Supplementary Material*

ACTIV-3/TICO Study Group. Efficacy and safety of ensovibep for adults hospitalized with COVID-19. A randomized controlled trial. Ann Intern Med. 2022. [Epub ahead of print]. doi:10.7326/M22-1503

Contents

* This supplementary material was provided by the authors to give readers further details on their article. The material was not copyedited.

Section 1: TICO Study Group

MP Supplemental Appendix: TICO 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., David Sahner, M.D., John Tierney, B.Sc.N., Susan E. Vogel, R.N., B.Sc.N., Betsey R. Herpin, M.Sc.N., C.C.R.C., R.N., Mary C. Smolskis, B.Sc.N., M.A., 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., Lisa Hensley, Ph.D., Joshua Lorenzo, M.P.H., Rebecca Mock Ph.D., R.A.C., Katy Shaw-Saliba Sc.M., Ph.D., Judith Zuckerman, B.S.N., 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.

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.

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, Greg Grandits, M.S., Birgit Grund, Ph.D., Merrie Harrison, Payton Kaiser, Joseph Koopmeiners, Ph.D., Sue Meger, Shweta Sharma Mistry, M.S., Thomas Murray, Ph.D., Kien Quan, M.S., Siu Fun Quan, Cavan Reilly, Ph.D., Lianne Siegel, Ph.D., Greg Thompson, David Vock, Ph.D., Jamie Walski, M.H.A., Deborah Wentworth, M.P.H.

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.

Baylor, Scott and White Health (16 participants enrolled): Uriel Sandkovsky, M.D., M.S., Robert L. Gottlieb, M.D., Ph.D., Michael Mack, M.D., Mezgebe Berhe, M.D., M.P.H., Clinton Haley, M.D., M.P.H., Emma Dishner, M.D., M.P.H., Christopher Bettacchi, M.D., Kevin Golden, M.D., Erin Duhaime, P.A.-C. Madison Ryan, Sarah Burris M.H.A., Catherine Tallmadge, B.A., C.M.A., Lorie Estrada, C.C.R.C., Felecia Jones, Samantha Villa, Samantha Wang, Raven Robert, Tanquinisha Coleman, Laura Clariday, Rebecca Baker, Mariana Hurutado-Rodriguez, Nazia Iram, Michelle Fresnedo, Allyson Davis, Kiara Leonard, Noelia Ramierez, Jon Thammavong, B.S., Krizia Duque, Emma Turner, Tammy Fisher, M.B.A, M.S.N, R.N, C.C.R.C., Dianna Robinson, Desirae Ransom, Nicholas Maldonado, BA, ACRP-CP, Erica Lusk, Aaron Killian, Pharm.D., Adriana Palacious, PharmD, Edilia Solis, Janet Jerrow, Matthew Watts, Heather Whitacre, Elizabeth Cothran.
Duke University Health System (58 participants enrolled): Peter K. Smith, M.D., Christina E. Barkauskas, M.D., Andrew M. Vekstein, M.D., Emily R. Ko, M.D., PhD., Grace R. Dreyer, PA-C, Neil Stafford, M.D., Megan Brooks, M.D., Tatyana Der, M.D., Marie Witte, M.D., Ruwan Gamarallage, M.D., John Franzone, M.D., Noel Ivey, M.D., Rebecca H. Lumsden, M.D., Nilima Mosaly, M.D., Ahmad Mourad, M.D., Thomas L. Holland, M.D., Mary Motta, B.Sc.N., R.N, Kathleen Lane, B.Sc.N., R.N., Lauren M. McGowan, B.Sc., E.M.T.B., Jennifer Stout, B.Sc., Heather Aloor, MPH,MS, Kennesha M. Bragg, MS, Barvina Toledo, MA, Beth McLendon-Arvik, Pharm.D., Barbara Bussadori, RPh, Beth A. Hollister, B.Sc.N., R.N., Michelle Griffin, MPH,EMTP, Dana M. Giangiacomo.

Lutheran Medical Group (2 participants enrolled): Vicente Rodriguez, M.D.

Ochsner Clinic (4 participants enrolled): Patrick E. Parrino, M.D., F.A.C.S., Stephen Spindel, M.D., Aditya Bansal, M.D., Katherine Baumgarten, M.D., F.A.C.P., F.I.D.S.A., Jonathan Hand, M.D., Derek Vonderhaar, M.D., Bobby Nossaman, M.D., Sylvia Laudun, D.N.P., M.B.A., R.N., C.P.H.Q., DeAnna Ames, M.S., Shane Broussard, Nilmo Hernandez, Geralyn Isaac, Pharm.D., Huan Dinh, Pharm.D., Yiling Zheng, Pharm.D., Sonny Tran, Pharm.D., Hunter McDaniel, Nicolle Crovetto, M.S.

Texas Heart Institute (2 participants enrolled): Emerson Perin, M.D., Ph. D., Briana Costello, M.D., Prasad Manian, M.D., M. Rizwan Sohail, M.D., Alexander Postalian, M.D., Punit Hinsu, Pharm.D., Carolyn Watson, James Chen, Melyssa Fink, Lydia Sturgis, Kim Walker, Kim Mahon, Jennifer Parenti, Casey Kappenman, Aryn Knight

University of Virginia Health Systems (4 participants enrolled): Jeffrey M. Sturek, M.D., Ph.D., Andrew Barros, M.D., M.S., Kyle B. Enfield, M.D., F.C.C.M., F.S.H.E.A., Alexandra Kadl, M.D., China J. Green, B.S., C.C.R.C., Rachel M. Simon, R.N., B.S.N., C.C.R.C., Ashley Fox, B.S., Kara Thornton, Pharm.D., M.Ed., C.C.R.P., Amy Adams, Pharm.D., C.C.R.P.
Minneapolis Heart Institute Foundation (1 participant enrolled): Jay H. Traverse, M.D., Frank Rhame, M.D., Joshua Huelster, M.D., Rajesh Kethireddy, M.D., Julianne Salamanca, Christine Majeski, Paige Skelton, Pharm.D., Maria Zarambo, Pharm.D., B.C.O.P., Andrea Sarafolean

Prevention and Early Treatment of Acute Lung Injury (PETAL) ICC, Massachusetts General Hospital, Boston, Massachusetts, USA: B. Taylor Thompson M.D., Crystal North M.D., Cathryn Oldmixon R.N., Nancy Ringwood 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., Neil R. Aggarwal, M.D., Karen Bienstock, PA-C, M.S.

ALIGNE Site Coordinating Center (SCC) Lead Investigators
Baystate Medical Center: Jay Steingrub, M.D.
Brigham and Women's Hospital: Peter Hou, M.D.

Baystate Medical Center (1 participant enrolled): 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, Sarah Romain, RN BSN

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

Beth Israel Deaconess Medical Center 4 participants enrolled): Konstantinos Andromidas, Valerie Banner-Goodspeed, M.P.H., Michael Bolstad, Katherine L. Boyle, M.D., Payton Cabrera, Arnaldo deVilla, R.N. M.P.H, Joshua C. Ellis, M.D., Ana Grafals, Sharon Hayes R.N., Conor Higgins, Lisa Kurt, Nicholas Kurtzman, M.D., Kimberly Redman, R.N B.S.N., Elinita Rosseto, Douglas Scaffidi, Nathan Shapiro, M.D. M.P.H., Daniel Talmor M.D., M.P.H.

Massachusetts General Hospital: Michael R. Filbin, M.D., M.Sc., Kathryn A. Hibbert, M.D., Blair Parry, C.C.R.C, B.A., Justin Margolin, B.S., Brooklynn Hillis, B.S.N, R.N., Rhonda Hamer
University of Mississippi: Alan E. Jones, M.D., James Galbraith, M.D., Utsav Nandi M.D.

California 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 (7 participants enrolled), University of San Francisco Mount Zion (1 participant enrolled): Michael A. Matthay M.D., Kirsten Kangelaris, M.D., M.A.S., Kimia Ashktorab, B.A., Rachel Gropper, B.S., Anika Agrawal, B.S.
University of California Fresno (12 participants enrolled): Eyad Almasri, M.D., Mohamed Fayed, M.D., Kinsley A. Hubel, M.D., Alyssa R. Hughes, B.S., Rebekah L. Garcia, C.C.R.P.

Ronald Reagan UCLA Medical Center (5 participants enrolled): George W. Lim, M.D., Steven Y. Chang, M.D., Gregory Hendey, M.D., Michael Y. Lin, M.D., Julia Vargas, B.S., Hena Sihota, B.S., Rebecca Beutler, M.S.

Stanford University: Angela J. Rogers, M.D., Jennifer G. Wilson, M.D., M.S., Rosemary Vojnik, B.S., Cynthia Perez, B.S., Jordan H. McDowell, M.S.
University of California Davis Health: Timothy Albertson, M.D., Erin Hardy, B.A./B.S., Richart Harper, M.D.
Colorado SCC Lead Investigators
University of Colorado Hospital: Adit A. Ginde, M.D., M.P.H, Marc Moss, M.D.

University of Colorado Hospital (7 participants enrolled): Adit A. Ginde, M.D., M.P.H., Amiran Baduashvili, M.D., Lakshmi Chauhan, M.D., David J. Douin, M.D., Flora Martinez, R.N., Lani L. Finck, M.P.H., Jill Bastman, R.N.

Michigan SCC Lead Investigators
University of Michigan: Robert C. Hyzy, M.D., Pauline K. Park, M.D.

University of Michigan (2 participants enrolled): Robert C. Hyzy, M.D., Pauline K. Park, M.D., Kristine Nelson, R.N., Jake I. McSparron, M.D., Ivan N. Co, M.D., Bonnie R. Wang, M.D., Jose Victor Jimenez, M.D., Barbara Sullins, Norman Olbrich.

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

Montefiore Medical Center Moses: Michelle N. Gong, M.D., M.S, Rahul Nair, M.D., Brenda Lopez, M.D., Omowunmi Amosu, M.S., Hiwet Tzehaie, B.S., William Nkemdirim, M.D., Sabah Boujid, B.S.
Banner University Medical Center Tucson (3 participants enrolled):Jarrod M. Mosier, M.D., Cameron Hypes, M.D., Elizabeth Salvagio Campbell, Ph.D., Billie Bixby, M.D., Boris Gilson, B.A./B.S., Anitza Lopez, B.S.

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

University of Cincinnati (3 participants enrolled): Kristin Hudock, M.D., Hammad Tanzeem, M.D., Harshada More, M.D., Jamie Martinkovic, C.N.P., Susan Sellers RN, BSN, CCRP, Judy Houston, PharmD, Mary Burns, PharmD.

Pacific Northwest 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 (3 participants enrolled): Catherine L. Hough, M.D., Akram Khan, M.D., Olivia F. Krol, Emmanuel Mills, M.D., Mistry Kinjal, Genesis Briceno, Raju Reddy, M.D., Kinsley Hubel M.D.

Cedars-Sinai Medical Center (15 participants enrolled): Peter Chen, M.D., Sam S. Torbati, M.D., Tanyalak Parimon, M.D., Antonina Caudill, M.P.H., C.P.H., Brittany Mattison, Susan E. Jackman, B.S.N., M.S., Po-En Chen, B.S.N., Emad Bayoumi, M.D., Cristabelle Ojukwu, B.S., Devin Fine, B.S., Gwendolyn Weissberg, B.S., Katherine Isip, B.S., Yunhee Choi-Kuaea, M.S.W., Shaunt Mehdikhani M.S., Tahir B. Dar, Ph.D., Fleury Augustin Nsole Biteghe, Ph.D., Dana Tran, B.S., Jennifer Emilow Dukov, B.S.

Swedish Hospital First Hill (4 participants enrolled): D. Shane O'Mahony, M.D., David M. Wilson, M.D., Julie A. Wallick, B.A./B.S., Alexandria M. Duven, R.N., Dakota D. Fletcher, B.S.
Southeast SCC Lead Investigators
Wake Forest Baptist Health: D. Clark Files, M.D., Chadwick Miller, M.D.

Wake Forest Baptist Health (5 participants enrolled): D. Clark Files, M.D., Kevin W. Gibbs, M.D., Lori S. Flores, D.N.P., Mary E. LaRose, R.N., B.S.N, Leigha D. Landreth R.N., B.S.N., D. Rafael Palacios, BSCR, Lisa Parks, R.N., and Madeline Hicks, BA.

Medical Center of South Carolina (1 participant enrolled): Andrew J. Goodwin, M.D., Edward F. Kilb, M.D., Caitlan T. Lematty, B.S., Kerilyn Patti
Utah SCC Lead Investigators
Intermountain Medical Center*:* Samuel Brown, M.D., Joseph Bledsoe, M.D.

Intermountain Medical Center (18 participants enrolled)*:* Kirk U. Knowlton, M.D., Samuel Brown, M.D., Michael Lanspa, M.D., Lindsey Leither, M.D., Ithan Pelton, M.D., Brent P. Armbruster, B.S., Quinn Montgomery, B.S., AEMT, Naresh Kumar, M.P.H., C.C.R.P., Melissa Fergus, B.S., Karah Imel, A. S., C.C.R.P., Ghazal Palmer, Pharm.D., Brandon Webb, M.D., Carolyn Klippel B.S., Hannah Jensen B.S., Sarah Duckworth, Andrew Gray B.S., Tyler Burke B.S., Dan Knox M.D., Jenna Lumpkin, B.S., Valerie T. Aston, M.B.A., R.R.T., C.C.R.P.

Vanderbilt 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 (2 participants enrolled): 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, Margaret Hays, R.N.

Division of Clinical Research, NIAID, NIH ICC:

Lincoln Medical Center (7 participants enrolled): Vidya Menon, MD, FACP., Moiz Kasubhai, MD., Anjana Pillai, MD., Jean Daniel, MD, MACP., Daniel Sittler, MD., Balavenkatesh Kanna, MD, MPH, FACP., Nargis Jilani, MD., Francisco Amaro, RN, FNP-BC., Jessica Santana, BA., Aleksandr Lyakovestsky, PharmD, BCPS., Issa Madhoun, PharmD., Louis Marie Desroches, RPH., Nicole Amadon, PharmD, BCGP., Alaa Bahr, PharmD, BCPS., Imaan Ezzat, PharmD., Maryanne Guerrero, BHSA, MA., Joane Padilla, Jessie Fullmer, Inderpreet Singh, Syed Hamad Ali Shah

CHRISTUS Spohn Shoreline Hospital (5 participants enrolled): Srikanth Ramachandruni, M.D., Rajeev Narang, M.D., Polly Mock, R.N, CCRC, CHRC, Melissa Shadle, R.N, B.S.N., OCN, CCRC, Brenda Hernandez, R.N., Kevin Welch, PharmD, Andrea Payne, PharmD, Gabriela Ertl, PharmD

Hendrick Medical Center (4 participants enrolled): Daniel Canario, M.D., Isabel Barrientos, MSN, APRN, Danielle Goss, MPH, MHA, Mattie DeVries, RPh, PharmD, Ibidolapo Folowosele, RPh.

