks associated with the investigational agents.

In some cases, especially where additional data about safety and feasibility are desired, a vanguard cohort/pilot phase may be incorporated into a trial of a given investigational agent. Details of such vanguard cohorts—including design features, additional safety monitoring, and sample size—will be specified in the agent-specific appendix.

3 Risk/Benefit Assessment

3.1 Known Potential Risks

Potential risks of participating in this trial are those associated with the product, and these are described in an agent-specific appendix and in the sample informed consent. Other risks include having blood drawn, intravenous (IV) catheterization, and breach of confidentiality. Given the significant disease-related risks faced by this target population, there is felt to be a favorable risk/benefit profile, and significant risk acceptability.

3.1.1 Risks of Drawing Blood and IV Catheterization

Drawing blood may cause transient discomfort and, rarely, fainting. Fainting is usually transient and managed by having the participant lie down and elevate his/her legs. Bruising at the blood collection sites may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. IV catheterization may cause insertion site pain, phlebitis, hematoma formation, and infusate extravasation; less frequent but significant complications include bloodstream and local infections. The use of aseptic (sterile) technique will make infection at the site of blood draw or at catheterization less likely.

3.1.2 Risks due to Study Treatments

Infusions of investigational agents likely to be used in this protocol are generally well-tolerated, except in rare cases of existing allergy to the products infused. However, each agent may have associated risks, which will be specified in the relevant agent-specific appendix.

3.1.3 Risks to Privacy

Participants will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the participant's PHI. All source records including electronic data

will be stored in secured systems in accordance with institutional policies and government regulations.

All study data that leave the site (including any electronic transmission of data) will be identified only by a coded number that is linked to a participant through a code key maintained at the clinical site. Names or readily identifying information will not be released. Electronic files will be password protected.

Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publication from this trial will not use information that will identify study participants. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the study monitor, other authorized representatives of the institutional review board (IRB), NIH, and applicable regulatory agencies (e.g. FDA).

3.2 Known Potential Benefits

While the trial is conducted to test the hypothesis that each investigational agent will improve participant status on an ordinal recovery outcome assessed at 90 days, the agents studied may or may not achieve these outcomes in any individual who participates in this trial. However, there is an anticipated benefit to society from a patient's participation in this trial, due to insights that will be gained about the investigational agent(s) under study as well as the natural history of the disease. While there may not be benefits for an individual, there will be benefits to society if a safe, efficacious therapeutic agent can be identified during this global COVID-19 outbreak.

4 Outcomes

This section describes the key outcome measures used in this phase III protocol. The complete approach to measurement and evaluation of trial endpoints will be specified in the statistical analysis plan before unblinding.

4.1 Primary and Secondary Outcomes to Evaluate Efficacy and Safety

The primary endpoint is an ordinal outcome that assesses participant recovery status at Day 90. The primary ordinal endpoint is referred to as ***recovery***. The outcome includes 6 categories, consisting of 3 ranked categories of the number of days alive, at home, and not receiving new supplemental oxygen ***at Day 90*** (77 or more consecutive days, 49–76 days, or 1–48 days) as well as an additional 3 categories for patients who are not recovered at Day 90: (1) discharged from the hospital but either not yet home, or home but receiving new supplemental oxygen, (2) still hospitalized or receiving hospice care, or (3) dead.

Consistent with the TICO protocol (NCT04501978), *home* is defined as the level of residence or facility where the participant was residing prior to onset of COVID-19 leading to the hospital admission that led to enrollment in this protocol. Residence or facility groupings to define home are: 1) **Independent/community dwelling** with or without help, including house, apartment, undomiciled/homeless, shelter, or hotel; 2) **Residential care facility** (e.g., assisted living facility, group home, other non-medical institutional setting); 3) **Other healthcare facility** (e.g., skilled nursing facility, acute rehab facility); and 4) **Long-term acute care hospital** (hospital

aimed at providing intensive, longer term acute care services, often for more than 28 days). Lower (less intensive) level of residence or facility will also be considered as home. By definition, “home” cannot be a “short-term acute care” facility. Participants previously residing in a “long-term acute care” hospital recover when they return to the same or lower level of care.

Since some patients will be receiving supplemental oxygen before their COVID-19 illness, we define new supplemental oxygen as any supplemental oxygen in participants who were not receiving supplemental oxygen before their COVID-19 illness or an increase in supplemental oxygen above pre-COVID-19 baseline among patients who were receiving supplemental oxygen before their COVID-19.

The “last-off” method for assessing recovery will be used, as has been customary in the use of similar ordinal endpoints in ARDS trials for decades. According to the “last-off” method, periods of recovery that are followed by hospital re-admission, change from home to a higher level of care, or receipt of new supplemental oxygen will *not be counted* toward the number of days of recovery. In other words, only days between the last time the patient entered a recovered state (returned home, free of new supplemental oxygen), and Day 90 are counted as days of recovery. The categories of the primary endpoint are displayed in Table 1.

Table 1 Categories of the primary endpoint

Category	Status at 90 days
1 (Best)	At home and off oxygen. No. of consecutive days at Day 90 ≥ 77
2	49-76
3	1-48
4	Not hospitalized AND either at home on oxygen OR not at home
5	Hospitalized for medical care OR in hospice care
6 (Worst)	Dead

Participants residing in a facility solely for public health or quarantine purposes will be considered as residing in the lowest level of required residence had these public health measures not been instated. If such patients are receiving new supplemental oxygen, they will not be classified as recovered.

4.1.1 Rationale for primary outcome

The primary ordinal endpoint, recovery, was selected given the high mortality in COVID-19 ARDS and the expectation that agents may have effects on both mortality and time to recovery among survivors. The common use of new supplemental oxygen after discharge (as high as

40% of discharged patients among ARDS patients in prior cohorts) and frequent rehospitalizations also motivated the structure of this endpoint.

The primary outcome is intended to identify relevant efficacy among investigational agents using an endpoint that is patient-centered, clinically relevant, and appropriately efficient.

Whereas mortality may be the most important ultimate outcome, the sample size to detect a plausible treatment effect for such an outcome would be much larger than outlined in this protocol. It was determined that use of a mortality-only endpoint would unduly increase the amount of time and resources necessary to make a determination of efficacy and was thus not feasible in current pandemic circumstances. Importantly, mortality was not considered to be the only relevant measure of efficacy in COVID-19—among survivors, the duration of recovery at Day 90, which also reflects length of hospitalization, is also an important benchmark. This position is consistent with decades of work in ARDS trials. Notably, while data specific to COVID-19 have not yet been generated, in general ARDS populations, a longer time to recovery has been associated with worse long-term outcomes, making recovery evaluated at Day 90 an important patient-centered endpoint.[41-44]

The primary outcome is assessed at 90 days of follow-up, which is longer than for other trials of investigational agents for COVID-19, which have typically been 28 days. The longer follow-up will allow better ascertainment of recovery from the longer-term consequences of the underlying disease, and hence the efficacy of the investigational agent. This is likely to be particularly true for the TESICO target population, who are critically ill. Based on data from COVID-19 observational cohorts and ARDS trials before the pandemic, it is also projected that excess mortality will be observed between Day 28 and Day 90. A single category of death at Day 90 is used for the worst category of the primary endpoint instead of time to death given the 90 day follow-up period. Time to death is a secondary endpoint.

4.1.2 Secondary outcomes

In addition to the primary endpoint, several secondary efficacy endpoints will be assessed. These endpoints will be assessed for all participants enrolled.

1. All-cause mortality through Day 90, dichotomous as well as time to death

2. (a) Composite endpoint that considers the number of days at home off new supplemental oxygen and the time to death as well as the other categories of the primary ordinal outcome;
   (b) a dichotomous composite endpoint of alive, at home, and off new supplemental oxygen at Day 90;
   (c) a three-category ordinal endpoint, measured at Day 90, with the following categories: recovered (alive, at home, and off new supplemental oxygen), alive and not recovered, and dead.

3. Time from randomization to recovery defined as alive, at home, and off oxygen (treating death as a competing risk).

4. Days alive outside of a short-term acute care hospital up to Day 90 (among survivors), using the “last off” method

5. Clinical organ failure or serious infections defined by development of any one or more of the following clinical events through Day 28 (see PIM for criteria for what constitutes each of these conditions; such conditions that existed at baseline are not counted):

    a. Worsening respiratory dysfunction
        1. Increase in the level of respiratory support from high-flow nasal cannula or non-invasive mechanical ventilation at baseline to mechanical ventilation or ECMO, or from invasive mechanical ventilation at baseline to ECMO.

    b. Cardiac and vascular dysfunction:
        1. Myocardial infarction
        2. Myocarditis or pericarditis
        3. Congestive heart failure: new onset NYHA class III or IV, or worsening to class III or IV
        4. Hypotension treated with vasopressor therapy
        5. Atrial or ventricular tachyarrhythmias

    c. Renal dysfunction:
        1. New requirement for renal replacement therapy

    d. Hepatic dysfunction:
        1. Hepatic decompensation

    e. Neurological dysfunction
        1. Acute delirium
        2. Cerebrovascular event (stroke, cerebrovascular accident [CVA])
        3. Transient ischemic events (i.e., CVA symptomatology resolving <24 hrs)
        4. Encephalitis, meningitis or myelitis

    f. Haematological dysfunction:
        1. Disseminated intravascular coagulation
        2. New arterial or venous thromboembolic events, including pulmonary embolism and deep vein thrombosis
        3. Major bleeding events (>2 units of blood within 24 hours, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding).

    g. Serious infection:
        1. Intercurrent, at least probable, documented serious disease caused by an infection *other than* SARS-CoV2, requiring antimicrobial administration and care within an acute-care hospital.

6. A composite of death, clinical organ failure or serious infections (see above) through Day 90.

7. Outcomes assessed in other treatment trials of COVID-19 for hospitalized participants in order to facilitate meta analyses and facilitate generation of norms, including an ordinal scale measuring the degree of oxygen support through Day 14, time to discharge from the initial hospitalization, and binary outcomes defined by worsening based on the worst 3 categories of the primary ordinal recovery outcome at day 90.

8. A composite of cardiovascular events (outcomes listed above in items 5b1, 5e2 and 5e3) and thromboembolic events (item 5f2) through Day 28 and Day 90.

9. Safety and tolerability as measured by
    a. A composite safety outcome of grade 3 and 4 clinical adverse events, SAEs, PSESEs (see 10.2.3), or death through Day 5 (*primary safety endpoint*) and through Day 28 (secondary safety endpoint)
    b. Infusion-related reactions of any severity
    c. Percentage of participants for whom the infusion was interrupted or stopped prior to completion for any reason and separately for an adverse event
    d. A composite of hospital readmissions or death through 90 days.

4.1.3 Rationale for secondary outcomes

The main secondary outcomes for the TESICO trial are constituents of the primary outcome (mortality, time to death, number of days home off oxygen) or closely related to them (days alive outside of the hospital). In addition, given the evolving information about the effects of COVID-19 outside of the lungs, measuring organ failure is important to understand the full range of COVID-19. Given that secondary infections are common among ARDS patients, including those with ARDS from COVID-19, measuring and monitoring secondary infections is also important to understanding the full scope of the effect of a COVID-19 therapeutic agent. In addition, the importance of understanding COVID-19 epidemiology (and supporting potential meta-analyses) across the range of therapeutic trials mandates collection of outcomes relevant to the calculation of endpoints from other trials. The rationale for the safety outcomes collected is presented in Section 10. If a specific secondary outcome is to be added for a given investigational agent, that additional outcome will be specified in the corresponding Appendix H.

5 Objectives

5.1 Primary Objective

The primary objective of this protocol is to determine whether investigational agents are safe and superior to control (initially and primarily placebo) when given with SOC for the primary endpoint of recovery (based on a 6-category ordinal outcome) evaluated at 90 days after randomization.

SOC may be modified (updated based on data from this or other trials) during the course of evaluating different investigational agents with this master protocol. SOC may also be studied in this master protocol along with investigational agents if data from trials indicate that efficacy is uncertain for this target population of patients with COVID-19 ARDS.

5.2 Secondary Objectives

Four key secondary objectives are to compare each investigational agent with control for:

1. Time to death through Day 90
2. A composite endpoint that considers the number of days at home off new supplemental oxygen and the time to death as well as the other categories of the primary ordinal outcome,
3. Time to recovery defined as alive, at home, and off new supplemental oxygen,
4. A three-category ordinal outcome, measured at Day 90, with the following categories: recovered (alive, at home, and off new supplemental oxygen), alive and not recovered, and dead.

Other secondary objectives are to compare each investigational agent with control for the secondary outcomes listed in section 4.

In addition, the primary ordinal endpoint of recovery will be evaluated for subgroups defined by the following characteristics measured at enrollment:

- Receipt of invasive mechanical ventilation or ECMO
- Age
- Biological sex
- Race/ethnicity
- Type of residence/facility (home)
- Body mass index (BMI)
- History of chronic conditions (cardiovascular disease, diabetes, asthma, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, hepatic impairment, or cancer)
- Geographic location
- Duration of symptoms prior to enrollment
- Concomitant treatments (including other randomized treatments) at enrollment
- SARS-CoV-2 vaccination status at baseline
- Disease progression risk score (defined using pooled treatment groups with the following baseline predictors of the primary outcome (recovery evaluated at 90 days): age, biological sex, duration of symptoms, receipt of invasive mechanical ventilation or ECMO vs. neither, and presence of chronic health conditions.

6 Study Design

TESICO (Therapeutics for Severely Ill Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of multiple investigational agents for COVID-19 ARDS. Master protocols can be a more efficient approach to the evaluation of multiple experimental interventions for a single disease such as COVID-19 in a continuous manner.

The trial described in this master protocol is a phase III randomized, blinded, controlled platform trial that allows investigational agents to be added and dropped during the study for efficient testing of new agents against placebo within the same trial infrastructure. When more than one agent is being tested concurrently, participants will be randomized across agents, as well as to agent/control. This general approach will allow rapid testing of multiple agents as the pooling of controls across agents requires fewer patients to be randomized to the matched control arm of each agent. However, this will only occur when feasible and when multiple agents are available to be tested at the same time. If an investigational agent shows superiority over placebo + SOC as initially defined, SOC for future investigational treatment evaluations will be modified accordingly.

In some cases, more than one dose of an investigational agent will be studied. For such agents, specific details of the dose selection will be outlined in the relevant Appendix H.

6.1 Randomization and Stratification

Patients will be equally allocated to each investigational agent + SOC or to placebo + SOC. For example, for a study of a single investigational agent, participants will be randomized in a 1:1 ratio to the investigational agent + SOC or to placebo + SOC. If a participant is eligible for two investigational agents, the allocation will be 1:1:1 to investigational agent A + SOC, agent B + SOC, or placebo + SOC. Because the two investigational agents (A and B) may require different placebos (for example, when infusion volumes or route of administration differ), the 1:1:1 allocation ratio will be achieved through a two-step randomization procedure: in *step 1*, the participant is randomized 2:1 to “active” versus “placebo”; in *step 2*, the participant is randomized 1:1 to A versus B. With k agents, this can be viewed as an initial k:1 allocation to “active” versus “placebo”, followed by a second, even allocation to one of the available agents (for example, if a participant was allocated to “placebo” in step 1, then the step 2 allocation will be 1:1 to “agent-specific placebo for A” versus “agent-specific placebo for B”). Sites will be informed of the specific investigational agent/placebo (e.g., A or B) to which the participant was randomized (see section 6.2) but not whether the patient is receiving active agent versus placebo. For the analysis, the concurrent agent-specific placebo groups will be pooled, resulting in a 1:1 allocation ratio for comparing each investigational agent versus the (pooled) placebo group.

If investigational agents are added or dropped, the allocation ratio to active versus placebo will be appropriately modified, and overall sample size will be recalculated as appropriate.

Randomization will be stratified by study site pharmacy (several clinical sites may share one study site pharmacy) and receipt of invasive mechanical ventilation or ECMO (vs. neither) at entry. Within each randomization stratum, mass-weighted urn randomization[45] will be used to generate the active and placebo assignments. This will ensure throughout the trial placebo allocation near the intended ratio while also ensuring near equal numbers of active and matched placebo assignments to each agent.

If more than one investigational agent is being compared with placebo and they have different contraindications, consideration will be given to allowing participants to enter with

randomization to each agent versus placebo separately as well as randomization to both agents. If the number of participants expected to have a contraindication is small, they will be excluded from the trial rather than establishing a separate randomization mechanism. Comparisons will be of each investigational treatment against its control arm. The control arm consists of all participants who were “at risk” for being randomized to the investigational agent but were randomized to a control group instead. This concept is relevant when the randomization includes investigational agents with different eligibility criteria or introduction into the platform trial at different time points. Formal randomization includes a matched placebo group for each agent, and the placebo groups will be pooled across agents, but only participants who (1) were eligible for the investigational agent under consideration, and (2) were randomized contemporaneously and at participating sites will be included in the control group for a given agent.

The default randomization allocation to agent (or its placebo) for which a participant is eligible is as outlined above. However, in some circumstances this allocation ratio may be changed by the (blinded) protocol leadership based on an overall assessment of how the master protocol framework is able to produce relevant and novel findings most effectively. In addition, some agents may undergo factorial randomization with other agents. Such details will be specified in the relevant agent-specific appendix.

6.2 Blinding

Investigational agents or placebo (as necessary) will be prepared by a pharmacist who is not blinded to the treatment assignment. All other study staff, including those at sites, and those in roles spanning multiple sites or spanning the protocol as a whole, will be blinded unless otherwise specified herein.

For investigational agents infused, blinding of the participant and clinical staff may be achieved by placing a colored sleeve over the infusion bags used for investigational agents and placebos. Placebo will consist of an isotonic crystalloid, referred to as an isotonic saline solution.

When more than one investigational agent is available for randomization, the clinical staff will be informed to which investigational agent/placebo the participant was randomly assigned for infusion, but they will remain blinded to whether the random assignment was to the active investigational agent or matching placebo.

If the blind is broken, whether by accident, or for safety reasons, this will be recorded, and the protocol chair will be notified of the event. In that situation, every attempt will be made to minimize the number of people unblinded. Specific unblinding procedures and instructions are found in the PIM.

6.3 Sample size assumptions

All sample size calculations are aimed at pairwise comparisons between a given investigational agent and its control arm. The following assumptions were made in estimating the required sample size for this phase III trial.

a. The primary analysis will be intention to treat.
b. A proportional odds model will be used to compare recovery at Day 90 for the investigational agent and placebo.
c. Patients will be assigned the worst category that applies at Day 90.
d. The "last-off" method (for return to home and liberation from new supplemental oxygen) is used to calculate days of recovery among those who are recovered on Day 90.
e. Approximately 80% of patients will enter the trial on high-flow nasal oxygen, while approximately 20% will enter with non-invasive or invasive mechanical ventilation or ECMO. Control-group event rates for these patients are based on findings from ACTT-1, the Intermountain Prospective COVID Registry (IPOC), ISARIC, and other data sources. This includes estimates of the percentage of patients in each category of respiratory support (i.e., high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO) at baseline.[46]
f. Most patients will be discharged in the first month after randomization; based on ACTT-1 and PETAL Network data, we estimate 25% will be discharged to their home and stay home for 14 days by day 28 following randomization; half of these patients will be discharged to their home on oxygen; and most will receive oxygen for 3-4 weeks. Thus, the category 1 percentage is approximately 12% considering re-initiation of home oxygen and re-hospitalization.
g. Categories 2 and 3 are wider and also consider home oxygen re-initiation and re-hospitalization.
h. Three categories of time at home off oxygen were considered because an intervention that shortened time on new supplemental oxygen and also decreased mortality was considered clinically relevant.
i. Based on data from PETAL Network and Intermountain Healthcare, 33% of participants will die by Day 90. A single category is used for death at Day 90 instead of time of death given the target population and planned follow-up.
j. At Day 90 < 10% of patients will be in the hospital; and about 10% will be on oxygen or not at home.
k. With type 1 error of 0.05 (2-sided) and 80% power to detect the OR of 1.5, sample size is 602. This is increased to 640 (320 in each group) to allow for a small percentage of patients who withdraw consent or are lost to follow-up before Day 90.

The estimated control and treatment arm distribution of endpoint categories used to calculate sample size and power is displayed in Table 2.

Table 2 Estimated Distribution of Endpoint Categories Used for Power Calculation

Category	Status at 90 days	Investigational Agent (%)	Control (%)
1	At home and off oxygen. No. consecutive days at Day 90 ≥ 77	17.0	12.0
2	49-76	27.7	23.0
3	1-48	17.2	17.0
4	Not hospitalized AND either at home on oxygen OR not at home	9.1	10.0
5	Hospitalized for medical care OR in hospice care	4.3	5.0
6	Dead	24.7	33.0
	Total	100.0	100.0

Sample size may be re-estimated before enrollment is complete to determine whether the pooled proportions are still consistent with 80% power to detect an OR 1.5.

6.4 Schedule of Assessments

Participants will be randomized and start therapy on Day 0. The primary endpoint and most secondary endpoints will be measured through Day 90. After Day 90 results are completed, data will be unblinded to allow expeditious reporting of primary results. In addition, all participants randomized will be followed through 180 days following randomization for collection of study data (Appendix B and section 9.1 for details).

6.5 Approach to Intercurrent Therapies and Clinical Trial Co-enrollment

In general, the study will take a pragmatic approach to the use of intercurrent, concomitant medications. Sponsor and/or protocol leadership may, based upon convincing new evidence, act in the interest of participant protection, and in avoidance of confounding, to exclude/disallow use of any specific concomitant therapy found to be reasonably contraindicated for a well-defined portion of the study population (see Appendix I). Such a determination may be made, communicated, and implemented by a Protocol Clarification Memo until it is reasonable to amend the protocol for other reasons.

Coenrollment in other trials will only be allowed where a coenrolling trial has been approved by trial leadership for coenrollment.

The planned analyses are by intention to treat (or modified intention to treat as noted). All participants will be compared throughout follow-up, irrespective of use of concomitant treatments or co-enrollment in other trials. Concomitant treatments will be recorded at baseline, daily through Day 7, and on Days 14 (which will reference Days 8–14), and 28.

7 Study Population

Pragmatic classifications of COVID-19 severity, largely based on an early WHO scale or variants, have been widely adopted in clinical trials. These scales generally specify the degree of respiratory impairment as determined by the location of care and the degree of organ support.[47] The target population of TESICO are patients with SARS-CoV-2 pulmonary involvement severe enough to cause acute hypoxemic respiratory failure that is treated with high flow nasal oxygen or mechanical ventilation (whether invasive or noninvasive). The TESICO target population is thus a subset of "critical COVID-19," as it is focused on hypoxemic respiratory failure due to COVID-19 pneumonia as the critical organ failure. The TESICO target population is also a subset of COVID-19 respiratory failure, since it is restricted to those with hypoxemia who are receiving advanced respiratory support. Based on unpublished data from a national and a regional cohort of hospitalized patients with COVID-19 pneumonia suggesting that >90–95% of patients in this target population would meet the Berlin consensus statement[48] oxygenation and radiographic criteria for ARDS, we at times use the term ARDS interchangeably with COVID-19-associated critical respiratory failure to describe our target population in this protocol. We anticipate that the members of the target population so defined will benefit from the investigational agents, as the vast majority will have bilateral pulmonary infiltrates from lung inflammation and injury due to life-threatening SARS-CoV-2 infection. (To facilitate inferences about generalizability and subsequent meta-analyses, we will record and report chest radiograph results and SF ratios to allow alignment with the Berlin definition and newly proposed modifications[49] at the conclusion of the trial.)

In the context of this understanding of COVID-19-associated critical respiratory failure, COVID-19 participants with ARDS will be enrolled at clinical trial sites globally. The estimated time from screening (Day -1 or Day 0) to end of study for an individual participant is 90 days for the primary endpoint and 6 months for some secondary endpoints.

Patient eligibility must be confirmed by study personnel named on the delegation log.

Protocol inclusion and exclusion criteria are intentionally straightforward and are NOT subject to exception for even minor deviations, e.g., by Study Medical Officers or by the Sponsor Medical Monitor.

7.1 Inclusion Criteria

1. Age ≥ 18 years;

2. Informed consent by the patient or the patient's legally-authorized representative (LAR)*;

3. Requiring admission for inpatient hospital acute medical care for clinical manifestations of COVID-19, per the responsible investigator, and NOT for purely public health or quarantine purposes.

4. Current respiratory failure (i.e., receipt of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO used to treat acute hypoxemic respiratory failure).

5. SARS-CoV-2 infection, documented by a nucleic acid test (NAT) or equivalent testing with most recent test within 14 days prior to randomization. (For non-NAT tests, only those deemed to have equivalent specificity to NAT by the protocol team will be allowed. A central list of allowed non-NAT tests will be maintained.)

6. Respiratory failure is believed to be due to SARS-CoV-2 pneumonia.

***Continuing consent**
Participants for whom consent was initially obtained from a LAR, but who subsequently regain decision-making capacity while in hospital will be approached for consent for continuing participation, including continuance of data acquisition.

7.2 Exclusion Criteria

1. Known allergy to investigational agent or vehicle
2. More than 4 days since initiation of support for respiratory failure (i.e., receipt of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or ECMO used to treat acute hypoxemic respiratory failure).
3. Chronic/home mechanical ventilation (invasive or non-invasive) for chronic lung or neuromuscular disease (non-invasive ventilation used solely for sleep-disordered breathing is not an exclusion).
4. Moribund patient (i.e., not expected to survive 24 hours)
5. Active use of “comfort care” or other hospice-equivalent standard of care
6. Expected inability to participate in study procedures;
7. In the opinion of the responsible investigator, any condition for which, participation would not be in the best interest of the participant or that could limit protocol-specified assessments;
8. Previous enrollment in TESICO

Exclusions that may be specifically appropriate for an investigational agent studied are referenced in the relevant appendix (H) for the investigational agent. The contraindications for use of components of SOC are outlined in Appendix I and in the PIM.

7.3 Costs to Participants

There is no cost to participants for the research tests, procedures/evaluations and study product while taking part in this trial. Procedures and treatment for clinical care including costs associated with hospital stay may be billed to the participant, participant’s insurance or third party.

8 Study Product

Investigational agents and SOC treatment to be used are described in Appendices H and I, respectively.

9 Study Assessments and Procedures

9.1 Screening/Baseline and Follow-up Assessments

Data collection at each visit is outlined below and summarized in Appendix B. Day 0 refers to the day on which randomization occurs and on which the investigational agent/placebo is first administered. Screening and randomization can be done in the same session. The term "baseline" refers to data that are collected prior to randomization.

9.1.1 Screening/Baseline Assessments

After obtaining informed consent, the following assessments are performed within 24 hours prior to randomization to confirm eligibility and to collect baseline data:

- Documentation of laboratory diagnosis of SARS-CoV-2 infection in the appropriate timeframe

- A focused medical history, including the following information:
    - Demographics including age, gender, and type residence or facility prior to current illness (i.e. "home")
    - Day of onset of COVID-19 signs and symptoms
    - History of chronic and current medical conditions, including targeted conditions for outcome analysis
    - Targeted concomitant medications and SARS-CoV-2 vaccine receipt or trial participation

- A focused physical examination including vital signs (at least heart rate, systolic and diastolic blood pressure, respiratory rate, temperature, and oxygen saturation), height and weight, baseline degree of oxygen supplementation/respiratory support

- Blood draw for local laboratory evaluations:
    - White blood cell count
    - Hemoglobin
    - Platelets
    - Lymphocyte and neutrophil counts
    - Ferritin
    - C-reactive protein
    - Basic metabolic panel
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)
    - Total bilirubin
    - INR
    - D-DIMER

- Plasma and serum specimens for future related research (four 1.0 mL aliquots of serum and four 1.0 mL aliquots of plasma). Two 9 mL tubes, one SST and one EDTA, of blood (18 mL total) will be drawn in order obtain 8 aliquots. This includes antibody status and viral antigen, among other assays.
- A mid-turbinate nasal swab for SARS-CoV-2
- Among those who provide consent for host genetics, whole blood will be collected and stored for RNA (one 2.5mL PAXgene tube) and DNA (one 9mL EDTA tube to produce six 1-mL aliquots) extraction
- Contact details (phone, e-mail or other types of contact) for the participant and at least two close relatives/friends, to ensure reliable data collection during follow-up in the trial.
- Urine or serum pregnancy test in women of childbearing potential who do not already have evidence of pregnancy

In some cases, it may not be possible to draw blood for local laboratory assessments and storage prior to the time of randomization. In these cases, the blood draw can be performed after the time of randomization but before the infusion of the blinded investigational agent/placebo.

The overall eligibility of the patient for the study will be assessed once all screening information is available. The screening process can be suspended prior to completion of the assessment at any time if exclusions are identified by the study team.

Participants who qualify will be randomized within 24 hours of consent and given the infusion of the blinded investigational agent/placebo. Immediately prior to randomization, receipt of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO by the participant should be verified.

On days of study drug administration, before and during study drug administration, the following data will be collected, and reported on appropriate case report forms as applicable:

- Adverse events of any grade severity present prior to the infusion (Day 0 only)
- Start and stop times of the infusion of the investigational agent/placebo
- Doses of study drug
- Infusion-related reactions to the investigational agent/placebo
- New adverse events of any grade severity during and up to 2 hours after the infusion
- On Days 0, 1, and 2, a blood draw for local laboratory evaluations

The details of monitoring during and immediately after the infusion will be specified in the agent-specific appendices. Participants who experience AEs during or immediately after the infusion should be followed closely until the resolution of the AE.

9.1.2 Follow-up Assessments

Participants will be followed through 180 days following randomization for collection of study data (Appendix B). Relevant clinical data will be collected on Days 0–7, 14, 28, 42, 60, 75, 90, and 180. These data will include discharge status, and interim changes in medical history (targeted to components of primary and secondary endpoints). Concomitant medications will be collected on Days 0-7, Day 14 (retrospectively for Days 8-14), and on Day 28, clinical (i.e.,

not limited to a laboratory abnormality) incident AEs of grade 3 and 4 severity through Day 28, and hospitalization readmissions and deaths through 180 days.

Components necessary to determine the ordinal WHO/NIH ordinal outcome and the TICO Pulmonary endpoint will be collected to allow the computation of the ordinal outcome for every day through Day 14 and on Day 28. On Days 14 and 28 AEs of any grade severity will also be collected.

At Day 3 and Day 5 for all participants still hospitalized, plasma and serum specimens for central testing for SARS-CoV-2 antibody determination, viral antigen, and storage (four 1.0 mL aliquots of serum and four 1.0 mL aliquots of plasma) will be obtained for future related research. Two 9 mL tubes, SST and EDTA, of blood (18 mL total) will be drawn in order obtain the 8 aliquots.

At Day 3, among those participants who provided consent for host genetics, a whole blood specimen for RNA extraction will be collected (sufficient for one 2.5 mL PAXgene tube).

At the time of discharge, the residence/place of living to which the participant was discharged and whether it was the type of residence (i.e. “home”) occupied at the time of onset of COVID-19 symptoms will be ascertained. All changes in this status (e.g., re-admission to another hospital or an intermediate care facility) will be collected at approximately 2-week intervals, starting with the day 14 visit, to determine the time of return “home” and time of liberation from new supplemental oxygen (as well as readmissions or resumption of new supplemental oxygen). Entry into hospice care will also be collected.

For visits on Days 7, 14, 42, 60, 75, 90, and 180, contact with the participant for study data collection may be performed by telephone. However, other information will be gathered, as outlined in Appendix B. At Day 90 and Day 180, the EQ-5D-5L will be administered by telephone, with additional patient-reported outcomes (MRC Dyspnea, PROMIS fatigue, CONNECTS Recovery) also collected by telephone at Day 90 and Day 180. Safety data collection and reporting are described further in Section 10.