Carilion Roanoke Memorial Hospital (2 participants enrolled): Dorothy Garner, M.D., Mariana Gomez, M.D., Justin Price, M.D., Ekta Bansal, M.D., Jim Wong, M.D., Jason Faulhaber, M.D., Tasaduq Fazili, M.D., Brian Yeary, M.D., Ruth Ndolo, R.N., Christina Bryant, R.N., Bridgette Smigeil, PharmD

Hoag Memorial Hospital Presbyterian (6 participants enrolled): Philip Robinson, M.D., Rana Najjar, MSHCA CRC, Patrice Jones, CRC, Julie Nguyen, RRT, CRC, Christina Chin, PharmD

Cotton O'Neil Clinical Research Center (4 participants enrolled): Hassan Taha, MD., Salah Najm, MD, MBA., Christopher Smith, PharmD., Jason Moore, PharmD., Talal Nassar, PharmD., Nick Gallinger, PharmD, Amy Christian, RN, CCRC, D'Amber Mauer, RN, BSN, Ashley Phipps, RN, BSN

Velocity Chula Vista (14 participants enrolled): Michael Waters, MD., Karla Zepeda, NP., Jordan Coslet, PA., Rosalynn Landazuri, BS., CRC., Jacob Pineda, CRC., Nicole Uribe, RPh., Jose Ruiz Garcia, CPhT., Cecilia Barbabosa, RN., Kaitlyn Sandler, BSN.

Velocity San Diego (16 participants enrolled): J. Scott Overcash, MD, Adrienna Marquez, Hanh Chu, MSN, NP-C, Kia Lee, MSN, ANP-BC, Kimberly Quillin, BSN, RN, Andrea Garcia MSN, RN, Pauline Lew, PharmD

Rhode Island Hospital (11 participants enrolled): Eleftherios Mylonakis MD, PhD, FIDSA, Ralph Rogers, M.D., Fadi Shehadeh, MSc, Evangelia K. Mylona, MSc, Matthew Kaczynski, BSc, Quynh-Lam Tran, BSc, Gregorio Benitez, MPH, Biswajit Mishra, PhD, Lewis Oscar Felix, PhD, Maria Tsikala Vafea, MD, Eleftheria Atalla, MD, Robin Davies, BSN, BA, RN, Salma Hedili, CPT, Maria Adnrea Monkeberg, MS, RPh, BCOP, Sandra Tabler, RPh, BCOP

The Miriam Hospital (23 participants enrolled): Eleftherios Mylonakis MD, PhD, FIDSA, Ralph Rogers, M.D., Fadi Shehadeh, MSc, Evangelia K. Mylona, MSc, Matthew Kaczynski, BSc, Quynh-Lam Tran, BSc, Gregorio Benitez, MPH, Biswajit Mishra, PhD, Lewis Oscar Felix, PhD, Maria Tsikala Vafea, MD, Eleftheria Atalla, MD, Robin Davies, BSN, BA, RN, Salma Hedili, CPT, Britt Harrington, PharmD.

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., Kimberley Viens, BS, CCRP, Melissa Turner, M.S.W., Michael J. Vjecha, M.D., Amy Weintrob, M.D.

Parkland Health and Hospital Systems (14 participants enrolled):
Mamta K. Jain, M.D., M.P.H., Rubria Marines-Price PhD, DNP, APRN, Alice Osuji, RN, BSN, MSN, Barbine Tchamba Agbor Agbor M.D., Tianna Petersen, M.Sc., MSN, Dena Kamel, B.S., Laura Hansen, M.A., Angie Garcia, MD, Christine Cha, Pharm.D., Azadeh Mozaffari, Pharm.D., Rosa Hernandez, Pharm.D., M.B.A.

University of Texas Southwestern Medical Center, Dallas TX (8 participants enrolled): Mamta K. Jain, M.D., M.P.H., Barbine Tchamba Agbor Agbor M.D., Alice Osuji, RN, BSN, MSN, Tianna Petersen, M.Sc., Dena Kamel, B.S., Laura Hansen, M.A., Angie Garcia, MD, Mina Kim, Pharm. D, Natalie DellaValle, Pharm.D., B.C.P.S., Sonia Gonzales, Pharm.D, B.C.O.P.

University of South Florida, Tampa General Hospital (7 participants enrolled): Kami Kim, M.D., Charurut Somboonwit, M.D.; Asa Oxner, M.D.; Lucy Guerra, M.D., Thanh Tran, M.P.H., Avenette Pinto

Lundquist Institute for Biomedical Innovation (5 participants enrolled): Timothy Hatlen, MD, Betty Anderson, B.S., Ana Zepeda-Gutierrez, B.S., Dannae Martin, B.A., Cindi Temblador, Avon Cuenca, B.A., Mario Guerrero, M.D., Eric Daar, M.D., Ramiro Correa, Gabe Hartnell

Medstar Health Research Institute (4 participants enrolled): Glenn Wortmann, M.D., Saumil Doshi, M.D., Theresa Moriarty, M.S.N.R.N., Melissa Gonzales, CRC III, Kristin Garman, C.R.N.

Hennepin Healthcare Research Institute, Minneapolis, MN (3 participants enrolled): Jason V. Baker, M.D., Anne Frosch, M.D., Rachael Goldsmith, B.Sc., Hodan Jibrell, B.Sc., Melanie Lo, M.D., Jonathan Klaphake, B.Sc., Shari Mackedanz, R.N., Linh Ngo, M.D., Kelly Garcia-Myers, B.Sc.

Minneapolis VA Medical Center (2 participants enrolled): Ken M. Kunisaki, M.D., M.S., Miranda Hassler, B.A., Mary Walquist, B.S.

SUNY Downstate Medical Center (2 participants enrolled): Michael Augenbraun, M.D., Jack Dehovitz, M.D.

University of Minnesota (2 participants enrolled):Mahsa Abassi D.O., Anne-Marie Leuck, MD, Via Rao, M.S.

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.

Michael E. DeBakey VA Medical Center, Houston, TX (8 participants enrolled): Barbara Trautner, M.D., Ph.D., Lavannya Pandit, M.D., M.S., Casey Hines-Munson, B.S., John Van, B.A., Laura Dillon, M.Sc., Yiqun Wang, M.A.

Salem VA Medical Center, Salem VA (3 participants enrolled): Stephanie Nagy-Agren, M.D., Shikha Vasudeva, M.D., Tracy Ochalek, B.S.N., Erin Caldwell, D.O., Edward Humerickhouse, M.D., David Boone, D.O., William McGraw, Pharm.D.

VA San Diego Healthcare System (1 participant enrolled): David J. Looney, M.D., Sanjay R. Mehta, M.D., Scott Thompson Johns, Pharm.D., Melissa St. John, Jacqueline Raceles, CCRC, Emily Sear, BSN, RN, Stephen Funk, Pharm.D., Rosa Cesarini, Michelle Fang, Pharm.D., Keith Nicalo, RN

VA TVHS Nashville Campus (5 participants enrolled): Wonder Drake, M.D.; Beatrice Jones, MSN, RN.; Teresa Holtman, D.Ph.

Sacramento VA Medical Center (1 participant enrolled): Hien H. Nguyen, M.D., Archana Maniar, M.D., Eric A. Johnson, M.D., Lam Nguyen, B.A., Michelle T. Tran, B.S.
Portland VA Health Care System (1 participant enrolled): Thomas W. Barrett, M.D., M.C.R., Tera Johnston, B.S.
Charleston VA Medical Center: Dr. John T. Huggins, M.D., Tatsiana Y. Beiko, M.D., Heather Y. Hughes, M.D., William C. McManigle, M.D., Nichole T. Tanner, M.D., Ronald G. Washburn, M.D., Magdalena Ardelt, ALM, Patricia A. Tuohy, B.S., Jennifer L. Mixson, RPh., Charles G. Hinton, Pharm.D., Nicola Thornley, M.P.H., Heather Allen, RN, Shannon Elam, RN, Barry Boatman RN, OCN, Brittany J. Baber, Rudell Ryant, M.B.A
Southern Arizona VA Health Care System: Brentin Roller, D.O., Chinh Nguyen, M.D., Amani Morgan Mikail, MSCRM, Marivic Hansen, Research RN
Miami Bruce Carter VA Health Care System: Paola Lichtenberger, M.D., Gio Baracco, M.D., Carol Ramos, M.D., Lauren Bjork, Pharm.D., Melyssa Sueiro, M.Sc.
San Francisco VA Health Care System: Phyllis Tien, M.D., Heather Freasier, M.Sc., R.D.

Bay Pines VA Healthcare System: Theresa Buck, M.D., Hafida Nekach, M.D.

Veterans Affairs Palo Alto Health Care System: Mark Holodniy, M.D., FACP, FIDSA; Aarthi Chary, M.D.; Kan Lu, PharmD.; Theresa Peters, RN, MS, CCRC.; Jessica Lopez, CCRC
VA Long Beach Healthcare System: Susanna Yu Tan, M.D., Robert H. Lee, M.D., Aliya Asghar, M.P.H, Tasadduq Karim, Karyn Isip, B.A., Katherine Le, Pharm D., Thao Nguyen, Pharm D., Shinn Wong, Pharm. D
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., Tomas O. Jensen, M.D., Bitten Aagaard, B.Sc.N., Charlotte B. Nielsen, Katharina Krapp, Ph.D., Bente Rosdahl Nykjær, Christina Olsson, Katja Lisa Kanne, M.Sc. B.Sc.N., Anne Louise Grevsen, M.Sc. Dent., Zillah Maria Joensen, B.Sc.N., Tina Bruun, B.Sc.N. Ane Bojesen, Frederik Woldbye, Nick E. Normand, B.Sc,

Denmark
Copenhagen University Hospital - Amager and Hvidovre, Center of Research & Disruption of Infectious Diseases, Department of Infectious Diseases (1 participant enrolled): Thomas Benfield, M.D, DMSc; Clara Lundetoft Clausen, M.D., Nichlas Hovmand, M.D., Simone Bastrup Israelsen, M.D., Katrine Iversen, M.D.; Cæcilie Leding, M.D., Karen Brorup Pedersen, M.D., Louise Thorlacius-Ussing, M.D., Michaela Tinggaard, M.D., Sandra Tingsgård, M.D.

Herlev-Gentofte Hospital, Respiratory Medicine Section, Department of Internal Medicine(1 participants enrolled): Jens-Ulrik Stæhr Jensen, M.D., Ph.D., Rikke Overgaard, R.N., Ema Rastoder, M.D., Christian Heerfordt, M.D., Caroline Hedsund, M.D., Christian Phillip Rønn, M.D., Peter Thobias Kamstrup, M.D., Dorthe Sandbæk Høgsberg, R.N., Christina Bergsøe, B. Sc.

Aarhus Universitetshospital, Skejby, Aarhus (1 participant enrolled): Lars Østergaard, M.D., Ph.D. D.M.Sc., Nina Breinholt Stærke, M.D., Yordanos Yehdego R.N., Ane Søndergaard R.N.

Odense University Hospital, Department of Infectious Diseases: Isik S. Johansen, M.D., DMSc.,
Inge K Holden, M.D., PhD., Susan O Lindvig, M.Sc.

Dept. of Infectious Diseases, Rigshospitalet, Copenhagen University Hospital: Marie Helleberg, M.D. Ph.D., D.M.Sc., Jan Gerstoft, M.D., D.M.Sc., Ole Kirk M.D. D.M.Sc., Tina Bruun R.N. MSc PH.

North Zealand University Hospital, Department of Pulmonary and Infectious Diseases (1 participant enrolled):
Tomas Østergaard Jensen, M.D., Birgitte Lindegaard Madsen, MD, Thomas Ingemann Pedersen, MD, Zitta Barrella Harboe MD.

Kolding Hospital, Department of Medicine:Birgit Thorup Røge, M.D., Ph.D., Thomas Michael Hansen M.D., Matilde Kanstrup Glesner M.D., Sandra Valborg Løfberg MD, Ariella Denize Nielsen MD

Aalborg University Hospital, Department of Infectious Diseases (2 participants enrolled): Henrik Nielsen, M.D., D.M.Sci., Rikke Krog Thisted, R.N., Kristine Toft Petersen, R.N., Maria Ruwald Juhl, R.N:

Department of Respiratory Medicine, Bispebjerg Hospital, Copenhagen, Denmark:
Daria Podlekareva, M.D., Ph.D, Stine Johnsen, MD, PhD

Department of Infectious Diseases, Zealand University Hospital Roskilde and Department of Internal Medicine, Zealand University Hospital Køge: Lothar Wiese, M.D., Ph.D., Lene Surland Knudsen, M.D., Ph.D.
Spain
INSIGHT SCC Spain, Hospital Universitari Germans Trias i Pujol, Badalona: Roger Paredes, M.D., Ph.D., Maria Expósito, B.Sc.; José Badillo, B.Sc.; Ana Martínez, B.Sc.; Elena Abad B.Sc.; Ana Chamorro, B.Sc.

Hospital Universitari Germans Trias i Pujol, Badalona (2 participants enrolled):
Lourdes Mateu, M.D., Ph.D.; Sergio España M.D.; Maria Constanza Lucero, MD., PhD; José Ramón Santos, M.D., Ph.D.; Gemma Lladós, M.D.; Cristina Lopez, M.D., Ph.D.; Lydia Carabias, M.D.

Hospital General Universitario Gregorio Marañón, Madrid: Eduardo Fernández-Cruz, M.D., Ph.D. Marisa Di Natale, MD. Sergiu Padure, Jimena Gomez MD MD. Cristina Ausin MD. Eva Cervilla MD. Héctor Balastegui MD. Carmen Rodríguez Sainz, PhD. Paco Lopez MD. Mariam Escobar R.N.

Barcelona Institute for Global Health (ISGlobal), Hospital Clínic - Universitat de Barcelona, Barcelona: Leire Balerdi MD,

Almudena Legarda, Montserrat Roldan, Laura Letona MD, José Muñoz, M.D., Ph.D.