9.1.3 Stored Samples and Future Research

The plasma, mid-turbinate, and serum specimens collected as outlined above will be stored at a central specimen repository in the US. In addition to the specified testing to be done per protocol (collected at baseline and Day 3 for all hospitalized participants and collected at Day 5 among participants still in the ICU on Day 5), the specimens will be available for later use in research concerning COVID-19, SARS-CoV-2, and the impact of the study treatment. The whole blood specimens for RNA and DNA extraction from those participants who provided consent for host genetics will also be stored at the same central specimen repository in the US. Proposed research utilizing these specimens will be reviewed and approved by the study scientific steering committee and overseen by an ethics committee as appropriate. Results of research tests on individual specimens will not be provided to participants or their clinicians. Aggregate research results will be made available.

10 Safety Assessment

The safety monitoring and assessment within this trial reflects attributes of the anticipated investigational agents and the target population.

First, investigational agents studied in this protocol are commonly expected to have short half-lives and low probability of triggering a pathologic process or demonstrating a toxicity that would not manifest during, or shortly after treatment. As a consequence, the mainstay of safety monitoring will be broad safety monitoring through Day 90 plus collection and reporting of serious and/or high-grade events thought to be at least possibly related to the investigational agent for the duration of participation. If agents with longer half-lives or a likelihood of demonstrating effects that may potentially manifest with substantial delay are included, a longer duration of broad safety monitoring will be employed for those agents. Details of such additional safety monitoring will be specified in the corresponding agent-specific Appendix H .

Second, patients with ARDS may each be reasonably anticipated to experience multiple serious adverse events regardless of any study procedures. Therefore, certain reasonably anticipated serious adverse events will be collected as study outcomes (these are termed protocol-specified exempt serious events (PSESEs); see Section 10.2.3), and will be monitored by the DSMB rather than reporting these as adverse events per se.

Safety events and PSESEs will be monitored to ensure real-time participant protection through frequent unblinded DSMB review. The DSMB will review unblinded safety reports on an at least monthly basis.

The safety evaluation of the study intervention includes several components, all of which will be regularly reviewed by the independent DSMB. For this protocol, the term "*study intervention*" refers to the investigational agent or placebo, and to any study provided SOC treatment(s).

Infusion-related reactions are only collected for the blinded investigational agent/placebo. All other AEs are collected for the study intervention (either the blinded investigational agent/placebo or any study provided SOC treatment).

Events will be reported to regulators and IRBs/ethics committees as appropriate/required.

Adverse events, infusion reactions and unanticipated problems will be regularly reviewed by the DSMB.

The following information will be collected on electronic case report forms, and will be regularly reviewed by the DSMB, to evaluate and help ensure safety:

- Infusion-related reactions during and within 2 hours post-infusion of the investigational agent/placebo.
- Clinical adverse events of grade 3 and 4 through study day 28 (isolated laboratory abnormalities that are not associated with signs or symptoms are not collected).
- Protocol-specified exempt serious events (see section 10.2.3) through Day 90.

- Serious adverse events, including laboratory-only serious events, through Day 90, if they are not being collected as clinical organ failure or serious infections (Item 5 of 4.1.2) or protocol-specified exempt serious events.
- Serious adverse events through Day 180 if they are related to study intervention
- Unanticipated Problems through Day 180
- Deaths through Day 180.
- Hospital readmissions through Day 180.

An overview of safety data collected during the study is given in Table 3.

Table 3 Overview of Safety Data Collection

	During and at least 2 hrs after infusion (all days on which infusion occurs)	Day 0–7	Day 14	Day 28	Day 90
Infusion-related reactions and symptoms of any grade[a]	X				
All grade 3 and 4 clinical AEs (new or increased in severity to Grade 3/4)	X	X	X[b]	X[b]	
Protocol-specified exempt serious events (PSESEs)[c]	Collected through Day 90				
SAEs that are not PSESEs	Collected through Day 90				
Unanticipated problems	Collected through End of Subject Participation (Day 180)				
Hospital admissions and deaths	Collected through End of Subject Participation (Day 180)				
Any SAE related[d] to study intervention	Collected through End of Subject Participation (Day 180)				

[a]This includes reporting of AEs of any grade present on day 0, before the first infusion. This allows assessment of whether a given AE is new after infusion.
[b]Participants will be asked about all new relevant adverse events of Grade 3 or 4 which have occurred since the last data collection, up to that time point. On these visits, AEs of any grade that are present on the day of the visit will also be collected.
[c]These are explained and defined in section 10.2.3.
[d]Relatedness determined as per protocol rules in section 10.

Definitions and methods of reporting each type of event are given below.

10.1 Definitions

10.1.1 Adverse Event (AE)

An AE is any untoward or unfavorable medical occurrence in a study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with their participation in research, whether or not considered related to the research. If a diagnosis is clinically evident (or subsequently determined), the diagnosis, rather than the individual signs and symptoms or lab abnormalities, will be recorded as the AE.

In Appendix H details are outlined for each investigational agent under study of the following: specific AEs observed to be possibly associated with the agent in question, and how to monitor for, clinically handle and report such AEs, should they arise.

10.1.2 Criteria for Seriousness

Events are serious if they lead to one of the following outcomes:

- Death
- Life-threatening (i.e., an immediate threat to life)
- Hospitalization or prolongation of hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital abnormalities/birth defects
- Other important medical events that may jeopardize the participant and/or may require intervention to prevent one of the outcomes listed above

10.1.3 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience or outcome that is:

1. Unexpected in terms of nature, severity, or frequency in relation to:
   a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents; and
   b. the characteristics of the population being studied; and
2. Possibly, probably, or definitely related to participation in the research; and
3. Places study participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized per the Investigator's Brochure(s) (IBs).

Furthermore, a UP could be an expected event that occurs at a greater frequency than would be expected based on current knowledge of the disease and treatment under study. The DSMB providing oversight to the study may make such an assessment based on an aggregate analysis of events.

10.1.4 Severity

The investigator will evaluate all AEs with respect to both seriousness (results in outcomes as above) and **severity** (intensity or grade). AEs will be graded for severity according to the

DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (also known as the DAIDS AE Grading Table; see Appendix D for the URL).

For specific events that are not included in the DAIDS AE Grading Table, the generic scale in Table 4 is to be used. Given the unique nature of the target population for this trial, hypotension will be graded according to the scale in Table 5 rather than the default DAIDS AE Grading Table.

Table 4 Generic AE Grading Scale

Grade 1	Events causing no or minimal interference with usual social and functional activities, and NOT raising a concern, and NOT requiring a medical intervention/ therapy.
Grade 2	Events causing greater than minimal interference with usual social and functional activities; some assistance may be needed; no or minimal medical intervention/therapy required.
Grade 3	Events causing inability to perform usual social and functional activities; some assistance usually required; medical intervention/therapy required.
Grade 4	Events causing inability to perform basic self-care functions; medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
Grade 5	Events resulting in death

Table 5. Hypotension AE Grading

AE GRADING	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 LIFE-THREATENING
SERIOUSNESS GUIDANCE*	No	No	No (usually)	Yes
Hypotension criteia that apply to all assessments	No intervention or complication meeting criteria for higher grade.	IVF ≥500 mL **OR** low-dose vasopressor (e.g. <0.1 NE [or equivalent])	Moderate-dose vasopressor (e.g. ≥0.1 NE [or equivalent]) **OR** ≥2 vasopressors **OR** multiple interventions	Life-threatening or clinically significant complications **OR** *persistent* clinically significant deterioration.
Additional hypotension criteria for aviptadil/placebo infusion days	No infusion change for hypotension	Decrease infusion rate *for hypotension* **OR** pause infusion with resumption *for hypotension*	Study drug discontinued for day *for hypotension* **OR** study drug not given for day *for hypotension* **OR** study drug discontinued permanently *for hypotension*	No additional criteria

* Guidance provides suggested seriousness alignment with AE grade but does not overrule investigator judgment. In particular, the presence of critical illness influences the threshold for considering a given hypotension AE 'life-threatening' or an 'important medical event.' Evaluation of other factors, including the intensity of intervention required and the event's impact on the patient, are required to determine event seriousness.

10.1.5 Causality

Causality refers to the likelihood that the event is related to the study intervention. It will be assessed for SAEs and UPs. This assessment will be made for both the blinded investigational agent/placebo and any study-supplied SOC treatment using the following guidelines:

- Reasonable possibility: There is a clear temporal relationship between the study intervention and the event onset, and the event is known to occur with the study intervention or there is a reasonable possibility that the study intervention caused the event.
  NOTE: Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the event.

- No reasonable possibility: There is no evidence suggesting that the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or a more reasonable/likely alternate etiology has been established.

The causality assessment is based on available information at the time of the assessment of the event. The investigator may revise these assessments as additional information becomes available.

10.1.6 Expectedness

Expectedness will be assessed for SAEs using the Reference Safety Information section of the IB(s) for the investigational agent(s) and any study-provided background therapy. Additional details of expectedness for a given agent will be specified in the relevant agent-specific appendix.

The expectedness assessment is based on available information at the time of the assessment of the event. The investigators and the sponsor may revise these assessments as additional information becomes available.

10.2 Schedule for Reporting of Specific Events

This section describes the schedule for reporting different types of safety outcomes on eCRFs as part of the protocol data collection plan. It is recognized that in the care of study participants, more information may be collected and recorded in the participant's medical record. The information collected in the medical record serves as source documentation of events (e.g., signs, symptoms, diagnoses) considered for reporting on eCRFs as part of protocol data collection.

10.2.1 Infusion-related reactions

Certain infusion-related signs/symptoms will be collected as protocol-specified exempt serious events (see section 10.2.3) and will not be separately reported as adverse events.

Adverse events that are
(a) not protocol-specified exempt serious events, AND
(b) are of grade 3 or 4 (whether new or as an increase in grade), AND
(c) occur during or within 2 hours post infusion
will be reported as adverse events on an eCRF.

10.2.2 Grade 3 and 4 clinical adverse events on days of study drug administration, and Days 0–7, 14, and 28

From Day 0 through Day 28, adverse clinical events reaching Grade 3 or 4 severity level will be reported on an eCRF. For a clinical adverse event that was present at baseline, only those which newly reach Grade 3 or 4 will be reported.

Beginning 2 hours post-infusion of the investigational agent or matched placebo, on Days 0–7, clinical AEs of Grade 3 or 4 that are new or that have increased in grade compared to their pre-infusion level will be reported on eCRFs.

Adverse clinical events reaching Grade 3 or 4 severity level that occur between Days 7 and 28 will be reported on an eCRF at the Day 14, and Day 28 visits. The date the event reached the indicated grade will be collected to permit time-to-event analyses. These reportable AEs should be assessed for SAE/UP reporting on the SAE eCRF or for protocol-specified exempt serious events reporting on the eCRF documenting the hospital course.

On Days 14 and 28, AEs of any grade that are present on the day of the visit will also be collected.

10.2.3 Protocol-specified exempt serious events (PSESEs)

Consistent with FDA guidance on protocol-specified serious adverse events, the TESICO trial will systematically collect certain adverse events that are expected to occur commonly in the target population even in the absence of study interventions. These events, termed protocol-specified exempt serious events (PSESEs), are in general exempted from the usual expedited reporting requirements for SAEs. This approach is taken to avoid creating a 'noisy' safety oversight environment, obscuring genuine safety signals, and imposing potentially unmanageable burdens on clinical/study staff, particularly in a pandemic critical care setting. Even as they are exempted from expedited reporting requirements, PSESEs will be reviewed regularly (unblinded, by treatment arm) by the DSMB to maintain the integrity of safety monitoring for the trial.

PSESEs will NOT be reported as SAEs, even if they meet one or more of the criteria for seriousness, ***unless considered related to study intervention (blinded investigational agent/ placebo or study-supplied SOC treatment) (see section 10.2.4)***. These events may occur during the initial hospitalization, lead to a re-admission, or occur in a later hospitalization during follow-up.

The following are **protocol-specified exempt serious events.**

- Death
- Stroke
- Meningitis
- Encephalitis
- Myelitis
- Myocardial infarction
- Myocarditis
- Pericarditis
- New onset of worsening of CHF (NYHA class 3 or 4)
- Arterial or deep vein thromboembolic events
- Renal dysfunction treated with renal replacement therapy
- Hepatic decompensation
- Neurologic dysfunction, including acute delirium and transient ischemic events
- Disseminated intravascular coagulation
- Major bleeding events
- Serious infections
- Worsening respiratory failure
- Hypotension treated with vasopressor therapy
- Atrial or ventricular arrhythmias

Consistent with this approach, sites will evaluate a potential adverse event to determine whether it is a PSESE:

- If the event is not a PSESE, it will be reported as an adverse event as outlined in section 10 of the protocol.
- If the event is a PSESE, it will be evaluated for relatedness.
  - If the PSESE is related to study interventions (either investigational agent or study-supplied SOC therapy), then the event will also be reported as an SAE. Thus, the event will be reported on both eCRFs, the SAE eCRF and the PSESE eCRF.
  - If, however, the event is a PSESE and is not related to study interventions, then the event will be recorded on the PSESE eCRF as a study endpoint and not as an SAE.

As noted earlier in this section, PSESEs are included in the unblinded safety reports reviewed by the DSMB to allow early detection of important imbalances in the distribution of these events between arms in the trial.

10.2.4 Reportable SAEs

Reportable SAEs for this study are:

- Clinical SAEs which are not exempt from expedited reporting per the protocol-specified exempt serious event list and associated rules (10.2.3); and
- Any SAE related to the study intervention

Deaths, life-threatening events, and other SAEs considered potentially *related to the blinded investigational agent/placebo or study-supplied SOC treatment*, that occur from the time of infusion of the study intervention through the Day 180 visit must be recorded by sites on the SAE eCRF **within 24 hours of site awareness**.

Suspected unexpected serious adverse reactions (SUSARs) are reportable SAEs that are assessed as related to a study intervention and are unexpected per the Reference Safety Information of the IB for that intervention. SUSARs are reported from the INSIGHT Safety Office to applicable regulators in an expedited fashion. SUSARs that result in death or are immediately life-threatening are reported to regulators within 7 calendar days of receipt. All other SUSARs are reported to regulators within 15 calendar days. The INSIGHT Safety Office will generate a Safety Report for each SUSAR for distribution to investigators and other parties. Investigators are responsible for submitting Safety Reports to their overseeing IRB/EC per requirements.

SAEs that are not PSESEs and that are not related to the study intervention must be reported on the SAE eCRF within 3 days of site awareness. Such SAEs will be recorded through day 90.

SAEs are followed until the outcome of the SAE is known. If the outcome of an SAE is still unknown at the time of the final follow-up visit, the outcome will be entered in the database as "unknown."

10.2.5 Unanticipated Problems (UPs)

UPs must be reported via the appropriate eCRF to the INSIGHT Safety Office no later than 7 calendar days after site awareness of the event. Investigators are responsible for submitting UPs that are received from the sponsor to their overseeing IRB/EC. Investigators must also comply with all reporting requirements of their overseeing IRB/EC.

10.2.6 Deaths

All deaths are reported on the eCRF for deaths. Deaths considered **related to the study intervention** (blinded investigational agent/placebo or study-supplied SOC) must **also** be reported as an SAE.

10.2.7 Pregnancy

The investigator will collect pregnancy information on any female participants who are or become pregnant while participating in this study. (Where the agent-specific appendix excludes pregnant women, this applies to participants who become pregnant.)

The participant will be followed to determine the outcome of the pregnancy.

Male participants with partners who become pregnant

If an investigator learns that a male participant's partner becomes pregnant while the male participant is in this study, the investigator is asked to attempt to obtain information on the pregnancy, including its outcome. Information obtained on the status of the mother and child will be forwarded to the sponsor. Whether such monitoring will be required is outlined in the agent-specific appendix.

10.3 Medical Monitor

A Medical Monitor appointed by the sponsor will be responsible for reviewing all SAEs, making an independent assessment of causality and expectedness, preparing sponsor safety reports, and communicating as needed with the DSMB and the Investigational New Drug (IND) holder through the study safety office or other mechanism mutually agreed to and documented.

10.4 Halting Enrollment for Safety Reasons

The sponsor medical monitor or the DSMB may request that enrollment be halted for safety reasons (e.g., unacceptably high rate of infusion-related reactions or other unanticipated AEs). If the study is temporarily halted or stopped for safety reasons, IRBs/ethics committees will be informed. The IND holder and sponsor, in collaboration with the protocol chair and the DSMB, will determine if it is safe to resume the study. The sponsor will notify the Site Investigators of this decision. The conditions for resumption of the study will be defined in this notification. The Site Investigators will notify their local IRBs/ethics committees of the decision to resume the study.

11 Statistical Analyses and Monitoring Guidelines

This section describes the analysis for primary and secondary outcomes stated in section 4. A more detailed statistical analysis plan (SAP) will be developed as a separate document. The SAP for each investigational agent may be updated by the blinded statisticians prior to unblinding for a specific treatment comparison.

All analyses will be intent to treat with comparisons to concurrent controls as described in section 6.3. It is anticipated that all study site pharmacies serving active sites will be randomizing all agents under study at any given time, but if this is not the case, comparisons will be restricted to the set of controls enrolled at study site pharmacies where the drug was available for randomization. Specifically, the control group for an investigational agent will consist of those participants who could have been randomized to the agent, but were randomized to a control group instead (i.e., randomized to the matched control group of one of the agents included in the randomization). Agents will be compared to controls, but not to each other, unless explicitly specified in the analysis plan.

All analyses will utilize 2-sided tests with a 5% significance level unless otherwise noted.

11.1 Analysis of the Primary Efficacy Endpoint

The primary ordinal outcome—*recovery*—assessed at Day 90 includes 6 ordered categories, best to worst, that assess 4 clinical states. The categories correspond to (1) the number of consecutive days at home off oxygen (3 categories); (2) receiving oxygen at home or living in a location other than home; (3) hospitalized for medical care or in hospice care; and (4) death. The percentage of patients in each category (6 total) will be compared at Day 90. The primary analysis will use a proportional odds model to estimate a summary odds ratio (OR) for being in a better category in the investigational agent group compared with placebo; an OR > 1.0 will reflect a more favorable outcome for patients randomized to the investigational agent vs. placebo.

The proportional odds regression model will include a treatment indicator, and an indicator for receipt of mechanical ventilation or ECMO (vs. neither) at enrollment.

A test for the proportional odds assumption will be carried out. Even if the proportional odds assumption is violated, the overall summary OR will be the basis for inference in the primary analysis, given the robustness of proportional odds regression to violation of the proportionality assumption. In order to further characterize the summary OR and any deviations from proportional odds, separate ORs will be estimated for different dichotomized definitions of improvement formulated from the components of the ordinal outcome (e.g., alive versus dead, alive and out of the hospital versus hospitalized or dead, etc.)

11.2 Analyses of Secondary Efficacy Endpoints, Safety Outcomes, and Subgroups

Four key secondary objectives are to compare investigational agent with placebo for the following endpoints

1. Time to death through Day 90.

2. A composite endpoint that considers the number of days at home off new supplemental oxygen and the time to death as well as the other categories of the primary ordinal recovery outcome.

3. Time to recovery defined as alive, at home, and off new supplemental oxygen.

4. A three-category ordinal outcome, measured at Day 90, with the following categories: recovered (alive, at home, and off new supplemental oxygen), alive and not recovered, and dead.

Time to death will be summarized using a log-rank test, stratified by receipt of invasive mechanical ventilation or ECMO vs. neither at randomization. The hazard ratio (investigational agent vs control) will be estimated using a stratified Cox proportional hazards model, and the proportion of participants who died by fixed time points (for example, Day 28 or Day 90) will be estimated using Kaplan-Meier estimates.

The composite outcome will be summarized with a win ratio statistic that ranks patients by time to death (instead of just survival status at Day 90), hospitalization at Day 90, home on oxygen or not at home, and duration of time (in days instead of weekly intervals) at home off new supplemental oxygen. Matching on mechanical ventilation (or ECMO) and a disease progression risk score at entry will be used to estimate the win ratio statistic.

The cumulative incidence functions for recovery (at home and off new supplemental oxygen) taking into account death as a competing risk will be estimated using the Aalen-Johansen method and compared using Gray's test. The recovery rate ratio will be estimated using a Fine-Gray regression model. The comparisons between treatment groups will be stratified by receipt of invasive mechanical ventilation or ECMO vs. neither at randomization. Recovery is defined using the last-off method, as described in section 4.

If there is evidence of benefit for an investigational agent versus placebo for the primary ordinal outcome, the comparison of the investigational agent with placebo for these three outcomes will help to inform the interpretation of the treatment effect.

The primary safety outcome is a composite of grade 3 or 4 events, SAEs, PSESEs (see 10.2.3), or death through Day 5, and tests for differences between treatment arms will be conducted with a Cochran Mantel Haenszel test stratified by receipt of invasive mechanical ventilation or ECMO at study entry, comparing the proportion of participants who had experienced any of these events by Day 5. Treatment differences for each of the components of this composite outcome will also be summarized. This composite safety outcome will also be assessed at Day 28. Time to event analysis will also be used to summarize this composite safety outcome. Proportions of participants who experienced any of these events will be compared using stratified Mantel Haenszel tests and logistic regression. SAEs and grade 3/4 events will be classified by system organ class according to MedDRA®.

Safety analyses also include infusion reactions collected during or within 2 hours after the infusion of the investigational agent or placebo. Proportions of participants who experienced infusion reactions or prematurely terminated infusions will be summarized by study arm, and Mantel Haenszel tests will be used to test for differences across arms.

Several other secondary efficacy outcomes will also be investigated. The models will include an indicator for treatment group, and stratify by receipt of invasive mechanical ventilation or ECMO at study entry as appropriate. Time from study entry to discharge from the hospital admission during which randomization took place will be analyzed using the same methods as described above for time to recovery. Readmissions will be summarized using methods for recurrent events (i.e. those who are readmitted will reenter the risk set).

Clinical organ failure is a composite of many different organ-specific events, listed in section 4.1.2, item 5. This outcome will be summarized as part of both safety and efficacy analyses. The incidence of organ failure, serious infection or death through Day 28 will be compared between arms using the log-rank test and Cox proportional hazards models. In addition, specific components (e.g., cardiac and vascular dysfunction, or the composite of cardiovascular outcomes, thromboembolic events described in section 4.1.2, item 10, and worsening respiratory failure) will be analyzed using time-to-event analyses under competing risks, as described above for the primary analysis. Proportions of participants who experienced organ failure, serious infection or death will be summarized and compared between treatment arms at fixed time points using stratified Mantel Haenszel tests, overall and for specific organ dysfunctions.

The impact of study arm on the primary efficacy (recovery) and safety outcomes (primary composite safety endpoint, composite of grade 3 or 4 events, SAEs, PSESEs, and death through Day 5 and through Day 28, composite of SAEs, PSESEs, and death, and composite of hospital readmissions and death through Month 6) along with mortality will be assessed for subgroups defined by baseline characteristics, including demographics, baseline classification of “home”, duration of symptoms at enrollment, clinical history and presentation, and tests for homogeneity of the treatment effect across subgroups will be carried out. Additionally, subgroup analyses will be conducted for subgroups formed by a disease progression risk score at baseline. The construction of this risk score is described in section 5.2. Subgroup analyses will be interpreted with caution due to limited power and uncontrolled type I error.

11.3 Data Monitoring Guidelines for an Independent DSMB

An independent DSMB will review interim data on a regular basis and use pre-specified guidelines to identify agents with evidence of harm based on a difference in all-cause mortality. The DSMB will also monitor other adverse events and safety signals.

As a guideline, we do not recommend early termination for benefit based on the primary endpoint, which is most reliably estimated at Day 90. In addition, given the relatively short follow-up period of 90 days for this target population, full follow-up for the primary and all secondary endpoints is considered important to evaluate the investigational agents to be studied. An exception to this guideline is if the DSMB believe there is clear and substantial evidence of a mortality benefit for an investigational agent

11.3.1 Monitoring Guidelines for Interim Analyses

Multiple distinctive features of potential therapies for COVID-19-associated ARDS contribute to the monitoring guidelines for interim analyses within the master protocol. (If a specific investigational agent requires an alternative approach to interim monitoring, those details will be specified in the relevant agent-specific appendix.)

First, in many cases, potential agents may be relevant not only to COVID-19-associated ARDS but to other forms of ARDS. As such, even if an agent did not achieve its efficacy endpoint, enrollment to the planned sample size is expected to provide important insights relevant to future investigations in ARDS. These insights may especially pertain to potential effects among subgroups of patients or less common safety events of interest.

Second, the primary endpoint of this trial requires 90 days of follow-up since the final classification of a patient's recovery requires knowledge of their status on Day 90. While this duration of follow-up for the primary endpoint is essential for a patient-centered result at the conclusion of the trial, in the context of the anticipated rapid enrolment of the trial, this endpoint is infeasible to use for stopping boundaries for either efficacy or futility on the basis of conditional power.

Third, enrollment should stop early for any agent that shows clear evidence for increased mortality. A stopping boundary for harm is thus indicated.

Fourth, while it is important to avoid premature stopping for a potentially non-reproducible efficacy signal for the primary endpoint, clear and substantial improvement in mortality may appropriately lead to a DSMB recommendation to stop early for efficacy.

On the basis of these and related factors, the monitoring guidelines for this master protocol will focus on a stopping boundary for harm, a stopping boundary for efficacy based on mortality, and ongoing close monitoring of safety by the DSMB, based on the totality of evidence.

As a guideline to the DSMB for assessment of harm, a Haybittle-Peto boundary using a 2.5 standard deviation (SD) for the first 100 participants enrolled and 2.0 SD afterwards. Harm will be assessed using all-cause mortality, specifically using a hazard ratio from a proportional hazard model for the time to death associated with the investigational agent. As an additional guideline to the DSMB for assessment of efficacy, a Haybittle-Peto boundary using a 3.0 SD threshold will be used after 100 patients have been enrolled and followed for at least 5 days. Efficacy will be assessed using all-cause mortality, specifically using a hazard ratio from a proportional hazard model for the time to death associated with the investigational agent.

12 Protection of Human Subjects and Other Ethical Considerations

12.1 Participating Clinical Sites and Local Review of Protocol and Informed Consent

This study will be conducted by major medical centers participating in INSIGHT and partnering networks, including especially NHLBI networks. It is anticipated that potential participants will be recruited by the site investigators (and/or their delegates, as appropriate) and/or that positive SARS-CoV-2 laboratory testing will be used to enquire about potential enrollment. Information about this study will be disseminated to health care workers at enrolling sites.

Prior to the initiation of the study at each clinical research site, the protocol, informed consent form and any participant information materials will be submitted to and approved by a central/national IRB/EC and/or the site's local IRB/EC as required. Likewise, any future amendments to the study protocol will be submitted and approved by the same IRB(s) or EC(s). After IRB/EC approval, sites must register for this study before screening potential

participants, and must register for any protocol amendments. Protocol registration procedures are described in the PIM.

12.2 Ethical Conduct of the Study

The study will be conducted according to the Declaration of Helsinki in its current version; the requirements of Good Clinical Practice (GCP) as defined in Guidelines, EU Clinical Trials Regulation (EU 536/2014)/EU Clinical Trials Directive (2001/20/EC), and EU GCP Directive (2005/28/EC); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines; Human Subject Protection and Data Protection Acts; the US Office for Human Research Protections (OHRP); or with the local law and regulation, whichever affords greater protection of human subjects.

12.3 Informed Consent of Study Participants

Informed consent must be obtained (see sample in Appendix A) prior to conducting any study-related procedures. Many of the patients approached for participation in this research protocol will often have limitations of decision-making abilities due to their critical illness. Hence, some patients will not be able to provide informed consent. For patients who are incapacitated, informed consent may be obtained from a legally-authorized representative (LAR). Because the investigational agents are intended to treat critical illness and the impairment of decisional capacity is intrinsic to the critical illness, the use of LARs for consent is appropriate for this trial. The use of consent from LARs will follow applicable legislation (e.g., in the United States, 45 CFR 46.116 and 45 CFR 46 102 (i)). Capacity will be assessed according to local standards and policies. Local standards and policies will also determine who is legally authorized to consent for an individual who is incapacitated. Should the individual regain capacity during the study, their direct reconsent should be obtained at the earliest feasible opportunity.

Electronic consent may be used when a validated and secure electronic system is in place to do so, if in compliance with national legislation and approved by the responsible IRB/EC. Other methods of obtaining documentation of consent may be used when site staff are unable to be in direct contact with a potential participant or a legally-authorized representative due to infection-control restrictions. No matter how the participant's consent is obtained and documented, it is expected that consent will be preceded by research staff providing an explanation of the research and an opportunity for the participant (or their LAR) to have questions answered. Sites should follow all available local or national guidance on suitable methods for obtaining documentation of participant (or their LAR) consent.

12.4 Confidentiality of Study Participants

The confidentiality of all study participants will be protected in accordance with GCP guidelines and national regulations.

12.5 Regulatory Oversight

Sites in the US will conduct this trial under the terms of the IND and will adhere to FDA regulations found in 21 CFR 312, Subpart D. Sites in countries other than the US will not conduct the trial under the IND. As stated in Section 12.2 above, all sites will conduct the

trial in accordance with the requirements of GCP as codified in their local law and regulation, under the oversight of their institution and competent regulatory authority.

As part of fulfilling GCP and FDA requirements for adequate trial monitoring, multiple modalities will be employed. The objectives of trial monitoring are to ensure that participant rights and safety are protected, to assure the integrity and accuracy of key trial data, and to verify that the study has been conducted in accord with GCP standards and applicable regulations.

A specific risk-based protocol monitoring plan will be developed. The plan will include strategies for central monitoring of accumulating data and will take into account site-level quality control procedures. On-site monitoring visits for targeted source document verification and review of regulatory and study pharmacy files will be conducted when possible, but these tasks will most likely need to be handled remotely during the pandemic. The monitoring plan will outline the frequency of this aspect of monitoring based on such factors as study enrollment, data collection status and regulatory obligations.

Appendix A Sample Informed Consent form

Short Title: Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO)

Sponsored by: The University of Minnesota (UMN)/National Institute of Allergy and Infectious Diseases (NIAID)

Funded by: The National Heart, Lung, and Blood Institute (NHLBI) and National Institute of Allergy and Infectious Diseases (NIAID), US National Institutes of Health (NIH)

Full Title of the Study: **A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Severely Ill Patients with COVID-19**

CONSENT FOR PARTICIPATING IN AN NIH-FUNDED RESEARCH STUDY

SITE INVESTIGATOR: _____ **PHONE:** _____

ALL SITE INSTRUCTION THAT IS INCLUDED IN A TEXT BOX SHOULD BE REMOVED FROM THE SITE'S INFORMED CONSENT FOR PARTICIPANTS

US Office for Human Research Protections (OHRP) Requirements to be read by the sites:

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB/EC REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB/EC WITH A COPY OF THIS SAMPLE LANGUAGE ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBs/ECs ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OR SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB/EC, AND NOTED IN THE IRB/EC MINUTES. JUSTIFICATION AND IRB/EC APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO THE INTERNATIONAL COORDINATING CENTER OR COLLABORATING NETWORK. SPONSOR-APPROVED CHANGES IN THE PROTOCOL MUST BE APPROVED BY THE LOCAL IRB/EC BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB/EC MAY OTHERWISE ADDITIONALLY REQUIRE.

PID: _____

Key information:

We are asking you to join a research study about COVID-19. It is your choice whether or not you want to join. This form gives you information about the study that will help you make your choice. You can discuss this information with your doctor or family or anyone else you would like before you make your choice. Your choice will not affect the care you are getting for COVID-19.

What is the research question we are trying to answer?

We are studying two treatments for COVID-19. We are asking you to join the study because you are in the hospital with COVID-19 and have significant trouble with your breathing.

First, we are studying an experimental medicine, aviptadil (also called VIP), supplied by NeuroRx. We are trying to find out if giving this experimental medicine can help sick people in the hospital with COVID-19 have fewer bad effects from the disease, and if it may possibly help them get better and go home faster. We are also trying to see if it is safe.

This experimental medicine is a man-made version of a naturally occurring hormone in the body. It may decrease COVID-19 virus levels, inflammation, and blood clotting, and help protect the lung against injury. We think this experimental medicine may possibly help patients with COVID-19, and we think it will be safe, but we are not sure and so we are doing this study.