Hospital Universitario La Paz, IdiPAZ, Madrid: Jose R Arribas, M.D., Rocio Montejano Sánchez, M.D., Ph.D., Beatriz Díaz-Pollán, M.D., Ph.D., Stefan Mark Stewart, M.D., Irene Garcia, M.D., Alberto Borobia, M.D., Ph.D.

Hospital Clínico San Carlos, Madrid: Vicente Estrada, M.D., Ph.D. Noemi Cabello, MD, Nuñez-Orantos MJ, MD; Sagastagoitia I, MD; Homen JR, MD; Orviz E, MD.

Hospital del Mar. Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Universitat Pompeu Fabra, Barcelona, Spain: Juan P. Horcajada, M.D., Ph.D., Silvia Castañeda M.D., Elena Sendra M.D., Joan Gómez-Junyent M.D. Ph.D., Inmaculada López-Montesinos M.D.
Hospital Universitary Vall d'Hebron, Barcelona: Adrián Sánchez Montalvá , MD, PhD, Juan Espinosa-Pereiro, MD, Pau Bosch-Nicolau, MD, Fernando Salvador, MD, PhD

Internal Medicine Department. University Hospital Arnau de Vilanova, Lleida: Jose Luis Morales-Rull M.D., Ph.D., Anna Maria Moreno Pena M.D., Cristina Acosta M.D.; Cristina Solé-Felip M.D.;

Switzerland
Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich and Institute of Medical Virology, University of Zurich, Zurich Switzerland (5 participants enrolled): Huldrych F. Günthard, M.D., Dominique L. Braun, M.D., Emily West, M.D., Khadija M'Rabeth-Bensalah, M.D., Mareile L. Eichinger, M.D., Manuela Grüttner-Durmaz, R.N., Christina Grube, R.N., Veronika Zink, M.Sc., pharmacist., Josefine Goes, pharmacist

Georgia
Georgia SCC, Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia:Tengiz Tsertsvadze M.D., Ph.D., Akaki Abutidze, M.D., MP.H., Ph.D., Nikoloz Chkhartishvili, M.D., M.S., Ph.D., Revaz Metchurtchlishvili, M.D., Marina Endeladze M.D.,
Poland
Poland SCC, Wojewodzki Szpital Zakazny Warsaw (2 participants enrolled). Marcin Paciorek MD, PhD, Dominik Bursa MD, PhD, Dominika Krogulec MD, Piotr Pulik MD, Anna Ignatowska MD
Ukraine
Central City Clinical Hospital of Ivano-Frankivsk City, Ukraine: Roman Fishchuk M.D, Olena Kobrynska, M.D, Khrystyna Levandovska, M.D; Ivanna Kirieieva; Mykhailo Kuziuk
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.

Tan Tock Seng Hospital, NCID, Singapore (21 participants enrolled): Barnaby E. Young, M.B.B.S., Ph.D., Po Ying Chia, M.B.B.S., Tau Hong Lee, M.B.B.S., Ray J. Lin, M.B.B.S., David C. Lye, M.B.B.S., Sean W.X. Ong, M.B.B.S., Ser Hon Puah, M.B.B.S., Tsin Wen Yeo, M.B.B.S., Ph.D., Shiau Hui Diong, B.Bio., M.Sc., Juwinda Ongko, B.Sc., He Ping Yeo, B.Sc.

Institute of Human Virology-Nigeria (IHVN) (9 participants enrolled): Nnakelu Eriobu, M.D, M.P.H, Vivian Kwaghe M.D, Habib Zaiyad M.D, Godwin Idoko M.D, Blessing Uche RM RN

Chennai Antiviral Research and Treatment Clinical Research Site, India: Poongulali Selvamuthu, M.B.B.S., M.Sc., Ph.D., Nagalingeswaran Kumarasamy, M.B.B.S., Ph.D., Faith Ester Beulah, B.Sc., M.A., M.Sc., Narayan Govindarajan, B.Pharm., Kowsalya Mariyappan, B.Pharm.

INSIGHT SCC Argentina, Coordinación en Investigación Clínica Académica en Latinoamérica: Marcelo H. Losso, M.D., M.S., Cecilia Abela, R.N., B.S.N., Renzo Moretto, M.D., Carlos G. Belloc, B.Sc., Ph.D., Jael Ludueña, T.B.A., Josefina Amar.

Hospital General de Agudos JM Ramos Mejia, Buenos Aires: Marcelo H. Losso, M.D., M.S., Javier Toibaro, M.D., B.C., Laura Moreno Macias, M.D., Lucia Fernandez, M.D., Pablo S. Frare, M.D., Sebastian R. Chaio, M.D., Valeria Pachioli, M.D., Stella M. Timpano, B.Pharm.

Hospital Italiano de Buenos Aires, Buenos Aires: Marisa del Lujan Sanchez, M.D., Mariana de Paz Sierra, M.D., Vanina Stanek, M.D., Waldo Belloso, M.D., Flavia L. Cilenti.

Centro de Educacion Medica e Investigaciones Clinicas, Buenos Aires: Ricardo N. Valentini, M.D., Martin E. Stryjewski, M.D., Nicolas Locatelli, M.D., Maria C. Soler Riera, M.D., Clara Salgado, M.D., Ines M. Baeck, M.D., Valentina di Castelnuovo, M.D., Stella M. Zarza.

INSIGHT London ICC, MRC Clinical Trials Unit at UC, London, UK: Abdel G. Babiker, Ph.D., Sarah L. Pett, M.D., Ph.D., Fleur Hudson, BA, Mahesh KB Parmar, Ph.D, Anna L Goodman, FRCP DPhil, Jonathan Badrock, BSc., Adam Gregory, M.A., Katharine Goodall BA, Nicola Harris, James Wyncoll, B.Sc.

United Kingdom SCC:
Royal Free Hospital (11 participant enrolled): S. Bhagani, MD, A. Rodger, Ph.D, A. Luntiel MD, C. Patterson, MD, J. Morales B.Sc, E.Witele BSc., A-M Preston, BSc, A. Nandani M.Pharm.

Royal Victoria Infirmary (3 participants enrolled): D.A Price MD., Jeremy Nell MD., Bijal Patel MSc., Carole Hays ADNS., Geraldine Jones BSc., Jade Davidson BTEC.Pharm

Greece SCC, Medical School, National & Kapodistrian University of Athens: Giota Touloumi, Ph.D., Nikos Pantazis, Ph.D., Vicky Gioukari, B.Sc. Tania.Souliou

Attikon University General Hospital, Medical School, NKUA (6 participants enrolled): A. Antoniadou MD, K. Protopapas MD, D. Kavatha MD, S. Grigoropoulou MD, R-N. Tziolos MD, C. Oikonomopoulo, C. Moschopoulos MD

1st Respiratory Medicine Department, Medical School, NKUA (6 participants enrolled): N. G. Koulouris MD, K. Tzimopoulos MD, A. Koromilias MD, K. Argyraki MD, P. Lourida MD, P. Bakakos MD

Department of Critical Care and Pulmonary Medicine, Evangelismos General Hospital, Medical School, NKUA (15 participants enrolled): I. Kalomenidis MD, V, Vlachakos MD, Z. Barmparessou MD, E, Balis MD, PhD , S. Zakynthinos MD, I. Sigala MD, N. Gianniou MD, E. Dima MD, S. Magkouta MD, E. Synolaki MD, S. Konstanta MD, M. Vlachou MSc, PHD, P. Stathopoulou MSc

Alexandroupolis General Hospital, Medical School, Democritus University of Thrace (3 participant enrolled): P. Panagopoulos MD, V. Petrakis MD, D. Papazoglou MD, E. Tompaidou MSc, E. Isaakidou

3rd Department of Medicine, Medical School, NKUA (30 participants enrolled): G. Poulakou MD, V. Rapti MD, K. Leontis MD, T. Nitsotolis MD, K. Athanasiou MD, K. Syrigos MD, M-D. Myrodia MD, K. Kyriakoulis MD, I. Trontzas MD, M. Arfara-Melanini MD, V. Kolonis, MD

Uganda SCC, JCRC/MRC/UVRI Uganda Research Unit: Joseph Lutaakome, MD., Cissy Kityo, MD., Ph.D., Henry Mugerwa, MD., Francis Kiweewa, MD. MPH, Ivan Kimuli, MD.

MRC/UVRI & LSHTM Uganda Research Unit (7 participants enrolled): Joseph Lukaakome MD, Christoher Nsereko MD, Gloria Lubega MD, Moses Kibirige MD, William Nakahima, Deus Wangi, Evelyne Aguti MD, Lilian Generous, Rosemary Massa, Margaret Nalaki, Felix Magala MD, Phiona Kaweesi Nabaggala.

Gulu Regional Referral Hospital (5 participants enrolled): Robert Kidega MD., Cissy Kityo MD., Ph.D., Henry Mugerwa MD., Oryem Daizy Faith RN, Apio Florence RN, Ocung Emmanuel BBLT, Mugoonyi Paul Beacham MD., Amone Geoffrey BSc., Dridah Nakiboneka B.Stat., Paska Apiyo MD.

Makerere University Lung Institute (6 participants enrolled): Francis Kiweewa MD. MPH., Bruce Kirenga MBChB, MMED, PhD., Ivan Kimuli MBChB, MMED, MPH., Angella Atukunda MBChB, MMED., Winters Muttamba MBChB MMED., Kyeyume Remmy B.MLT., Ivan Segawa B.Pharm., Nsubuga Pheona B.Pharm, MPH., David Kigere DN., Queen Lailah Mbabazi MBChB , Ledra Boersalino MBChB., Grace Nyakoolo BSc.

Lira Regional Referral Hospital (12 participants enrolled): Francis Kiweewa MD. MPH., Aniongo Fred B.MLT., Alice Alupo

RN, Doryn Ebong BSN, Edson Monday BSN, Ritah Norah Nalubwama MD., Milton Kainja MD., Munu Ambrose DMLT, Vanon Kwehayo RN, Mary Grace Nalubega RN., Augustine Ongoli MBChB, Stephen Obbo MBChB, MMED, MPH., Nicholus Sebudde MBChB., Jeniffer Alaba, Geoffrey Magombe B.Pharm, Harriet Tino B.Pharm., MSc. PHSM., Emmanuel Obonya., EE.

Masaka Regional Referral Hospital (4 participants enrolled): Joseph Lutaakome MD, Jonathan Kitonsa MD, Martin Onyango MD, Tukamwesiga Naboth MD, Hadijah Naluyinda, Regina Nanyunja, Muttiibwa Irene, Biira Jane, Kyobejja Wimfred, Ssemazzi Leonard, Tkiinomuhisha Deus, Namasaba Babra, Paul Taire

St. Francis Hospital, Nsambya (2 participants enrolled): Joseph Lutaakone MD, Evelyn Nabankema MD, Joseph Ogavu MD, Oscar Mugerwa MD, Ivan Okoth MD, Raymond Mwebaze MD, Timothy Mugabi MD, Anthony Makhoba MD, Phiona Arikiriza, Nabuuma Theresa, Hope Nakayima, Kisuule Frank.

CISPOC: Centro de Investigação e Treino em Saúde da Polana Caniço, Maputo, Mozambique: Patrícia Ramgi, MD Kássia Pereira, MD and all site team

Gilead Sciences, Foster City, CA, USA: Anu Osinusi, M.D., M.P.H., Huyen Cao, M.D.

Molecular Partners and Novartis: Philippe Legenne, Michael Stumpp, Susana Goncalves, Krishnan Ramanathan, Richa Chandra

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., Mabel Asomah, M.S.H.S, Yvonne Jato, M.P.H, April Stottlemyer. A.A., Olivia Tang, B.S., Sharon Vanderpuye, B.A., Lindsey Yeon, 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., Marylu Schaffhauser, B.A., 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.

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, Ph.D.., Tauseef Rehman, Ph.D., Danielle Lynam, M.S., Tom Imamichi, Ph.D., Sylvain Laverdure, Ph.D.., Sharada Paudel, Ph.D., Kyndal Cook, B.S., Kendra Haupt, B.S., Ayub Khan, Ph.D., Allison Hazen, M.S., Yunden Badralmaa, M.S

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

PCI Pharma Services: Craig Brown, Nadine DuChateau, Sadie Ellis, Adam Flosi, Lisa Fox, Les Johnson, Rich Nelson, Jelena Stojanovic, Amy Treagus, Christine Wenner, Richard Williams.

Section 2: Supplementary Methods

Trial Design and Treatments

Randomization and Use of Shared Placebo

The TICO (Therapeutics for Inpatients with COVID-19) is a Phase III randomized, blinded, controlled, platform trial in which multiple candidate therapies in a multigroup, multistage, double-blind design are investigated in parallel, or staggered with overlapping times; investigational agents may be added or dropped (1-3). When more than one agent is being tested concurrently, where possible, participants are randomly allocated across agents (as well as between the agent and its matched placebo), and the control group is pooled across the concurrently randomized, agent-specific matched placebo groups. Thus, each investigational agent and the corresponding pooled control group form their own randomized trial, and several agents may (at least partially) share their pooled control groups.

Ensovibep, (MP0420, Molecular Partners) was the 5th agent entering TICO, on June 11, 2021. Ensovibep was tested concurrently with tixagevimab/cilgavimab through September 20, 2021; placebo was shared, and the randomization allocation was 2:1:2:1 at sites approved for both agents. Eligibility criteria were the same for each agent. Out of the 241 participants in the placebo group 185 were assigned a matching placebo to ensovibep and 56 were assigned a matching placebo to tixagevimab/cilgavimab.

Randomization was carried out with stratification by site pharmacy (several clinical sites shared a site pharmacy, in cases of geographical proximity) and disease severity. A flexible web-based randomization application was developed, which was able to vary allocation according to stratum (i.e., pharmacy or disease severity). Using the mass-weighted urn scheme (4,5), the underlying Active:Placebo sequence is generated to ensure an approximate 1:1 balance for each active versus pooled placebo comparison within strata throughout the trial. After confirming eligibility and obtaining informed consent, designated personnel at the clinical sites used the application to verify eligibility and 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 the only unblinded study member and prepared the infusion bag for the patient.

<u>The two strata that defined disease severity were</u>:
Disease severity stratum 1: Absence of all of the following: stroke, meningitis encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, symptomatic congestive heart failure (NYHA class III or IV), arterial or deep venous thrombosis or pulmonary embolism, requirement for invasive mechanical ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new renal replacement therapy.

Disease severity stratum 2: Presence of at least one of the excluded conditions or treatments in disease severity stratum 1.