Second, we are studying a drug called remdesivir (also called Veklury) supplied by Gilead. Remdesivir is approved in the United States and many other countries for the treatment for COVID-19 in people who are in the hospital. We are trying to find out if remdesivir helps patients with your level of COVID-19 illness get better and go home faster. Remdesivir may decrease COVID-19 virus levels and lung injury. Currently we do not know if remdesivir will help people with your level of COVID-19 illness which is why we are doing this study.

What do you have to do if you decide to be in the study?

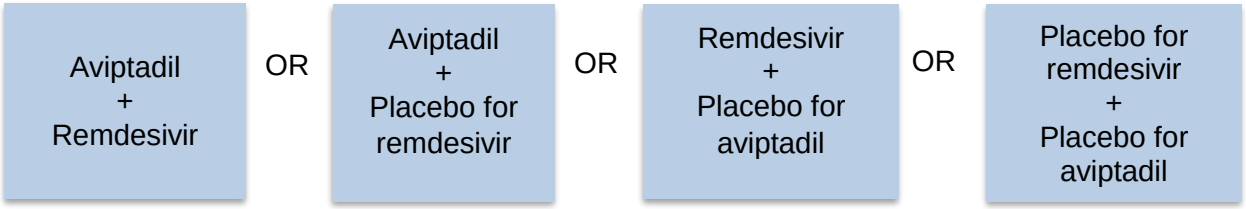
The study staff at your hospital will check to see if there is any reason you should not be in the study. They will check your medical history. They will look at tests commonly done for your condition. They will also check to see if you are able to get both of the drugs we are studying or just one of the drugs. For example, if you are pregnant you will not be able to receive the aviptadil or matching placebo (inactive salt solution) but you will be able to receive the remdesivir or matching placebo.

If you agree to be in the study, and you are able to get both treatments, we will assign you to one of four study groups. This will be done by random chance -- like flipping a

PID: _____

coin. You will have an equal chance of getting either the active drug or placebo (salt solution) for each drug.

You will be assigned to one of the following 4 groups:



Your doctor will NOT decide and will not know which of these four options you will get. The study staff will also not know which option you will get.

If you agree to be in the study, and you are ONLY able to get Aviptadil we will assign you to one of two study groups. This will be done by random chance -- like flipping a coin. You have an equal chance of being in each group.

If you agree to be in the study, and you are ONLY able to get remdesivir we will assign you to one of two study groups. This will be done by random chance -- like flipping a coin. You have an equal chance of being in each group.

Aviptadil: You will receive the Aviptadil study product (either the experimental medicine or the matching placebo) for three consecutive days starting on the day you join the study (study Day 0). You will get it by an intravenous (IV) drip through a tube in your vein. This is called an infusion. The infusion will take about 12 hours on each day that it is given.

Aviptadil is the only thing you may be given that is experimental. It is NOT approved for use in people with COVID-19 by the United States Food and Drug Administration (FDA) or any other regulatory body in the world. It is approved in some countries outside the US for another condition but is given in a different way. Its use in the United States is strictly limited to research.

Remdesivir: You will receive the remdesivir study product (either the active medicine or matching placebo) once per day for up to 10 days. You will also get this by an IV drip through a tube in your vein, which will generally take 1-2 hours. Remdesivir is approved

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in the United States for the treatment of COVID-19 in people who are in the hospital. It's not known whether it works in people with more severe COVID-19.

Other treatments: As part of the study you may also get a drug called a steroid for up to 10 days while you are in the hospital, as care for your COVID-19, unless your doctor thinks the steroid would not be safe for you to take. Steroids have been shown in prior studies to help people survive COVID-19. Steroids are available for other diseases in the United States, so your doctor will be using it "off-label," which means that while there is not formal FDA approval for this use, your doctors think it is reasonable. It is likely that you would receive steroid medicine even if you were not in the study.

Any other medications or treatments you will be given will be what you would usually receive in this hospital for your condition. There may be some additional procedures or testing done for study purposes. We will describe these below.

You will be in the study for 180 days. We will check on your health every day while you are in the hospital, and regularly after you leave the hospital.

We will swab your nose to see how much of the virus that causes COVID-19 is present. We will take blood samples from you to better understand the body's response to the infection. Some of the blood may be used in future studies.

To be in the remdesivir/placebo part of the study, you will need to agree to not have sex that could make you or a partner pregnant for seven days after you finish the remdesivir or placebo infusion. This may involve not having sex at all (abstinence), or you may use effective contraception (hormonal contraception or barrier methods with spermicide) to avoid pregnancy. Methods like rhythm, sympto-thermal or withdrawal are not effective for the purpose of the study. You can ask the study team about this if you have questions or concerns.

If you are pregnant, you cannot be in the aviptadil/placebo part of the study. You can still be in the remdesivir/placebo part of the study.

If you become pregnant during the study, please let your study team know as soon as possible. We will ask to follow you until your pregnancy is over, to see if there were any problems that may have been caused by any of the study treatments.

PID: _____

We will need to do the following things with you, and gather detailed information at these times:

Study Timepoint	**What will happen & what we will check**
Up to 1 day before you get study product	• Informed consent (this document) • Check to see how you are feeling • Your medical history • Whether you are taking certain medicines • A swab of your nose for virus detection • Blood tests to check your health (9 mL, about ½ tablespoon) • Blood for future research (18 mL, about 1 tablespoon) • Collection of urine or blood for a pregnancy test • Contact information like telephone numbers and addresses for you and at least two close relatives or friends
Day 0, Day 1, Day 2	• Infusion of study product (the experimental medicine or else placebo) if able to get this drug • Infusion of remdesivir study product (active drug or placebo) if able to get this drug (you may get this treatment for up to 10 days) • Blood tests to check your health (9 mL, about ½ tablespoon), unless your treatment team has already performed those tests
Day 3, Day 5	• How you are feeling • Blood for future research (18 mL, about a tablespoon) • If you're not in the hospital, we will not draw your blood and the visit may take place by phone
Day 2, Day 4, Day 5, Day 7, Day 14, Day 42, Day 60, Day 75	• How you are feeling (Days 2, 4, 7, 14, 60) • Update on return to home (Days 14, 42, 60, 75) • On Days 0-7 and 14, also whether you have taken certain medicines These "visits" may take place by phone.
Day 28, Day 90, and Day 180	• How you are feeling • On Day 28, also whether you have taken certain medicines • On day 90 and 180 only: we will ask you additional questions about your health These "visits" will take place by phone.

We may need to get some information from your medical record.

- By signing this consent, you agree to let us get information for this study from your medical record.

PID: _____

- By signing this consent, you are giving us permission to contact other hospitals or medical facilities if you are admitted there during the time you are in the study. We will contact them to be sure we know how you are doing.
- We will ask you to give us information about other people we can contact if we are not able to reach you after you leave the hospital, so we can find out how you are doing.

We will send the information we collect to the University of Minnesota (UMN) in the US where it will be stored and analyzed. In this information, only a code number, your year of birth, and a 3-letter code that the study staff chooses identifies you.

The study staff here at this site are responsible for keeping your identifying information safe from anyone who should not see it.

We will send the blood samples to a laboratory in the US for storage. We will keep them for as long as we have the funding and space to do so, which we expect to be many years. There is more information below about how we will use these samples.

Why would you want to be in the study?

If you get study drug, it is possible it may help you get better, or that you may get home faster, but we do not know that.

It is important to remember that some people in this study will get inactive placebo and will not get study drug.

By being in this study, you will help doctors learn more about how to treat COVID-19 in people in the hospital. Because so many people are getting hospitalized with COVID-19, this could help others. There may be a large health impact if a treatment proves to be safe and is shown to be effective.

Why would you NOT want to be in the study?

Since only some people in this study will get study drug, you may not receive it. Even if you do get study drug, it may not be useful, or it may have harmful side effects, so being in the study would not be of any direct help to you.

What are the risks or side effects of the study treatments?

All treatments have risks and may cause side effects. These may happen to you from the study treatment.

You may have an allergic reaction, including hives, trouble breathing, or other allergic responses. Allergic reactions like these are likely to be rare, but may be severe or life-threatening.

PID: _____

You will be monitored very closely while you are being given the infusion of the study product (aviptadil or placebo) and for at least 2 hours after the infusion is finished. We will give you prompt medical care if needed to treat any side effects from the infusion.

There are discomforts and risks associated with blood draws. You will have these things done while you are in the hospital even if you are not in the study. These discomforts and risks are no different from what you would experience if they were performed as part of your regular hospital care for COVID-19.

What are the risks or side effects of Aviptadil?

One effect of aviptadil is that it relaxes smooth muscle such as in your lungs, blood vessels, and intestines. Relaxing this type of muscle opens up your airways so it is easier to breathe and get oxygen into your body.

The most common side effect of aviptadil infusion is decreased blood pressure. In early studies of very ill patients with lung injury, about 1 in 5 people (20%) had lower blood pressure during the infusion of aviptadil. The decrease was usually small and went away within 10 minutes of stopping the infusion.

Facial flushing is common with aviptadil and is not dangerous. It is caused by relaxation of the blood vessels in the skin and goes away when the infusion is stopped.

Increases in heart rate are common and usually not dangerous. The increase in heart rate is mostly due to blood vessel relaxation.

Some people getting aviptadil have had mild to moderate diarrhea. The diarrhea goes away when the infusion is stopped.

What are the risks or side effects of Remdesivir?

The most common side effects of remdesivir included abnormal liver function test results, abnormal blood clotting test results, constipation, diarrhea, nausea, vomiting, decreased appetite, and headache. The abnormal liver function tests lasted longer than a few days in some people but went back to normal within a few weeks or less.

Remdesivir might affect the way that other medications are processed by your body. They might stay in your body longer, or shorter, at higher or lower levels. At the time this document was written, one person in another study had an increase in the level of a medication in their blood that was considered by study doctors to be at least possibly related to having taken remdesivir. There did not appear to be any harm from this temporary change. You can ask the study team more about this if you are concerned.

PID: _____

Some people may have some side effects after the infusion of remdesivir. Other people may have no side effects.

What are the risks and benefits of taking steroids?

Steroids may cause your sodium (salt) and glucose (sugar) levels to rise in your blood. You may feel anxious while taking steroids. You may be given steroids to treat your COVID-19 even if you do not join this study.

What if you are pregnant or breastfeeding?

If you are pregnant or breastfeeding, you can still join this study, although you cannot participate in the aviptadil portion of the study. However, we do not have any information about how either aviptadil or remdesivir may affect your baby. The risks to a pregnant woman or an unborn baby might be serious. Please take this into account as you make your decision about whether to join this study.

Additional information:

Here is some additional information about the study that may help you make your choice about whether you want to be in the study.

The NIH, an agency of the US Federal government, is paying for this study.

We are required to comply with all rules and regulations for human research as well as the laws of each country where the study is taking place.

This study is taking place in several countries. We expect to enroll about 800 people around the world.

You do not have to join this research study if you do not want to. If you choose to join the study, you can stop at any time. If you choose not to join or to stop, the medical care you are getting now will not change.

If we get any new information that might change whether you want to join or stay in the study, we will tell you right away.

If you do not want to be in this study, you will still get the usual care to treat COVID-19. However, you cannot get Aviptadil because it is experimental.

What are the costs to you?

We will give you the study treatment at no cost. We will pay for all clinic visits, lab work, and other tests that are part of this study.

THE NEXT PARAGRAPH IS FOR UNITED STATES SITES ONLY. SITES IN OTHER COUNTRIES SHOULD DELETE THE NEXT PARAGRAPH.

PID: _____

You, your insurance company, or some other third-party payer must pay for all other medicines and hospital costs.

SITES OUTSIDE THE UNITED STATES: Please replace the paragraph above with language appropriate for your location

Will you be paid to be in the study?

We will compensate you for your time and inconvenience participating in the study. *[Specific details to be completed by site.]*

What if you are hurt as part of this study?

If you are hurt because of being in this study, *[insert the name of the hospital/clinic]* will treat your injury right away. You or your insurance will have to pay for this treatment. The study cannot pay you or pay for any care for study-related injuries or for your illness.

If the above is not true for your site, i.e., if trial insurance covers such cost, please replace the above with appropriate language.

[The following section, up to "What happens to the blood samples?" is for US sites only.]

A Declaration under the Public Readiness and Emergency Preparedness (PREP) Act was issued by the Secretary of the United States Department of Health and Human Services on March 10, 2020. This Declaration limits the legal rights of a subject participating in clinical studies utilizing COVID-19 countermeasures. Because this study is covered by the Prep Act Declaration, covered persons, such as the manufacturers, study sponsor, researchers, healthcare providers and others have liability immunity (that is, they cannot be sued by you or your family under the laws of the United States).

If you believe that you may have been harmed as a result of this research study, certain claims for serious injury or death caused by the countermeasure may be eligible for compensation through the Countermeasures Injury Compensation Program. This is a program set up by the United States Government.

Information about this program can be found at https://www.hrsa.gov/cicp/about/index.html or by calling 1-855-266-2427. If you are

eligible for this program, you must file a claim within one year of the administration or use of the covered countermeasure.

What happens to the blood samples?

We will send the blood samples to a central laboratory in the United States. You and your doctor will **not** get the results of any tests done on these samples. We will not sell your samples and they will not be used for research aimed at making money (commercial research). The laboratory where the samples are stored will not have any information that could identify you.

The blood samples will measure how many COVID-19 antibodies are in your blood. This will tell us how your immune system responded to your COVID-19. The blood samples will also measure the amount of virus in your blood and other results related to your COVID infection.

Any blood samples that are left over after these tests will be stored at the central laboratory for as long as we are able to keep them. We hope to use these in the future to answer other questions about COVID-19, the virus that causes it, and how people respond to treatment. You and your doctor will **not** get any results from these tests.

You can withdraw your consent for us to keep these specimens at any time. Let your study team know if you do not want the study to keep your specimens anymore, and every effort will be made to destroy all of your specimens that are still at the central laboratory.

How do we protect your privacy?

We will take every reasonable step to keep your health information private and to keep anyone from misusing it.

Your information (data) and samples will not be identified by name, or in any other way, in anything published about this study.

We will do everything we can to keep your personal information private, but we cannot guarantee that nobody will get it. We may have to release your personal information if required by law.

These people may see your medical and research information:

- the ***[insert the name of the hospital/clinic]*** ethics committee (institutional review board [IRB]);
- the sponsor, the group paying for the research (US NIH), other study research staff and study monitors
- US and other participating countries' health regulatory agencies, including the US FDA.

They are committed to protecting your privacy.

As the research staff at *[inset the name of the hospital/clinic]*, we are required to make sure that people not involved with this study cannot see your research and medical information. We will keep your research files in a safe place and will handle your personal information very carefully.

Your study data are sent electronically to the UMN in the US through a secure system. By signing this consent, you agree to having your data sent to UMN. No information that could directly identify you is sent to UMN. This is called "pseudonymized data." Access to the data at UMN is limited through security measures, and no data breach or unauthorized access has ever occurred in this system. After the study is over, the data will be stored securely for the period required by law.

Your study data will be shared with the US National Institutes of Health (which is paying for this study), and with regulators that oversee the study, including the US FDA, as required by law. Your study data will also be shared with the drug company that provides the study medicine to help them develop the drug.

UMN may share your data and specimens with other people who study COVID-19. UMN will remove any information that could possibly be used to identify you before sharing. This is called "anonymizing the data." We will not ask you for additional consent for this sharing. UMN will only share data and specimens for research projects that are approved by the group that is conducting this study.

This study has a Certificate of Confidentiality from the US Federal Government. This means that UMN cannot share any data it has about you with national, state, or local civil, criminal, administrative, legislative, or other authorities unless you specifically allow us to share it.

A description of this clinical trial will be available at http://www.ClinicalTrials.gov, and on the EudraCT website (https://eudract.ema.europa.eu/). These websites will not include your name or any other direct identifiers such as your contact information. These websites will include a summary of the results of this research once the study has been completed. You can search either website at any time.

[Note for US sites: The following brief HIPAA authorization is provided. Your site-specific consent should be modified to reflect the HIPAA authorization language requirements at your site.]

To do this research, we will collect and use your personal data, as described above and in any HIPAA Authorization Form we have given you. Please tell us whether you agree to have us collect and use your personal data by placing your initials in front of your selection.

____**Yes**, I agree to the collection and processing of my personal data.

PID: _____

____**No**, I do not agree to the collection and processing of my personal data.

It is your choice whether you allow us to collect and use your data. However, you will not be able to be in this study if we cannot collect and use your data.

*[The following section (up to "What are your rights regarding your data?") is for **US sites only.**]*

There are a lot of studies trying to find out more about COVID-19 and how people do after they have had COVID-19. Sometimes other researchers studying COVID-19 may ask if we know of people who might be interested in being in a study. If you think you might be interested in future studies, you can let us know now. We are asking you for permission to share your contact information (name, email, phone number, mailing address) with other researchers outside the study team who ask us to help them. We would only share your contact information with researchers who have appropriate ethics approval for their study. We will never share your contact information with researchers doing studies aimed at making money ("commercial research"). Even if you let us give other researchers your contact information, you do not have to be in any future studies. You always have the choice to say "no" if someone contacts you for a future study. If you tell us now that we can share your contact information but later you change your mind, let us know. If you change your mind, we will no longer share your contact information with other COVID-19 researchers.

Please put your initials by your choice:

____**Yes**, you **can** share my contact information with other qualified researchers.

____**No**, **do not** share my contact information with other qualified researchers.

It is your choice whether to let us share your contact information with other researchers studying COVID-19. You can still be in this study even if you do not want us to share your contact information.

*[The following section (up to "What if you have problems or questions?") is for **only for countries subject to the GDPR or similar legislation requiring this information**. It should only be included in consents for sites subject to such legislation. It will vary from place to place whether it must be in this consent document, a separate consent document, or an information sheet that does not require signature. The amount of information provided may be reduced to meet the requirements of a particular country (e.g., not all countries/ECs require an enumeration of all of a data subject's rights).]*

What are your rights regarding your data?

The UMN is a public research university, and this study is funded primarily by a grant from the US Federal government. UMN and the study funding source require the sponsor (UMN) to follow regulations and policies that are meant to protect your privacy.

PID: _____

UMN is also required to comply with the General Data Protection Regulation (GDPR), because it processes data obtained from people in Europe.

There is no specific independent supervisory authority overseeing the processing of data in the US. Any complaint you might have about the use of your data would be made to your national data protection authority.

The GDPR gives you additional rights which we would like to inform you about below.

Right to Information: You have the right to know what data about you is being processed. You can also get a free copy of this data provided.

Right to Correction: You have the right to correct any information about you which is incorrect or had become incorrect.

Right to Erasure/Anonymization: The sponsor is required under both EU and US law to retain data from research studies like this one for many years. However, you have the right to request that your personal data be completely anonymized. This is done by destroying the information at your study center that links your identity to the pseudonymized data held by the sponsor. This means that no one would ever be able to link the data held by the sponsor to you personally.

Right to Restriction of processing: Under certain conditions, you have the right to demand processing restrictions, i.e. the data may then only be stored, not processed. You must apply for this. Please contact your study physician or the data protection officer of the study center if you want to do so. This right may be limited if the restriction would affect the reliability of the study results.

Right to Data portability: You have the right to receive the personal data that you have provided to the study center. This will allow you to request that this information be transmitted either to you or, where technically possible, to another agency designated by you.

Right to Contradiction: You have the right to object at any time to any specific decision or action taken to process your personal data. This right is limited for data that have already been processed and may be limited if your objection would affect the reliability of the study results.

Right to Withdrawal of this consent: You may withdraw your consent at any time with effect for future data collection. This withdrawal may be in an informal or verbal communication to your investigator. If you withdraw your consent this will not affect the

lawfulness of the data processing that has been or will be done with data collected until you withdraw consent. Data already collected will be anonymized.

If you would like to use one of these rights, please first contact the person responsible for the data collection at your study center:

Person responsible for data collection at the study center:
Name:
Address:
Phone:
Email

For concerns about data processing and compliance with data protection requirements you can also contact the data protection officer responsible for the study center:

Data protection officer responsible for the study center:
Name:
Address:
Phone:
Email

In addition, you have the right to lodge a complaint with the competent authority if you believe that the processing of personal data concerning you is contrary to the GDPR:

Data protection authority responsible for the study center:
Name:
Address:
Phone:
Email

What if you have problems or questions?

If you ever have questions about this study, or about the storage or use of your data or samples, or if you are hurt by being in the study, contact:

- *[name of the investigator or other study staff]*
- *[telephone number of the above]*

If you have questions about your rights as a research participant, you can call:

- *[name or title of person on the ethics committee (IRB) or other organization appropriate for the site]*
- *[telephone number of the above]*

PID: _____

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE TESICO STUDY

I have read the consent or have had it explained to me. I believe that I understand the information. By signing and dating this consent, I am stating that I want to join this study. I understand that I do not waive any of my legal rights as a study participant by signing this consent. I understand that I will receive a copy of the signed and dated consent.

If you agree to be in this study, please sign below.

_____ Date: _____

Signature of participant

_____

Printed name of participant

_____ Date: _____

Signature of investigator/designee

_____

Printed name of investigator/designee

FOR ADULTS NOT CAPABLE of GIVING CONSENT

_____ Date: _____

Signature of Legally Authorized Representative (LAR)

_____

Printed name of LAR

PID: _____

_____

Relationship of LAR to Participant

(Indicate why the LAR is authorized to act as a surrogate health care decision-maker under state or applicable local law)

Witness to Consent Interview

On the date given next to my signature, I witnessed the consent interview for the research study named above in this document. I attest that the information in this consent form was explained to the subject, and the subject indicated that his/her questions and concerns were adequately addressed.

_____ Date: _____

Signature of witness

_____

Printed name of witness

NOTE: This consent form, with the original signatures, MUST be retained on file by the Investigator of Record. A copy of the signed and dated consent must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

If no-touch / electronic consent is used, the participant must be provided with a copy of the consent in a manner appropriate to the method used to obtain it. A record of the act of consent must also be appropriately retained in the participant's medical record.

Additional Consent for Genetic Testing on Stored Specimens

WHY IS GENETIC TESTING BEING DONE? The study team would like your permission to collect a small amount of your blood and store them for researchers who will do genetic testing (testing on your genes) and other related tests in the future. These tests will help us understand how the genetic makeup of people affects the COVID-19 virus and how it makes people sick.

Any future research done on the blood collected for this study will be related to the COVID-19 virus for which you are being studied in ***this trial.***

WHAT WILL HAPPEN DURING GENETIC TESTING?

If you agree to take part in this study, three blood specimens will be collected along with other blood being drawn for the study, approximately 15 mL (about 1 tablespoon) in total. The blood will be taken with other laboratory test samples so you will not get an extra needle stick.

HOW WILL YOUR BLOOD BE USED? Your blood will be used to learn more about the health problems that may be caused by COVID-19. This may include tests to better understand why some people have more severe complications (get sicker) than others and why medicines to prevent or treat these infections might work better in some people than in others.

Researchers involved with this blood collection project do not know yet exactly which tests will be done.

You and your study doctor or nurse will not get any results from the tests done on your blood collected for this genomics study. These tests will only be used for research and may not apply to your medical care.

Your blood sample collected for this study will:

- Become the property of INSIGHT.
- Not be sold or used to make commercial products.
- Not be tested for any specific research study unless the plan for using your blood is approved - based on scientific and ethical considerations - by the INSIGHT Scientific Steering Committee, the U.S. National Institutes of Health (NIH), and a special committee (an Institutional Review Board or Ethics Committee) at the researcher's institution.

HOW WILL YOUR PRIVACY AND THE CONFIDENTIALITY OF YOUR INFORMATION BE PROTECTED?

PID: _____

Every reasonable step will be taken to protect your privacy and the confidentiality of your health information and to prevent misuse of this information, and to make sure your blood sample is handled with care at the storage facility. For example, your research records will be identified only by a code. Your blood sample and results of any genetic testing will be identified by a second code. Only a few statisticians (persons who analyze the study results) associated with the INSIGHT studies will have access to both codes in order to analyze the test results. These statisticians will not have access to any information that can identify you.

Researchers will write reports, including information they learn from future tests on your blood. These reports will be shared with participating research sites. These findings will also be submitted for publication in scientific or medical journals. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

However your records may be seen by:

- Institutional Review Boards (IRBs) or Ethic Committees (ECs) who review the study to make sure it is ethically acceptable
- Agencies of the U.S. government that fund or oversee this research, for example, the U.S. National Institutes of Health (NIH) or the U.S. Office for Human Research Protections (OHRP)
- Research staff and study monitors, and their designees.

Staff at ***[insert the name of the site]*** will handle your personal information very carefully. They are required to make sure that people not involved with this study do not have access to your research and medical records.

[For U.S. Sites Only]

In addition to these efforts to keep your information confidential, the INSIGHT Genomics study is covered by a *Certificate of Confidentiality* from the U.S. Department of Health and Human Services. This certificate means that researchers cannot be forced to give information collected as part of this study to people who are not involved with the study, for example, the court system. However, this certificate has limited protection rights. You should know that it does not stop the doctor in charge of this study from taking appropriate steps to prevent serious harm to yourself or others. Federal and state laws also help protect research participants and others who have genetic testing done.

[For International Sites Only]

Efforts will be made to keep your personal information confidential, but we cannot guarantee complete confidentiality. Your personal information may be released if

required by law. Any publication of this study will not use your name or identify you personally.

HOW LONG WILL YOUR BLOOD BE KEPT?

Your blood specimen will be stored as long as funding is available for storage and testing.

[Alternative to Previous Paragraph for non-US Sites Only]

Your blood specimen will be stored safely and securely at a special facility called a specimen repository. The repository may be located in the United States. This facility follows strict procedures so that only approved researchers can use the stored specimen for future testing. The employees at this facility who will store and track your blood specimen will not have information that identifies you by name.

Risks: There are few risks involved with your participation in this study. Having your blood drawn may result in a little pain and slight bruising where the needle goes into your skin. You may also feel lightheaded, bleed, develop a small blood clot where the needle goes into your skin, or faint. Very rarely, your skin may get infected. Another small but unlikely risk is the possibility of others finding out about your participation in this study.

Benefits: You will not receive any direct benefit from your samples. Information obtained from the tests may provide useful information, to help other patients, about the causes, risks, and prevention of the COVID-19 virus.

WHAT IF YOU DON'T WANT YOUR BLOOD FOR GENETIC TESTING STORED ANY LONGER? If you sign the consent that your blood can be stored for research to be done at a later date you can change your mind at any time. If you change your mind, you must write a letter to ***[insert the name of the principal investigator*]** at the ***[insert the name and address of the site]*** to let them know that you do not want your blood specimen collected for this study used for future research. A sample letter will be given to you as a guide to help you express your request in writing.

When ***[insert the name of the principal investigator]*** receives your letter, the research staff will contact you to come to the clinic to verify your decision by signing and dating this original informed consent form. A second copy of this consent will be given to you as proof that we received your request. If we do not hear from you within 30 days after getting your letter to withdraw from this study, we will send your request to the storage facility.

If you decide to withdraw consent for this study, your blood sample, including any parts separated from the sample, will not be used. Every effort will be made to destroy your

blood sample and any parts separated from it. If some testing has already been done on your blood sample, the results from this testing will remain as part of this research. The research staff at the ***[insert the name of the site]*** will notify you of the date your blood specimen and any of its parts were destroyed.

Costs or compensation of study: There will be no costs to you or compensation.

Consent: Please ***mark the box for*** yes or no and ***sign your name***, indicating you have freely given your answers and consent:

- My blood samples may be stored and used for future genetic research in COVID-19 or other serious illness: **Yes** ☐ **No** ☐

_____ _____

Signature (subject or surrogate) Date

_____

Subject or Surrogate Printed Name

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name and Title of Person

Appendix B Schedule of Assessments

	Screen or Day 0	Day 0	Study Day													
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**180**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+ 10**	**± 14**
ELIGIBILITY & BASELINE DATA																
Informed consent	X															
Baseline medical and social history	X															
Baseline concomitant medications	X															
Symptom-directed physical exam by the clinical team (includes vital signs)	X															
Nasal swab for virus detection and review SARS-CoV-2 test results	X															
Baseline study labs (CBC with differential, ferritin, CRP, BMP, INR, D-DIMER, AST, ALT, bilirubin)[2]	X															
Research sample storage (includes DNA and RNA at baseline among patients who consent to genetics)	X															
Urine pregnancy test or other documentation of pregnancy status	X															
STUDY INTERVENTION																
Randomization		X														

	Screen or Day 0	Day 0	Study Day													
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**180**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+ 10**	**± 14**
Study Drug/Placebo Administration[3]		X	X	X												
Assess infusion completion and adverse reactions[3]		X	X	X												
STUDY PROCEDURES																
Post-randomization concomitant medications		X	X	X	X	X	X	X	X	X[4]	X					
On-study labs (BMP, CBC with differential, INR, D-DIMER, AST, ALT, bilirubin)[2,5]		X	X	X												
Clinical labs (BMP, CBC with differential, INR, D-DIMER, AST, ALT, bilirubin)[5,6]					X[7]		X[8]									
Research sample storage (includes RNA at day 3 among patients who consent to genetics)[4,5]					X[7]		X[8]									
Vital signs[5]	X	X	X	X			X			X						
Hospitalization status					X		X		X	X	X	X	X	X	X	X
Changes in residence/facility										X	X	X	X	X	X	
Interim medical history									X	X	X	X	X	X	X[9,10]	X[9,10]
Oxygen support (for WHO/NIH/TICO ordinal outcome)	X	X	X	X	X	X	X	X	X	X[4]						

	Screen or Day 0	Day 0	Study Day													
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**180**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+ 10**	**± 14**
Clinical AEs of grade 3 and 4 severity		X	X	X	X	X	X	X	X	X	X					
Clinical AEs of any grade on day indicated										X	X					
SAEs and PSESEs		Report through 90 days														
SAEs related to study interventions		Report as they occur														
Unanticipated problems		Report as they occur														
Deaths and readmissions		Report as they occur														
Hospitalization Summary		Report upon hospital discharge														

[1] Screening must be performed within 24 hours of randomization.
[2] These laboratory evaluations will only be performed as study procedures if they are unavailable clinically on that study day
[3] Duration of study drug administration may vary by investigational agent; the sample provided here is for 3 successive days. Where the duration of study drug administration varies from this schedule, the duration will be specified in the relevant agent-specific Appendix H .
[4] The Day 14 visit will record values for Days 8–14.
[5] These will be not be collected after hospital discharge.
[6] These laboratory assessments will only include clinically available results
[7] It is acceptable to perform the Day 3 draw on Day 4.
[8] It is acceptable to perform the Day 5 draw on Day 5±1, but the Day 3 and Day 5 draws cannot both be performed on Day 4.
[9] Includes telephone administration of the Euro-QOL-5D-5L instrument.
[10] Includes telephone administration of Patient-Reported Outcomes (MRC Dyspnea, PROMIS fatigue, CONNECTS Recovery)

Appendix C TESICO / ACTIV-3b protocol team

To oversee the implementation of this master protocol, a protocol team will be formed and include:

- Protocol co-chair(s)
- NIAID, Division of Clinical Research representatives
- NHLBI Program Officers
- INSIGHT University of Minnesota representatives
- INSIGHT International Coordinating Center representatives
- Representatives from collaborating trials networks, including PETAL, CTSN, and VA
- Representatives from collaborating laboratory representatives
- Representatives from collaborating manufacturers of investigational agents
- Representatives from site investigators
- Study biostatisticians
- Community representative(s)

A core team consisting of the co-chair(s), ICC leaders, NIH representatives, study statisticians, representatives from collaborating trials networks, and other representatives and the INSIGHT PI will also regularly convene to review study progress and address study conduct and administrative issues that arise.