In the initial stage of the trial, only patients in disease severity stratum 1 were eligible. Once an agent passed the initial futility assessment, eligibility could be expanded to disease stratum 2.

In the trial of ensovibep, all patients randomized were in disease severity stratum 1.

Analysis Population

According to the statistical analysis plan, comparisons of safety outcomes was to be analyzed by modified intention to treat (mITT), defined as the population of participants who received a complete or partial infusion. For the comparison of efficacy outcomes, the analysis was to be by intention to treat (all randomized participants).

In the trial of ensovibep, only 11 participants did not receive all or part of an infusion of the study agent or placebo,

10 of which withdrew consent between the time of randomization and time of infusion and did not have day 5 data recorded. Thus, only 1 patient with outcome data did not receive a complete or partial infusion. Because of this, all analysis were carried out with the mITT population. This approach allowed potential risks and benefits to be evaluated in the same population.

Blinding
Investigational agents or placebo (as necessary) was prepared by a pharmacist who was 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, were blinded. For investigational agents infused, blinding of the participant and clinical staff was achieved by placing a colored sleeve over the infusion bags used for investigational agents and placebos. Placebo consisted of a 50ml infusion of an isotonic crystalloid, referred to as an isotonic saline solution. When more than one investigational agent was available for randomization, the clinical staff was informed to which investigational agent/placebo the participant was randomly assigned for infusion, but they remained blinded to whether the random assignment was to the active investigational agent or matching placebo.

Plan for Early futility assessment
TICO is an adaptive trial and was designed for each agent to undergo an early futility assessment. Only agents that pass the early futility assessment progress to enroll the full sample size. Prior to the early futility assessment, patients with moderate and severe COVID-19 are enrolled. The futility assessment is conducted based on the analysis of two intermediate seven-category ordinal efficacy outcomes assessed at day 5 referred to as the pulmonary ordinal outcome and the pulmonary-plus ordinal outcome (detailed below). Early futility assessments include approximately 150 participants in an interventional group (one agent) and 150 participants in the placebo group (contemporaneous pooled common placebo group). This was intended to provide 95% power to detect a summary odds ratios of 1.60 or greater in the pulmonary and pulmonary-plus ordinal scales, using one sided tests with type I error rates of 0.30. However, these criteria were non-binding and the DSMB was encouraged to assess the data comprehensively. Agents with more favorable scores than placebo on the pulmonary and pulmonary-plus ordinal outcome scales with one-sided p-values <0.3 continue enrollment for a full efficacy assessment.

Futility Assessment Carried out by DSMB for Ensovibep
The DSMB recommended stopping enrollment on 15 November 2021. Prior to this recommendation, the DSMB reviewed day 5 ordinal pulmonary outcomes from 297 participants on 18 October 2021. At the October evaluation, the adjusted odds ratio for the day 5 pulmonary outcome was 1.07 [95% CI: 0.70 to 1.62] with a one-sided p-value of 0.38, above the 0.3 threshold for recommending study continuation. However, given a trend for benefit in the ordinal outcome on day 28 and a trend for lower mortality in the ensovibep group, the DSMB recommended that enrollment continue, and that futility would be evaluated again at the next DSMB meeting. The next DSMB meeting was held on 15 November 2021, at which time 496 participants had been randomized, 421 of whom had day 5 outcome data. The adjusted odds ratio for the pulmonary outcome on day 5 was 0.93 [95% CI: 0.67 to 1.30], with a one-sided p-value of 0.68. Based on these results along with a decrease in the favorable trend for ensovibep in the day 28 ordinal outcome and for mortality seen at the previous DSMB meeting, the DSMB recommended that enrollment be stopped.

Statistical Analysis and Study Population
For the comparison of the primary outcome, Gray's test was used. Gray's test with rho=0 is the analogue of the log-rank test in the presence of competing risks; it is used here to account for the competing risk of death when analyzing time to sustained recovery.

With an estimated sustained recovery rate ratio of 1.25 for the investigational agent versus control, it was calculated that if an agent passes the early futility assessment, enrollment was to be expanded to include patients with critical COVID-19 and continue until 843 patients combined in the active agent arm and concurrent placebo arm have experienced the primary outcome of sustained clinical recovery. For 2 groups, we assumed that the sample size should be approximately 20% higher than the number of recoveries, to account for deaths, a small number of withdrawals of consent, and a small number of patients remaining in the hospital at Day 90. The total sample size

for 2 groups was set at approximately 1,000 patients (500 in an active agent group and 500 patients in the placebo group).

The distributions of the pulmonary and pulmonary-plus ordinal scales were compared between treatment groups using proportional odds models. The proportional odds model estimates a summary OR; that is, the ratio of the cumulative odds of being in a better category of the ordinal outcome for ensovibep versus placebo. The models included a single indicator for treatment, indicators based on participant clinical state at entry (categories of pulmonary ordinal scale at day 0) and study site pharmacy (sites with less than 20 participants were pooled within country or region as appropriate, See also Supplement Table 3 in the Supplementary Appendix). Proportional odds models were fit with the same covariates for the ordinal outcomes at days 1-7, 14, and 28. The protocol specified that an agent would pass the futility assessment if the one-sided p-values for both the day 5 pulmonary and pulmonary-plus ordinal scales were less than 0.30 in favor of ensovibep.

Assessment of the Treatment Effect Heterogeneity

- Duration of symptoms prior to enrollment
- Age (18-49, 50-59, 60-69, 70-79, 80+)
- Biological sex
- Race/ethnicity
- Geographic location
- Level of residence (home) at the time COVID-19 symptoms developed
- Baseline pulmonary status (mutually exclusive subgroups: not on supplemental oxygen, supplemental oxygen < 4 L/min, supplemental oxygen > 4 L/min, HFNC or NIV; invasive mechanical ventilation or ECMO)
- Body mass index (BMI)
- History of chronic conditions (cardiovascular disease, diabetes, asthma, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, hepatic impairment, or cancer), and number of chronic conditions (none, 1, 2, 3 or more).
- Plasma antibody status.
- Plasma antigen level.
- SARS-CoV-2 viral RNA level based on mid-turbinate swab.
- Biomarkers of inflammation and coagulation (including IL-6, hsCRP, and D-dimer)
    - Vaccine status
    - Immunosuppressive status
    - Viral strain
- Concomitant medications, including subgroups formed by:
    - Use of remdesivir prior to study entry
    - Use of corticosteroids

Additional details of the rationale and design of TICO are available in the trial protocol and statistical analysis plan (both available as supplementary materials), the TICO design manuscript (2) and references that guided the design of the trial (3-5).

Study Population and Inclusion/Exclusion Criteria

For each investigational agent, an estimated 1,000 COVID-19 participants would be enrolled at clinical trial sites globally. The time from screening (Day -1 or Day 0) to end of study for an individual participant was 18 months. Initially, approximately 300 participants in the disease severity stratum 1 would be enrolled. For investigational agents passing an initial futility assessment for these participants, enrollment would be expanded, seamlessly and without any data unblinding, to include participants in disease severity stratum 2 as well as those in disease severity stratum 1.

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

Inclusion Criteria

- Age ≥ 18 years;
- Informed consent by the patient or the patient's legally authorized representative
- SARS-CoV-2 infection, documented by a nucleic acid test (NAT) or equivalent testing within 3 days prior to randomization OR documented by NAT or equivalent testing more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator (For non-NAT tests, only those deemed with equivalent specificity to NAT by the protocol team will be allowed. A central list of allowed non-NAT tests will be maintained.);
- Duration of symptoms attributable to COVID-19 ≤ 12 days per the responsible investigator;
- 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.

Exclusion Criteria

- Prior receipt of:
  - Any SARS-CoV-2 hIVIG, convalescent plasma from a person who recovered from COVID-19 or
  - SARS-CoV-2 nMAb at any time prior to hospitalization.
- Not willing to abstain from participation in other COVID-19 treatment trials until after Day 5 (with the approval of study leadership, enrollment before or on Day 5 is permitted for trials comparing different approaches for implementing SOC interventions that are recommended in Appendix I;
- 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.
- Expected inability to participate in study procedures.
- Women of child-bearing potential who are not already pregnant at study entry and who are unwilling to acknowledge the strong advice to abstain from sexual intercourse with men or practice appropriate contraception through 18 months of the study.
- Men who are unwilling to acknowledge the strong advice to abstain from sexual intercourse with women of child-bearing potential or to use barrier contraception through 18 months of the study.
- Prior to the initial futility assessment for an investigational agent, the following two additional exclusions (7 and 8) which define disease severity stratum 2 apply:
  - Presence at enrollment of any of the following: a. stroke; b. meningitis; c. encephalitis; d. myelitis; e. myocardial infarction; f. myocarditis; g. pericarditis; h. symptomatic CHF (NYHA class III-IV); i. arterial or deep venous thrombosis or pulmonary embolism
  - Current requirement for any of the following: j. invasive mechanical ventilation; k. ECMO; l. mechanical circulatory support; m. vasopressor therapy; n. commencement of renal replacement therapy at this admission (i.e., not patients on chronic renal replacement therapy).

Patients who were vaccinated against SARS-CoV-2 were eligible for enrolment.

Approach to Intercurrent Therapies and Clinical Trial Co-enrollment

The study adopted a pragmatic approach to the use of intercurrent, concomitant medications. Except for use of convalescent plasma, hyperimmune SARS-CoV-2 immunoglobulin or nMAb which is not permitted prior to entry or before Day 5, there were few restrictions. Participants were asked at screening to agree to refrain from participation in other clinical trials until at least the assessment at Day 5 except for certain trials approved by trial leadership. It was recognized that, in the case of progression during follow-up to life-threatening disease and end-organ failure (broadly categories 5 and 6 of the intermediate outcome measure) participation in an additional clinical trial at that time would not be restricted. Prior participation in clinical trials (except receipt of hIVIG, convalescent plasma or another nMAb) was not restricted, recognizing for example that participants may have enrolled in a study for mild disease prior to progression and then may wish to participate in this study at the onset of progression.

Outcomes for Early Futility Assessment

The early futility assessment was based on two ordinal outcome scales measured at day 5 — the seven-category pulmonary ordinal outcome scale and the seven-category pulmonary-plus ordinal outcome scale. Patients were

classified according to the highest level met during the calendar day of study day 5. Both scales were derived from ACCT-1 and WHO-recommended ordinal scales and have been used in previous COVID-19 trials.
The pulmonary ordinal outcome scale primarily reflects supplemental oxygen requirements and includes the following categories:

The 7-category pulmonary ordinal outcome scale:

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements) *
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements) *
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen) *
5. Non-invasive ventilation or high-flow oxygen (high flow nasal cannula)
6. Invasive ventilation, extracorporeal membrane oxygenation (ECMO), mechanical circulatory support, or new receipt of renal replacement therapy
7. Death

The pulmonary-plus ordinal outcome scale includes the same categories as the pulmonary outcome scale but incorporates additional extrapulmonary conditions into categories 4-6.

The 7-category pulmonary-plus ordinal outcome scale:

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements) *
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements) *
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen) * or any of the following: stroke (NIH Stroke Scale [NIHSS] ≤14), meningitis, encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, new onset congestive heart failure New York Heart Association class III or IV or worsening to class III or IV, arterial or deep venous thromboembolic events.
5. Non-invasive ventilation or high-flow oxygen, or signs and symptoms of an acute stroke (National Institutes of Health Stroke Scale score >14)
6. Invasive ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new receipt of renal replacement therapy
7. Death

* For patients on chronic supplemental oxygen therapy prior to COVID-19, categorization on the pulmonary ordinal scale was based on oxygen flow rates above the pre-COVID oxygen flow rate. For example, a patient who chronically used supplemental oxygen at 2 liters/minute prior to COVID-19 would be categorized as category 2 if using 2 liters/minute at randomization, category 3 if using >2 liters per minute and <6 liters/minute, and category 4 if using ≥6 liters/minute of supplemental oxygen.

Primary Efficacy Outcome

The primary endpoint is ***time from randomization to sustained recovery***, where sustained recovery is defined as being discharged from the index hospitalization, followed by being alive and *home* for 14 consecutive days prior to Day 90.
Home is defined as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this trial (the index hospitalization).

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 affiliated with a "long-term acute care" hospital recover when they return to the same or lower level of care.

Readmission from "home" may occur and if this occurs within 14 days of the first discharge to "home", then the primary endpoint will not be reached until such time as the participant has been at home for 14 consecutive days. 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.

Safety Outcomes

Infusion-related reactions were reported on a checklist during and for 2 h after infusion. After the infusion and for the first 7 days of hospitalization, patients were assessed in-person daily and adverse event data were collected via direct interaction between the study team and the patient and via medical record review. After hospital discharge, adverse event data were collected via in-person visits and telephone visits. Relatedness of adverse events to study procedures was assessed.

A specific reporting system was developed for rash. On December 7, 2021, all participants for whom rash adverse events had been reported through Day 28 were identified. Sites were asked to complete an eCRF for each event. The number and percentage of participants with a rash event were summarized by treatment group; rash events associated with myalgia, arthralgia, or generalized aches and pains were also summarized by treatment group. Line listing of events included MedDRA Preferred Term (PT), severity grade, rash characteristics, location, and other solicited events that occurred simultaneously. In a supplemental analysis for the Day 28 composite safety outcome which includes deaths, SAEs (6), organ failure, serious infection and grade 3 or 4 adverse events the rash adverse events were included as a separate component.

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) grade 3 or 4 adverse events, 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)

Adverse events were graded for severity using a toxicity table of the Division of AIDS, NIAID (4). For adverse events not in the table, a generic grading scheme was used. Adverse events were categorized according to codes in the Medical Dictionary for Regulatory Activities (MedDRA®), version 23.1

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. Respiratory dysfunction:
    a. Respiratory failure defined as receipt of high flow nasal oxygen, noninvasive ventilation, invasive mechanical ventilation or ECMO
2. Cardiac and vascular dysfunction:
    a. Myocardial infarction
    b. Myocarditis or pericarditis
    c. CHF: new onset NYHA class III or IV, or worsening to class III or IV
    d. Hypotension requiring institution of vasopressor therapy
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 thanSARS-CoV2, requiring antimicrobial administration and care within an acute-care hospital.