Appendix D REFERENCES ON THE INSIGHT WEBSITE

The INSIGHT website (**www.insight-trials.org**) will maintain updated links to the following documents referenced in the INSIGHT 014 protocol and to other information pertinent to the study:

- DAIDS toxicity table: (https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables)

- INSIGHT Publications and Presentations Policy (http://insight.ccbr.umn.edu/resources/P&P_policy.pdf)

- Centers for Disease Control and Prevention (CDC) and European Centre for Disease Prevention and Control (ECDC) guidance on how to handle infection control measures (https://www.cdc.gov/sars/guidance/i-infection/healthcare.html and https://www.ecdc.europa.eu/en/publications-data/infection-prevention-and-control-and-preparedness-covid-19-healthcare-settings).

- Treatment guidelines, incl from NIH and WHO (https://www.covid19treatmentguidelines.nih.gov/, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/, https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation and https://www.ersnet.org/covid-19-guidelines-and-recommendations-directory)

Appendix E LIST OF ACRONYMS

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ACTT	Adaptive COVID-19 Treatment Trial
AE	adverse event
ARDS	acute respiratory distress syndrome
CDC	Centers for Disease Control and Prevention (US)
CHF	Congestive heart failure
CI	confidence interval
COVID-19	Coronavirus-Induced Disease 2019
CTSN	Cardiothoracic Surgical Trials Network
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
EU	European Union
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HR	hazard ratio
ICC	International Coordinating Center
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Institutional Ethics Committee
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IQR	interquartile range
IRB	Institutional Review Board

IV	intravenous
LAR	Legal Authorized Representative
MI	Myocardial infarction
mL	milliliter
NAT	Nucleic acid test (to identify genomic material; some uses amplification)
NHLBI	National Heart, Lung, and Blood Institute, NIH (US)
NIAID	National Institute of Allergy and Infectious Diseases, NIH (US)
NIH	National Institutes of Health (US)
NIHSS	National Institutes of Health Stroke Scale/Score
nMAb	Neutralizing Monoclonal Antibodies
OHRP	Office for Human Research Protections (US)
OR	odds ratio
PCR	polymerase chain reaction
PETAL	Prevention and Early Treatment of Acute Lung Injury Network
PHI	personal health information
PIM	Protocol Instruction Manual
RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TOC	trial oversight committee
UMN	University of Minnesota
UP	Unanticipated problem
US	United States of America
VA	Veterans Administration
WHO	World Health Organization

Appendix F This Is Intentionally Blank

Appendix G This Is Intentionally Blank

Appendix H Investigational Agent.

This appendix will include the following information for each investigational agent studied. The rationale for studying the agent and the description and administration of the agent. Also, as appropriate, specific AEs observed to be possibly associated with the agent in question, and how to monitor for, clinically handle and report such AEs, should they arise. Changes in endpoint, SOC, inclusion and/or exclusion criteria, sample size estimation and approach to interim analyses and data analyses will also be included if appropriate for the investigation of the agent in question relative to what is stated in the master protocol. Finally, the text will also clarify whether the manufacturer of the investigational agent plans to pursue licensure in the countries where the trial will occur, should the investigational agent be demonstrated in the trial to have overall benefit.

Introduction/Rationale for studying the agent

  - Potential risks and benefits of agent
  - Motivation for agent selection with consideration of results from trials of other agents
- Agent-specific eligibility criteria
- Description of investigational agent
  - Administration and duration
  - Formulation and preparation
  - Supply, distribution, and accountability
  - Contraindicated medications
  - Precautionary medications
- Clinical and laboratory evaluations in addition to master protocol
  - Timing
  - Special instructions
- Clinical management issues
  - Infusion-related reactions
  - Hypersensitivity
- Pregnancy and breast-feeding considerations
- Criteria for discontinuation of infusion
- References

Appendix I Standard of Care

I1. Overview

Currently, the only licensed treatment for COVID-19 is remdesivir, but the *registration trials for remdesivir were too small to demonstrate efficacy in patients with critical illness from COVID-19.* Considering the number of randomized trials being conducted to study treatments for COVID-19, it is likely that other effective treatments will be identified during performance of this master protocol.

When treatments for COVID-19 are demonstrated to have safety and efficacy, those treatments should be considered in designing new studies. Depending on the scientific question, an experimental treatment will be coupled with or compared to a known effective treatment. When such known effective treatments are incorporated into both arms, they are called "background therapy" or standard of care (SOC). In this case, the scientific question addressed is whether a new treatment added to an already effective treatment is superior to the established effective treatment alone.

SOC may include general supportive care appropriate to the participant's clinical status, and specific therapeutic agents, and measures to reduce risk of SARS-CoV-2 transmission to the participant and health care givers.

As stated in section 5.1, the objective of this protocol is to evaluate investigational agents - aimed at treating patients with critical illness from SARS-CoV-2 infection - for safety and efficacy compared to placebo control, when all eligible participants receive background therapy that is considered effective. Consistent with precedent, we refer to background therapy as standard of care (SOC). All participants will receive an investigational agent + SOC vs. placebo + SOC.

Below, principles for defining SOC are provided, and recommendations and guidance on SOC are given. Whether an individual SOC treatment is provided by the trial or not is based on multiple factors, including clinical and scientific considerations. In some cases, the decision to administer an SOC treatment is left entirely to the research participant's primary medical team.

I2. Guiding principles for inclusion of measures as part of SOC

The SOC will be regularly updated based on review of the scientific literature and updated authoritative treatment guidelines on this topic. The standard for including one or more measures as SOC, includes a careful review of the existing literature and current guidelines (see Appendix D). As for therapeutic agents, those having been shown to be clinically effective in properly powered Phase III or Phase IV trials (i.e., high quality/level 1 evidence) and with a reasonable safety profile will be considered by the protocol team for inclusion, if recommended by at least one major treatment guideline. This evaluation may also lead to a statement that one or more agents are either not recommended or should not be used as part of SOC. As knowledge will likely continue to accumulate rapidly, the protocol leadership team may occasionally decide to include or exclude an intervention as part of SOC before it is recommended in at least one major treatment guideline. In such cases, the relevant literature that lead to the determination will be cited.

The use of a given SOC intervention may apply to all or to a subgroup of the participants in the master protocol based on available evidence – the subgroup may be defined based on severity of disease, a clinical or laboratory defined feature, or a clinically or laboratory defined contraindication for using the SOC treatment. An SOC agent may be mandated for participants (required for protocol entry); mandated where not contraindicated (participants may enter if that SOC is unsuitable, and not receive that SOC); or recommended subject to clinical discretion. SOC may be protocol-supplied where mandated.

The master protocol acknowledges that there may be local variation in the clinical availability of one or more agents chosen to be part of mandated protocol-supplied SOC from site to site. While acknowledging risks of inadvertent coercion, the importance of the scientific question (how candidate agents perform against the background of the current SOC treatments) is a crucial, high-priority question. There is no possible way to answer the question of efficacy against the background of an already proven effective agent without providing the agent – if not readily available - within the trial.

I3. Current SOC in the master protocol:

I3.1 Remdesivir

Although remdesivir is licensed for use in the United States and is SOC for most hospitalized patients with COVID-19, the key registration trials[50] included insufficient patients in this subgroup to provide strong evidence in favor of remdesivir for critically ill patients. It is anticipated that this master protocol may include a placebo-controlled investigation of remdesivir, possibly in a factorial design, in this patient population. Thus remdesivir is not considered SOC presently for this protocol: the protocol does not recommend routine initiation of remdesivir in this patient population (except potentially as an investigational agent). For patients who have already initiated remdesivir by the time of enrollment, this protocol makes no recommendation regarding whether to continue or discontinue remdesivir as part of background therapy. (For patients enrolling in a remdesivir randomization, see the remdesivir appendix for further guidance on receipt of remdesivir prior to randomization.)

I3.2 Dexamethasone and Other Corticosteroids

Based on the findings of the RECOVERY trial,[39] a meta-analysis of glucocorticoid trials,[51] and in line with NIH treatment guideline (Appendix D), it is recommended to consider initiation of corticosteroid therapy in participants with COVID-19 who have respiratory failure—the target population of this master protocol. Corticosteroids may increase the probability of reactivating latent infections including herpes viruses and tuberculosis, hyperglycemia, hypernatremia, secondary infections, and may delay clearance of SARS-CoV-2, but the balance of evidence favors glucocorticoid therapy. Treatment with a corticosteroid is recommended for a total of 10 days, using doses outlined in this table.

Corticosteroid name	Daily dose
Dexamethasone	6 mg PO or IV
Prednisone	~40 mg PO
Methylprednisolone	~32 mg IV
Hydrocortisone	~160 mg IV

I3.3 Other Supportive Care

All participants will be given *supportive care* for most complications of severe COVID-19 including: pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization, including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy. Links to details of such care can be found in Appendix D. Supportive care components of SOC include lung-protective ventilation for patients who require invasive mechanical ventilation[52] (high quality evidence) and prone positioning for mechanically ventilated patients with more than moderate ARDS (high quality evidence[53,54]), treatment with anti-bacterial agents for patients believed to have bacterial infection (high quality evidence), guidelines-compliant management of sepsis when it is present (moderate quality evidence).[55] Use or non-use of extra-corporeal life support (ECLS) is not mandated as part of SOC; nor is any specific approach to renal replacement therapy.

Consideration should be given to the use of pharmacological thromboprophylaxis (thrombosis prevention) in line with local clinical guidelines for hospitalized patients as appropriate for an individual participant, in addition to approaches to maintain mobility and minimize other thrombotic risks. Standard approaches to thromboprophylaxis supported by high quality evidence include the use of low molecular weight heparin (for example, enoxaparin 0.5 m/kg daily), which is the preferred agent in some COVID-19 treatment guidelines. However other standard approaches in accordance with local and institutional guidelines and the medical circumstances of an individual participant may also be considered, including the use of low (prophylactic) dose unfractionated heparin (high quality evidence). Specialist advice should be sought for participants with pre-existing prothrombotic states, or who are pregnant.

I3.4 Cautions and Contraindications

It is not recommended to use chloroquine as SOC due to excess harm and no demonstrable benefit. Neither hydroxychloroquine nor chloroquine have documented clinical benefit, and hence are not recommended for use as SOC. Similarly, it is not recommended to use lopinavir/ritonavir as SOC, since there are studies suggesting no clinical benefit.[56,57] These recommendations are consistent with current guidelines by the Infectious Disease Society of America, as included in Appendix D.

I3.5 SARS-CoV-2 Infection Control

Minimum standards of protection to *reduce the risk of SARS-CoV-2 transmission* from trial participants to research personnel, participants in other trials, or patients treated in the same facility can be found in links displayed in Appendix D.

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TESICO Appendix H1: Aviptadil version 3.0, 08 March 2022

The content of this appendix is confidential and should only be viewed by persons covered by the relevant CDA between NIAID and the collaborating companies.

This appendix provides detailed information pertaining to the study of this investigational agents. If not stated otherwise in this appendix, the text in the TESICO master protocol provides the approach that will be taken to study this agent.

The principal difference of the study of this agent with the master protocol is that it will be studied, in part, using a 2x2 factorial design with remdesivir. Study objectives, randomization and data analyses take this factorialization into account and are described in Appendix H2 for remdesivir.

At the outset of this study, there will not be a shared placebo with another investigational agent.

1. Introduction and rationale for studying aviptadil

Vasoactive Intestinal Peptide (VIP; aviptadil is the generic name for the synthetic peptide) is a 28-amino acid signaling peptide that belongs to the glucagon-secretin superfamily. VIP is an abundant biologically active peptide endogenous in humans as well as in other species. It is produced by neurons in the peripheral and central nervous system, by endocrine cells such as pituitary lactotrophs, cells of the endocrine pancreas as well as T-lymphocytes, and B-lymphocytes. This natural peptide is one of the signal molecules of the neuroendocrine-immune network. VIP is an inhibitory neurotransmitter that binds G-protein coupled receptors named VPAC1 and VPAC2, generally leading to an increase in cAMP in target cells. Originally described in the intestinal tract,[1] it is expressed widely in the body, with multiple functions. The lung is the primary location of binding of VIP, as evidenced by radiolabeled VIP perfusion experiments (within 30 minutes, 45% of all infused VIP is bound in the lung, with minimal binding in other organs[2]). Cells expressing VIP receptors in the lung include vascular and bronchial smooth muscle cells as well as alveolar type 2 cells (ATII).[3] Critically, ATII cells are also a primary target for SARS-CoV2, the virus causing COVID-19.

The effects of aviptadil are pleiotropic, with key effects being (1) antiviral effects, (2) immune modulation, (3) increase in ATII surfactant production, (4) ATII cell protection, (5) smooth muscle relaxation (leading to bronchodilation and vasodilation), (6) decrease in platelet activation.

Antiviral effects. VIP is known to decrease HIV production within monocytes,[4,5] which drove interest in evaluating antiviral properties for SARS-CoV2. In a series of experiments, Temerozo and colleagues established that VIP decreased viral replication within infected Calu-3 cells (an immortalized lung cancer cell line), plus increased monocyte and Calu-3 viability after SARS-CoV2 infection.[6] These experiments also established that VIP treatment decreased the production of inflammatory cytokines within SARS-CoV2-infected monocytes.[6]

Immune modulation. VIP has multiple immune-modulatory effects.[7] In the lung, VIP decreases inflammation through multiple interdependent mechanisms, including inhibition of effector T cells and supplementation of regulatory T cells, with an associated decrease in local cytokines, as observed in sarcoid.[8] In a rat ATII cell model of smoke-associated lung inflammation, VIP decreased inflammation and proteinase activity.[3] Similar pre-clinical data in sepsis demonstrated decreases in TNFa and TGFb with VIP administration.[9-11] In terms of post-inflammatory injury, VIP has been shown to decrease myofibroblast proliferation in cell models.[12]

Surfactant production. In a lung explant model, VIP directly increased phosphatidylcholine production via PKC and C-Fos mechanisms.[13,14] In a similar model, VIP increased surfactant protein A production in ATII cells.[15]

ATII cell protection. VIP prevents apoptosis of ATII cells via multiple mechanisms including Granzyme and Fas-ligand.[16,17] In multiple animal models of ARDS, VIP is protective against acute lung injury.[17-21]

Smooth muscle relaxation. VIP is a non-adrenergic pulmonary and systemic vasodilator that in ex vivo pulmonary artery is substantially more potent at muscle relaxation than prostacyclin.[22] The increases in muscle relaxation are independent of the endothelium. VIP is also a direct bronchodilator based on relaxation of bronchial smooth muscle.[23] In a cat bronchoconstriction model, intravenous (but not inhaled) VIP resulted in significant bronchodilation.[24]

Platelet effects. VIP inhibits pro-inflammatory platelet activation via inhibition of platelet activating factor.[25]

These mechanistic observations in cell and animal models have been corroborated in various human observations in a variety of conditions, including ARDS and COVID-19.

Clinical experience with aviptadil

Non-randomized data in other disease states

Sarcoidosis. Twenty patients with chronic sarcoidosis were treated with nebulized aviptadil, which was associated with increases in regulatory T cells and decreases in macrophage activation.[8] There were no important safety concerns.

Checkpoint inhibitor pneumonitis. Inhaled VIP was used successfully to treat pneumonitis caused by checkpoint inhibitor therapy in a patient with advanced melanoma. The pneumonitis had recurred after an initial course of steroid therapy, and VIP was used in hopes of avoiding a second course of steroids.[26] The patient recovered from the pneumonitis, and no safety concerns were identified.

Pulmonary hypertension. Twenty patients with pulmonary hypertension (PH) of various etiologies received 100mcg of inhaled VIP during right heart catheterization, with an immediate decrease in vascular resistance. Among patients with lung disease as the cause of PH, increases in oxygen saturation were observed.[27] Similar results were observed in a smaller cohort of PH patients.[28] No important safety concerns were identified.

Non-randomized data in ARDS and COVID-19

Currently, there are multiple case reports and case series of patients with either septic ARDS or COVID-19 ARDS who have been treated with intravenous VIP or in whom biological samples have been collected.

In the mid-2000s, Youssef, Said and colleagues treated 8 patients with septic ARDS with VIP. They used 50 pmol/kg/hr in 5 patients, of whom one had hypotension requiring decrease to 25 pmol/kg/hr. The other three patients received 100 pmol/kg/hr, in whom one patient required temporary reduction (to 85 pmol/kg/hr) for hypotension. The target dosing duration was 6 or 12 hours. (An intended increase to 150 pmol/kg/hr was not undertaken because the senior author retired.) All but 2 patients

survived their ARDS.[29] VIP infusion appeared safe and feasible, and mortality appeared to be on the low end for septic ARDS, suggesting possible clinical efficacy.

During the COVID-19 pandemic, Youssef and colleagues studied 21 patients receiving intravenous aviptadil under an expanded access program (EAP). The patients receiving aviptadil were compared to non-randomized concurrent controls who were either admitted by physicians who were not investigators on the VIP trial or in the two weeks before and after this cohort was assembled. Four-week survival in the EAP cohort (primarily but not exclusively patients with immune suppression or undergoing ECMO therapy who were excluded from a concurrent randomized trial) was 90%; 4 of 5 ECMO patients were "successfully decannulated." All patients were treated with glucocorticoids, 18 of 21 patients were treated with tocilizumab, and 6 of 21 were treated with remdesivir before VIP infusion. Hypotension occurred in 5 of 21 (24%) of patients receiving VIP infusion, primarily among those on ECMO and/or receiving vasopressors. In the other 16 patients, blood pressure was stable or improved during aviptadil infusion. Diarrhea was present in 4 of 21 patients; prophylactic or therapeutic loperamide was used in 86% of patients. The survival among the non-randomized concurrent controls was substantially lower, suggesting possible clinical efficacy. Approximately 200 patients have been studied under this EAP at multiple centers in the United States as of December 16, 2020. Reports from the full EAP cohort are pending.

In terms of observational data, Temerozo et al studied 24 patients with severe COVID-19 (i.e., requiring ICU admission), demonstrating significantly higher endogenous VIP levels among survivors than non-survivors.[5] In this observational cohort, no aviptadil was administered.

Randomized data in COVID-19. A randomized controlled trial (NCT04311697) has enrolled 196 patients (2:1 randomization) using the same intravenous dosing schedule as the Phase 1 trial in septic ARDS patients and the COVID-19 EAP experience. Final results from this trial are pending; preliminary results suggested survival of 71–72% at 28 days in both groups with exploratory signals suggesting possible benefit in time to recovery in the largest subgroup, those receiving high-flow nasal cannula at randomization. The DSMB did not identify any important safety concerns during interim monitoring; hypotension has been uncommon and has not generally resulted in changes to aviptadil infusion. Mild-moderate diarrhea occurred in approximately a third of patients.

1.1 Potential risk and benefits from aviptadil

Primary effects of VIP infusion, generally dose dependent, include facial flushing, changes in heart rate, decrease in blood pressure, and diarrhea. Effects on renal function and fluid status are transient and mild, with the possible exception of patients with advanced liver disease.

Facial flushing is common with VIP and is not dangerous. It is generally well tolerated and resolves when the VIP infusion is stopped. It is caused by dilation of cutaneous vasculature.

Increases in heart rate are common and rarely clinically significant. The increase in heart rate primarily reflects changes in cardiac preload and an adrenergic response to decreased afterload.

The primary known risk of intravenous VIP infusion is of decreased blood pressure. The clinician investigators with the most experience with the agent report (personal communication) approximately 25% incidence of hypotension during infusion in ICU patients with shock present before initiation of VIP. These rates are observed in treatment protocols that do not exceed 150 pmol/kg/hr. When present, the decrease in blood pressure appears to be approximately 10% of mean arterial pressure (e.g., a decrease from 80 mmHg to 72 mmHg). In other settings (generally healthy volunteers at

higher doses), a modest decrease in mean arterial pressure in most (but not all) studied populations has been observed. This is generally in the range of 10–15% decrease in MAP. The findings in normal volunteers are presented in Table 1.

Table 1. Hypotensive Effects Observed During VIP Infusion in Phase 1 or Similar Experience

Patient type	Patients infused with VIP	Rate in pmol/kg/hr	Blood pressure change	Study
Stable patients with stable cancer	79	300 pmol bolus (not adjusted for body mass)	7mm Hg nominal decrease (probably not significant)	Virgolini et al[2]
Healthy volunteers	6	400 pmol/kg/hr	MAP decrease by 12%	Frase et al[30]
Healthy volunteers	6	180 pmol/kg/hr	MAP decrease by 15%	Erikkson et al[31]
Healthy volunteers	8	360 pmol/kg/hr	MAP decrease by 5–10%	Unwin et al[32]
Healthy volunteers	4	198 pmol/kg/hr	DBP decrease by 15%/stable SBP	Domschke et al[33]
Healthy volunteers	6	360 pmol/kg/hr	MAP decrease by 7%	Calam et al[34]
Healthy volunteers	22	400 pmol/kg/hr	No change in blood pressure	Krejs et al[35]
Healthy volunteers	2	720 pmol/kg/hr	No change in blood pressure	Unwin et al[36]
Outpatient asthmatics	7	360 pmol/kg/hr	DBP decrease by 10%/stable SBP	Morice et al[37]
Cirrhotic patients	6	360 pmol/kg/hr	BP decrease by 10%	Calam et al[38]
BP: blood pressure; MAP: mean arterial pressure; DBP: diastolic blood pressure; VIP: vasoactive intestinal peptide				

The infusion rates used in this study are substantially lower than those used in healthy volunteers. Relevant to the proposed population for TESICO is the experience with aviptadil administered to patients with ARDS at infusion rates ranging from 50 to 150 pmol/kg/hr. In patients with septic ARDS, approximately 25% of patients encountered some decrease in blood pressure during infusion.[29] In the EAP experience with aviptadil for COVID-19 (unpublished data supplied to investigators by NeuroRX), which included patients on vasopressors, ECMO, CRRT, approximately 25% had hypotension during infusion, while the balance of patients either had stable or increased blood pressure, including several patients who weaned off vasopressors during aviptadil infusion. In the preliminary results of the randomized trial, hypotension was observed in 25.2% of aviptadil patients and 18.5% of placebo patients.

Diarrhea, which can lead to bicarbonate wasting and metabolic acidosis, was observed in 5 healthy volunteers receiving 400 pmol/kg/hr of VIP, reproducing the syndrome of “pancreatic cholera” associated with VIP-producing tumors.[39] Youssef and colleagues report (personal communication) that the diarrhea observed during infusion rates of 50–150 pmol/kg/hr are easily managed with enteral loperamide.

Hemoconcentration, presumably through diarrhea, has been observed with VIP infusion, primarily manifesting as a modest increase in hematocrit or serum albumin concentration. While urine output may decrease during aviptadil infusion, the glomerular filtration rate (GFR) does not.[34] The hemoconcentration does not persist after discontinuation of aviptadil infusion.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of aviptadil may be found in the Investigator's Brochure(s) (IB) and Participant Information Leaflet.

Given the high morbidity and mortality of COVID-19 ARDS, the short half-life of aviptadil, the close monitoring and early detection of abnormal vital signs present in the settings where the trial will be performed, and the ease of management of expected adverse events in care environments treating critically ill patients, the overall benefit-risk assessment of this study is considered favorable in the clinical settings where the trial will be performed.

1.2 Motivation for agent selection by the ACTIV Agent Selection Committee (ASC) and Trial Oversight Committee (TOC)

The ACTIV Agent Prioritization Committee (APC) Subteam reviewed the NeuroRX agent aviptadil (VIP) and voted in favor of the agent proceeding into ACTIV-3, and the TOC endorsed that recommendation. NeuroRX's aviptadil was supported because it binds to VPAC receptors on the pulmonary Alveolar Type II cell that is a selective target of SARS-CoV-2. The agent has suggested positive effects on lung function and clinical outcomes in small clinical studies of ARDS.

While the reviewers noted the mechanism of action in SARS-CoV-2 infection is not yet well elucidated, some published preclinical tests show a ~50% reduction in viral replication in infected Calu-3 cells, suggesting partial efficacy as an antiviral[5]; however, the agent has shown promising effects in clinical trials against SARS-CoV-2. In addition, the company provided a preprint of in vitro data, which suggests that this compound is efficacious as an antiviral. The Subteam also noted that its target within the host is a good candidate for preventing fluid accumulation and inflammation in the lung, which is a major factor in COVID-19, and the natural endogenous peptide is increased in survivors of severe COVID-19. Aviptadil is available in both IV and nebulized formulations, but the inhaled version may cause some nasal and respiratory epithelium degeneration; thus, the IV formulation is preferred for this trial. At the time of APC review, the Phase 2a trial of 50–150 pmol/kg/hr was close to completion—the company shared promising interim results from that trial.

Based on the positive response to the data presented for the agent, the Subteam discussed which ACTIV trial platform should test it. The agent already has safety data from indications other than COVID-19, which could allow it to proceed to a Phase III trial. The Subteam selected ACTIV-3 for effective testing of the agent, and the agent would fill a void in the more severely ill patients screened for that trial that are not eligible for the neutralizing antibodies currently being tested in the trial.

Finally, the APC Subteam found the manufacturing and scalability strategy for aviptadil sufficient for the full trial and beyond.

Statement regarding plans for licensure: NeuroRx, Inc., has filed IND 149,152 for Intravenous Use of Aviptadil with the FDA and been awarded Fast Track designation. FDA has indicated in writing that all preclinical data have been submitted that are required for NDA and that an NDA would be accepted based on efficacy as demonstrated in adequately controlled studies. EMA licensure will be sought by Relief Therapeutics AG (Geneva, Switzerland).

1.3 Justification for dose selected

Given temporal constraints imposed by the pandemic, selection of the dose and duration of therapy are based on preliminary observations from multiple sources, which together provide a reasonable basis for the dose and duration selected. Lines of evidence include pre-clinical observations, observations from cell models of SARS-CoV-2 infection, known serum pharmacokinetics, rapid trafficking to and accumulation in the target organ, lung, and an observational human cohort suggesting relevant differences in serum VIP concentrations between survivors and non-survivors.

Half life of VIP. The well-established serum half-life of VIP, due to degradation by serum peptidases, is 1 minute. In dogs, only repeat daily administration for 4 weeks was associated with effects that persisted for more than a few minutes after discontinuation of the infusion. The precise elimination dynamics from lung are not well established, but empirically, the accumulation of aviptadil in lung increases over time. In addition, concentrations in serum slowly increase over the course of a prolonged infusion.

Observations from cell models of SARS-CoV-2 infection. Temerozo and colleagues identified in multiple cell models of SARS-CoV-2 infection that a VIP concentration of approximately 10nM provided maximal anti-viral and cell-protective effects, especially in lung cells (Calu-3 cells) and monocytes. In some additional experiments, concentrations of 1nM demonstrated a relevant effect.[6]

An observational cohort of patients with COVID-19 ARDS. In a complementary observational cohort of 24 patients with severe COVID-19, Temerozo and colleagues demonstrated that VIP levels of 10–12 pg/ml were present among non-survivors (N=13), as opposed to 20 pg/ml among survivors (N=11). While these data are observational and do not provide causal evidence of the effect of ~10 pg/ml change in serum VIP levels, they nevertheless suggest the possibility that increases in VIP levels may be clinically relevant.

Expected blood and/or lung levels achieved with a given infusion. The infusion rates necessary to achieve serum levels have been demonstrated in pre-clinical experiment in dogs. Unverferth and colleagues infused 0.02 and 0.05 mcg/kg/min (360 and 900 pmol/kg/hr, respectively) in 12 dogs. The dogs had a baseline VIP blood level below the level of detection (<50 pg/ml), and the two infusion rates achieve blood levels of 540 pg/ml and 1200 pg/ml, respectively.[40] Extrapolating from these experiments (assuming a consistent relationship between infusion rate and resulting blood concentrations), 50 pmol/kg/hr would be expected to result in 71 pg/ml, and 100 pmol/kg/hr would result in 143 pg/ml in this model. These blood levels are substantially higher than those observed among survivors in the Temerozo cohort and also substantially higher than the difference between survivor and non-survivor VIP levels.

In a 10-hour infusion of 400 pmol/kg/hr of VIP among healthy volunteers, blood VIP levels rose over the course of infusion, achieving 782 pg/ml by the end of the 10-hour infusion.[39] Extrapolating this observed relationship between infusion rate and resulting blood concentrations to a 100 pmol/kg/hr infusion rate, we anticipate a blood level of 195 pg/ml by the 10-hour timepoint.

Following an intravenous dose, aviptadil rapidly distributes into tissue with approximately 45% of the dose distributing to the lungs within 30 minutes of administration.[2] The apparent volume of distribution following a 300 pmol dose is 135 mL/kg. Therefore, an initial aviptadil plasma concentration is estimated to be 0.03 nM for a 70 kg patient for which 45% of the plasma concentration is anticipated to be distributed into the lungs. Assuming dose-proportionality and drug-tissue accumulation, where dose escalation proportionally increases drug exposure, a 100 pmol/kg/hr aviptadil dose over 12 hours is estimated to achieve pulmonary concentrations within 10 nM for a 70 kg patient. A

150 pmol/kg/hr for 12 hours would with greater confidence achieve 10nM in lung. The 10nM concentration in lung is specific to a cell model of SARS-CoV-2 infection; lower concentrations may be protective. Extrapolation from serum concentrations suggest that rates as low as 50 pmol/kg/hr may have efficacy. The time course of subsequent decreases in lung concentrations is not well established, but the approach of interrupted infusion envisioned in this protocol is thought to represent the optimal balance of risk and benefit on the basis of current information.

Clinical experience. When Said and colleagues selected the range of doses/durations for the initial phase 1 trial in patients with septic ARDS,[29] they did so in the context of the infusion rates that were well tolerated in healthy volunteers (~300–400 pmol/kg/hr) and the awareness that even low infusion rates were associated with substantial increases in plasma VIP levels. That phase 1 trial envisioned dose escalation in small cohorts of patients, from 50 pmol/kg/hr for 6 hours up to 150 pmol/kg/hr for 12 hours. The investigators completed dosing through the 100 pmol/kg/hr for 12 hours (3 patients treated at that infusion rate). According to investigators (personal communication), VIP was infused daily for 3 days in the Phase 1 trial.

The COVID-19 experience to date (~200 patients in a 2:1 randomized trial and another ~200 treated open label under an expanded access program [EAP]) have employed a sequential dose escalation strategy, in which a 12-hour infusion is performed daily for 3 days. The initial dose is 50 pmol/kg/hr, followed on day 2 by 100 pmol/kg/hr and on day 3 by 150 pmol/kg/hr. Treatment is not continued after the patient leaves the ICU. If a patient develops intolerance at a given infusion rate, the infusion period is increased (commonly to 18 hours) without a change in the overall dose administered. These rates have been reasonably well tolerated (personal communication). The EAP experience (compared with non-randomized concurrent controls) suggested the possibility of clinical efficacy; the Phase 2a trial has not yet read out. Unpublished reports (personal communication from Dr. Youssef) from the EAP experience suggest that intolerance may be somewhat higher at the conclusion of the 100 pmol/kg/hr infusion and with the 150 pmol/kg/hr infusion among patients with ARDS and shock.

The maximum infusion rate used to date in COVID-19 (150 pmol/kg/hr) is substantially below the infusion rates used in healthy volunteers (300–400 pmol/kg/hr) which either elicited no hypotension or elicited an average of 10% decrease in mean arterial pressure. The approach taken in the present trial is thus designed to optimize tolerability while achieving adequate blood levels and lung tissue concentrations of aviptadil.

Given this context and background, the vanguard cohort of 40 participants (see below) is planned to evaluate and fine-tune the approach to managing aviptadil infusions and further assess anticipated feasibility/tolerance in the target population.

1.4 Vanguard cohort

In order to assure timely and sufficient evaluation of aviptadil using an optimal approach to managing aviptadil infusion in this target population, a vanguard cohort will be incorporated. It is recognized that prior experience with aviptadil in similar populations appears to be safe and well-tolerated, and that additional insights relevant to the conduct of the present trial can be gleaned from a vanguard cohort. The target population for the vanguard cohort will be identical to the overall trial, with the exception of the requirement that vanguard participants be admitted to an intensive care unit to facilitate more intensive monitoring. The vanguard cohort will be limited to approximately 10 sites and approximately 40 patients (randomized 1:1 to aviptadil vs. control). The focus in the vanguard cohort will be in understanding the usability and feasibility of infusion management guidelines and making minor adjustments to “fine-tune” the infusion guidelines. Investigators will received blinded adherence reports for receipt of study drug infusion as would be typical of a DSMB open report. Extensive unblinded data will also be provided on a regular basis to the DSMB, detailing blood pressure, heart

rate, vasopressors, fluid administration as well as data on the study drug infusions. These features will be monitored during the infusions and through 2 hours after the conclusion of the infusion.