The protocol specified some serious events anticipated to be common in COVID-19, that were exempt from being reported as serious adverse events, except when the event was classified as related or possibly related to study procedures. These “protocol-specified exempt 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
- Respiratory failure defined as receipt of high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO
- Hypotension requiring vasopressor therapy
- 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

Laboratory Methods
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 or serum and four 1 mL aliquots of plasma were collected at baseline, and on follow-up days 1, 3, 5, 28 and 90. Two 9mL tubes, one SST and one EDTA of blood was drawn to obtain the 8 aliquots.

SARS-CoV-2 Viral RNA was assessed at baseline from mid-turbinate nasal swabs. Qualitative and quantitative assessments of the SARS-CoV-2 RNA in viral transport media (proxy for viral load) by RT-PCR were made centrally by ABML.

- *Qualitative RT-PCR analysis:* Extraction, master mix preparation, and RT-PCR were performed as described in the CDC 2019-Novel Coronavirus Real-Time RT-PCR Diagnostic Panel. RT-PCR was performed on an Applied Biosystems QuantStudio 7 Flex. Ct scores <40 for both nCoV N1 and nCoV N2 probe sets are scored as positive for the presence of SARS-CoV-2 RNA.
- *Quantitative RT-PCR analysis:* Quantitative RT-PCR analysis of the samples used the same RNA extracts prepared for the qualitative assay. Assay conditions were the same as outlined in the CDC protocol except the RNaseP probe was not used.

For subgroup analyses, RNA levels in viral transport media were categorized as (<56,000 cp/mL [low] versus >56,000 cp/mL [high]); the cut-point is close to the median viral RNA level.

SARS-CoV-2 variants Beginning in February 2021, the presence of the Delta variant versus other variants was determined using an RT-PCR assay specifically designed to amplify nucleocapsid of SARS-CoV-2 and N-terminal domain of the Spike gene of delta variant. Thus, specimens that were positive for both nucleocapsid and N-terminal domain of the Spike gene of Delta variant were designated as the Delta. The assessment of Delta with this method was concordant with the sequencing results for the subset of patients who had results for both.

Antibody Levels, Antigen Levels and Outcomes SARS-CoV-2 antibody and antigen levels were measured in plasma specimens collected at baseline (Day 0), Day 1, Day 3, and Day 5. Antibody and antigen levels were determined centrally, by the Frederick National Laboratory, blinded to treatment group.

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, US) measuring total (IgA, IgG, and IgM) anti-nucleoprotein (Anti-N) antibodies. Results of this antibody measurement are reported as “specimen ratios”. Specimen ratios are defined as the specimen optical density (OD) divided by the optical density of the cut-off control R4 (ODMR4). According to the manufacturer, specimen ratios less than 0.8 are considered negative, those with a specimen ratio between 0.8 and 1.0 are considered equivocal, and those > 1.0 are considered positive for the presence of antibodies.

Levels of neutralizing antibodies (nAbs) directed against the SARS-CoV-2 receptor binding domain (RBD) were determined using the GenScriptSARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) assay (GenScript, Piscataway, NJ, USA). Levels of nAbs reported as “percent binding inhibition”. Specimens with levels <30% are considered nAb negative, levels > 30% are considered positive for nAbs (30% is the manufacturer’s cutoff for positivity).

Plasma Antigen Levels
SARS-CoV-2 nucleocapsid antigen levels were determined in 90 µL plasma in duplicate using

a Quanterix assay (Simoa® SARS-CoV-2 N Protein Advantage, Quanterix, Bellerica, MA, USA). The lower limit of quantification for the assay is 3 ng/L. Antigen levels < 3 ng/L are considered "antigen negative". When analyzed as continuous variable, Quanterix antigen levels <3 were imputed as 2.9 ng/L.

References to the Supplementary Methods

1. Murray DD, Babiker AG, Baker JV, Barkauskas CE, Brown SM, Chang CC, et al. Design and implementation of an international, multi-arm, multi-stage platform master protocol for trials of novel SARS-CoV-2 antiviral agents: Therapeutics for Inpatients with COVID-19 (TICO/ACTIV-3). Clin Trials. 2022;19(1):52-61.
2. ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Inf Dis, December 23, 2021. (https://doi.org/10.1016/S1473-3099(21)00751-9)
3. Beigel JH, Tomashek K, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - preliminary report. N Engl J Med. 2020; 383:992-994.
4. Zhao W. Mass weighted urn design — A new randomization algorithm for unequal allocations. Contemporary Clinical Trials 2015;43:209–16.
5. WHO. COVID-19 Therapeutic Trial Synopsis. Available at https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis accessed May 11, 2022.
6. 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. Available at https://rsc.niaid.nih.gov/clinical-research-sites/grading-severity-adult-pediatric-adverse-events-corrected-version-two-one accessed March 20, 2022.

Supplemental Tables Descriptions

Supplement Table 1: Enrollment by Country

A little over two-thirds (68%) of participants enrolled were from the United States, followed by Greece (12%), Uganda (7%) and Singapore (5%).

Supplement Table 2: Enrollment by Month

Enrollment began in June 2021 and ended in November 2021. October 2021 was the largest recruitment month.

Supplement Table 3: Strata used for Analysis

Sites with more than 20 participants formed their own strata; smaller sites were combined by country or geographic region. The largest site was in the United States (site 301-006) with 57 participants enrolled.

Supplement Table 4: Baseline Covid-19 Vaccination

Approximately one-quarter (26%) of participants were fully vaccinated by enrollment; 69% were not vaccinated.

Supplement Table 5: Baseline Medical History

Hypertension was the most common medical condition (39%) followed by diabetes (23%); 58% of participants reported at least one medical condition.

Supplement Table 6: Baseline Concomitant Medications

Approximately three-quarters of participants were taking antiplatelets or anticoagulants at baseline, most of these were on heparin; 72% of participants were on corticosteroids.

Supplement Table 7: Baseline Antibody, Antigen, and Viral Load Distributions

62% of participants were antinucleocapsid antibody positive and 58% were anti-spike neutralizing antibody positive at enrollment; 95% were antigen positive with a median [IQR] of 1374 [165-4758] pg/mL. Approximately 90% were viral load positive.

Supplement Table 8: Concomitant Medication Use During Follow-up

Medication use at day 5 and day 8 were similar between ensovibep and placebo groups. Use of corticosteroids by day 28 was reduced to approximately 6% of participants.

Supplement Tables 9-10: Day 5 Ordinal Pulmonary and Pulmonary plus Outcomes

The distribution of pulmonary outcome categories were similar between the ensovibep and placebo groups. Overall, approximately 20% were able to resume usual activities with minimal or no symptoms. There was little difference between the pulmonary and pulmonary plus distributions.

Supplement Table 11: Change from Baseline to Day 5 in Pulmonary Outcome

This table classified patients by change from baseline to day 5 in pulmonary categories: 1) better category on day 5; 2) same category on day 5 and 3) worse category on day 5. Approximately 45% of participants were in a better category by day 5 and the distribution was similar between groups.

Supplement Table 12: Components of Ordinal Outcome at Day 5

Odds ratios between 6 cutoffs of the ordinal pulmonary outcome showed no evidence of unequal slopes using a conventional significance level.

Supplement Table 13: Odds Ratios for Pulmonary Outcomes, Days 1-7

Odds ratios for the pulmonary outcome across days 1-7 were similar and all 95% confidence intervals included one.

Supplement Table 14-15: Ordinal Pulmonary Outcome on Days 14 and 28

The odds ratio for the pulmonary outcome on day 14 was 1.10 [0.77-1.55] and at day 28 was 1.13 [0.77-1.65], slightly favoring ensovibep. Improvements from day 14 to day 28 were seen in both groups. At day 28, over one-half of participants were independently able to undertake usual activities with minimal symptoms.

Supplement Table 16-17: Infusion Reactions by Type and Grade

Few participants in either group experienced infusion reactions and, of those that did, nearly all were grade 1.

Supplement Table 18-21: Adverse Events Through Day 7, at Day 14, and at Day 28

Adverse events are presented by MedDRA System Organ Class (SOC). The highest rate was for Respiratory, Thoracic, and Mediastinal at each visit but decreased over time in both groups. Rates were similar between groups for each SOC except for the Nervous System which was lower at each visit in the ensovibep group than the placebo group. Grade 3 or 4 events were slightly higher in the placebo group than in the ensovibep group.

Supplement Table 22: SAEs through Day 90 by SOC

Thirty participants experienced an SAE through day 90, 14 in the ensovibep group and 16 in the placebo group; 7 participants experienced an SAE related to Respiratory condition.

Supplement Table 23: Safety Summary through Day 5

This table presents events in a 6 category hierarchy through day 5. Results were similar between groups. The odds ratio for the combined 6 category is presented in Table 2 of the main manuscript.

Supplement Table 24: Safety Summary through Day 28.

This table presents events in a 7 category hierarchy through day 28. Odds ratio were all less than one indicating a lower rate in the ensovibep group. However, all 95% CI included one.

Supplement Table 25: Safety Summary through Day 90.

This table presents events in a 4 category hierarchy through day 90; grade 3 and 4 events were not collected after day 28 and are not included in these analysis. All 95% CI included one.

Supplement Table 26: Clinical Organ Failure and Serious Infections through Day 90

This tables presents percentages of participants experiencing various organ failures and serious coinfections through day 90. Approximately one-quarter of participants in each group experienced one or more of these diagnosis.

Supplement Table 27: Rash Events through Day 28

Seven participants in the ensovibep group experienced a rash event compared to 4 in the placebo group. Most of these were not associated with other conditions.

Supplement Tables 28-37: Subgroup Analysis

For each of the major outcomes analysis were run separately by age groups, gender, race, region, days since symptom onset, baseline pulmonary category, BMI, history of chronic condition, vaccination status, immunosuppression status, and date of enrollment. Since the study was stopped before full enrollment, there is very low power for these analysis. There were few qualitative differences (HR > 1 in one subgroup and HR < 1 in another) observed. In all cases considered, evidence for heterogeneity was weak and there was no reason to assume the best estimate of the relative treatment difference was not the overall OR/HR.

Supplement Figure 1: Time to Discharge from Index Hospitalization, Cumulative Incidence

This figure displays the cumulative incidence function for time to index hospitalization discharge for ensovibep and placebo groups. The pattern is similar for the two groups.

Supplement Figure 2: Kaplan-Meier for Composite Safety Outcome through Day 28

This figure display the Kaplan-Meier plot for the composite safety outcome at Day 28 for ensovibep and placebo groups. The ensovibep showed a lower rate than the placebo group throughout follow-up.

Supplement Figure 3: Kaplan-Meier for Composite Safety Outcome through Day 90

This figure displays the Kaplan-Meier plot for the composite safety outcome at Day 90 for ensovibep and placebo groups. The pattern is similar for the two groups. Table 2 in the main manuscript shows the HR and 95% CI which includes one.

Supplement Figure 4: Sustained Recovery Cumulative Incidence Plot by Baseline Supplemental O2

This figure displays separately for four O2 categories at baseline the cumulative incidence plot for sustained recovery. The highest sHR was for participants not on O2 and for participants on high flow or NIV. All 95% CI include one.

Section 3: Supplemental Tables and Figures

Supplement Table 1: Enrollment by Country

Country	*No. randomized*	*No. infused (mITT)*
Denmark	7	7
Greece	60	60
Nigeria	9	9
Poland	2	2
Singapore	23	23
Spain	2	2
Switzerland	5	5
Uganda	36	36
United Kingdom	14	10
United States	338	331
Total	496	485

Supplement Table 2: Enrollment by Month

Month Randomized	*Group A*	*Group B*	*Total*
Jun 2021	15	5	20
Jul 2021	40	45	85
Aug 2021	43	35	78
Sep 2021	44	43	87
Oct 2021	72	80	152
Nov 2021	33	30	63
Total	247	238	485

Supplement Table 3: Strata used for analysis

Strata	*Country*	*No. Sites*	*No. Participants*
1	United States (080-039)	1	22
2	United States	45	252
3	United States (301-006)	1	57
4	Singapore (612-201)	1	23
5	Denmark	1	7
5	Poland	1	2
5	Spain	1	2
5	Switzerland	1	5
5	United Kingdom	2	10
6	Nigeria	1	9
6	Uganda	5	36
7	Greece	2	60
Total		62	485

Supplement Table 4: Baseline Covid-19 Vaccination

	Ensovibep		Placebo	
No. randomized	247		238	
	No.	Pct.	No.	Pct.
Vaccination Status*				
Fully vaccinated	62	25.1	62	26.1
Partially vaccinated	12	4.9	17	7.1
Not vaccinated	173	70.0	159	66.8
Fully vaccinated				
2-dose course completed	54	87.1	55	88.7
1-dose course completed	8	12.9	7	11.3
Partially vaccinated				
2-dose course completed, symptoms within 14 days after last dose	1	8.3	2	11.8
1-dose course completed, symptoms within 14 days after dose	4	33.3	1	5.9
2-dose course, only 1 dose received	7	58.3	14	82.4
Not vaccinated				
First dose received after symptoms start	4	2.3	1	0.6
No doses received or unknown	169	97.7	158	99.4

* Fully vaccinated = full course completed, symptoms started at least 14 days after the last dose

Partially vaccinated = full course complete and symptoms started within 14 days after last dose, or 2-dose course and only 1 dose received

Not vaccinated = first dose received after symptoms start, or no doses received / unknown

Supplement Table 5: Baseline Medical History

	Ensovibep		Placebo	
No. participants	247		238	
	No.	**Pct.**	**No.**	**Pct.**
Medical History*				
Asthma	20	8.1	25	10.5
Cerebrovascular event	4	1.6	3	1.3
COPD	12	4.9	18	7.6
Diabetes mellitus requiring medication	62	25.1	52	21.8
Heart failure	10	4.0	9	3.8
Hepatic impairment	1	0.4	2	0.8
HIV or other immune suppression	9	3.6	8	3.4
Hypertension requiring medication	102	41.3	89	37.4
Malignancy	7	2.8	9	3.8
MI or other acute coronary syndrome	3	1.2	10	4.2
Renal impairment	23	9.3	23	9.7
Any of above	*143*	*57.9*	*138*	*58.0*
Admission to randomization - median days (IQR) **	2 (1, 2)		2 (1, 2)	
BMI kg/m^2				
< 30	135	54.7	121	50.8
30-30.9	80	32.4	83	34.9
≥ 40	32	13.0	33	13.9
Unknown	0	0.0	1	0.4
Pre-morbid need for continuous supplemental oxygen	4	1.6	4	1.7
Pre-morbid need for renal replacement therapy	5	2.0	4	1.7

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

** Admission date collected at time of discharge

Supplement Table 6: Baseline Concomitant Medications

	Ensovibep		Placebo	
No. randomized	247		238	
Concomitant Medication	No.	Pct.	No.	Pct.
Antibiotics	91	36.8	101	42.4
IV antibiotic	72	29.1	87	36.6
Oral antibiotic	37	15.0	29	12.2
Antifungals	2	0.8	3	1.3
ACE inhibitor	19	7.7	14	5.9
ARB	20	8.1	18	7.6
Antiplatelets/anticoagulants	187	75.7	185	77.7
Aspirin	33	13.4	34	14.3
Other antiplatelet	7	2.8	7	2.9
Heparin prophylactic dose	128	51.8	120	50.4
Heparin intermediate dose	23	9.3	22	9.2
Heparin therapeutic dose	15	6.1	17	7.1
Warfarin	1	0.4	4	1.7
DOAC	7	2.8	10	4.2
Antiviral	0	0.0	1	0.4
Favipiravir	0	0.0	0	0.0
Lopinavir	0	0.0	0	0.0
Other antiviral	0	0.0	1	0.4
Antirejection meds	10	4.0	6	2.5
Immune modulator	22	8.9	20	8.4
IL1	0	0.0	0	0.0
IL6	6	2.4	9	3.8
Interferons	0	0.0	0	0.0
JAK inhibitor	14	5.7	10	4.2
TNF inhibitor	0	0.0	1	0.4
Other immune modulator	2	0.8	0	0.0
NSAID	14	5.7	17	7.1
Corticosteroids	180	72.9	170	71.4
Biologic meds for cancer/autoimmune disease	3	1.2	1	0.4

Note - concomitant medications used within the last 24 hours.

Supplement Table 7 : Baseline Antibody, Antigen and Viral Load Data by Treatment Group

BioRad Antinucleocapsid Ab [a] Sample/Cutoff Ratio	Ensovibep n=240	Placebo n=227	Total n=467
n (%) positive	154 (64%)	134 (59%)	288 (62%)
n (%) equivocal	1 (0%)	3 (1%)	4 (1%)
min, max	0.04, 5.95	0.05, 5.95	0.04, 5.95
median (IQR)	2.95 (0.22, 3.55)	2.95 (0.21, 3.90)	2.95 (0.22, 3.86)
mean ±SD	2.39 ± 1.93	2.24 ± 1.82	2.32 ± 1.88

GenScript Anti-Spike Neutralizing Ab [b] Binding Inhibition (%)	Ensovibep n=240	Placebo n=227	Total n=467
n (%) positive	154 (64%)	118 (52%)	272 (58%)
min, max	-13, 98	-11, 98	-13, 98
median (IQR)	48 (17, 87)	33 (10, 76)	44 (13, 83)
mean ±SD	50.4 ± 35.1	42.5 ± 35.5	46.6 ± 35.5

Quanterix Antigen [c] Concentration (pg/mL)	Ensovibep n=240	Placebo n=226	Total n=466
n (%) positive	229 (95%)	212 (94%)	441 (95%)
min*, max	2.9, 60896	2.9, 39946	2.9, 60896
median (IQR)	1386 (142, 5899)	1361 (206, 4196)	1374 (165, 4758)
mean ±SD	4335 ± 7860	3261 ± 5598	3814 ± 6871
median (IQR) $\log_{10}$	3.14 (2.15, 3.77)	3.13 (2.31, 3.62)	3.14 (2.22, 3.68)
mean ±SD $\log_{10}$	2.91 ± 1.05	2.83 ± 1.05	2.87 ± 1.05
n (%) ≥ 1000	133 (55%)	123 (54%)	256 (55%)

* 2.9 is imputed for an antigen <LOQ (<3)

Quanterix Antibody [d] (ng/mL)	Ensovibep n=240	Placebo n=227	Total n=467
n (%) positive	142 (59%)	114 (50%)	256 (55%)
min, max	1, 2.03E6	0, 2.13E6	0, 2.13E6
median (IQR)	1786 (230, 22713)	789 (117, 6666)	1108 (154, 11536)
mean ±SD	95426 ± 301482	55042 ± 206946	75796 ± 260373

Viral Load (ng/mL)	Ensovibep [e] n=232	Placebo [e] n=217	Total [e] n=449
n (%) positive	204 (88%)	196 (90%)	400 (89%)
min, max[f]	0, 1.97E8	0, 8.42E8	0, 8.42E8
median (IQR)[f]	51021 (3364, 986783)	50188 (4031, 924922)	50525 (3692, 979115)
mean ±SD[f]	4.76E6 ± 2.04E7	7.69E6 ± 6.11E7	6.2E6 ± 4.52E7

[a] positive = ≥ 1.0 S/C

[b] positive = ≥ 30%

[c] positive = ≥ 3 pg/ml

[d] positive = ≥ 770 ng/mL

[e] Only includes patients with antibody result

[f] Of patients viral load positive

Supplement Table 8: Concomitant Medications Use During Followup

	Reported at Day 5				Reported at Day 28			
	Ensovibep (n=240)		Placebo (n=228)		Ensovibep (n=203)		Placebo (n=191)	
Concomitant Medication	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
Antibiotics	60	25.0	63	27.6	9	4.4	19	9.9
IV antibiotic	47	19.6	46	20.2	7	3.4	10	5.2
Oral antibiotic	21	8.8	25	11.0	3	1.5	10	5.2
Antifungals	4	1.7	2	0.9	3	1.5	5	2.6
ACE inhibitor	20	8.3	15	6.6	11	5.4	16	8.4
ARB	13	5.4	10	4.4	13	6.4	16	8.4
Antiplatelets/anticoagulants	143	59.6	147	64.5	58	28.6	57	29.8
Aspirin	27	11.3	32	14.0	22	10.8	22	11.5
Other antiplatelet	9	3.8	11	4.8	6	3.0	8	4.2
Heparin prophy dose	83	34.6	88	38.6	12	5.9	7	3.7
Heparin intermediate dose	16	6.7	17	7.5	0	0.0	0	0.0
Heparin therapeutic dose	18	7.5	11	4.8	4	2.0	9	4.7
Warfarin	1	0.4	3	1.3	1	0.5	2	1.0
DOAC	8	3.3	13	5.7	21	10.3	12	6.3
Antiviral	0	0.0	0	0.0	0	0.0	0	0.0
Favipiravir	0	0.0	0	0.0	0	0.0	0	0.0
Lopinavir	0	0.0	0	0.0	0	0.0	0	0.0
Other antiviral	0	0.0	0	0.0	0	0.0	0	0.0
Antirejection meds	9	3.8	5	2.2	8	3.9	1	0.5
Immune modulator	24	10.0	18	7.9	4	2.0	1	0.5
IL1	0	0.0	0	0.0	0	0.0	0	0.0
IL6	1	0.4	2	0.9	0	0.0	0	0.0
Interferons	0	0.0	0	0.0	0	0.0	0	0.0
JAK inhibitor	20	8.3	15	6.6	1	0.5	0	0.0
TNF inhibitor	0	0.0	0	0.0	0	0.0	0	0.0
Other immune modulator	4	1.7	1	0.4	3	1.5	1	0.5
NSAID	5	2.1	6	2.6	5	2.5	6	3.1
Corticosteroids	136	56.7	114	50.0	14	6.9	11	5.8
Biologics for cancer/autoimmune disease	1	0.4	0	0.0	2	1.0	0	0.0

Note - concomitant medications used within the last 24 hours.

Supplement Table 9 : Day 5 Ordinal Pulmonary Outcome	Ensovibep			Placebo		
Day 5 Category	No.	%	Cum. %	No.	Pct.	Cum. %
1 Can independently undertake usual activities with minimal/no symptoms	45	18.6	18.6	51	21.9	21.9
2 No supplemental oxygen; symptomatic & unable to independently undertake usual activities	58	24.0	42.6	49	21.0	42.9
3 Supplemental oxygen < 4 liters/min [a]	37	15.3	57.9	45	19.3	62.2
4 Supplemental oxygen ≥ 4 liters/min [a]	39	16.1	74.0	30	12.9	75.1
5 Non-invasive ventilation or high-flow oxygen	46	19.0	93.0	45	19.3	94.4
6 Invasive ventilation, ECMO, mechanical circulatory support, or renal replacement therapy	16	6.6	99.6	10	4.3	98.7
7 Death	1	0.4	100.0	3	1.3	100.0
TOTAL	242	100.0		233	100.0	
Unadjusted Odds ratio (95% CI) [b]			*0.89 (0.65, 1.23)*			
Odds ratio (95% CI) [c]			*0.93 (0.67, 1.30)*			

[a] Compared to premorbid use, if applicable.

[b] Summary odds ratio (E/P) of being in a better category, using proportional odds.

[c] Summary odds ratio (E/P) of being in a better category, using proportional odds model with adjustment for patient's baseline ordinal level and pharmacy site (see Supplement Table 3 for strata)

Supplement Table 10 : Ordinal Pulmonary Plus Outcome on Day 5

	Category	Ensovibep No.	Ensovibep %	Ensovibep Cum. %	Placebo No.	Placebo %	Placebo Cum. %
1	Can independently undertake usual activities with minimal/no symptoms	45	18.6	18.6	51	21.9	21.9
2	No sup. oxygen; symptomatic & unable to independently undertake usual activities	58	24.0	42.6	49	21.0	42.9
3	Supplemental oxygen < 4 liters/min [a]	37	15.3	57.9	45	19.3	62.2
4	Supplemental oxygen ≥ 4 liters/min [a] *or end-organ manifestations* [b]	39	16.1	74.0	29	12.4	74.7
5	Non-invasive ventilation, high-flow oxygen or vasopressor *or severe stroke (NIHSS > 14)*	46	19.0	93.0	44	18.9	93.6
6	Invasive ventilation, ECMO, mechanical circulatory support, renal replacement therapy *or vasopressor*	16	6.6	99.6	12	5.2	98.7
7	Death	1	0.4	100.0	3	1.3	100.0
	TOTAL	242	100.0		233	100.0	
	Unadjusted Odds ratio (95% CI) [c]			*0.90 (0.66, 1.24)*			
	Odds ratio (95% CI) [d]			*0.95 (0.69, 1.32)*			

[a] Compared to premorbid use, if applicable.

[b] Stroke, meningitis, myocardial infarction, encephalitis, myelitis, myocarditis, pericarditis, CHF (NYHA III or IV), arterial or deep venous thromboembolic events.

[c] Summary odds ratio (E/P) of being in a better category, using proportional odds model.

[d] Summary odds ratio (E/P) of being in a better category, using proportional odds model with adjustment for patient's baseline ordinal level and site pharmacy (see Supplement Table 3 for strata)

Supplement Table 11 : Change from Baseline to Day 5 in Ordinal Outcome

	Ensovibep		Placebo	
Baseline Category*	No.	Pct.	No.	Pct.
No oxygen use	45	100.0	47	100.0
Better category on Day 5	19	42.2	20	42.6
Same category on Day 5	18	40.0	18	38.3
Worse category on Day 5	8	17.8	9	19.1
Conventional supplement O2 < 4 L/min	66	100.0	75	100.0
Better category on Day 5	40	60.6	42	56.0
Same category on Day 5	16	24.2	21	28.0
Worse category on Day 5	10	15.2	12	16.0
Conventional supplement O2 ≥ 4 L/min	81	100.0	63	100.0
Better category on Day 5	32	39.5	33	52.4
Same category on Day 5	26	32.1	14	22.2
Worse category on Day 5	23	28.4	16	25.4
High flow or non-invasive ventilation	50	100.0	48	100.0
Better category on Day 5	17	34.0	14	29.2
Same category on Day 5	25	50.0	29	60.4
Worse category on Day 5	8	16.0	5	10.4
All participants	242	100.0	233	100.0
Better category on Day 5	108	44.6	109	46.8
Same category on Day 5	85	35.1	82	35.2
Worse category on Day 5	49	20.2	42	18.0

* Baseline category of ordinal pulmonary endpoint.

Supplement Table 12 : Components of Ordinal Outcome Summarized at Day 5

Status on Day 5	Ensovibep No.	Ensovibep Pct.	Placebo No.	Placebo Pct.
Category 1 vs. 2-7				
Can undertake usual activities with no/minimal symptoms	45	18.6	51	21.9
Symptomatic, on oxygen, or died	197	81.4	182	78.1
Adj. OR (95% CI)*		*0.85 (0.51, 1.43)*		
Category 1-2 vs. 3-7				
Not on oxygen	103	42.6	100	42.9
On oxygen or died	139	57.4	133	57.1
Adj. OR (95% CI)*		*1.15 (0.74, 1.78)*		
Category 1-3 vs. 4-7				
Not on oxygen or oxygen use < 4 L/min	140	57.9	145	62.2
Oxygen needs ≥ 4 L/min or died	102	42.1	88	37.8
Adj. OR (95% CI)*		*0.90 (0.57, 1.42)*		
Category 1-4 vs. 5-7				
No oxygen needed beyond conventional supplement O2	179	74.0	175	75.1
Non-invasive ventilation, HFNC, or life support needed, or died	63	26.0	58	24.9
Adj. OR (95% CI)*		*1.03 (0.63, 1.70)*		
Category 1-5 vs. 6-7				
Not on life support	225	93.0	220	94.4
Intubated, ECMO, mech. circulatory support, dialysis, or died	17	7.0	13	5.6
Adj. OR (95% CI)*		*0.80 (0.37, 1.72)*		
Category 1-6 vs. 7				
Alive	241	99.6	230	98.7
Dead	1	0.4	3	1.3
No. Participants with Day 5 Outcome	*242*		*233*	

Proportional Odds Assumption:	p-value
• Test from partial proportional odds model with unequal slopes across outcome categories, but equal slopes across stratification covariates	.40

* Odds ratio (E/P) for being in the *better* category with adjustment for ordinal category at baseline and pharmacy site (see Supplement Table 3 for strata)

Supplement Table 13 : Odds Ratios for Ordinal Outcomes, Days 1-7

		Pulmonary Outcome		Pulmonary+ Outcome	
Visit	No.	OR*	95% CI	OR*	95% CI
Day 1	480	0.90	0.61, 1.32	0.95	0.65, 1.38
Day 2	478	0.93	0.65, 1.31	0.97	0.68, 1.37
Day 3	478	0.82	0.59, 1.15	0.84	0.60, 1.18
Day 4	475	0.80	0.57, 1.11	0.82	0.59, 1.14
Day 5	475	0.93	0.67, 1.30	0.95	0.69, 1.32
Day 6	474	1.07	0.77, 1.48	1.09	0.78, 1.51
Day 7	474	1.13	0.81, 1.57	1.12	0.81, 1.56

*** Summary odds ratio (E/P) of being in a better category, using proportional odds model with adjustment for patient's baseline clinical category and pharmacy site (see Supplement Table 3 for strata)**

s

Supplement Table 14: Ordinal Pulmonary Outcome on Day 14

	Day 14 Category	Ensovibep No.	Ensovibep %	Ensovibep Cum. %	Placebo No.	Placebo %	Placebo Cum. %
1	Can independently undertake usual activities with minimal/no symptoms	101	43.5	43.5	93	41.7	41.7
2	No supplemental oxygen; symptomatic & unable to independently undertake usual activities	43	18.5	62.1	54	24.2	65.9
3	Supplemental oxygen < 4 liters/min [a]	33	14.2	76.3	25	11.2	77.1
4	Supplemental oxygen ≥ 4 liters/min [a]	14	6.0	82.3	7	3.1	80.3
5	Non-invasive ventilation or high-flow oxygen	10	4.3	86.6	8	3.6	83.9
6	Invasive ventilation, ECMO, mechanical circulatory support, or renal replacement therapy	13	5.6	92.2	19	8.5	92.4
7	Death	18	7.8	100.0	17	7.6	100.0
	TOTAL	232	100.0		223	100.0	
	Odds ratio (95% CI) [b]			*1.10 (0.77, 1.55)*			

[a] Compared to premorbid use, if applicable.