In order to protect the overall blind and allow inclusion of vanguard participants in the final analytic cohort, investigators will only review (1) interviews with treating clinicians and site investigators regarding the utility and clarity of the infusion management guidelines, (2) blinded aggregate data on adherence with study drug infusion, and (3) recommendations from the DSMB. Standard firewalls between the DSMB and investigators will be maintained during the vanguard cohort.

The vanguard cohort is intended to assess and finetune guidelines for study drug infusion management. It is recognized that the small size of the vanguard cohort will not support conclusive inferences about safety or efficacy and is focused on feasibility and tolerance. If experience with the vanguard cohort reveals that the original infusion management guidelines are infeasible, the infusion management guidelines may undergo modification. If necessary, a second vanguard cohort may be enrolled to allow further assessment of feasibility/tolerance and further finetuning of the approach to management of aviptadil infusion. If a second vanguard cohort is required, the patients in the first vanguard cohort will not be included in the final trial analysis.

In general modifications to infusion management guidelines will not require an enrollment pause or protocol amendment, but will be managed through a protocol clarification memo and revision to the case report forms and PIM. The DSMB will also advise the study team and sponsor on the need for changes (or not) to the informed consent based on the experience in the vanguard cohort.

2. Agent-specific eligibility criteria

2.1 There is no change in inclusion criteria for this agent

2.2 Agent specific exclusion criteria

- *Refractory hypotension*, defined as infusion of vasopressors at or above norepinephrine equivalent of 0.1 mcg/kg/min (or infusion of more than one simultaneous vasopressor) in prior 4 hours to maintain MAP > 65 mmHg OR systolic blood pressure <90 mmHg or MAP < 65 mmHg at time of enrollment (or randomization, if the patient has already been enrolled) confirmed on two consecutive measurements at least 5 minutes apart (if a single measurement meets those criteria, a second measurement is required). Since aviptadil may induce hypotension, as noted above, patients with critical hypotension have a different risk:benefit profile that is less likely to favor aviptadil even where aviptadil is efficacious.
- *Severe diarrhea*, defined as 3 or more liquid bowel movements within the last 24 hours. Since diarrhea is a common side effect of aviptadil, if patients already have severe diarrhea, they may have a different risk:benefit profile that is less likely to favor aviptadil.
- *Current C. difficile infection (CDI)*. CDI generally causes diarrhea, its severity is often gauged in part by the volume of diarrhea, and anti-motility agents that may be used to manage aviptadil-associated diarrhea are contraindicated in CDI. These factors suggest that the risk:benefit ratio in patients with CDI may not be favorable.
- *Pregnancy or current breast-feeding*. Aviptadil was associated with involution of embryos in animal models and may be associated with changes in visceral and/or placental perfusion. It is thus felt not appropriate to infuse aviptadil in pregnant patients or in women who are breastfeeding.
- *End-stage liver disease (ESLD)*, defined as hepatic decompensation in a person with or without cirrhosis, usually associated with ascites (fluid in the peritoneal cavity), jaundice, variceal hemorrhage or hepatic encephalopathy (confusion, change in behavior, forgetfulness).

Liver function tests and/or coagulation profile are usually abnormal. An isolated elevation in serum bilirubin does not meet criteria for end-stage liver disease.

3. Description of investigational agent

3.1. Administration and duration

The approach to infusion is based on prior clinical experience with the use of aviptadil. Aviptadil is infused over 12 hours per day for three days. The day 1 infusion rate is 50 pmol/kg/hr, the day 2 infusion rate is 100 pmol/kg/hr, while the day 3 infusion rate is 150 pmol/kg/hr. The primary factors defining intolerance to aviptadil infusion are hypotension or diarrhea. The PIM will include infusion management guidelines to assist clinicians in responding to hypotension or diarrhea among patients receiving aviptadil. The total volume of the infusion (aviptadil vs. saline placebo) is generally less than 100 ml per day, although infusion volumes will vary by patient weight and dosing day.

3.2. Formulation and preparation

Aviptadil is a sterile drug product that must be formulated by a hospital pharmacist under sterile conditions according to the supplied pharmacy manual. Formulation is in 0.9% sodium chloride, with standard mixing procedures. Standard intravenous bags and tubing are used. Dosing is at 50/100/150 pmol/kg/hr.

3.3 Supply, distribution, and accountability

Procedures for ordering and accepting drug, for maintaining inventory of aviptadil, and for breaking the blind in the event of a medical emergency will be described in the Pharmacy Procedures.

3.4. Contraindicated medications

There are no known contraindicated medications. There is a theoretical consideration about use of nitric oxide or prostanoid therapy, but there is no compelling data to date to suggest that such medication should be restricted. Use of pulmonary vasodilators will thus be tracked with concomitant medications.

3.5. Precautionary medications

The clinical site should have necessary equipment and medications for the management of any infusion reaction. These include capacity to monitor vital signs, ability to infuse and monitor vasopressor agents if necessary, and capacity to manage diarrhea and electrolyte loss. Unrelated to aviptadil but centrally related to COVID-19, sites must be able to manage progression of respiratory failure.

4. Clinical and laboratory evaluations

Clinical and laboratory evaluations will follow the master protocol schedule of assessments.

4.1 Timing of Assessments

All assessments are outlined in the relevant section of the master protocol.

4.2. Pharmacokinetic Assessments

Pharmacokinetic assessments are being performed in a Phase 2 trial performed by NeuroRX.

5. Clinical management issues

All participants should be monitored closely for hypotension and diarrhea and any additional adverse events, with special attention to treatment-emergent adverse events.

5.1. Symptoms and Signs
Symptoms and signs that may occur as part of an infusion reaction, include, but are not limited to, decrease in mean arterial pressure, diarrhea, facial flushing. Infusion-related reactions' severity will be assessed and reported using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected version 2.1. Given the unique nature of the target population for this trial, hypotension will be graded according to the scale in Table 5 (Section 10) of the master protocol rather than the DAIDS AE Grading Table.

5.2. Site Needs
The clinical site should have necessary equipment, medications, adequately qualified and experienced staff with appropriate medical cover for the management of any infusion reaction, which may include, but is not limited to, hypotension and diarrhea.

5.3. Management of Infusion Reactions including Discontinuation
Infusion of aviptadil or its placebo will be guided by infusion management guidelines in the context of clinician judgment. If the complete infusion is not administered, all follow-up procedures and reporting outlined in the master protocol should be adhered to as indicated.

6. Agent-specific safety monitoring activities

Safety monitoring for aviptadil will be as specified in the master protocol. However, grade 3 or 4 diarrhea in the peri-infusion period will only be included in the composite safety endpoint if the diarrhea is a serious adverse event, or results in discontinuation of the study drug infusion. "Peri-infusion" refers to the time period during and up to 2 hours after an infusion.

The primary safety outcome was modified in order to avoid mistaken inferences regarding safety, because diarrhea is common with aviptadil and is generally well managed with loperamide in prior clinical experience. For example, diarrhea treated with loperamide would generally be classified as a grade 3 adverse event. All grade 3 or 4 diarrhea that occurs outside the peri-infusion time period will still be included in the primary safety outcome, as part of incident grade 3 or 4 AEs. Also, all peri-infusion diarrhea events will be reported to the DSMB as part of the infusion reaction summaries.

Specific to aviptadil study drug, there is one change to the safety monitoring schedule displayed in Table 3 of the master protocol: hypotension of any grade will be recorded daily through Day 28.

Note that as part of the oversight of this trial, the DSMB will review unblinded safety data regularly during the trial.

Hypotension is defined as a lower arterial blood pressure or low arterial blood pressure/perfusion leading to (1) initiation or clinically meaningful increase in vasopressor therapy, (2) administration of an intravenous fluid bolus (≥500 ml of crystalloid solution or equivalent volume of colloid), or (3) modification or discontinuation of study drug infusion. Specific grading of hypotension will be according to Section 10, Table 5 of the master protocol. Specific to the aviptadil vs. placebo comparison, in addition to standard data summaries for hypotension AEs, hypotension associated with organ dysfunction within the first 5 days after study entry will also be compared between aviptadil and its placebo. Hypotension associated with organ dysfunction is defined as hypotension plus concomitant or subsequent organ dysfunction. Organ dysfunction in this setting is a composite outcome consisting of items 5a-5f (excluding item 5b4) of the secondary outcome of clinical organ failure and serious infections (section 4.1.2 of the TESICO master protocol).

For regulatory reporting purposes, including identification and potential expedited reporting of 'SUSAR' events, the following serious and/or non-serious Adverse Events/Reactions are considered expected for this study as applies to the aviptadil factor.

- Hypotension*
- Diarrhea

* For regulatory reporting purposes, hypotension up to Grade 3 is considered expected for aviptadil in this specific study, population, disease and setting. Hypotension occurring at Grade 4 or higher as described in Table 5 in the main protocol document is **not** considered expected.

In addition, the following adverse events/reactions are considered expected unless serious:

- Bradycardia
- Tachycardia
- Flushing

The DSMB reviews safety data on an ongoing and unblinded manner. If a pattern, frequency, or other characteristic of concern becomes evident to the DSMB with regard to the 'expected' events listed above, the study team and sponsor will be promptly notified and action will be taken as may be indicated for subject protection and/or reporting purposes.

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TESICO Version 2.0 (11 August 2021): Major changes from Version 1.0 (01 April 2021)

- Changes made in Letter of Amendment #1 dated 30 April 2021 have been incorporated into the main protocol document (Section 6.5, Approach to Intercurrent Therapies and Clinical Trial Co-enrollment).
- A secondary outcome of worsening respiratory dysfunction has been added to Section 4.1.2.
- A new grading table for hypotension has been added to Section 10.1.4.
- Appendix A, Sample Informed Consent: the genomics signature page has been reorganized for clarity.
- Appendix H-1 (aviptadil) Sections 5 (Clinical management issues) and 6 (Agent-specific safety monitoring activities): these have been modified to change the criteria used for grading hypotension and assessing its expectedness with this drug in this patient population.

Minor editorial changes for clarity were made throughout.

TESICO Table of changes – Version 2.0 (11 Aug 2021) to Version 3.0 (08 Mar 2022)

Major change	Location	Rationale
Day 5 specimens now collected from all participants in hospital on Day 5, rather than only those in the ICU	Section 9.1.2 page 26; also in sample informed consent	Allows comparison of trajectories between rapid recovering patients and slower recovering patients to better characterize the biological mechanisms of recovery.
Additional health-related outcomes added to existing patient-reported outcomes obtained at Day 90 and Day 180	Section 9.1.2 page 26	Undertaken at the recommendation of the NIH working group on long-term outcomes in order to facilitate understanding of long-term outcomes across the many COVID trials conducted under NIH sponsorship. See next item.
Language added to consent to permit the sharing of contact information (applicable to US sites only)	Appendix A, sample informed consent	NIH has developed the RECONNECTS registry to perform independent long-term follow-up of patients enrolled in NIH-sponsored trials of COVID. This new language will make it easier to help facilitate the connection between TESICO trial participants and investigators conducting important, non-commercial research. The RECONNECTS registry and any similar study that might be covered by this consent language would take place after study procedures are completed for TESICO.
Added daily recording of hypotension (through Day 28) to safety measurements	Appendix H1: Aviptadil	Obtains more granular information on this important side effect of aviptadil.

Minor changes:

- Cover page: ClinicalTrials.gov and EudraCT registration numbers added
- Consent: US PREP Act language added (was inadvertently omitted in previous versions of sample informed consent)
- 9.1.1 Screening and Baseline Assessments; Consent: additional clarification that viral antigen will be measured on stored specimens at baseline. Note: Previously only antibodies were noted as measured, however antigen testing was always intended to be done as well, but inadvertently had not been specified in the protocol
- 9.1.2 Follow-up Assessments: Consent: additional clarification that viral antigen will be measured on stored specimens at Days 3 and 5 (for participants still hospitalized). Note: Previously only antibodies were noted as measured, however antigen testing was always intended to be done as well, but inadvertently had not been specified in the protocol.

- Appendix H-1 (VIP): changed from “weekly” to “regular” DSMB review of unblinded safety data, to allow for spacing reviews more widely when enrollment is very slow

9 Statistical Analysis Plan

This section presents the original statisical analysis plan and a subsequent amendment for the futility analysis.

Statistical Analysis Plan

Version 1.0

Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO)

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

Clinicaltrials.gov identifier: NCT04843761
EudraCT number: 2021-001650-56

Version	Date	Who	Comments
1.0	05 August 2021	BG	TESICO ACTIV-3b INSIGHT 015 Protocol v2.0, August 2021, Investigational agents: aviptadil and remdesivir

Contents

1 Introduction

1.1 Objective of the Statistical Analysis Plan

The objective of this statistical analysis plan (SAP) is to provide a description of the general analytic strategy and the statistical methods that will be used to analyze the data for the TESICO (Therapeutics for Severely Ill Inpatients with COVID-19) protocol. The goal of TESICO is to evaluate the safety and efficacy of investigational agents aimed at improving outcomes for patients with acute respiratory failure related to COVID-19. TESICO is a sister protocol to the TICO master protocol, with focus on patients with critical respiratory failure (i.e., those receiving high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or ECMO to treat acute hypoxemic respiratory failure caused by SARS-CoV-2 pneumonia).

The master protocol is for a phase III randomized, blinded, placebo-controlled platform trial that allows investigational agents to be added and dropped during the course of the study for efficient testing of new agents against control within the same trial infrastructure. When more than one agent is being tested concurrently, a factorial design may be employed, or participants may be randomly allocated in parallel arms.

This version of the SAP describes statistical analyses for the first two investigational products, Vasoactive Intestinal Peptide (VIP; aviptadil is the generic name for the synthetic peptide, developed by NeuroRX, Inc.) and remdesivir (Gilead Sciences, Inc.). All participants receive standard of care (SOC) and will be randomized to receive one or two investigational agents or matching placebo in addition to SOC, as described in section 1.2.

This SAP:

- Provides a short description of the study design (sections 1.2-1.4)
- Describes goals of the interim reviews by the independent DSMB and the planned format of the review meetings (section 2)
- Describes the planned data analyses presented in the reports to the DSMB (sections 3-13). General analysis principles are summarized in section 3, safety analyses are described in section 7, efficacy analyses in section 8, and interim monitoring guidelines in section 10.
- Describes data summaries to be provided regularly to study leadership to aid in monitoring trial conduct and data quality; these data summaries will be pooled across treatment groups, and will be restricted to enrollment, baseline data, and summaries of data completeness and study conduct.

The SAP for TESICO will be updated by the blinded study statisticians prior to unblinding. It may also be updated based on protocol amendments.

1.2 Description of the Study Design

This section is adapted from Section 1 and Appendix H1 of the TESICO protocol version 2.0.

Design

TESICO (Therapeutics for Severely Ill Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of investigational agents aimed at improving outcomes for patients with critical acute respiratory failure caused by SARS-CoV-2 pneumonia.

The protocol is for a phase III randomized, blinded, controlled platform trial that allows investigational agents to be added and dropped during the course of the study for efficient testing of new agents against control within the same trial infrastructure.

In this section, we are describing the trial design for the first two investigational products, aviptadil and remdesivir. In short, the trial consists of a 2x2 factorial for aviptadil versus matched placebo and remdesivir versus matched placebo, and participants who are not eligible to be randomized in the factorial will be randomized 1:1 to one of two treatment groups, either aviptadil versus matched placebo, or remdesivir versus matched placebo, depending on eligibility. All participants receive standard of care (SOC), plus the randomized treatment assignment. Corticosteroid therapy is recommended as part of SOC for all participants, unless contraindicated.

Specifically, the trial includes four strata of participants (referred to as "**design strata**") (Figure 1 on the next page):

Stratum 1: Participants who are eligible for aviptadil and remdesivir, and have not received any remdesivir prior to randomization. These participants will be randomized in a 2x2 factorial to the four possible combinations of aviptadil, remdesivir, and the matching placebos for these drugs: 1) aviptadil + remdesivir placebo; 2) aviptadil placebo + remdesivir; 3) aviptadil + remdesivir; and 4) aviptadil placebo + remdesivir placebo.

Stratum 2: Participants who are not eligible to receive remdesivir (contraindication). These participants will be randomized to aviptadil versus placebo only.

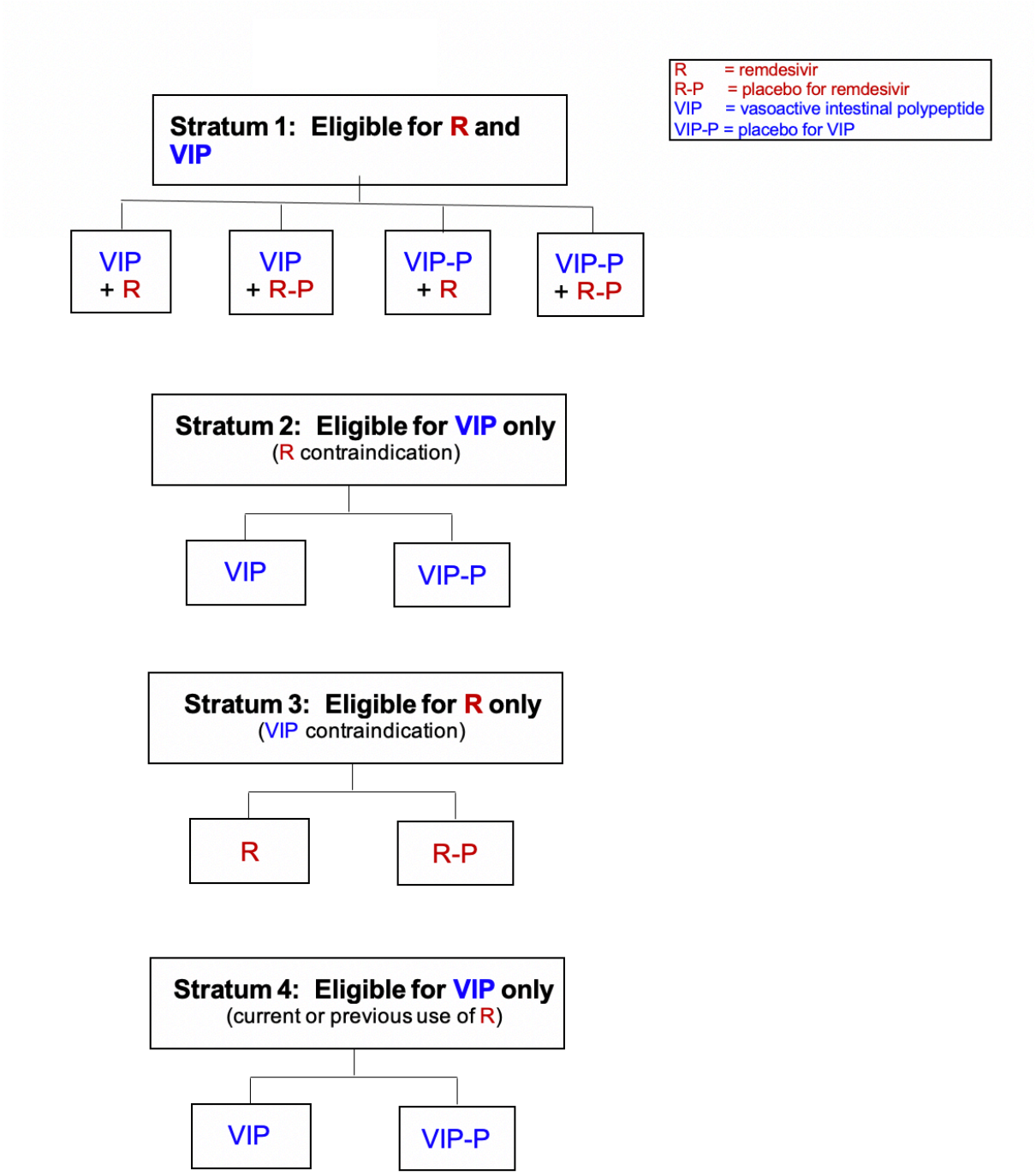
Stratum 3: Participants who are not eligible to receive aviptadil (contraindication). These participants will be randomized to remdesivir versus placebo only.

Stratum 4: Participants who have received remdesivir prior to randomization, and are eligible for aviptadil. These participants will be randomized to aviptadil versus placebo only.

Each randomization of investigational agent versus placebo will use a 1:1 allocation, and equal allocation to the four treatment combinations in the 2x2 factorial. Statistical analyses will compare aviptadil versus placebo, pooling participants in strata 1, 2, and 4, and will compare remdesivir versus placebo, pooling participants in strata 1 and 3. To achieve this, it is estimated that 800 participants will have to be enrolled (640 for each pairwise comparison: aviptadil vs. placebo, and remdesivir vs. placebo).

The design assumes that the effects of aviptadil and remdesivir are independent of each other; a possible interaction between the two investigational agents will be assessed in the 2x2 factorial, although power is limited for the interaction test.

Figure 1: Study Design of TESICO. The study includes 4 "design strata": a 2x2 factorial for aviptadil (VIP) versus placebo and remdesivir versus placebo, and 3 strata with 1:1 randomizations to either investigational agent versus placebo.



Stratum	Percent of Patients
1	60
2	10
3	10
4	20

Sample size for VIP = strata 1, 2 and 4
Sample size for R = strata 1 and 3

Population
The study population consists of inpatient adults (≥18 years) who have documented SARS-CoV-2 infection within 14 days of enrollment and are receiving high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO at enrollment, in whom the current respiratory failure is thought to be due to SARS-CoV-2 infection and in whom respiratory support was initiated within 4 days prior to randomization.

Additional eligibility criteria apply for aviptadil and remdesivir. Participants who have received remdesivir prior to study entry are excluded from randomization to remdesivir.

The **primary endpoint** is a 6-category ordinal outcome that assesses the recovery status of the patient at Day 90, described in Appendix A, and is referred to as "**recovery"**. The categories of the ordinal outcome, from best to worst, start with 3 categories of "recovery" defined by the number of days alive at home and not on new supplemental oxygen, followed by 3 categories for "not recovered" defined as a) discharged but not to home or at home but still requiring continued new supplemental oxygen**,** b) hospitalized or receiving hospice care, and c) death at day 90.

Primary Objectives
1. To determine whether aviptadil is superior to placebo when given with standard of care for the primary outcome of recovery based on a 6-category ordinal outcome evaluated at 90 days after randomization.
2. To determine whether remdesivir is superior to placebo when given with standard of care for the primary outcome of recovery based on a 6-category ordinal outcome evaluated at 90 days after randomization.

Duration
The primary and most secondary outcomes will be collected during the first 90 days of follow-up. In addition, participants will be followed through 180 days for hospitalizations and deaths. SAEs that are related to study interventions will also be reported through 180 days.

Sample size
This Phase III trial is planned to provide 80% power to detect an odds ratio of 1.5 for improvement in recovery status at Day 90 for an investigational agent versus placebo, comparing treatment groups by intention to treat using a proportional odds model for the ordinal outcome. The planned sample size is 640 participants (320 per group) for each investigational agent versus placebo comparison. The sample size is not adjusted for inflation of Type I error due to multiple comparisons (separate tests for the two investigational agents).

The sample size may be re-estimated before enrollment is complete. The re-estimation will be performed by study personnel who are blinded to any data by treatment group.

Randomization Stratification
Randomization will be stratified by study design stratum (Figure 1), by disease severity (2 strata, defined by receipt of *mechanical ventilation or ECMO* at enrollment), and by study site pharmacy.

Monitoring
An independent DSMB will review interim data on a regular basis for safety and efficacy. Initially, monthly full reviews are planned, and weekly safety reviews for the aviptadil versus

placebo comparison. Prior to expanding enrollment to all sites, a full review by the DSMB will be conducted after approximately 40 participants have been randomized by the vanguard sites and have Day 5 data available.

After enrollment increases with the inclusion of non-vanguard sites, the DSMB will use asymmetric Haybittle-Peto monitoring boundaries for ***mortality*** to assess interim data for harm or benefit due to the investigational agents; the DSMB may recommend discontinuation of an investigational agent if the risks are judged to outweigh the benefits. No formal futility assessments are planned.

For an investigational agent, if the trial is stopped early, further enrollment of the investigational agent will be terminated if applicable, and the trial data for the investigational agent will be unblinded and reported with data through 90 days of follow-up. Follow-up of all participants will continue through 6 months using the data collection plan described in the master protocol.

1.3 Randomization

The randomization is described in section 6.1 of the protocol.

For the first two investigational agents, aviptadil and remdesivir, the study population consists of four “trial design strata”, described in section 1.2 (Figure 1).

- Participants in stratum 1 are eligible for aviptadil and remdesivir, and have not used remdesivir prior to study entry. These participants will be randomized in equal proportions to one of the four treatment combinations in the 2x2 factorial formed by aviptadil/aviptadil placebo and remdesivir/remdesivir placebo.
- Participants in each of the other 3 trial design strata will be randomized 1:1 to the investigational agent versus matched placebo.

Within each design stratum, randomization will be stratified by study site pharmacy (several clinical sites may share one study site pharmacy) and by disease severity (receipt of *invasive mechanical ventilation or ECMO*) at entry. Within each randomization stratum, mass-weighted urn randomization[1] will be used to generate the treatment assignments, with equal allocations across the treatment groups. The number of treatment groups depends on the design stratum.

With this approach, participants will be equally allocated to aviptadil versus matched placebo (strata 1, 2, and 4) and to remdesivir versus matched placebo (strata 1 and 3).

1.4 Sample Size Estimates

The sample size calculations are aimed at the pairwise comparisons between each of the two investigational agents and its matched placebo. A total sample size of 800 participants is estimated.

To address the first primary objective, participants who are randomized to aviptadil will be compared to those randomized to the matched aviptadil placebo, pooled over design strata 1,

2 and 4. For the second primary objective, participants who are randomized to remdesivir will be compared to those randomized to the matched remdesivir placebo, pooled over design strata 1 and 3. Treatment groups will be compared by intention-to-treat for the 6-category ordinal outcome of recovery on Day 90 (primary outcome) using proportional odds models.

The planned sample size for each pairwise comparison is 640 participants (320 participants in each group, pooled across the corresponding design strata). The sample size is sufficient to detect an odds ratio (OR) of 1.5 with 80% power, using a two-sided test with a significance level of 0.05.

Participants in design stratum 1 (2x2 factorial) will contribute to both comparisons; assuming that 60%, 10%, 10%, and 20% will be enrolled in trial design strata 1-4, respectively, 800 participants in total will result in 640 participants for each of the two pairwise comparisons. The total sample size, which depends on the percentage of participants enrolled in the factorial design, will be periodically assessed by the protocol team.

Sample size calculations are described in detail in Section 6.3 of the protocol.

Blinded sample size re-estimation will be carried out before enrollment is complete to determine whether the planned sample size of 640 participants for each of the pairwise comparisons, followed for 90 days, will be sufficient to adequately power the trial. The blinded sample size re-estimation does not involve unblinding of the treatment difference. It will be based on the pooled outcome data, the relative enrollment into the two disease strata and four design strata, the number of withdrawals prior to the infusion, adherence to the blinded infusions, and the amount of missing data.

2 Interim DSMB Reviews: Goals and Format

Each investigational agent versus control will be reviewed as a separate clinical trial. For full DSMB reviews, a joint open report will be provided for aviptadil and remdesivir, with separate data summaries for the aviptadil and remdesivir cohorts (defined below), and key summaries by the four design strata. Separate closed reports will be provided for aviptadil and remdesivir, with similar layouts of the data summaries.

Analysis cohorts: Safety and efficacy analyses (closed reports) will be conducted for the Aviptadil and Remdesivir cohorts, and the Factorial cohort will be used to assess whether the effects of aviptadil and remdesivir are independent:

1. ***Aviptadil cohort:*** Participants who were randomized to aviptadil or its placebo (design strata 1, 2, and 4)
2. ***Remdesivir cohort:*** Participants who were randomized to remdesivir or its placebo (design strata 1 and 3)
3. ***Factorial cohort:*** Participants who were randomized to the four treatment combinations formed by the aviptadil/placebo and remdesivir/placebo pairs (2x2 factorial design; design stratum 1).

    For the factorial cohort, analyses will focus on assessing whether the effects of aviptadil and remdesivir are independent of each other, described in section 9.

Goals of the interim reviews:

- Protect the safety of study participants.
- Advise on stopping or modifying the trial for patient safety in case of emerging data on harm, or for efficacy in case of evidence of overwhelming benefit.
- After the first 40 participants are enrolled for the aviptadil vs placebo comparison, review safety and study implementation
- Review the conduct of the trial

Timing of the reviews: The DSMB will conduct frequent safety reviews. The initial safety review for either investigational agent will be conducted after approximately 40 participants are enrolled and have Day 5 data available, or earlier. Subsequent full reviews will be timed according to the recommendations of the DSMB and study leadership.

After the initial safety review, weekly safety reports for aviptadil versus placebo will be provided to the DSMB. At the discretion of the DSMB, the frequency of these (initially weekly) safety reports may be modified. ***The DSMB may request interim reports that are focused on safety at any time***.

Review meetings will typically consist of an Executive session (optional; closed), open session, closed session, and a second open session to give feedback to study leadership (optional).

Masking of treatment group labels in interim reports: In the open reports, any data reports will be pooled across all treatment groups. In the closed reports, treatment group labels will masked; for example as “Group A” through “Group D”. The treatment group labels will be consistent across all analyses and over subsequent reports. The DSMB will be unmasked to the treatment group labels.

Open report to the DSMB

The open report will contain:

- A synopsis of the trial design and current status of the platform trial
- Responses of the study team to DSMB requests
- A summary prepared by the study leadership
- Data summaries for enrollment
- Separate data summaries for the Aviptadil and Remdesivir cohorts:
    - Enrollment and baseline characteristics
    - Summary of adherence to infusions
    - Eligibility violations and protocol deviations
    - Summary reports for data completeness and study conduct
- Emerging external data, e.g., results of phase I or II trials on the investigational agent, will also be provided to the DSMB by the study leadership. This is usually included with the open report, but may be shared confidentially if needed.

All data summaries in the open report will be pooled across the treatment groups. The open reports will be prepared by the blinded statisticians in cooperation with the unblinded statisticians. In addition to the DSMB, open reports will be provided to the study team, and posted on the website for access by study investigators.

While the study is ongoing, summaries by treatment group, and comparisons of the investigational agents versus their placebo are restricted to the confidential closed report to the DSMB. Additionally, all summaries of follow-up data other than the data completeness and study conduct reports (pooled across treatment groups) will be restricted to the confidential closed report. For the **planned sample size re-estimations prior to completion**, pooled outcome data will be provided to the blinded study statisticians and study leadership. On a case-by-case basis, other pooled follow-up data may be provided if explicitly approved by the DSMB. ***Data that allow estimation of the treatment differences will remain blinded.***

Closed reports to the DSMB (full review)

A separate closed report will be provided for each investigational agent. All data summaries in the closed reports will be by (masked) treatment group. Closed reports for a full review will contain:

- Specific data summaries requested by the DSMB or study leadership
- Data summaries in the open report, by treatment group (enrollment, baseline characteristics, eligibility violations), described in sections 4 and 5.
- Data summaries to assess safety of the investigational treatment, described in sections 6 and 7. Data summaries for selected "efficacy outcomes" will also be included in each report, because these data contain information about the risk/benefit profile of the investigational agent. Analyses are described in section 8.
- Data summaries on data completeness and study conduct, described in section 11
- Interim monitoring boundaries for efficacy or harm (section 10)
- Listings of incident grade 3 and 4 adverse events, serious adverse events (SAE), protocol-specified exempt events (PSESE) described in Appendix C, unanticipated problems (UP), suspected unexpected serious adverse reactions (SUSAR), and deaths.
- Listings of early discontinuation of aviptadil or remdesivir (or matched placebo) with reason of discontinuation.