[b] Summary odds ratio (E/P) of being in a better category, using proportional odds model with adjustment for patient's baseline ordinal level and pharmacy site (see Supplement Table 3 for strata)

Supplement Table 15 : Ordinal Pulmonary Outcome on Day 28

	Day 28 Category	Ensovibep No.	Ensovibep %	Ensovibep Cum. %	Placebo No.	Placebo %	Placebo Cum. %
1	Can independently undertake usual activities with minimal/no symptoms	128	56.4	56.4	123	55.9	55.9
2	No supplemental oxygen; symptomatic & unable to independently undertake usual activities	33	14.5	70.9	39	17.7	73.6
3	Supplemental oxygen < 4 liters/min [a]	25	11.0	81.9	13	5.9	79.5
4	Supplemental oxygen ≥ 4 liters/min [a]	5	2.2	84.1	5	2.3	81.8
5	Non-invasive ventilation or high-flow oxygen	5	2.2	86.3	0	0.0	81.8
6	Invasive ventilation, ECMO, mechanical circulatory support, or renal replacement therapy	9	4.0	90.3	15	6.8	88.6
7	Death	22	9.7	100.0	25	11.4	100.0
	TOTAL	227	100.0		220	100.0	
	Odds ratio (95% CI) [b]			*1.13 (0.77, 1.65)*			

[a] Compared to premorbid use, if applicable.

[b] Summary odds ratio (E/P) of being in a better category, using proportional odds model with adjustment for patient's baseline category and pharmacy site (see Supplement Table 3 for strata)

Supplement Table 16 : Infusion Reactions by Type and grade

	Ensovibep (no. infused=247)				Placebo (no. infused=238)			
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%)
Bronchospasm	1 (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%)	0 (0%)	0 (0%)	0 (0%)
Confusion	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%)
Fever	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	1 (0%)	2 (1%)	0 (0%)
Headache	2 (1%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)	1 (0%)	0 (0%)
Hypotension	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Pruritus	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (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%)	2 (1%)	0 (0%)	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	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tachycardia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (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%)	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%)
Other reaction	7 (3%)	0 (0%)	0 (0%)	1 (0%)	3 (1%)	1 (0%)	0 (0%)	0 (0%)
Any of above	15 (6%)	1 (0%)	0 (0%)	1 (0%)	8 (3%)	3 (1%)	3 (1%)	1 (0%)

*** Collected via checklist during and within 2 hours following the completion of administration off blinded study medication. Limited to signs and symptoms that are new or increased in grade (as compared to pre-infusion). A participant with multiple *other* reactions is counted once according to highest grade of *other reaction* recorded.**

Supplement Table 17 : Infusion Reactions by Grade

	Ensovibep (no. infused=247)				Placebo (no. infused=238)			
Infusion Reaction*	Grade ≥ 1 No. (%)	Grade ≥ 2 No. (%)	Grade ≥ 3 No. (%)	Grade 4 No. (%)	Grade ≥ 1 No. (%)	Grade ≥ 2 No. (%)	Grade ≥ 3 No. (%)	Grade 4 No. (%)
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%)
Bronchospasm	1 (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%)	0 (0%)	0 (0%)	0 (0%)
Confusion	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%)
Fever	2 (1%)	0 (0%)	0 (0%)	0 (0%)	5 (2%)	3 (1%)	2 (1%)	0 (0%)
Headache	3 (1%)	1 (0%)	0 (0%)	0 (0%)	3 (1%)	2 (1%)	1 (0%)	0 (0%)
Hypotension	2 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)	1 (0%)	1 (0%)
Pruritus	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (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%)	2 (1%)	0 (0%)	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	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tachycardia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (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%)	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%)
Other reaction	8 (3%)	1 (0%)	1 (0%)	1 (0%)	4 (2%)	1 (0%)	0 (0%)	0 (0%)
Any of above	16 (6%)	2 (1%)	1 (0%)	1 (0%)	12 (5%)	6 (3%)	3 (1%)	1 (0%)

*** Collected via checklist during and within 2 hours following the completion of administration of blinded study medication. Limited to signs and symptoms that are reported as new or increased in grade (as compared to pre-infusion). *Other* reactions are counted once per patient according to highest grade.**

Supplement Table 18 : Adverse Events of Any Grade through Day 7 by MedDRA System Organ Class

System Organ Class (MedDRA SOC)	Ensovibep (n=247) Pts w/ events	Ensovibep (n=247) Pct w/ events	Placebo (n=238) Pts w/ events	Placebo (n=238) Pct w/ events
Blood and Lymphatic System	3	1.2	2	0.8
Cardiac	16	6.5	13	5.5
Congenital, Familial, Genetic	0	0.0	0	0.0
Ear and Labyrinth	1	0.4	1	0.4
Endocrine	0	0.0	0	0.0
Eye	0	0.0	1	0.4
Gastrointestinal	30	12.1	36	15.1
General and Administration Site	32	13.0	45	18.9
Hepatobiliary	0	0.0	1	0.4
Immune System	0	0.0	0	0.0
Infections and Infestations	9	3.6	9	3.8
Injury, Poisoning, Procedural	0	0.0	1	0.4
Investigations	3	1.2	3	1.3
Metabolism and Nutrition	19	7.7	21	8.8
Musculoskeletal, Connective Tissue	7	2.8	11	4.6
Neoplasms - Benign and Malignant	0	0.0	0	0.0
Nervous System	17	6.9	32	13.4
Pregnancy, puerperium, perinatal	0	0.0	0	0.0
Psychiatric	13	5.3	15	6.3
Renal and Urinary	9	3.6	4	1.7
Reproductive System and Breast	0	0.0	0	0.0
Respiratory, Thoracic, Mediastinal	54	21.9	58	24.4
Skin and Subcutaneous Tissue	2	0.8	6	2.5
Social Circumstances	0	0.0	0	0.0
Surgical and Medical Procedures	0	0.0	0	0.0
Vascular	10	4.0	13	5.5
Not yet MedDRA coded	0	0.0	0	0.0
Any of above	103	41.7	111	46.6

Supplement Table 19 : Adverse Events of Any Grade Present at Day 14 Visit by MedDRA System Organ Class

System Organ Class (MedDRA SOC)	Ensovibep (n=247) Pts w/ events	Ensovibep (n=247) Pct w/ events	Placebo (n=238) Pts w/ events	Placebo (n=238) Pct w/ events
Blood and Lymphatic System	0	0.0	3	1.3
Cardiac	2	0.8	6	2.5
Congenital, Familial, Genetic	0	0.0	0	0.0
Ear and Labyrinth	1	0.4	0	0.0
Endocrine	0	0.0	0	0.0
Eye	1	0.4	0	0.0
Gastrointestinal	5	2.0	7	2.9
General and Administration Site	27	10.9	31	13.0
Hepatobiliary	0	0.0	1	0.4
Immune System	0	0.0	0	0.0
Infections and Infestations	3	1.2	8	3.4
Injury, Poisoning, Procedural	0	0.0	0	0.0
Investigations	0	0.0	1	0.4
Metabolism and Nutrition	8	3.2	9	3.8
Musculoskeletal, Connective Tissue	10	4.0	4	1.7
Neoplasms - Benign and Malignant	1	0.4	0	0.0
Nervous System	7	2.8	15	6.3
Pregnancy, puerperium, perinatal	0	0.0	0	0.0
Psychiatric	6	2.4	4	1.7
Renal and Urinary	1	0.4	3	1.3
Reproductive System and Breast	0	0.0	0	0.0
Respiratory, Thoracic, Mediastinal	40	16.2	39	16.4
Skin and Subcutaneous Tissue	5	2.0	1	0.4
Social Circumstances	0	0.0	0	0.0
Surgical and Medical Procedures	0	0.0	0	0.0
Vascular	1	0.4	5	2.1
Not yet MedDRA coded	0	0.0	0	0.0
Any of above	67	27.1	68	28.6

Supplement Table 20 : Adverse Events of Any Grade Present at Day 28 by MedDRA System Organ Class

System Organ Class (MedDRA SOC)	Ensovibep (n=247)		Placebo (n=238)	
	Pts w/ events	Pct w/ events	Pts w/ events	Pct w/ events
Blood and Lymphatic System	2	0.8	3	1.3
Cardiac	3	1.2	2	0.8
Congenital, Familial, Genetic	0	0.0	0	0.0
Ear and Labyrinth	1	0.4	1	0.4
Endocrine	0	0.0	0	0.0
Eye	1	0.4	0	0.0
Gastrointestinal	5	2.0	5	2.1
General and Administration Site	26	10.5	23	9.7
Hepatobiliary	0	0.0	0	0.0
Immune System	0	0.0	0	0.0
Infections and Infestations	2	0.8	7	2.9
Injury, Poisoning, Procedural	0	0.0	0	0.0
Investigations	0	0.0	0	0.0
Metabolism and Nutrition	8	3.2	3	1.3
Musculoskeletal, Connective Tissue	9	3.6	9	3.8
Neoplasms - Benign and Malignant	0	0.0	1	0.4
Nervous System	9	3.6	11	4.6
Pregnancy, puerperium, perinatal	0	0.0	0	0.0
Psychiatric	3	1.2	2	0.8
Renal and Urinary	1	0.4	0	0.0
Reproductive System and Breast	1	0.4	0	0.0
Respiratory, Thoracic, Mediastinal	30	12.1	28	11.8
Skin and Subcutaneous Tissue	0	0.0	4	1.7
Social Circumstances	0	0.0	0	0.0
Surgical and Medical Procedures	0	0.0	0	0.0
Vascular	2	0.8	1	0.4
Not yet MedDRA coded	0	0.0	0	0.0
Any of above	57	23.1	53	22.3

Supplement Table 21: Incidence of Grade 3/4 Adverse Events through Day 28 by MedDRA System Organ Class

System Organ Class (MedDRA SOC)	Ensovibep (n=247)		Placebo (n=238)	
	Pts w/ events	Pct w/ events	Pts w/ events	Pct w/ events
Blood and Lymphatic System	2	0.8	4	1.7
Cardiac	7	2.8	7	2.9
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	5	2.0	8	3.4
General and Administration Site	15	6.1	21	8.8
Hepatobiliary	1	0.4	1	0.4
Immune System	0	0.0	0	0.0
Infections and Infestations	7	2.8	14	5.9
Injury, Poisoning, Procedural	0	0.0	0	0.0
Investigations	1	0.4	1	0.4
Metabolism and Nutrition	8	3.2	12	5.0
Musculoskeletal, Connective Tissue	1	0.4	3	1.3
Neoplasms - Benign and Malignant	0	0.0	0	0.0
Nervous System	4	1.6	3	1.3
Pregnancy, puerperium, perinatal	0	0.0	0	0.0
Product Issues	0	0.0	0	0.0
Psychiatric	8	3.2	9	3.8
Renal and Urinary	7	2.8	8	3.4
Reproductive System and Breast	0	0.0	0	0.0
Respiratory, Thoracic, Mediastinal	47	19.0	47	19.7
Skin and Subcutaneous Tissue	0	0.0	2	0.8
Social Circumstances	0	0.0	0	0.0
Surgical and Medical Procedures	0	0.0	0	0.0
Vascular	11	4.5	14	5.9
Not yet MedDRA coded	0	0.0	0	0.0
Any of above	64	25.9	77	32.4

Supplement Table 22 : SAEs through Day 90 by MedDRA System Organ Class

System Organ Class (MedDRA SOC)	Ensovibep (n=247) Pts w/ events	Ensovibep (n=247) Pct w/ events	Placebo (n=238) Pts w/ events	Placebo (n=238) Pct w/ events
Blood and Lymphatic System	0	0.0	1	0.4
Cardiac	1	0.4	1	0.4
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	0.8	2	0.8
General and Administration Site	2	0.8	0	0.0
Hepatobiliary	1	0.4	0	0.0
Immune System	0	0.0	0	0.0
Infections and Infestations	0	0.0	0	0.0
Injury, Poisoning, Procedural	2	0.8	1	0.4
Investigations	1	0.4	0	0.0
Metabolism and Nutrition	0	0.0	1	0.4
Musculoskeletal, Connective Tissue	0	0.0	1	0.4
Neoplasms - Benign and Malignant	0	0.0	3	1.3
Nervous System	1	0.4	0	0.0
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	1	0.4
Reproductive System and Breast	0	0.0	0	0.0
Respiratory, Thoracic, Mediastinal	3	1.2	4	1.7
Skin and Subcutaneous Tissue	0	0.0	0	0.0
Social Circumstances	0	0.0	0	0.0
Surgical and Medical Procedures	1	0.4	0	0.0
Vascular	0	0.0	3	1.3
Not yet MedDRA coded	0	0.0	0	0.0
Any of above	14	5.7	16	6.7