Closed Weekly Safety Report

Weekly DSMB reviews of safety data for the aviptadil versus placebo comparison will include the following data summaries:

- Summaries of the composite primary safety outcome of grade 3 or 4 AEs, SAEs, PSESEs, or death through Days 5 and 28, and its components
- Safety summaries for infusion reactions: infusion dose, peri-infusion grade 1-4 AEs, modifications in the infusion rates due to AEs, peri-infusion hypotension incidence, vasopressor use.
- Event listings for incident grade 3 and 4 AEs, SAEs, PSESEs, SUSARs, UPs and deaths (events that were reported since the previous review will be highlighted).
- Narratives for selected SAEs, SUSARs or UPs, particularly those judged related to study treatment.
- Incidence of grade 3 or 4 laboratory abnormalities

At the discretion of the DSMB, the frequency and content of these (initially weekly) safety reports may be modified.

3 Analysis Principles

Each investigational agent versus control will be treated as a separate clinical trial. Separate closed reports will be provided for each investigational agent and its corresponding randomized control group. The trial design does not allow to compare investigational agents (aviptadil and remdesivir) against each other. The pairwise comparisons of each agent versus control will **not** be adjusted for potential inflation of Type I error due to multiple comparisons.

The following principles apply for the comparisons of each investigational treatment against its randomized control arm (matched placebo).

Analysis populations for safety and efficacy outcomes:

- Comparisons for ***safety outcomes*** will be ***by modified intention-to-treat (mITT)***. The modified intention-to-treat analysis is restricted to participants who received a complete or partial infusion of the investigational agent/placebo; participants who did not receive ***any*** of the investigational agent/placebo are excluded.
- Comparisons for ***efficacy endpoints*** will be ***by intention-to-treat (ITT),*** unless otherwise stated. Sensitivity analyses by modified intention-to-treat will be carried out for primary outcomes and key secondary outcomes.
- Under certain circumstances, the efficacy analyses may be performed by mITT instead of ITT. For example, if enrollment is stopped due to a safety concern, it is customary to not initiate study treatment in participants who were randomized but did not yet start treatment. In this case, it would be appropriate to exclude such participants from efficacy analyses, because the reason for not starting treatment is independent of the treatment assignment.
  In general, prior to the unblinding of data, the blinded statisticians and study leadership will decide whether the efficacy analyses should be by mITT.

Analysis cohorts for individual investigational agents:

- ***Aviptadil cohort:*** The study population for the aviptadil versus placebo comparisons consists of design strata 1, 2 and 4; in stratum 1, participants are pooled across the two remdesivir arms.
- ***Remdesivir cohort:*** The study population for the remdesivir versus placebo comparisons consists of design strata 1 and 3; in stratum 1, participants are pooled across the two aviptadil arms.
- ***Factorial cohort:*** Participants who were randomized to the four treatment combinations formed by the aviptadil/placebo and remdesivir/placebo pairs (2x2 factorial design; design stratum 1).
  - The primary analysis to assess whether the effects of aviptadil and remdesivir are **independent** of each other will be conducted in the factorial cohort, by testing for an interaction effect. If there is evidence for an interaction ($p<0.05$), the effect of aviptadil versus placebo will be estimated for those who were randomized to remdesivir, and for those who were randomized to remdesivir-matched placebo. Analyses that will be conducted in the factorial cohort are described in Section 9.

Comment: Additionally, the independence of the effects of aviptadil and remdesivir will also be assessed in subgroup analyses within the aviptadil and remdesivir cohorts. For example, in subgroup analyses for aviptadil versus placebo, heterogeneity of the treatment effects across subgroups by remdesivir use (use at baseline or randomized to remdesivir versus neither) will be assessed by testing for an interaction between treatment and subgroup indicators. The assessment of independence is protected by randomization in the factorial cohort, but not in the subgroup analyses in the aviptadil or remdesivir cohorts.

Descriptive statistics will be reported overall and by randomized group. For categorical outcomes, the number and percent in each category will be reported; percentages will be of non-missing values, if data are not complete. Continuous variables will be summarized by median (interquartile range [IQR]) and/or mean (SD). Continuous variables may be categorized (e.g., age may be broken into categories to investigate the distribution across age groups).

Stratification: Tests comparing the investigational agent versus control for primary outcomes and key secondary outcomes will be stratified by disease severity (2 strata, by receipt of *invasive mechanical ventilation or ECMO* versus neither).

There are several exceptions:

- Early in the trial, analyses will be unstratified, until sufficiently many participants are enrolled such that each of the two disease severity strata contains at least 20 participants. This guideline on the minimal size of the strata aims to avoid unstable analyses and/or loss of power that may result from the use of sparse strata. In the case of time-to-event data, analyses will be stratified when sufficiently many events have accrued, e.g., at least 10 events per stratum.
- Sensitivity analyses exploring the effect of stratification will be provided for key analyses that may prompt the DSMB to recommend stopping or modifying the trial. In particular, extensive sensitivity analyses will be provided for the treatment difference in *mortality*, when test statistics approach the interim monitoring boundaries. Such sensitivity analyses will include the following:
    - Unstratified analyses
    - Stratification by study design stratum (3 strata in the aviptadil cohort, 2 strata in the remdesivir cohort)
    - Stratification by disease severity and study design stratum (6 strata in the aviptadil cohort, or 4 in the remdesivir cohort)
    - Additional stratification by geographical region (U.S, Europe, other), provided individual strata are sufficiently large (20 participants or more).

For time-to-event analyses, stratification by disease severity usually implies separate baseline hazard functions for the two strata; if event numbers in strata are too small, however, the strata indicator may be included in the model as an additive covariate instead.

Comment: Randomization in TESICO will be stratified by disease severity, by study site pharmacy, and by the four design strata. The randomization strata were designed to ensure balanced treatment groups. Statistical analyses (treatment comparisons) will be stratified by disease severity only (unless specified otherwise), in order to avoid potentially unstable analyses due to small strata.

For **binary outcomes**, probabilities will be compared between the investigational agent and its control group using Cochran-Mantel-Haenszel tests (CMH) or logistic regression. The CMH tests will be stratified by disease severity, as described above under "stratification". Odds ratios (OR) with 2-sided 95% confidence intervals (CI) will be estimated using logistic regression models.

For longitudinally measured binary outcomes, the treatment effect through follow-up will be estimated with 95% confidence intervals using generalized estimating equations (GEE) with a logit link function; the treatment effect is estimated via the interaction between the indicator for treatment group and the indicator for follow-up (versus baseline) visits. When there is more than one follow-up visit, "visit number" (day) may be included as categorical variable in the model, for variance reduction; alternatively, "time" may be included as a continuous variable.

Ordered categorical outcomes (e.g., recovery) will be compared between treatment groups using proportional odds models, and the summary OR will be estimated with a 2-sided 95% CI.[2] Additionally, to aid the interpretation, the ordinal outcome will be dichotomized according to cumulative probabilities of the ordered categories, comparing treatment groups for proportions of participants in category 1, in the "best 2 categories", "best 3 categories", etc.; these comparisons will be performed using logistic regression (or stratified CMH tests).

Models will be adjusted for disease severity at study entry (2 categories, by use of *invasive mechanical ventilation or ECMO* versus neither), by including the corresponding indicator variable in the model.

The validity of the proportional odds assumption will be assessed by testing for heterogeneity in the log ORs (for the treatment effect) across the dichotomized cumulative ordered categories in the corresponding logistic regression model (partial proportional odds model, test for "unequal slopes").

- The primary sensitivity analysis testing the proportional odds assumption will compare the unadjusted proportional odds model for the treatment comparison (null model) versus a partial proportional odds model that allows for "unequal slopes" across the dichotomized cumulative categories (i.e., when testing the proportional odds assumption for the treatment comparison with respect to the recovery outcome on a given day, the model will allow for heterogeneous ORs across the outcome categories) as well as across the stratification covariate (i.e., the strata defined by disease severity) (full partial proportional odds model).

Continuous outcomes will be compared between treatment groups using ANCOVA models for comparing means, if the ANCOVA model assumptions hold. If the distributions of the continuous outcomes are skewed, outcomes may be transformed, or compared between treatment groups using rank-based methods, such as the Wilcoxon test, or quantile (median) regression. For example, biomarker levels often require log-transformation to meet model assumptions for ANCOVA analyses.

Comparisons between treatment groups for a continuous outcome will be adjusted for baseline values of the outcome, for the purpose of variance reduction, unless there are

concerns over model stability with such an adjustment. For this purpose, the baseline value will be included as covariate in the model (e.g., ANCOVA, linear mixed models).

To estimate the treatment effect for *longitudinally measured continuous outcomes*, the outcome will usually be defined as "change from baseline" (difference at follow-up visit minus baseline value). The treatment effect through follow-up will then be estimated with 95% confidence intervals using generalized estimating equations (GEE) with an indicator for treatment group, or, in the case of Gaussian responses, the corresponding mixed effects models with random effects for participants. To improve the model fit and reduce error variance, "visit number" (day) may be included as categorical variable in the model; alternatively, "time" may be included as continuous variable. Models will also be adjusted for the baseline values of the outcome variable.

Time-to-event outcomes will be summarized with Kaplan-Meier estimates for cumulative probabilities over time, and compared between treatment groups using stratified log-rank tests or Cox proportional hazards models, or their competing risk analogues.

In case "death" is a competing risk for the outcome (e.g., for time to hospital discharge), the following competing risk methods will be used:

- Aalen-Johannsen estimator for the cumulative incidence function (analogue to the Kaplan-Meier estimate)[3]
- Gray's test with $\rho=0$ (analogue to the log-rank test)[4]
- Fine-Gray estimates and tests for the sub-distribution hazard ratio (analogue to the Cox proportional hazards model).[5,6]

The proportional hazards assumption will be tested by adding an interaction term for time by treatment group to the model. The cumulative proportions of participants who experienced the event will also be compared at given time points (specified in secondary objectives, e.g., at 28 days); in this case, the cumulative proportions will be estimated using Kaplan-Meier estimates or the competing risks analogue, and/or as proportion of participants who reached the time point (e.g., time since randomization $\geq$ 28 days).

The **administrative follow-up time** is defined as the minimum of (cut date minus randomization date) or the analysis time period. For example, the analysis time period for the time to hospital discharge is 180 days, and the analysis time period for the important safety endpoint, the composite of *grade 3 and 4 events, SAEs, PSESEs, or death*, is 5 days or 28 days. The **administrative censoring date** is the earlier of the cut-date of the dataset or the randomization date plus analysis time period.

> **Comment:** The notion of "administrative censoring" is important in time-to-event analyses in the presence of competing risks. For example, the Fine-Gray method for estimating the sub-hazard ratio for time to hospital discharge can be approximated by using a Cox proportional hazards model where follow-up time for participants who died without being discharged is not censored at death, but is carried forward to the administrative censoring date with event status "not recovered".

Censoring for time-to-event analyses

For **interim** analyses, the type of censoring used will depend on the data collection schedule.

- If the reporting of the endpoint is data-driven (e.g., SAEs and deaths are reported as they occur), then follow-up is censored at the administrative censoring date, at the date of withdrawal, or loss to follow-up, whichever occurs earliest.
- If the date of the event is elicited retrospectively at fixed study visits spaced more than one week apart, follow-up will be censored at the last day the endpoint status was ascertained. For example, this applies to endpoints that require information on whether the patient has been "at home" for a given period of time, such as time to *sustained recovery*.
- Sensitivity analyses will be provided for key analyses when the outcome status is uncertain.

For **final** analyses, follow-up will be censored on the last day the outcome status was ascertained.

Adverse events (AEs) will be classified by system organ class according to MedDRA®[1] (currently version 24.0 [March 2021] is used; when new versions are implemented, items are recoded). AEs will be graded according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, *Corrected Version 2.1 (July 2017)* (also referred to as the *DAIDS AE Grading Table*).[7] Hypotension AEs will be graded according to Table D-3 in Appendix D; this table is replicated from the TESICO protocol, version 2.0, Table 5. Cause of death will also be coded according to MedDRA®.

> **Comment:** Under version 1 of the TESICO protocol, hypotension AEs were graded according to the DAIDS AE Grading Table.

The number and percent of participants with peri-infusion grade 1-4 AEs will be summarized by day and grade, and by type and grade. The percentage of participants with AEs will be compared between treatment groups according to grade cut-offs, e.g., "percent of participants with any AE", "percent of participants with grade 2 or higher AEs", etc., using CMH tests. The total number of events and median (IQR) number of events per participant will also be summarized.

Additionally, the incidence of grade 3 and higher AEs will be summarized (number and percent of participants) by MedDRA® System Organ Class and grade using stratified CMH tests. Incidence of grade 3 and 4 AEs will also be compared between treatment groups as part of composite safety endpoints using time-to-event methods.

Significance level, two-sided tests: Unless noted otherwise, statistical tests and confidence intervals will be 2-sided, confidence intervals will have approximate 95% coverage probability, and test results with P-values $\leq$ 0.05 will be considered "significant".

Cut-date for interim reviews: Analysis data sets will be locked several days (or weeks) prior to the review date, to allow the unblinded statisticians time to prepare a consistent report.

[1] The Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

The cut-date may be earlier than the date of the data lock, to allow for lag time in the reporting of events. Early in the trial, the cut date and lock date will be very close to the review date, to ensure timely safety reviews.

4 Enrollment and Eligibility

For the open report, the following enrollment and eligibility summaries will be provided:

- Enrollment over calendar time: plot by day or week, cumulative and increments.
- Enrollment by study design stratum (4 strata), and pooled across the relevant design strata for the aviptadil/placebo and remdesivir/placebo comparisons.
- Enrollment by site pharmacy and by country: number (%)
- Eligibility: number (%) and reasons for eligibility violations

These summaries will be provided overall, and by disease severity randomization stratum.

For the closed report, enrollment and eligibility violations will be summarized by treatment group.

5 Baseline Characteristics

Baseline characteristics will be based on information collected on baseline and screening forms. Separate summaries will be provided for the Aviptadil and Remdesivir analysis cohorts.

For the open report, data will be pooled across treatment groups. In addition to the overall summaries, selected baseline characteristics will also be summarized by disease severity at study entry (2 strata, by use of *invasive mechanical ventilation or ECMO*).

For the closed report, baseline characteristics will be summarized by treatment group. For interim closed reports, baseline characteristics will usually be summarized by **modified intention-to-treat (mITT),** for consistency with the safety summaries.

Unless noted otherwise, categorical variables will be summarized with the number and percentage (N, %) of participants in each category, and continuous variables will be summarized with the median and interquartile range (IQR); in the open report, in addition, the mean (SD) and range may be provided.

The following baseline characteristics will be reported:

- Number of participants with baseline data, overall and by study design stratum (N, %)
- Demographics
  - Age: distribution in categories 18-39, 40-49, 50-59, 60-69, 70-79, ≥80 years; and summary as continuous variable
  - Sex at birth
  - Ethnic group: Asian, Black, Latino/Hispanic, White, other
  - Country of enrollment

- Type of residence prior to COVID-19 ("home")
- COVID-19 related characteristics
  - Duration of symptoms prior to enrollment
  - Level of care: non-ICU versus ICU
  - Respiratory support (4 categories: high-flow nasal cannula [HFNC], non-invasive ventilation [NIV], invasive mechanical ventilation without ECMO, or ECMO)
  - Time since initiation of oxygen support
  - Extent of lung infiltrates (3 categories: none, unilateral, bilateral)
  - ARDS (defined as bilateral lung infiltrates and SF ratio <315)
  - Receipt of SARS-CoV-2 vaccination (N, %)
    - Fully vaccinated at the onset of COVID-19 symptoms (≥ 14 days after the final vaccine dose [≥ 14 days since second dose, or since first dose if only one dose is required])
    - Type of vaccine
    - Received as part of a blinded clinical trial
- Vital signs (median [IQR] and categories)
  - Respiratory rate (categories: ≤20 vs >20 breaths/minute)
  - Oxygen saturation (SpO2) (categories: <92%, 92-96%, >96%)
  - Fraction of inspired oxygen (FiO2) (categories: <0.30, 0.31-0.40, 0.41-0.70, >0.70)
  - SpO2:FiO2 (SF ratio) (categories: <315, ≥315)
  - Temperature (categories: <38º C, ≥ 38º C)
  - Heart rate (categories: <100, ≥100 bpm)
  - Systolic blood pressure (SBP) (categories: <90 mmHg, 90-110 mmHg, >110 mmHg)
  - Mean arterial pressure (MAP) (4 categories: <65 mmHg with vasopressor use, <65 mmHg without vasopressor use, ≥65 mmHg with vasopressor use, ≥65 mmHg without vasopressor use)
  - Current vasopressor use
  - ARDS: SF ratio < 315 and bilateral pulmonary infiltrates
- Acute organ dysfunction during the index COVID-19 illness
  - Cardiac and vascular dysfunction
  - Hematologic dysfunction
  - Hepatic decompensation (exclusion criterion for aviptadil)
  - Serious infection other than SARS-CoV-2 (respiratory and non-respiratory)
  - Neurologic dysfunction
  - Renal dysfunction
- History of chronic conditions (present prior to the index COVID-19 illness)
  - Compromised immune function, defined as current use of antirejection medication after transplant, cytotoxic chemotherapy, or treatment with biological medicine for autoimmune disease or cancer; HIV; or immunosuppressive disorder other than HIV.
  - Metabolic/vascular co-morbidities, defined as history of diabetes mellitus requiring treatment, a cerebrovascular event (thrombotic or hemorrhagic), heart failure, or an MI or other acute coronary syndrome, overall and by components
  - Hypertension with and without history of other metabolic and vascular co-morbidity (4 groups):
    i) no hypertension or other metabolic/vascular co-morbidity;
    ii) hypertension without metabolic/vascular co-morbidity;
    iii) metabolic/vascular condition without hypertension; and
    iv) hypertension and a metabolic/vascular co-morbidity.

Metabolic/vascular co-morbidities include a history of diabetes, a cerebrovascular event, heart failure, or an MI or other acute coronary syndrome
    - Renal impairment or requirement of renal replacement therapy, overall and by components
    - Chronic obstructive pulmonary disease (COPD)
    - Chronic continuous supplemental oxygen use
    - Hepatic impairment
    - Cancer
- Other clinical characteristics
    - BMI (<30, 30-39.9, 40+)
    - Pregnancy, and gestational age (remdesivir cohort only, as pregnancy is an exclusion criterion for aviptadil)
- COVID-19 treatments
    - Receipt of remdesivir prior to randomization (N, %), and number of days
    - Corticosteroid use, summarized overall, and by disease severity at study entry (receipt of *invasive mechanical ventilation or ECMO*)
    - Antiplatelet/anticoagulant therapy (none; prophylactic heparin; intermediate or therapeutic heparin or other anticoagulant therapy; aspirin; or other antiplatelet therapy)
    - Immune modulators (IL-1 inhibitors, IL-6 inhibitors, interferons, JAK inhibitors, TNF inhibitors, other)
    - Convalescent plasma for SARS-CoV-2 infection
    - Hyperimmune intravenous immunoglobulin (hIVIG)
    - Neutralizing monoclonal antibodies for SARS-CoV-2
- Pulmonary vasodilators, by type
- Sedatives, by type
- Blood pressure lowering medications, by type
- Other concomitant medications
    - Antidiarrheals
    - Antifungals
    - Antirejection medications
    - Biologics for cancer or autoimmune disease
    - Cytotoxic chemotherapy
    - NSAIDs (at least 7 days)
- Laboratory values: as continuous outcomes, and number (%) of grade 3 or 4 lab abnormalities according to the *DAIDS AE Grading Table.*
- Co-enrollment in other trials, by trial
- Genomics consent

Some biomarkers will be measured centrally from stored samples, for example, SARS-CoV-2 antigen and antibody levels in plasma and SARS-CoV-2 viral RNA from nasal mid-turbinate swabs. If these measures are available, they will be included in interim reports.

Open report only:
In addition to the overall summaries, selected baseline characteristics will also be summarized by study design stratum, including age, gender, race/ethnicity, geographic region, disease severity, admission to ICU, duration of symptoms prior to enrollment, and duration of support for respiratory failure.

6 Administration of Study Treatment

These data are an important part of the safety review, with particular emphasis on infusion-related reactions and symptoms occurring during or within up to 2 hours after the infusion. These reactions and symptoms will be graded according to the DAIDS AE Grading Table.

The administration of study treatment is also an essential element of study conduct. The data summaries described in this section will be provided:

- In the closed report to the DSMB, by treatment group
- In the open report, selected summaries describing adherence, pooled across treatment groups

Summaries of AEs or infusion-related reactions are restricted to the closed report. Selected summaries will also be provided separately for the two disease severity strata.

Analyses will be by modified intention-to-treat (mITT), unless specified otherwise. The treatment comparisons will be performed using the methods described in section 3 for binary and continuous outcomes: stratified CMH test or logistic regression for comparing percentages, Wilcoxon rank-sum test [or quantile regression] for comparing medians, ANCOVA models for comparing means.

6.1 Infusion of Aviptadil (Active or Placebo)

Study population *(Aviptadil cohort, mITT)*: Unless otherwise noted, the study population consists of participants who were randomized to aviptadil or its placebo, excluding those who did not receive **any** aviptadil/placebo (modified intention-to-treat [mITT]).

Aviptadil (and its placebo) will be administered by intravenous infusion for 3 days, over a continuous 12 hour period each day. The protocol-specified infusion rate for the first infusion day is 50 pmol/kg/hr (Day 0), to be increased to 100 pmol/kg/hr on Day 1 and 150 pmol/kg/hr on Day 2. This corresponds to a protocol-specified dose of 600, 1200, or 1800 pmol/kg for infusions on Days 0-2. Infusions may be paused or discontinued due to side effects, or the target dose may be decreased.

In the following, "aviptadil" refers to the blinded aviptadil infusion (active or placebo). "Peri-infusion" refers to the time period during or within 2 hours after the infusion.

The following statistics will be used to summarize the infusions in each treatment group (active and placebo) for the closed reports, or pooled across treatment groups for open reports shared with investigators. For the closed report, treatment groups will be compared for the various outcomes using methods described in section 3.

For all participants who were randomized ***(Aviptadil ITT cohort)***:

- Non-administration of aviptadil:
  Number and percentage of participants who did not receive any aviptadil, and reasons

All other analyses will use the ***Aviptadil mITT*** cohort (i.e., analyses will exclude those who did not receive any blinded aviptadil in the study).

- For each of the Days 0-2: number and percentage of participants who did not receive any aviptadil, and reasons
- Adherence to the study treatment on Days 0-2 will be summarized over time: percent of participants who received no infusion, some (<50% of the day's protocol-specified infusion dose), most (50-90%) and full infusion (>90%) for each of the three days, and overall.
    - For each day, for each participant, the "percent dose infused" will be the estimated dose delivered expressed as percentage of the protocol-specified dose for the day (600, 1200, or 1800 pmol/kg).
    - For the summary across Days 0-2 ("overall"), categories are formed by the average of the three daily percent doses infused.
- Day of first infusion (same day as randomization, next day, or > 1 day after randomization), and time between randomization and start of infusion (median hours, IQR).
- For each of the Days 0-2: **Infusion of aviptadil**, rate, dose, and infusion time
    - Pre-infusion summary:
        - starting (patient-specific planned) infusion rate (categories: at versus below the protocol-specified rate for the day)
        - blood pressure (MAP, SBP)
        - use of vasopressors and dose
        - receipt of antidiarrheal agents to prevent infusion reactions
    - Dose infused (as percent of goal): median, 25th and 75th percentile, and according to categories (full [>90% of goal]; most [50-90%]; some [<50%]; no infusion)
    - For participants who received an incomplete infusion of the study drug on any day, reasons for the incomplete infusion (all that apply)
    - Timing of administration
        - Duration of infusion: median, 25th and 75th percentile of infusion time
        - Infusion start times (8am-12:00 noon; 12:01pm- 6:00pm, > 6pm)
    - Decrease in the infusion rate during the day (overall: worst category across Days 0-2; and worst category by day) (closed report only):
        - No decrease
        - Flow rate decreased, but no intermittent stop. The reasons for the decrease will be summarized (due to AE versus other reasons)
        - Infusion was paused (stopped but resumed), and not discontinued prematurely for the day; and reasons (AE versus other)
        - Premature discontinuation for the day (infusion duration <12 hours, and patient-specific planned dose not delivered), and reasons for discontinuation (AE or other)
        - Permanent discontinuation, and reasons
    - Listings of participants for whom the infusion was discontinued early, with reason for discontinuation, dose infused per day, disease severity at baseline, age, sex.
    - Concomitant medications peri-infusion (i.e., during or within 2 hours after the infusion) (overall: any use peri-infusion on Days 0-2; and by day)
        - Vasopressors, with dose in norepinephrine equivalent (NE)
        - IV bolus or colloids
        - Other medications to treat AEs, as collected on the infusion eCRF

Safety: infusion-related signs/symptoms, AEs, and lab markers (closed report only)
The primary safety outcome of *grade 3 or 4 AEs, SAEs, PSESEs, or death through Day 5* includes potentially infusion-related outcomes; the analysis of the primary safety outcome is described in section 7. The current section describes safety analyses that are focused on the peri-infusion time period (i.e., during and within 2 hours after the infusion).

Peri-infusion signs and symptoms are reported as AEs (with grade and action taken) on eCRFs. Local labs are reported at baseline, Days 1 and 2 for all participants, and Days 3 and 5 if clinically available. Labs on Day 5 are reported for participants who are treated in the ICU.

Side effects of aviptadil observed in previous studies include:

- Hypotension with and without vasopressor
- Diarrhea
- Facial flushing
- Bradycardia
- Tachycardia

For the aviptadil versus placebo comparisons, incidence and management of hypotension in particular will be monitored in detail. Blood pressure is recorded prior to the start of the infusion and every 2 hours peri-infusion on each infusion day. Vasopressor use and dose are reported: prior to the start of the infusion, the highest dose peri-infusion, and the dose at 2 hours after the infusion.

The following data summaries will be provided overall for Days 0-2, and separately by day. Treatment groups will be compared using statistical methods described under “analysis principles” in section 3; comparisons will be stratified by disease severity at study entry (2 categories, by use of *invasive mechanical ventilation or ECMO*).

- Number and percentage of participants with infusion-related signs or symptoms (reported during the infusion or within 2 hours after the infusion), by type and grade, by type and grade cut-off (i.e., $\geq$ grade 2, $\geq$ grade 3, etc.), and by type and action taken.

  Comments:
  1. For aviptadil, ***diarrhea is not included in the composite safety outcome*** of incident grade 3 or 4 AEs, SAEs, PSESEs or death unless it is a SAE or leads to discontinuation of the infusion (for the day, or permanent discontinuation). Therefore, peri-infusion diarrhea AEs will be summarized in two ways: (1) as reported, and (2) restricted to diarrhea AEs that lead to discontinuation of the investigational agent.
  2. Hypotension, diarrhea, facial flushing, bradycardia, and tachycardia are collected as part of the infusion-related signs and symptoms, and will be summarized by type and grade, and by type and action taken in response to the AE, as described above.

- **Peri-infusion hypotension summary**
  - Peri-infusion hypotension AEs reported on infusion eCRF (by grade: highest grade on Days 0-2, or highest grade on the day for the day-specific summaries)
  - Blood pressure (across days 0-2, and on each day)

        - MAP decrease by > 20 mmHg from daily pre-infusion baseline
        - Lowest peri-infusion MAP (mean [SD] across participants)
        - Incidence of MAP < 65 mmHg (compared to daily pre-infusion baseline)
        - Percentage of peri-infusion BP data points with MAP <65 mmHg (mean [SD] of percentage across participants)
    - Infusion modifications for hypotension (prevalence on ≥ 1 day)
        - Infusion not attempted for hypotension/vasopressor use
        - For those with any infusion modification, summary of the highest-intensity infusion modification (across Days 0-2, and for each day): Rate decreased but infusion not paused; infusion paused but resumed; infusion discontinued for the day; infusion discontinued permanently
    - Vasopressor use peri-infusion
        - New peri-infusion vasopressor use on any day among patients not receiving vasopressors pre-infusion on Day 0 (Number in subgroup, N, %)
        - New or increased peri-infusion vasopressor use on any day among patients who received vasopressors pre-infusion on Day 0 (Number in subgroup, N, %)
        - Maximum peri-infusion vasopressor rate increase within a study day from pre-infusion to peak (in NE units; max over Days 0-2, then mean across patients; 0 NE is imputed for time points when no vasopressor is used. If the maximal peri-infusion vasopressor dose is lower than the pre-infusion dose, then 0 NE will be imputed).
        - Percent with vasopressor rate higher at 2 hours post infusion than pre-infusion
        - Incidence of vasopressor rate increase by > 0.03 mcg/kg/min NE units peri-infusion relative to daily pre-infusion baseline (N, %)
        - Incidence of peak (absolute) vasopressor rate of > 0.1 mcg/kg/min NE units
    - IV fluid use peri-infusion in response to hypotension AE
        - IV fluid (crystalloid ≥ 500 mL or equivalent colloid volume) peri-infusion, prevalence
        - For those who received IV fluid or colloid: maximum IV fluid volume on one day (max across days for each participant, then mean across participants)

- Summary of *SBP and MAP trajectories*, from infusion start to 2 hours after infusion
    - Mean trajectories will be plotted by treatment group, and compared using longitudinal models.
    - For selected participants, *individual trajectories* for MAP and SBP will be plotted for each of the infusion days. In particular, individual trajectories will be plotted for participants who used vasopressors, who experienced peri-infusion hypotension (MAP < 65 mmHG or hypotension AE), or for whom the infusion flow rate was decreased, the infusion paused, or discontinued. These events will be marked on the individual trajectories. Thus, the individual trajectories serve as “line listings” for hypotension events.

- Heart rate:
    - Mean trajectories over time, similar to MAP
    - Percent of participants for whom the peri-infusion heart rate decreased to below 60 bpm at any time, stayed between 60-100 bpm at all times, or reached >100 bpm at any time.

- Medications (other than vasopressors) received in response to AEs during or within 2 hours after infusion, number and percentage of participants and type of medication

- Listings of participants who died or experienced grade 3 or 4 AEs, SAEs, or PSESEs are provided as part of the safety analyses described in section 7.

6.2 Infusion of Remdesivir (Active or Placebo)

Study population *(Remdesivir cohort, mITT)*: Unless otherwise noted, the study population consists of participants who were randomized to remdesivir or its placebo, excluding those who did not receive **any** remdesivir/placebo (modified intention-to-treat [mITT]).

Remdesivir (and its placebo) will be administered once-daily by intravenous infusion (over 30 minutes) for up to 10 days, or until hospital discharge, whichever comes sooner. Remdesivir will be administered on Day 0 as a 200 mg IV loading dose, followed by a 100 mg maintenance dose on subsequent days. Remdesivir may be discontinued after 5 or more days, per discretion of the treating clinician, if the participant is no longer requiring respiratory support.

In this section, "remdesivir" refers to the blinded remdesivir infusion (active or placebo).

The following statistics will be used to summarize the infusions in each treatment group (active and placebo) for the closed reports, or pooled across treatment groups for reports shared with investigators:

- Number and percent of participants who received (any) remdesivir/placebo, by day
- Number of days remdesivir was administered: median, IQR, distribution.
- Number and percent of participants for whom remdesivir was discontinued, and reasons for discontinuation.
- Number and percent of participants for whom the complete target volume was not administered, by day; and reasons for incomplete administration (pooled over days).
- Number and percent of participants for whom a daily remdesivir infusion was discontinued prematurely, by day, and pooled across days.
- Pooled across days:
    - Number and percentage of participants with infusion-related signs or symptoms (reported during the infusion or within 2 hours after the infusion), by type and grade, and by type and action taken. (Closed report only)
    - Number and percent of participants for whom a remdesivir infusion was discontinued prematurely due to an AE

- Number and percent of participants for whom medications were prescribed during or within 2 hours following the infusion *in response to an AE*, and type of medication

7 Safety Analyses

The planned timing of safety reviews is described in section 2. An overview of the safety data collection is provided in Appendix D.

Analysis cohorts: Safety analyses will be conducted by modified intention-to-treat (mITT), unless otherwise stated, for the following three cohorts:

1. ***Aviptadil cohort, mITT:*** Participants who were randomized to aviptadil or its placebo, excluding those who did not receive any aviptadil/placebo
2. ***Remdesivir cohort, mITT:*** Participants who were randomized to remdesivir or its placebo, excluding those who did not receive any remdesivir/placebo
3. ***Factorial cohort, mITT:*** Participants who were randomized to the four treatment combinations formed by the aviptadil/placebo and remdesivir/placebo pairs (2x2 factorial design), excluding those who did not receive any of the aviptadil/placebo OR any of the remdesivir/placebo.
   In the factorial cohort, the presence of interactions between aviptadil and remdesivir will be assessed, for the primary safety endpoint and other key outcomes. If there is evidence for interactions ($p<0.05$) in a given outcome, the analyses described in Section 9 will be performed.

Comment: Because the safety profile of remdesivir has been well-described, safety summaries for the remdesivir cohort will be provided only after more than 40 participants are randomized to remdesivir vs placebo; the frequency of the safety reports for remdesivir will be determined by the DSMB.

A comprehensive safety review includes:

- Comparison of the treatment groups for the primary safety endpoint, its components, and analyses of secondary safety outcomes (described in this section)
- Analyses of infusion-related reactions and symptoms, described in section 6
- Evaluation of selected efficacy outcomes (e.g., recovery at Day 90, time to recovery, time to hospital discharge), which contain important safety information. Described in section 8.

In addition to the full DSMB reviews, more frequent, shorter safety reports will be provided to the DSMB, for example, weekly safety reports early in the trial.

This section describes the primary safety outcome, and the analyses of AEs, SAEs, UPs, SUSARs, and deaths. Comparisons between treatment groups will be stratified by disease severity at study entry (as described in section 3 under “stratification”).

In order to streamline the reporting of events, it was decided that certain protocol-specified exempt events (PSESE) are *not reported as SAEs*, unless they are considered related to the study treatment by the investigator. The PSESE in TESICO encompass a collection of serious events that are expected to occur commonly in the target population even in the absence of study interventions. While the PSESEs in this protocol are similar in severity to

SAEs, PSESEs are reported not on the SAE eCRF, but are reported as study endpoints on various other eCRFs. AEs that are considered PSESEs are listed in Appendix C. The composite outcome of *clinical organ failure or serious infections*, defined in Appendix B, is comprised of all PSESEs, except all-cause mortality (death is a PSESE, but is included in the composite of *clinical organ failure or serious infections* only if the cause of death corresponds to one of the components listed in Appendix B).

7.1 Safety Analyses for the Aviptadil and Remdesivir Cohorts

The following safety and tolerability outcomes will be analyzed; models will be stratified by disease severity (receipt of invasive mechanical ventilation or ECMO at study entry), as described in section 3 under "stratification", unless noted otherwise:

- The **primary safety endpoint** is a composite of incident grade 3 or 4 AEs, SAEs, PSESEs, or death through Day 5. The number and proportion of participants experiencing one of these events up through Day 5 will be tabulated, and treatment groups will be compared using a CMH test stratified by disease severity at study entry (2 categories, by receipt of *invasive mechanical ventilation or ECMO* vs. neither). The OR comparing the investigational treatment versus placebo will be estimated with a 95% CI using a logistic regression model that includes the treatment group indicator and the indicator for disease severity at study entry.
    - Mortality will be analyzed as a key secondary outcome, see below.
    - The individual components of the composite outcome will be summarized.
    - Sensitivity analyses for the primary safety outcome: After completion of enrollment, if the Day 5 status for the primary safety outcome is unknown for more than 2% of participants in the mITT cohort, then treatment groups will also be compared for time to event through Day 5 using a log-rank test, stratified by disease severity at study entry; the HR will be estimated with a 95% CI using a stratified Cox proportional hazards model, and the cumulative proportion of participants with events over the first 5 days in each treatment group will be estimated using Kaplan-Meier curves.

  Comments:
  1. For aviptadil, ***peri-infusion diarrhea is not included in the composite safety outcome*** of *incident grade 3 or 4 AEs, SAEs, PSESEs or death* unless it is a SAE or leads to discontinuation of the infusion (Appendix H1 of the TESICO protocol). After completion of the infusion, all incident grade 3 or 4 diarrhea AEs are included.
  2. Because most participants in the remdesivir cohort will also be randomized to aviptadil versus placebo, we will use the same composite safety outcome for the remdesivir versus placebo comparison as for aviptadil (i.e., diarrhea occurring during and up to 2 hours after the aviptadil/placebo infusion will be excluded as described above).

- All-cause mortality through follow-up will be analyzed using time-to-event methods. Cumulative proportions of participants who died in each treatment group will be estimated using Kaplan-Meier estimates, and summarized in tables (proportion of participants who died by Days 5, 14, 28, 60, 90, month 6) and figures (Kaplan-Meier curves with pointwise 95% CIs). Treatment groups will be compared for time to death using log-rank tests,

stratified by disease severity at study entry, and HRs will be estimated with 95% CIs using stratified Cox proportional hazards models.

- Cause of death will be MedDRA® coded and summarized by treatment group.

- The following composite endpoints will be analyzed using time-to-event methods (cumulative proportions of participants with events will be estimated using Kaplan-Meier curves with pointwise 95% CIs; treatment groups will be compared using log-rank tests; numbers and percent of participants with events will be summarized by treatment group, and overall HRs with 95% CI will be estimated using Cox proportional hazards models):
    - Composite of incident grade 3 or 4 clinical adverse events, SAEs, PSESEs, or death through Day 28
        - Components of the composite endpoint will be also be summarized.
        - In addition to time-to-event analyses, the treatment groups will be compared for the proportion of participants who experienced the composite endpoint by Day 28 using a stratified CMH test, similar to the primary safety analysis on Day 5.
    - Composite of SAEs, PSESEs, or death through Day 28 and Day 90
    - Composite of hospital re-admission or death through Day 90 and Month 6.

- Grade 3 or 4 AEs, SAEs, and UPs will be classified by MedDRA® system organ class. AEs will be graded for severity according to the *DAIDS AE Grading Table*, except for peri-infusion hypotension AEs, which are graded according to Table D-3 in Appendix D.

- Incident **grade 3 and 4 clinical AEs** are reported through Day 28. (A grade 3 or 4 AE is considered "incident" if the event was not present at baseline or increased to grade 3 or 4 from grades 1 or 2, or increased to grade 4 from grade 3.)
    - AEs that were reported to have occurred on Day 0 prior to the first infusion will be considered "baseline" and thus will be excluded from the analysis of incident AEs.
    - Grade 3 and 4 AEs that occur peri-infusion (i.e., during and within 2 hours after the infusion) on Days 0-2 and are reported on the infusion eCRFs will be included as incident grade 3 or 4 AEs, unless noted otherwise.
    - The number and percent of participants with incident grade 3 and 4 AEs will be summarized by MedDRA® system organ class and grade, and by MedDRA® system organ class and grade cut-off (i.e., grade $\geq$3, grade 4). Comparisons between treatment groups will be for the proportion of participants who experienced AEs of grade 3 or higher through Day 28, using stratified CMH tests or logistic regression, stratified by disease severity at study entry (*invasive mechanical ventilation or ECMO* vs. neither). Treatment groups will be compared for incidence of grade 3 or 4 AEs overall, and by system organ class.
    - System organ classes may be split up into MedDRA® preferred terms (PT) for the most frequent system organ classes, particularly for classes where the treatment difference is significant.
    - Other clinically meaningful AE groupings (beyond system organ class) may be developed by the study team, who are blinded to the treatment effect.

- Grade 1-4 clinical AEs are reported at baseline (Day 0 prior to infusion of the investigational agent), on Days 0-2 peri-infusion (during and within 2 hours after the

infusion), as well as on Days 14 and 28. The peri-infusion AEs are collected as "signs and symptoms" via checklist on the infusion eCRFs.

The analysis of peri-infusion AEs is described in section 6. In particular, the number and percent of participants with peri-infusion AEs will be summarized by day and grade, by type and grade, and by type and action taken (i.e., modification or discontinuation of the infusion).

- Treatment groups will be compared for the proportion of participants who developed **PSESEs** through Day 28 and through Day 90, using stratified CMH tests. In addition to the overall comparison, individual components of the composite PSESE outcome will be tabulated, and compared between treatment groups using stratified CMH tests. The components of the PSESE outcome are listed in Appendix C.

  Comment: The composite outcome of *clinical organ failure, serious infections, or death* is identical to the composite of all PSESEs; individual components of clinical organ failure are listed in Appendix B.

  Treatment groups will also be compared for the incidence of PSESEs using time-to-event methods; because death is a PSESE, the overall comparison will use Cox proportional hazards models, while comparisons for individual components will use the Fine-Gray model to account for the competing risk of death. Models will be stratified by disease severity at study entry (*invasive mechanical ventilation or ECMO* vs. neither) if event numbers permit.

- Treatment groups will be compared for incidence of a composite of cardiovascular and thromboembolic events, a subset of the organ failure outcome (items b1, e2, e3, and f2 in Appendix B). Time-to-event methods will be used that take into account the competing risk of death (as described in section 3, using Aalen-Johansen estimates for the cumulative incidence functions, and Gray's and Fine-Gray's methods to compare treatment groups and estimate the sub-hazard ratio).

- **Subgroup analyses:** The impact of study arm on the primary safety outcome (composite of grade 3 or 4 events, SAEs, PSESEs, or death through Day 5) and other important safety outcomes will be assessed for subgroups defined by baseline characteristics, including demographics, duration of symptoms at enrollment, baseline classification of "home", clinical history and presentation (including disease severity at study entry), use of concomitant medications, and, if available, baseline levels of antibodies, antigen and viral RNA; tests for homogeneity of the treatment effect across subgroups will be carried out. Outcomes and methods for subgroup analyses are described in detail in section 8.5.

- Treatment groups will be compared for mean changes in laboratory test values from baseline to Day 3, and for incidence of grade 3 and 4 laboratory abnormalities at Day 3 (new abnormality or increase in grade). Laboratory tests include the basic metabolic panel (BMP), complete blood count (CBC) with differential, international normalizing ratio (INR), D-dimer, AST, ALT, and bilirubin. Statistical methods are described in section 3. Biomarkers will be log-transformed as needed.

  - For all participants, these biomarkers will be determined locally on Days 0, 1, and 2. Treatment groups will be compared for mean changes from baseline through

Day 2, overall using longitudinal models, and pointwise at Days 1 and 2 using ANCOVA models; models will be adjusted for baseline biomarker levels.
    - For participants who are in the ICU on Day 5, these biomarkers are also collected on Day 5. For this cohort, trajectories of mean biomarker values will be described, and treatment groups will be compared for mean changes in biomarker values from baseline through Day 5.
    - For renal function lab tests, participants who are on dialysis at study entry will be excluded.

- Pregnancy outcomes will be summarized.

Listings of SAEs, PSESEs, incident grade 3 and 4 AEs, UPs, SUSARs, and deaths (with cause of death) by treatment group will be provided at each DSMB meeting, with new events highlighted. The listings will include important baseline characteristics, such as age, sex, and level of respiratory support at study entry.

Further safety assessments may be considered.

Concomitant medication use is collected at baseline, and daily through Day 7; additionally, any use between Days 8 and 14, and use on Day 28 is reported. Vasopressor use is reported daily for Days 0-14. The following categories of concomitant medications will be summarized by treatment group:

- Corticosteroid use (daily for Days 0-7, any use through Day 14)
- Vasopressor use (daily for Days 0-14)
- Anticoagulation and antiplatelet therapy, by type
- COVID-19 treatments other than corticosteroids, by type
- Other summaries will be provided by request of the DSMB or study leadership.

7.2 Additional Safety Analyses for the Aviptadil Cohort

Limited safety data are available for aviptadil. Therefore, infusion reactions to aviptadil will be carefully monitored. Side effects of aviptadil observed in previous studies include:

- Hypotension with and without vasopressor
- Diarrhea
- Facial flushing
- Bradycardia
- Tachycardia

Data summaries that address these potential side effects during or within 2 hours after the infusion are described in section 6.1, under “Safety”.

In addition, the aviptadil and placebo groups will be compared for *hypotension associated with organ dysfunction* within the first 5 days after study entry. *Hypotension associated with organ dysfunction* is defined as hypotension plus concomitant or subsequent organ dysfunction. Organ dysfunction in this setting is a composite outcome consisting of items 5a-5f (excluding item 5b4) of the secondary outcome of *clinical organ failure and serious infections* (section 4.1.2 of the TESICO master protocol). The composite outcome will be assessed on Day 5, and compared between treatment groups using CMH tests, stratified by

disease severity at baseline; the ORs will be estimated with 95% CIs using logistic regression, adjusted for disease severity at baseline.

8 Efficacy Analyses

Analysis cohorts: Separate efficacy analyses will be conducted for the ***Aviptadil*** cohort (comparison of aviptadil versus placebo), and the ***Remdesivir*** cohort (comparison of remdesivir versus placebo). Interactions between aviptadil and remdesivir will be assessed in the ***Factorial*** cohort (assessment whether the effects of aviptadil and remdesivir are independent of each other, section 9).

Efficacy analyses will be by intention-to-treat, unless otherwise stated.

8.1 Primary Efficacy Endpoint

The **primary endpoint** of the trial is a 6-category ordinal outcome that assesses the participants' recovery status at Day 90, referred to "**recovery**". The six ordered categories of recovery are shown in Table 1 below; they consist of 3 ranked categories that describe the number of days alive, at home, and not receiving new supplemental oxygen ***at Day 90*** (77 or more consecutive days, 49–76 days, or 1–48 days) as well as an additional 3 categories for patients who are not recovered at Day 90. The ranking is from 1=best to 6=worst (death).

Table 1. Categories of the primary endpoint of *recovery at Day 90*

Category	Status at 90 days
1 (Best)	At home and off oxygen. No. of consecutive days at Day 90 ≥ 77
2	49-76
3	1-48
4	Not hospitalized AND either at home on oxygen OR not at home
5	Hospitalized for medical care OR in hospice care
6 (Worst)	Dead

Definition of *Home* for the primary endpoint:
According to the protocol, section 4.1, and consistent with the TICO protocol (NCT04501978), *Home* is defined as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this protocol.

Residence or facility groupings to define home are:

1) **Independent/community dwelling** with or without help, including house, apartment, undomiciled/homeless, shelter, or hotel

2) **Residential care facility** (e.g., assisted living facility, group home, other non-medical institutional setting)

3) **Other healthcare facility** (e.g., skilled nursing facility, acute rehab facility)

4) **Long-term acute care hospital** (hospital aimed at providing intensive, longer term acute care services, often for more than 28 days).

Lower (less intensive) level of residence or facility will also be considered as home. By definition, "home" cannot be a "short-term acute care" facility. Participants previously residing in a "long-term acute care" hospital recover when they return to the same or lower level of care.

Participants residing in a facility solely for public health or quarantine purposes will be considered as residing in the lowest level of required residence had these public health measures not been instated.

Since some patients may have been receiving supplemental oxygen before their COVID-19 illness, we define **new supplemental oxygen** as any supplemental oxygen in participants who were not receiving supplemental oxygen before their COVID-19 illness or an increase in supplemental oxygen above pre-COVID-19 baseline among patients who were receiving supplemental oxygen before their COVID-19.

The **"last-off" method** for assessing recovery will be used, as has been customary in the use of similar ordinal endpoints in ARDS trials for decades. According to the "last-off" method, periods of recovery that are followed by hospital re-admission, change from home to a higher level of care, or receipt of new supplemental oxygen will *not be counted* toward the number of days of recovery. In other words, only days between the last time the patient entered a recovered state (returned home, free of new supplemental oxygen), and Day 90 are counted as days of recovery.

8.2 Primary Analysis

Primary analysis
The investigational agent will be compared to the corresponding placebo group for *recovery at Day 90* by intention-to-treat. The primary analysis will use a proportional odds regression model to estimate a summary odds ratio (OR) for being in a better category in the investigational agent group compared with placebo; an OR > 1.0 will reflect a more favorable outcome for patients randomized to the investigational agent vs. placebo. The model will include a treatment indicator, and will be stratified by disease severity by including an indicator for receipt of *mechanical ventilation or ECMO* at enrollment.

Comments:

1. The primary endpoint can be ascertained only after 90 days of follow-up are completed (except in the case of death), since it is possible that a participant gets re-admitted to the hospital at any time after the initial discharge.
2. Ascertainment of the primary endpoint requires knowledge of the hospitalization status, type of residence ("home"), and oxygen use over time through Day 90. After the first hospital discharge, these will be assessed every 2 weeks (starting at Day 14, usually through phone contact).

3. At interim analyses, tests that compare treatment groups for the ordinal endpoint of "recovery at 90 days" need to account for the censoring of follow-up for all participants who have not yet completed 90 days. A novel statistical method combining proportional odds models with methods for competing risks is currently under review at a peer-reviewed journal (Tsiatis and Davidian 2021, personal communication). When published, this method will be implemented for interim analyses of the primary endpoint. The method requires that a certain proportion of participants has completed the 90 day follow-up, and such is not suitable for very early reviews.
4. **Missing data at the final analysis:** If the proportion of missing data is low and data are missing at random, the method by Tsiatis and Davidian (2021) described under item 3 will be applied. Prior to unblinding, the proportion, pattern, and reasons for missing data will be reviewed by the unblinded statisticians, and the method for treating missing data will be defined in cooperation with the blinded statisticians.

- The number and percentage of participants in each of the six categories on Day 90 will be tabulated, and the adjusted summary OR of the active versus control group will be estimated with a 95% CI, using a proportional odds model as described above.

  Sensitivity Analyses:
  - In addition to the adjusted summary OR, the unadjusted summary OR with 95% CI will be shown (estimated using a proportional odds model without adjustment for disease severity). In the case that the adjusted OR differs substantially from the unadjusted OR, the reason for the deviation will be explored.
  - The primary comparison will be repeated after excluding participants who did not receive any of the investigational agent/placebo (modified intention-to-treat).

- To supplement the overall summary odds ratio for the 6-category *recovery* outcome, each dichotomized definition of improvement that can be formulated from the components of the ordinal outcomes will be considered separately; for example, treatment groups will be compared for the proportions of participants in category 1 on Day 90; for the proportions in categories 1 or 2 ("best two categories"), in categories 1-3, etc. Proportions will be tabulated, and odds ratios for active versus control groups will be estimated with 2-sided 95% CIs using logistic regression models. These analyses need to be interpreted with caution, because they are not adjusted for inflation of type I error due to multiple comparisons.
  - The validity of the proportional odds assumption for the primary endpoint will be assessed by testing for heterogeneity in the log ORs (for the treatment effect) across the dichotomized cumulative ordered categories in the corresponding logistic regression model and across the stratification covariate (partial proportional odds model, test for "unequal slopes"), as described in section 3.

- **Subgroup analyses** will be carried out for the primary outcome. The goal is to determine whether the treatment effect differs across subgroups, and to aid the DSMB in considerations on whether there are safety concerns in specific subgroups. Principles for subgroup analyses are described in section 8.5; here, subgroup analyses are based on the proportional odds models. In particular, heterogeneity of the treatment effect by disease severity at baseline will be assessed.

8.3 Key Secondary Outcomes

The TESICO protocol identifies four key secondary outcomes (protocol section 11.2):

- **Mortality** through Day 90 is a key secondary outcome; analyses are described in section 7.1. In addition, interim monitoring boundaries are based on time to death (rather than the primary ordinal endpoint of *recovery*). Corresponding analyses are described in section 10.2.

- To supplement the separate analyses of *recovery at day 90* and *time to death*, a composite endpoint that considers the number of days at home off oxygen and the time to death (instead of just survival status at day 90) as well as the other categories of the primary ordinal recovery outcome will be analyzed jointly using the "**win ratio**" method.[8] (This analysis will be performed when the trial is completed).

  The win ratio will be calculated using the matched pairs method described in Pocock (2012).[8] Pairs will be formed by matching participants by disease severity (requiring invasive mechanical ventilation or ECMO), and by ranking the participants in each treatment group according to a risk score, described in section 13.1, and pairing the participants in groups A (here referring to the investigational drug) and B (referring to control) with equal ranks. Details are given below.

  - If both treatment groups have the same number of observations, the win ratio is calculated as follows:
    Step 1: Calculate the risk score for all participants, and order participants by the risk score in each treatment group. If needed, break ties at random. Each participant forms a "matched pair" with the participant of equal rank order in the other treatment group.
    Step 2: For each pair, determine whether the participant in group A wins, loses, or neither:
    a. Compare pairs for *time to death,* for all pairs where one or both participants died. If the participant in group A died, wins and losses are computed as follows:
       - If the matched participant in group B has longer follow-up, then A loses and B wins.
       - If the matched participant in group B has shorter follow-up and is alive at the censoring date, then neither group wins.

       Repeat for pairs where the participant in group B died.
    b. Compare remaining pairs for category 5 of the primary outcome, *hospitalized for medical care OR in hospice care*
    c. Compare remaining pairs for category 4 of the primary outcome, *not hospitalized AND either at home on oxygen OR not at home*
    d. Compare remaining pairs for *days off oxygen at home*.
       - If time at home off oxygen is longer for A, then A wins and B loses; vice versa for B.
       - If A achieved recovery (discharged home and off oxygen) at the latest follow-up date, and B was censored without reaching recovery before A reached recovery, then neither group wins; vice versa for B.
       - Otherwise, neither group wins.

Step 3: Calculate the win ratio as the number of wins in group A divided by the total number of pairs with a win or a loss in group A. Calculate the 95% CI for the win ratio and p-value as described in Pocock (2012).[8]

- If one treatment group has more participants than the other, select $|n_A - n_B|$ participants at random from the larger group and delete. Calculate the win ratio, 95% CI and p-value for the resulting matched pairs. Repeat the random selection of observations to delete 501 times (or more); identify the matched pairs data set that corresponds to the median win ratio; the final values of the win ratio, 95% CI and p-value are those calculated from this data set.
- If both treatment groups have the same number of observations, but some ranked risk scores are tied within a treatment group, a similar process may be used to repeat the random breaking of ties, with the final win ratio chosen as the median over repeated random tie breaks.

With this approach, time to death is first used to determine the winning group (i.e., longer time to death), then categories 4 and 5 followed by days off oxygen at home are used to determine the winning group: in this manner, the win ratio combines these conflicting outcomes into a composite while recognizing the importance of mortality.

- **Time to recovery** through Day 90, defined as *alive, at home, and off new supplemental oxygen*. Here, "new supplemental oxygen" is defined as supplemental oxygen above the level used prior to the COVID-19 infection. The cumulative incidence functions for recovery taking into account death as a competing risk will be estimated using the Aalen-Johansen method and compared using Gray's test with ρ=0. The recovery rate ratio will be estimated using a Fine-Gray regression model. The comparisons between treatment groups will be stratified by disease severity at study entry.
  - Per protocol, the recovery status in the primary ordinal outcome is defined using the "last-off" method, i.e., hospital re-admission, change from home to a higher level of care, or receipt of new supplemental oxygen changes the status to "not recovered". In contrast, the cited statistical methods for time-to-first-event analyses require that "recovery" is defined as an absorbent state, i.e., once a participant achieved "recovery", they will not revert to a different state later. Therefore, we will present two analyses:
    - Time to *first* being discharged from the hospital, at home, and off new oxygen.
    - Time to *last* being discharged from the hospital, at home, and off new oxygen; this corresponds to the "last-off" method. Results will have to be interpreted with caution, as the last-off method violates assumptions for the standard time-to-(first-)event analyses.
  - Time to first being *discharged from the hospital, at home and off oxygen for 14 consecutive days* will be analyzed to aid in the interpretation of "time to recovery".

- Status on a 3-category ordinal outcome that includes (a) recovered (alive, at home, and off new oxygen), (b) alive but not recovered, and (c) dead, assessed at Day 90. Here, *new oxygen* is defined as supplemental oxygen above the level that was used prior to COVID-19.
  Treatment groups will be compared using proportional odds models, stratified by disease severity.

8.4 Other Secondary Outcomes

The protocol defines a number of secondary endpoints in addition to the four key endpoints described in section 8.3 above. These analyses will be carried out for the final report. Selected secondary endpoints may also be analyzed for interim monitoring reports, to help evaluate the safety and efficacy of the investigational agent.

Below, the secondary outcomes from section 4.1.2 of the protocol are cited, with a short description of the analysis methods. For each outcome, the treatment groups will be compared by intention-to-treat, stratified by disease severity at study entry, as described in section 3 under "stratification".

- Time to discharge from the initial hospitalization. Treatment groups will be compared using time-to-event methods that take into account the competing risk of death, similar to the analyses for time to recovery described in section 8.3.
    - Hospital readmissions will be summarized using methods for recurrent events (i.e. those who are readmitted will re-enter the risk set).[9]
- *Hospital-free days to Day 90* (days alive outside of a short-term acute care hospital up to day 90). For this analysis, the "last-off" method will be used, i.e., days from the latest hospital discharge to day 90 will be counted. A person who dies within 90 days will be assigned a value of -1, consistent with the approach taken in many trials of intensive care-based interventions. We will present the median days by group and test the hypothesis of no difference between arms with a Wilcoxon rank sum test.
    - For interim analyses, only participants who have reached Day 90 (administrative follow-up for those who died) will be included, to avoid bias. Alternatively, the current follow-up time may be used, censored at the time point when the outcome status was last known for participants who were alive.
- A composite of death, clinical organ failure, or serious infection through Days 28 and 90 (see Appendix B). Analyses were described in section 7, under "PSESE".
- **Time to sustained recovery** through Day 90, defined as being discharged from the index hospitalization, followed by being alive and *home* for 14 consecutive days. (This is the primary endpoint in the ACTIV-3/INSIGHT 014/TICO protocol.) The analyses methods will take into account the competing risk of death, using the Aalen-Johansen method to estimate cumulative incidence functions, and Gray's test and the Fine-Gray method for treatment comparisons.
- Outcomes assessed in other treatment trials of COVID-19 for hospitalized participants in order to facilitate meta analyses and facilitate generation of norms, including an ordinal scale measuring the degree of oxygen support through Day 14, time to discharge from the initial hospitalization, and binary outcomes defined by worsening based on the worst 3 categories of the primary ordinal recovery outcome at day 90. We will try to match the analyses in the other trials, to get results that can be compared. These analyses will not be performed for interim reports to the DSMB, unless requested.

- A composite of cardiovascular events (outcomes listed in items b1, e2 and e3 in Appendix B) and thromboembolic events (item f2) through Day 28 and Day 90. Time to event methods will be used that take into account the competing risk of death, e.g., Gray's test to compare treatment groups.

8.5 Subgroup Analyses

As stated in the protocol, subgroup analyses for the primary efficacy outcome (recovery at Day 90), and for key safety outcomes (composite of *grade 3 and 4 AEs, SAEs, PSESEs, or death* through Day 5 and Day 28, composite of SAEs, PSESEs, or death through Day 90, time to hospitalization or death through Month 6, and for time to death) will be performed to determine whether and how the treatment effect (active versus control) differs qualitatively across various **subgroups defined at baseline**, and whether there are safety concerns in specific subgroups.

Key subgroup analysis are by disease severity at study entry and by study design stratum; other important subgroups include subgroups by age, by sex, by categories of oxygen support at baseline, by duration of symptoms prior to enrollment, by pre-existing conditions, and by use of concomitant medications (in particular, corticosteroid use).

Subgroup analyses will be performed by the following baseline factors:

- Study design stratum (defined in section 1.2)
  - for aviptadil, design stratum 1 versus strata 2 and 4
  - for remdesivir, design stratum 1 versus stratum 4
- Disease severity (*invasive mechanical ventilation or ECMO* versus neither).
- Oxygen requirement at baseline (HFNC, NIV, invasive mechanical ventilation without ECMO, ECMO)
- Duration of symptoms prior to enrollment
- Age
- Sex at birth
- Race/ethnicity
- Geographic location
- Residence (home) at the time COVID-19 symptoms developed
- Body mass index (BMI)
- Presence of chronic medical conditions. Only conditions with $\geq$ 5% prevalence will be considered.
  - Compromised immune function, defined as current use of antirejection medication after transplant; cytotoxic chemotherapy; treatment with biological medicine for autoimmune disease or cancer, HIV, or immunosuppressive disorder other than HIV.
  - Metabolic/vascular co-morbidities, defined as history of diabetes mellitus requiring treatment, a cerebrovascular event (thrombotic or hemorrhagic), heart failure, or an MI or other acute coronary syndrome
  - Hypertension with and without history of other metabolic and vascular co-morbidity (4 groups, as described in section 5)
  - Cancer
  - COPD
  - Asthma

  - Renal impairment or renal replacement therapy
  - Hepatic impairment
- Use of selected concomitant medications
  - Use of corticosteroids (recommended as SOC in this study), overall and by oxygen requirement at baseline
  - Use of antiplatelet/anticoagulant therapy (prophylactic heparin, intermediate or therapeutic heparin or other anticoagulant therapy, none)
  - Use of vasopressors
  - Use of IL-6 inhibitors or JAK inhibitors
- SARS-CoV-2 vaccination status at baseline, overall and by whether or not the immune function was impaired.
- ***In the Aviptadil cohort:*** Use of remdesivir at study entry or randomization to remdesivir in design stratum 1 (the 2x2 factorial).

  Comment: This subgroup analysis will provide information on whether the effect of aviptadil is independent of remdesivir. The assessment of independence in the subgroup analysis is not protected by randomization and would complement the assessment of independence in the factorial cohort, which is protected by randomization.
- ***In the Remdesivir cohort:*** Randomization to aviptadil.

When SARS-CoV-2 antibody and antigen levels in plasma and RNA levels from mid-turbinate nasal swabs (viral load) are available, subgroups will also be considered by upper respiratory SARS-CoV-2 viral load, by antibody level, by neutralizing antibody level, and by antigen level at baseline.

Subgroup analyses for the primary endpoint of recovery will use proportional odds models, stratified by disease severity at study entry (if the sample size permits). Summary ORs with 95% CIs comparing the investigational agent versus control will be estimated for each subgroup. Global tests for heterogeneity of the treatment effect across subgroups will be carried out, by adding the interaction between the subgroup indicator and the treatment group indicator to the model. In case the subgroups were formed by categorizing a continuous variable, the interaction term will be formed between the subgroup indicator and the continuous variable.

Subgroup analyses for the primary safety endpoint at Day 5 will use logistic regression, stratified by disease severity at study entry (if the sample size permits). Subgroup analyses for safety endpoints that are analyzed using time-to-event methods (those analyzed through Day 28 or longer) will use stratified Cox proportional hazards models, since death is part of the composite endpoints and not a competing risk. HRs will be estimated for each subgroup, and global tests of heterogeneity of the treatment effect will be carried out, as described above.

Additionally, subgroup analyses will be conducted for subgroups formed by a disease progression risk score at baseline. The construction of this risk score will be finalized later, see section 12.1.

Subgroup analyses will not be adjusted for multiple comparisons; they are supportive to the primary endpoint analyses. Subgroup analyses will be interpreted with caution due to limited power and uncontrolled type I error.

9 Assessment of Independence in the Factorial Cohort

Participants in the factorial cohort were randomized 1:1:1:1 to each of the four treatment combinations formed by aviptadil / matched placebo *and* remdesivir / matched placebo in a 2x2 factorial design. In this cohort, we will assess whether the effects of aviptadil and remdesivir are independent of each other (additive in the corresponding models). If there is evidence for an interaction effect (i.e., the effect of the two treatments is not independent), then the nature of the interaction will be investigated.

The presence of interactions between aviptadil and remdesivir will be investigated for the following outcomes:

- The composite of incident grade 3 or 4 AEs, SAEs, PSESEs, or death through Day 5 (**primary safety outcome**) and through Day 28.
    - For the final analyses, the test for an interaction between aviptadil and remdesivir at Day 5 will be performed using a logistic regression model that contains indicator variables for the aviptadil/ placebo main effect, the remdesivir/ placebo main effect, their interaction, and the indicator for disease severity at study entry (the stratification variable used in the main analysis). Similar for Day 28.
    - For interim analyses, the interaction tests will be performed using the corresponding Cox proportional hazards models.

- **Time to death**: The test for an interaction between aviptadil and remdesivir will be performed using a Cox proportional hazards regression model that contains indicator variables for the aviptadil/ placebo main effect, the remdesivir/ placebo main effect, and their interaction; the model will be stratified by disease severity at study entry.

- **Primary efficacy outcome** (recovery at 90 Days): The test for an interaction between aviptadil and remdesivir will be performed using a proportional odds regression model that contains indicator variables for the aviptadil/ placebo main effect, the remdesivir/ placebo main effect, their interaction, and the indicator for disease severity at study entry (the stratification variable used in the main analysis). The interaction test for the primary efficacy outcome will be performed after the 90-day follow-up is completed.

If there is evidence for an interaction between aviptadil and remdesivir ($p \leq 0.05$ for the interaction effect), then the four treatment groups will be described:

- Number and percent of participants with events in each group
- Kaplan-Meier curves for the time-to-event outcomes.

Comment: For the aviptadil versus placebo comparison in the full aviptadil cohort, the presence of differential treatment effects across subgroups by remdesivir use (randomized to remdesivir or use of remdesivir at study entry versus neither) also provides information about possible interactions between aviptadil and remdesivir. However, participants are not randomized to these subgroups (other than those in the factorial cohort); therefore, comparisons across these subgroups may be confounded with other patient characteristics.

10 Interim Monitoring Guidelines for the DSMB

Each investigational agent (aviptadil and remdesivir) versus placebo comparison will be treated as a separate clinical trial; stopping boundaries will be derived to allow for multiple interim looks, but will not be additionally inflated to adjust for simultaneous analysis of two different agents.

The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of benefit or harm.

As a guideline, **early termination for benefit or futility** based on the primary endpoint (*recovery* at Day 90) is not recommended, as the endpoint requires follow-up through Day 90. Given the anticipated rapid enrollment, this endpoint would be infeasible to use for stopping boundaries for either efficacy or futility. In addition, given the relatively short follow-up period of 90 days for this target population, full follow-up for the primary and all secondary endpoints is considered important to evaluate the investigational agents to be studied. An exception to this guideline is if the DSMB believe there is clear and substantial evidence of a mortality benefit for an investigational agent.

10.1 Early Assessment of Safety

Because data on aviptadil are limited, the pace of enrollment will be initially restricted. A comprehensive safety review will be conducted after the first 40 participants have been enrolled for the aviptadil vs. placebo comparison and Day 5 data are available. An initial safety review may be conducted earlier, e.g., after approximately 20 participants are enrolled for the aviptadil/placebo comparison and have Day 5 safety data available.

After the initial safety review, weekly safety reviews will be conducted. At the discretion of the DSMB, the frequency and content of these (initially weekly) safety reports may be modified. The DSMB may also request additional data summaries.

Monitoring of safety will be based on the totality of evidence, as described in section 7.

10.2 Interim Monitoring Boundaries

The monitoring guidelines for this master protocol focus on asymmetric stopping boundaries for harm or efficacy **based on mortality**, and ongoing close monitoring of safety by the DSMB, based on the totality of evidence. The stopping boundaries are provided as a guideline to the DSMB.

- For assessment of **harm**, a Haybittle-Peto boundary using 2.5 standard deviations (SD) of the test statistic under the null hypothesis for the first 100 participants enrolled and 2.0 SD afterwards. Harm will be assessed using **all-cause mortality**, specifically using a hazard ratio from a proportional hazard model for the time to death associated with the investigational agent.

- For interim assessment of **efficacy**, a Haybittle-Peto boundary using a 3.0 SD threshold will be used after 100 participants have been enrolled and followed for at

least 5 days. Efficacy will be assessed using **all-cause mortality**, specifically using a hazard ratio from a proportional hazard model for the time to death associated with the investigational agent.

Comment: The proportional hazards models for time to death will include the treatment indicator; if event numbers permit, the model will be stratified by disease severity at study entry (receipt of mechanical ventilation or ECMO vs. neither) (as described in section 3 for time to event analyses).

At each full interim review after the first 100 participants have been enrolled and followed for at least 5 days, the following will be provided:

- Z-value of the test statistic comparing treatment groups for time to death, plotted over information time, and the asymmetric Haybittle-Peto boundaries for harm and superiority described above.

  In addition to the current value of the test statistic, the corresponding values of the test statistic at the previous reviews will be plotted over information time, (1) as presented at the previous DSMB meetings, and (2) re-calculated with current data (using the cut-dates of the previous reports).

  Comment: Assuming that Z>0 denotes superiority of the investigational treatment and Z<0 denotes harm, then the Haybittle-Peto boundary for harm would be crossed when Z<-2, and the boundary for efficacy would be crossed when Z>3.

- History of the estimated hazard ratios for time to death with 95% CIs and p-values at previous DSMB reviews, as presented, and recalculated with the current data (using the cut-date of the previous reports). The latter provides information on the influence of a possible time lag in the ascertainment of deaths.

10.3 Interim Monitoring for Futility

No interim monitoring for futility is planned.

11 Data Completeness and Study Conduct

According to the protocol, clinical data will be collected on eCRFs to be submitted on Days 0, 1, 2, 3, 5, 7, 14, 28, 42, 60, 75, 90 and 180; mortality and re-hospitalizations will be assessed through Day 180 (6 months), SAEs and PSESEs through Day 90. (SAEs that are related to the investigational agent and Unanticipated Problems [UPs] are reported through Day 180). After hospital discharge, visits may be conducted by phone. Plasma and serum for central testing and for storage will be collected at baseline, at Day 3 (for participants who are hospitalized) and on Day 5 (for participants who are at the ICU or equivalent). The data collection schedule is included in Appendices D and E of this SAP.

Data completeness and study conduct reports will be provided by treatment group (for the closed report) and pooled across treatment groups (for the open report). Data summaries for the infusion of the investigational agents on Days 0-2 are described in Section 6; several of

those reports are also relevant for monitoring study conduct and will be included in the open report or provided to study leadership, pooled across treatment groups.

The following data summaries will be provided to assess data completeness and study conduct:

- Number and percent of participants with protocol deviations, and type of protocol deviation
- Expected and observed number (% of expected) of participants who completed visits on Days 0-3, 5, 7, 14, 28, 42, 60, 75, and 90.
- ***For the Aviptadil cohort:*** Expected and observed number (% of expected) of participants with infusion forms on Days 0, 1, and 2.
- Length of follow-up: Median, IQR, range
- Number and percent of participants who withdrew consent or were (potentially) lost to follow-up (no contact and unknown vital status for 30+ days).
- If substantial numbers of participants are lost to follow-up (e.g., more than 10% of participants), Kaplan-Meier estimates for the cumulative proportion of participants who are lost to follow-up over time, by treatment group, will be provided (closed report only).
- Listing of participants who withdrew consent, including dates of randomization, disease severity stratum at baseline, receipt of study treatment, oxygen requirement and hospitalization status at last visit, date of withdrawal, and reason of withdrawal.
- **Ascertainment of the primary endpoint** (recovery at Day 90, a 6-category ordinal outcome) requires knowledge of the hospitalization status, type of residence ("home"), and oxygen use over time through Day 90. After the first hospital discharge, these will be assessed every 2 weeks (starting at Day 14, usually through phone contact). To assess the data completeness for ascertaining the primary endpoint, the expected and observed number (% of expected) of participants with *known status for the components* will be provided for Days 14, 28, 42, 60, 75, and 90:
    - vital status (also for Day 180);
    - status of hospitalization;
    - status of oxygen use;
    - if discharged, the status of the residence ("home" versus other).
- Collection of specimens: Expected and observed number (% of expected) of participants with specimens collected as specified by the protocol, by visit.

A visit counts as "expected" if the visit window has closed or the data have been received.

12 SARS-CoV-2 Antigen, Antibody, and RNA Levels

SARS-CoV-2 antigen and antibody levels will be determined centrally, from stored plasma samples, and thus may not be available at interim analyses. Similarly, SARS-CoV-2 RNA levels will be determined centrally from mid-turbinate nasal swabs. If data are available, analyses will be included in interim reports. Analysis plans will be developed when more information is available.

13 Exploratory Analyses

13.1 Disease Progression Risk Score

A disease progression risk score, calculated at baseline, will be used to form subgroups of participants with low or high predicted risk for subgroup analyses for safety and efficacy outcomes, and to pair participants for the win ratio analyses described in section 8.3.

The risk score will be developed for the final analyses, and the method will be specified at a later time. A possible method is to derive the risk score using a proportional odds model for the primary outcome of recovery (ordinal outcome), with baseline predictors including the oxygen requirement at study entry, age, sex, and indicator variables for the following risk factors: asthma/COPD, diabetes, CVD, heart failure, hypertension, immune impairment, and renal impairment. The risk score will be derived from the pooled data for the investigational agent/placebo groups. Thus, the risk score will be specific to each investigational agent.

14 Unblinding of Treatment Comparisons

For any investigational agent, trial results will be unblinded when all participants have completed 90 days of follow-up; results may be unblinded earlier upon the recommendation of the DSMB if the sponsor and study leadership concur. In this case, trial results for the investigational agent will be unblinded and reported with available data through 90 days of follow-up. After that, data collection will continue through 180 days as outlined in the data collection plan.

While the trial is ongoing, access to any data summaries by treatment group (investigational agent or control groups) will be restricted to the members of the DSMB, the DSMB's Executive Secretary, and the unblinded statisticians.

When the trial for an investigational agent is concluded, data for the investigational agent and the corresponding pooled control group will be unblinded and provided to the study team.

15 Distribution of Reports

- Open report: ACTIV-3b leadership team; DAIDS Medical Officer; selected NIAID staff; representatives of the companies; and all recipients of the unblinded closed report. After the DSMB meeting, the open report and the DSMB summary statement will be posted to the trial's web site, open to all investigators.
- Closed report: DSMB members, Executive Secretary of the DSMB, unblinded statisticians.
- Web reports (accessible by all investigators and study staff):
    - Enrollment summaries by site and over time (updated daily)
    - Baseline characteristics
    - Selected summary measures on data quality and study conduct (pooled across treatment groups).

- Additionally, selected summary measures on study conduct will be provided to study leadership upon request (pooled across treatment groups).

16 References

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Appendix A. Categories of the Primary Outcome (Recovery)

The primary endpoint is a 6-category ordinal outcome that assesses participant recovery status at Day 90. The primary ordinal endpoint is referred to as ***recovery***.

Table A-1 Categories of the primary endpoint

Category	Status at 90 days
1 (Best)	At home and off oxygen. No. of consecutive days at Day 90 ≥ 77
2	49-76
3	1-48
4	Not hospitalized AND either at home on oxygen OR not at home
5	Hospitalized for medical care OR in hospice care
6 (Worst)	Dead

Home is defined as the level of residence or facility where the participant was residing prior to onset of COVID-19 leading to the hospital admission that led to enrollment in this protocol. Residence or facility groupings to define home are: 1) **Independent/community dwelling** with or without help, including house, apartment, undomiciled/homeless, shelter, or hotel; 2) **Residential care facility** (e.g., assisted living facility, group home, other non-medical institutional setting); 3) **Other healthcare facility** (e.g., skilled nursing facility, acute rehab facility); and 4) **Long-term acute care hospital** (hospital aimed at providing intensive, longer term acute care services, often for more than 28 days). Lower (less intensive) level of residence or facility will also be considered as home. By definition, “home” cannot be a “short-term acute care” facility. Participants previously residing in a “long-term acute care” hospital recover when they return to the same or lower level of care. Participants residing in a facility solely for public health or quarantine purposes will be considered as residing in the lowest level of required residence had these public health measures not been instated. If such patients are receiving new supplemental oxygen, they will not be classified as recovered.

The “last-off” method for assessing recovery at Day 90 will be used, i.e., in case a higher level of care is required after an initial discharge home, only days between the last time the patient entered a recovered state (returned home, free of new supplemental oxygen), and Day 90 are counted as days of recovery.

Appendix B. Definition of Clinical Organ Failure and Serious Infection

According to the protocol, section 4.1.2., *clinical organ failure* is defined by development of any one or more of the following clinical events (see PIM for criteria for what constitutes each of these conditions):

a. Worsening respiratory dysfunction
    1. Increase in the level of respiratory support from high-flow nasal cannula or non-invasive mechanical ventilation at baseline to mechanical ventilation or ECMO, or from invasive mechanical ventilation at baseline to ECMO.

b. Cardiac and vascular dysfunction:
    1. Myocardial infarction (MI)
    2. Myocarditis or pericarditis
    3. Congestive heart failure (CHF): new onset NYHA class III or IV, or worsening to class III or IV
    4. Hypotension treated with vasopressor therapy
    5. Atrial or ventricular tachyarrhythmias

c. Renal dysfunction:
    1. New requirement for renal replacement therapy

d. Hepatic dysfunction:
    1. Hepatic decompensation

e. Neurological dysfunction
    1. Acute delirium
    2. Cerebrovascular event (stroke, cerebrovascular accident [CVA])
    3. Transient ischemic events (i.e., CVA symptomatology resolving <24 hrs)
    4. Encephalitis, meningitis or myelitis

f. Haematological dysfunction:
    1. Disseminated intravascular coagulation
    2. New arterial or venous thromboembolic events, including pulmonary embolism and deep vein thrombosis
    3. Major bleeding events (>2 units of blood within 24 hours, bleeding at a critical site [intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal], or fatal bleeding).

Serious infection is defined as:

g. Serious infection:
    1. Intercurrent, at least probable, documented serious disease caused by an infection *other than* SARS-CoV-2, requiring antimicrobial administration and care within an acute-care hospital.

Appendix C. Protocol-specified Exempt Serious Events (PSESE)

Protocol-specified exempt serious events (PSESE) are defined in the TESICO protocol section 10.2.3. These events are usually of similar severity as SAEs, but are **not** reported as SAEs, **unless** the investigator considered that there was a reasonable possibility that the study intervention (blinded investigational agent/ placebo or study-supplied SOC treatment) caused the event.

- Death
- Stroke
- Meningitis
- Encephalitis
- Myelitis
- Myocardial infarction
- Myocarditis
- Pericarditis
- New onset of worsening of CHF (NYHA class 3 or 4)
- Arterial or deep vein thromboembolic events
- Renal dysfunction treated with renal replacement therapy
- Hepatic decompensation
- Neurologic dysfunction, including acute delirium and transient ischemic events
- Disseminated intravascular coagulation
- Major bleeding events
- Serious infections
- Worsening respiratory failure
- Hypotension treated with vasopressor therapy
- Atrial or ventricular arrhythmias

Comment: PSESEs include all events in the composite outcome of *organ failure or serious infections* (described in Appendix B above), plus *death*.

Appendix D. Safety Data Collection

Table D-1. Overview of Safety Data Collection (protocol version 2.0, section 10).

	During and at least 2 hrs after infusion (all days on which infusion occurs)	Day 0–7	Day 14	Day 28	Day 90
Infusion-related reactions and symptoms of any grade[a]	X				
All grade 3 and 4 clinical AEs (new or increased in severity to Grade 3/4)	X	X	X[b]	X[b]	
Protocol-specified exempt serious events (PSESEs)[c]	Collected through Day 90				
SAEs that are not PSESEs	Collected through Day 90				
Unanticipated problems	Collected through End of Subject Participation (Day 180)				
Hospital admissions and deaths	Collected through End of Subject Participation (Day 180)				
Any SAE related[d] to study intervention	Collected through End of Subject Participation (Day 180)				

[a] This includes reporting of AEs of any grade present on day 0, before the first infusion. This allows assessment of whether a given AE is new after infusion.
[b] Participants will be asked about all new relevant adverse events of Grade 3 or 4 which have occurred since the last data collection, up to that time point. On these visits, AEs of Grade 1 or 2 that are present on the day of the visit will also be collected.
[c] These are explained and defined in section 10.2.3 of the protocol, and Appendix B of this SAP.
[d] Relatedness determined as per protocol rules in protocol section 10.1.5.

Table D-2. Overview of Safety Data Collection for Remdesivir (stratum 3) (protocol version 2.0, Appendix H2, Table 1).

	Day 0–7	Day 14	Day 28	Day 90
All grade 3 and 4 clinical AEs (new or increased in severity to Grade 3/4)	X	X[a]	X[a]	
Protocol-specified exempt serious events (PSESEs)[b]	Collected through Day 90			
SAEs that are not PSESEs	Collected through Day 90			
Unanticipated problems	Collected through End of Subject Participation (Day 180)			
Hospital admissions and deaths	Collected through End of Subject Participation (Day 180)			
Any SAEs related[c] to study intervention	Collected through End of Subject Participation (Day 180)			

[a] Participants will be asked about all new relevant adverse events which have occurred since the last data collection, up to that time point. On these visits, AEs of Grade 1 or 2 that are present on the day of the visit will also be collected.

[b] PSESEs are collected on designated forms and consist of events most likely occurring due to the underlying disease. PSESEs are study endpoints and will be reviewed by the DSMB regularly, but will be "exempt" from additional collection and reporting as adverse events for safety. See section 10.2.3 of the master protocol for further details

[c] Relatedness determined as per protocol rules in section 10.

Table D-3. Hypotension AE grading (protocol version 2.0, section 10.1.4, Table 5)

AE GRADING	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 LIFE-THREATENING
SERIOUSNESS GUIDANCE*	N	N	N (usually)	Y
Hypotension criteia that apply to all assessments	No intervention or complication meeting criteria for higher grade.	IVF ≥500 mL **OR** low-dose vasopressor (e.g. <0.1 NE [or equivalent])	Moderate-dose vasopressor (e.g. ≥0.1 NE [or equivalent]) **OR** ≥2 vasopressors **OR** multiple interventions	Life-threatening or clinically significant complications **OR** *persistent* clinically significant deterioration.
Additional hypotension criteria for aviptadil/placebo infusion days	No infusion change for hypotension	Decrease infusion rate *for hypotension* **OR** pause infusion with resumption *for hypotension*	Study drug discontinued for day *for hypotension* **OR** study drug not given for day *for hypotension* **OR** study drug discontinued permanently *for hypotension*	No additional criteria

* Guidance provides suggested seriousness alignment with AE grade but does not overrule investigator judgment. In particular, the presence of critical illness influences the threshold for considering a given hypotension AE 'life-threatening' or an 'important medical event.' Evaluation of other factors, including the intensity of intervention required and the event's impact on the patient, are required to determine event seriousness.

Appendix E. Schedule of Assessments

Table E-1. Schedule of Assessments (protocol version 2.0, Appendix B)

	Screen or Day 0	**Day 0**	**Study Day**													
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**180**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+ 10**	**± 14**
ELIGIBILITY & BASELINE DATA																
Informed consent	X															
Baseline medical and social history	X															
Baseline concomitant medications	X															
Symptom-directed physical exam by the clinical team (includes vital signs)	X															
Nasal swab for virus detection and review SARS-CoV-2 test results	X															
Baseline study labs (CBC with differential, ferritin, CRP, BMP, INR, D-DIMER, AST, ALT, bilirubin)[2]	X															
Research sample storage (includes DNA and RNA at baseline among patients who consent to genetics)	X															
Urine pregnancy test or other documentation of pregnancy status	X															
STUDY INTERVENTION																
Randomization		X														
Study Drug/Placebo Administration[3]		X	X	X												
Assess infusion completion and adverse reactions[3]		X	X	X												

	Screen or Day 0	Day 0	Study Day													
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**180**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+ 10**	**± 14**
STUDY PROCEDURES																
Post-randomization concomitant medications		X	X	X	X	X	X	X	X	X[4]	X					
On-study labs (BMP, CBC with differential, INR, D-DIMER, AST, ALT, bilirubin)[2,5]		X	X	X												
Clinical labs (BMP, CBC with differential, INR, D-DIMER, AST, ALT, bilirubin)[5,6]					X[7]		X[8]									
Research sample storage (includes RNA at day 3 among patients who consent to genetics)[4]					X[7]		X[8]									
Vital signs[5]	X	X	X	X			X			X						
Hospitalization status					X		X		X	X	X	X	X	X	X	X
Changes in residence/facility										X	X	X	X	X	X	
Interim medical history									X	X	X	X	X	X	X[9]	X[9]
Oxygen support (for WHO/NIH/TICO ordinal outcome)	X	X	X	X	X	X	X	X	X	X[4]						
Clinical AEs of grade 3 and 4 severity		X	X	X	X	X	X	X	X	X	X					
Clinical AEs of any grade on day indicated										X	X					
SAEs and PSESEs		Report through 90 days														
SAEs related to study interventions		Report as they occur														
Unanticipated problems		Report as they occur														
Deaths and readmissions		Report as they occur														
Hospitalization Summary		Report upon hospital discharge														

[1] Screening must be performed within 24 hours of randomization.

[2] These laboratory evaluations will only be performed as study procedures if they are unavailable clinically on that study day

[3] Duration of study drug administration may vary by investigational agent; the sample provided here is for 3 successive days. Where the duration of study drug administration

varies from this schedule, the duration will be specified in the relevant agent-specific Appendix.

[4] The Day 14 visit will record values for Days 8–14.

[5] These will be not be collected after hospital discharge.

[6] These laboratory assessments will only include clinically available results

[7] It is acceptable to perform the Day 3 draw on Day 4.

[8] The Day-5 draw will occur only among patients who remain in the intensive care unit (ICU) or equivalent. It is acceptable to perform the Day 5 draw on Day 5±1, but the Day 3 and Day 5 draws can not both be performed on Day 4.

[9] Includes telephone administration of the Euro-QOL-5D-5L instrument.

Appendix F. List of Acronyms

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ACTT	Adaptive COVID-19 Treatment Trial
ADE	Antibody-dependent enhancement
AE	Adverse event
ARDS	Acute respiratory distress syndrome
BMP	Basic metabolic panel
CHF	Congestive heart failure
CI	Confidence interval
CIF	Cumulative incidence curve
CMH	Cochran-Mantel-Haenszel [test]
COVID-19	Coronavirus-Induced Disease 2019
CVA	Cerebrovascular accident
DSMB	Data and Safety Monitoring Board
ECMO	Extracorporeal membrane oxygenation
EU	European Union
FDA	Food and Drug Administration (US)
FiO2	Fraction of inspired oxygen
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GEE	Generalized estimating equations
GMT	Geometric mean titer
HFNC	High-flow nasal cannula oxygen
HR	Hazard ratio
ICC	International Coordinating Center
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IgG	Immunoglobulin G
IL-6	Interleukin 6
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IQR	Interquartile range
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	Intravenous
nMAb	Neutralizing monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	modified intention-to-treat
mL	Milliliter
MV	(Invasive) mechanical ventilation
NE	Norepinephrine equivalent (dose)
NEW	National Early Warning [score]
NIAID	National Institute of Allergy and Infectious Diseases, NIH (US)
NIH	National Institutes of Health (US)
NIHSS	National Institutes of Health Stroke Scale/Score
NIV	Non-invasive ventilation
NYHA	New York Heart Association

nMAb	Neutralizing Monoclonal Antibodies
OR	Odds ratio
PCR	Polymerase chain reaction
PIM	Protocol Instruction Manual
PT	Preferred term
PSESE	Protocol-specified exempt serious event
RNA	Ribonucleic acid
RR	Rate ratio
RRR	Recovery rate ratio
SAE	Serious adverse event
SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAP	Statistical analysis plan
SOC	Standard of care
SpO2	Oxygen saturation by pulse oxymeter
SUSAR	Suspected unexpected serious adverse reaction
UMN	University of Minnesota
UP	Unanticipated problem
U.S.	United States of America
VIP	Vasoactive Intestinal Peptide
WHO	World Health Organization

Addendum to the Statistical Analysis Plan for the ACTIVE 3b/TESICO Trial
May 1, 2022

According to the TESICO protocol, no interim monitoring for futility was planned. When the trial was designed, futility assessments were not planned because completing the trial, in the absence of safety concerns, could provide valuable information for future investigations, rapid enrollment was anticipated, and the primary endpoint requires 90 days of follow-up to classify patients into the appropriate category of the ordinal outcome. Randomized patients who have not completed 90 days of follow-up would not contribute to an interim assessment of futility with respect to the primary outcome. Two paragraphs from section 11.3.1 of the protocol are cited below:

> "First, in many cases, potential agents may be relevant not only to COVID-19-associated ARDS but to other forms of ARDS. As such, even if an agent did not achieve its efficacy endpoint, enrollment to the planned sample size is expected to provide important insights relevant to future investigations in ARDS. These insights may especially pertain to potential effects among subgroups of patients or less common safety events of interest.
>
> Second, the primary endpoint of this trial requires 90 days of follow-up since the final classification of a patient's recovery requires knowledge of their status on Day 90. While this duration of follow-up for the primary endpoint is essential for a patient-centered result at the conclusion of the trial, in the context of the anticipated rapid enrolment of the trial, this endpoint is infeasible to use for stopping boundaries for either efficacy or futility on the basis of conditional power."

As a consequence of the enrollment decline since January 2022, most randomized patients have now completed 90 days of follow-up. For example, as of April 24, 2022, 466 of the planned 640 patients (73%) have been enrolled to the aviptadil/placebo group and 457 (98%) of those patients will have a day-90 anniversary by May 25, the date of the next Data and Safety Monitoring Board (DSMB) review.

It is costly to maintain the infrastructure of the TESICO trial. For example, the team continues to work with NRx on new manufacturing supply chains for drugs, continues to ship aviptadil to study sites when current supplies reach their expiry date, and continues to maintain staff at our international coordinating centers.

Therefore, we considered it important to develop a plan for assessing futility for the TESICO trial.

The purpose of this addendum to the Statistical Analysis Plan (SAP) is to document the results of the sample size re-estimation which was carried out in March 2022 using blinded (pooled outcome data for the aviptadil and placebo groups combined), and to describe our plan for futility assessments that will be carried out for future meetings of

the DSMB.

Sample Size Re-estimation for TESICO

Marginal (both treatment groups combined) category proportions for the Day 90 primary ordinal outcome were provided on March 22, 2022 by the unblinded TESICO statisticians to the blinded leadership of TESICO for the initial 352 patients enrolled and followed to day 90. These proportions are given in the 2nd column of the table below. The 3rd column gives the marginal proportions that had been assumed in the design for estimating sample size.

Category Status at Day 90	Observed pooled category proportions (n=352)	Hypothesized pooled category proportions; OR=1.5; alpha = 0.05 (2-sided); power=0.80; and total n=602; increased to 640 to allow for some missing data and patients who withdraw before their infusion
1 (home off oxygen ≥ 77 consecutive days)	.196	.145
2 (home off oxygen 49-76 consecutive days)	.168	.254
3 (home off oxygen 1-48 consecutive days)	.134	.171
4 (not hospitalized, at home on oxygen or not at home)	.106	.096
5 (hospitalized for medical care or in hospice care	.056	.047
6 (dead)	.341	.289
	1.00	1.00

The formula for total sample size (n) assuming 1:1 allocation of treatments based on Whitehead (Stat Med 1993) is given below. The sum of the cubed marginal proportions (the p_i's and numbers in the table) for the 6 categories is in the denominator of the formula. Other parameters were fixed as stated at the top of the 3rd column above. Using this formula, solving for Z_β, power was re-estimated.

$$n= 12 (Z_{\alpha/2} + Z_\beta)^2 / \ln(OR)^2 [1- \Sigma p_i^3]$$

Using the observed marginal proportions, power is slightly less than 0.80 for n=602. The sample size for 0.80 power is 608 with the category percentages in the 2nd column.

In the report for the February 2022 meeting of the DSMB, the percentage of patients with unknown recovery status at day 90 was 9.4%. This is somewhat higher than planned.

The observed percentage of deaths at day 90 in the table above is 5% higher than the pooled estimate used for sample size. This is likely due to enrolling more patients on non-invasive or mechanical ventilation or ECMO than anticipated. We assumed 80% of patients would enter on a high flow nasal cannula (HFNC), 5% on non-invasive ventilation (NIV), and 15% on mechanical ventilation or ECMO (VENT). Mortality for these 3 groups in the control group was assumed to be 30%, 40% and 45%, respectively.

Among the 352 patients who completed day 90, 195 (55%) are on HFNC at entry. At the time of the February DSMB meeting, the percentages on HFNC, NIV, and VENT at study entry were 53%, 6% and 41%, respectively. Using the original mortality estimates, the 90-day mortality estimate for the control group assuming these percentages persist is 36.8%. Assuming an OR of 1.5, the resulting aviptadil mortality would be 28.0%. The pooled estimate using these percentages assumed for the aviptadil (28.0%) and placebo (36.8%) groups is 32.4%, close to the observed pooled rate of 34.1%.

Recommendation: No change in sample size is required if missing data at day 90 can be reduced to 5%. The goal should remain 640 participants.

Futility Assessment Plan for TESICO

As a guideline, we propose futility be assessed at the May 25, 2022 DSMB meeting using conditional power estimates for the primary 6-category ordinal outcome. We also propose that the recommendation by the DSMB on futility consider the time required to complete enrollment in the trial in addition to conditional power. For example, if enrollment can be completed in 3 months, then conditional power > 0.10 might be acceptable for continuing the trial; if the completion of enrollment requires another 12 months, then conditional power of > 0.50 might be more appropriate.

For the May 25 review we assume the following:

- Outcome data will be available for 70% of the 640 planned patients.
- By the time of the meeting, the number enrolled to the aviptadil/placebo group will increase by 6 patients to 472. This leaves an additional 168 patients to enroll.
- Enrollment will be completed in 7 months by December 31, 2022 (an average of 24 patients per month from June through December). This assumption is based on steady enrollment of 15 new sites in Brazil which will begin enrollment in July or August, enrollment in Europe which may begin in September, and an increase

in enrollment in the U.S. The rate required to complete enrollment by the end of 2022 is similar to that for the month of February 2022 when it was 22.

We propose that conditional power be estimated based on assuming the following for the 30% of patients (largely not enrolled) without day 90 information (future data):

- Assume an odds ratio (OR) of 1.5 as in the design for future data.
- Assume the OR observed for the future data.

<u>As a guideline</u>, it is recommended that conditional power be at least 0.20 based on either of the 2 assumptions to continue the trial.

It is also recommended that the DSMB consider other information in making their recommendation. For example, the following results should be considered:

- The magnitude of the OR required for the remaining 30% of patients in order to obtain a significant result.
- The observed mortality differences between treatment groups (mortality is an important secondary endpoint).
- Subgroup findings for the primary endpoint for the two disease strata by oxygen requirement at baseline (high flow nasal cannula and non-invasive ventilation versus mechanical ventilation and ECMO).
- The primary safety outcome at day 28.
- A repeat of the aforementioned analyses excluding participants who were not infused (currently 9 patients) in the event a modified intention to treat (mITT) analysis is carried out instead of an ITT analysis.

If the review on May 25 leads to a recommendation to continue the trial as planned, we would like the DSMB to reassess futility using conditional power in August 2022, irrespective of how much additional data (completed day 90 visits) are available. If the rate of enrollment has not increased substantially by August and it is unlikely that enrollment will be completed by December 31, 2022, we recommend using conditional power > 0.5 as the criteria for continuing the trial. Conditional power estimates will be estimated in the same way and similar supporting analyses will be provided for the August DSMB review.

The results of the sample size re-estimation and the plan for futility assessments were shared with the DSMB on April 28, 2022, and they responded on April 29, 2022 that they agreed with “staying with the current sample size of 640” and “with the guidelines for futility as spelled out”. They also stated the following: “The Board affirms the study teams’ recognition that what is suggested are guideline for the Board to use rather than rules.”