Supplement Table 23 : Safety Summary through Day 5

	Ensovibep (n= 247)		Placebo (n= 238)	
Events through Day 5	Pts	Pct.	Pts	Pct.
Death	1	0.4	3	1.3
Death or SAE	4	1.6	6	2.5
Death, SAE, or Grade 4 AE	25	10.1	21	8.8
Death, SAE, or Grade 3/4 AE	47	19.0	53	22.3
Death, SAE, Grade 3/4 AE, or Organ Failure	61	24.7	67	28.2
Death, SAE, Grade 3/4 AE, Organ Failure, Serious Infection	61	24.7	69	29.0
Organ Failure or Serious Infection	41	16.6	35	14.7

Supplement Table 24 : Safety Summary through Day 28 Including Rash Events

	Ensovibep (n= 247)		Placebo (n= 238)		Hazard Ratio*	
Events though Day 28	Pts	Pct.	Pts	Pct.	HR	95% CI
Death	22	8.9	25	10.5	0.87	0.49, 1.54
Death or SAE	30	12.1	33	13.9	0.87	0.53, 1.43
Death, SAE, or Grade 4 AE	41	16.6	49	20.6	0.81	0.53, 1.22
Death, SAE, or Grade 3/4 AE	69	27.9	86	36.1	0.74	0.54, 1.02
Death, SAE, Grade 3/4 AE, or Organ Failure	83	33.6	94	39.5	0.82	0.61, 1.11
Death, SAE, Grade 3/4 AE, Organ Failure, Serious Infection	84	34.0	96	40.3	0.81	0.60, 1.09
Death, SAE, Grade 3/4 AE, Organ Failure, Serious Infection, Rash	88	35.6	98	41.2	0.83	0.62, 1.11
Organ Failure or Serious Infection	58	23.5	56	23.5	0.99	0.69, 1.44

* Hazard ratio by Cox proportional hazards model stratified by pharmacy site (see Supplement Table 3 for strata)

Supplement Table 25 : Safety Summary through Day 90

	Ensovibep (n= 247)		Placebo (n= 238)		Hazard Ratio*	
Events though Day 90	Pts	Pct.	Pts	Pct.	HR	95% CI
Death	30	12.1	35	14.7	0.83	0.51, 1.35
Death or SAE	43	17.4	45	18.9	0.92	0.61, 1.40
Death, SAE, or Organ Failure	74	30.0	67	28.2	1.06	0.76, 1.48
Death, SAE, Organ Failure, or Serious Infection	78	31.6	70	29.4	1.07	0.77, 1.47
Organ Failure or Serious Infection	63	25.5	59	24.8	1.02	0.72, 1.46

* Hazard ratio by Cox proportional hazards model stratified by pharmacy site (see Supplement Table 3 for strata)

NOTE - grade 3 and 4 AEs are only collected through day 28, therefore not included in this composite outcome.

Supplement Table 26 : Clinical Organ Failure and Serious Infections through Day 90

	Ensovibep (n =247)		Placebo (n=238)	
Diagnoses (through day 90)	No.	Pct.	No.	Pct.
Cardiac and vascular dysfunction				
MI +	1	0.4	2	0.8
CHF NYHA class III or IV	1	0.4	0	0.0
Hypotension requiring vasopressor	19	7.7	25	10.5
Myocarditis	0	0.0	0	0.0
Pericarditis	0	0.0	0	0.0
Hematological dysfunction				
Major bleeding event	2	0.8	3	1.3
DIC	1	0.4	0	0.0
Thromboembolic events +	13	5.3	10	4.2
Hepatic dysfunction				
Hepatic dysfunction	4	1.6	1	0.4
Infection				
Intercurrent serious coinfection	26	10.5	19	8.0
Neurologic dysfunction				
Acute delirium	6	2.4	9	3.8
Cerebrovascular accident/stroke +	1	0.4	1	0.4
Encephalitis	0	0.0	0	0.0
Meningitis	0	0.0	0	0.0
Myelitis	0	0.0	0	0.0
TIA +	0	0.0	1	0.4
Renal dysfunction				
Renal replacement therapy	6	2.4	6	2.5
Respiratory dysfunction				
Respiratory failure	42	17.0	35	14.7
Any of above	63	25.5	59	24.8
Any CVD	15	6.1	12	5.0

+ Included in any CVD category

Supplement Table 27 : Rash Events through Day 28

Events Concurrent with Rash	Ensovibep (n=247)		Placebo (n=238)	
	Pts w/ events	Pct w/ events	Pts w/ events	Pct w/ events
Myalgia	0	0.0	0	0.0
Arthralgia (joint ache/pain)	0	0.0	0	0.0
Generalized aches and pains	1	0.4	0	0.0
Elevated creatinine	0	0.0	1	0.4
Abnormal urinalysis and/or urine sediment	0	0.0	0	0.0
Elevated AST	0	0.0	0	0.0
Elevated ALT	1	0.4	1	0.4
Other	2	0.8	0	0.0
No concurrent events	4	1.6	3	1.3
Has rash event	7	2.8	4	1.7

Supplement Table 28 : Subgroup Analysis for Sustained Recovery

	Ensovibep		Placebo		sHR*	
Baseline Subgroup	Pts	N (%)	Pts	N (%)	sHR	95% CI
Age* (years)						
< 50	79	71 (90%)	83	70 (84%)	1.04	0.77, 1.42
50-59	53	47 (89%)	50	45 (90%)	1.07	0.73, 1.57
60-69	56	43 (77%)	55	40 (73%)	1.31	0.87, 1.98
70-79	49	33 (67%)	27	21 (78%)	0.78	0.46, 1.32
80 +	10	9 (90%)	23	14 (61%)	1.56	0.76, 3.20
Gender						
Male	147	120 (82%)	128	100 (78%)	1.12	0.87, 1.44
Female	100	83 (83%)	110	90 (82%)	1.01	0.76, 1.34
Race						
Black	60	50 (83%)	60	52 (87%)	0.84	0.59, 1.21
Hispanic	40	33 (83%)	38	27 (71%)	1.75	1.07, 2.86
White/other	147	120 (82%)	140	111 (79%)	1.02	0.80, 1.31
Region						
Africa	22	16 (73%)	23	20 (87%)	0.61	0.33, 1.13
Asia	12	10 (83%)	11	10 (91%)	0.95	0.41, 2.20
Europe	41	35 (85%)	45	37 (82%)	1.06	0.68, 1.64
N. America	172	142 (83%)	159	123 (77%)	1.16	0.92, 1.46
Days since symptom onset						
≤ 5	62	55 (89%)	59	51 (86%)	1.19	0.83, 1.71
6-8	77	62 (81%)	96	75 (78%)	0.94	0.69, 1.30
9 +	108	86 (80%)	83	64 (77%)	1.13	0.83, 1.55
Baseline pulmonary category						
Not on supplemental O2	47	45 (96%)	48	44 (92%)	1.51	1.01, 2.23
Sup O2, flow rate < 4 L/min	68	63 (93%)	77	67 (87%)	1.11	0.81, 1.53
Sup O2, flow rate ≥ 4 L/min	82	64 (78%)	65	54 (83%)	0.78	0.55, 1.11
HF or NIV	50	31 (62%)	48	25 (52%)	1.50	0.90, 2.50
BMI kg/m^2						
≤ 30	135	112 (83%)	122	94 (77%)	1.12	0.86, 1.46
> 30	112	91 (81%)	116	96 (83%)	1.03	0.78, 1.35
History of chronic condition						
Yes	142	110 (77%)	133	107 (80%)	0.94	0.72, 1.21
No	105	93 (89%)	105	83 (79%)	1.30	0.98, 1.72
Covid-19 vaccination status						
Fully vaccinated	62	54 (87%)	62	48 (77%)	1.26	0.88, 1.82
Partially vaccinated	12	11 (92%)	17	15 (88%)	1.85	0.85, 4.01
Not vaccinated	173	138 (80%)	159	127 (80%)	0.98	0.78, 1.24
Immunosuppressed						
Yes	18	16 (89%)	12	8 (67%)	1.55	0.72, 3.33
No	229	187 (82%)	226	182 (81%)	1.04	0.86, 1.26
Date of Enrollment						
Before 19Jul21	27	23 (85%)	27	20 (74%)	1.10	0.63, 1.94
On or after 19Jul21	220	180 (82%)	211	170 (81%)	1.06	0.87, 1.29

* subhazard ratio (E/P), from a Fine-Gray model.

Supplement Table 29 : Subgroup Analysis for Day 28 Composite Safety Outcome

	Ensovibep		Placebo		Hazard Ratio*	
Baseline Subgroup	**Pts.**	**N (%)**	**Pts.**	**N (%)**	**HR**	**95% CI**
Age* (years)						
< 50	**79**	**24 (30%)**	**83**	**24 (29%)**	**1.03**	**0.58, 1.81**
50-59	**53**	**12 (23%)**	**50**	**19 (38%)**	**0.59**	**0.28, 1.21**
60-69	**56**	**19 (34%)**	**55**	**24 (44%)**	**0.73**	**0.40, 1.34**
70-79	**49**	**24 (49%)**	**27**	**15 (56%)**	**0.86**	**0.45, 1.64**
80 +	**10**	**5 (50%)**	**23**	**14 (61%)**	**0.78**	**0.28, 2.16**
Gender						
Male	**147**	**49 (33%)**	**128**	**52 (41%)**	**0.82**	**0.55, 1.21**
Female	**100**	**35 (35%)**	**110**	**44 (40%)**	**0.83**	**0.53, 1.29**
Race						
Black	**60**	**21 (35%)**	**60**	**19 (32%)**	**1.14**	**0.61, 2.11**
Hispanic	**40**	**13 (33%)**	**38**	**19 (50%)**	**0.63**	**0.31, 1.27**
White/other	**147**	**50 (34%)**	**140**	**58 (41%)**	**0.78**	**0.54, 1.14**
Region						
Africa	**22**	**7 (32%)**	**23**	**5 (22%)**	**1.54**	**0.49, 4.87**
Asia	**12**	**3 (25%)**	**11**	**2 (18%)**	**1.50**	**0.25, 9.00**
Europe	**41**	**11 (27%)**	**45**	**13 (29%)**	**0.91**	**0.41, 2.04**
N. America	**172**	**63 (37%)**	**159**	**76 (48%)**	**0.73**	**0.52, 1.01**
Days since symptom onset*						
≤ 5	**62**	**21 (34%)**	**59**	**24 (41%)**	**0.77**	**0.43, 1.39**
6-8	**77**	**26 (34%)**	**96**	**37 (39%)**	**0.87**	**0.53, 1.43**
9 +	**108**	**37 (34%)**	**83**	**35 (42%)**	**0.79**	**0.50, 1.26**
Baseline pulmonary category*						
Not on supplemental O2	**47**	**4 (9%)**	**48**	**14 (29%)**	**0.26**	**0.09, 0.80**
Sup O2, flow rate < 4 L/min	**68**	**15 (22%)**	**77**	**22 (29%)**	**0.75**	**0.39, 1.45**
Sup O2, flow rate ≥ 4 L/min	**82**	**38 (46%)**	**65**	**29 (45%)**	**0.97**	**0.60, 1.57**
HF or NIV	**50**	**27 (54%)**	**48**	**31 (65%)**	**0.87**	**0.52, 1.45**
BMI kg/m^2*						
≤ 30	**135**	**44 (33%)**	**122**	**52 (43%)**	**0.73**	**0.49, 1.09**
> 30	**112**	**40 (36%)**	**116**	**44 (38%)**	**0.93**	**0.61, 1.43**
History of chronic condition**						
Yes	**142**	**58 (41%)**	**133**	**59 (44%)**	**0.91**	**0.63, 1.30**
No	**105**	**26 (25%)**	**105**	**37 (35%)**	**0.68**	**0.41, 1.12**
Covid-19 vaccination status**						
Fully vaccinated	**62**	**20 (32%)**	**62**	**26 (42%)**	**0.73**	**0.41, 1.30**
Partially vaccinated	**12**	**2 (17%)**	**17**	**7 (41%)**	**0.35**	**0.07, 1.68**
Not vaccinated	**173**	**62 (36%)**	**159**	**63 (40%)**	**0.89**	**0.63, 1.26**
Immunosuppressed**						
Yes	**18**	**8 (44%)**	**12**	**5 (42%)**	**0.97**	**0.32, 2.97**
No	**229**	**76 (33%)**	**226**	**91 (40%)**	**0.80**	**0.59, 1.09**

*** Hazard ratio by Cox proportional hazards model.**

Supplement Table 30 : Subgroup Analysis for Day 90 Composite Safety Outcome

	Ensovibep		Placebo		Hazard Ratio*	
Baseline Subgroup	**Pts.**	**N (%)**	**Pts.**	**N (%)**	**HR**	**95% CI**
Age* (years)						
< 50	**79**	**18 (23%)**	**83**	**18 (22%)**	**1.04**	**0.54, 1.97**
50-59	**53**	**11 (21%)**	**50**	**14 (28%)**	**0.77**	**0.35, 1.68**
60-69	**56**	**19 (34%)**	**55**	**19 (35%)**	**0.98**	**0.53, 1.83**
70-79	**49**	**26 (53%)**	**27**	**9 (33%)**	**1.73**	**0.81, 3.68**
80 +	**10**	**4 (40%)**	**23**	**10 (43%)**	**0.88**	**0.29, 2.63**
Gender						
Male	**147**	**45 (31%)**	**128**	**43 (34%)**	**0.93**	**0.62, 1.40**
Female	**100**	**33 (33%)**	**110**	**27 (25%)**	**1.35**	**0.82, 2.24**
Race						
Black	**60**	**19 (32%)**	**60**	**14 (23%)**	**1.40**	**0.71, 2.77**
Hispanic	**40**	**11 (28%)**	**38**	**18 (47%)**	**0.54**	**0.26, 1.14**
White/other	**147**	**48 (33%)**	**140**	**38 (27%)**	**1.23**	**0.81, 1.87**
Region						
Africa	**22**	**7 (32%)**	**23**	**3 (13%)**	**2.62**	**0.69, 9.96**
Asia	**12**	**3 (25%)**	**11**	**2 (18%)**	**1.50**	**0.28, 8.16**
Europe	**41**	**11 (27%)**	**45**	**8 (18%)**	**1.52**	**0.62, 3.73**
N. America	**172**	**57 (33%)**	**159**	**57 (36%)**	**0.91**	**0.64, 1.31**
Days since symptom onset*						
≤ 5	**62**	**17 (27%)**	**59**	**13 (22%)**	**1.19**	**0.58, 2.45**
6-8	**77**	**26 (34%)**	**96**	**25 (26%)**	**1.37**	**0.80, 2.35**
9 +	**108**	**35 (32%)**	**83**	**32 (39%)**	**0.83**	**0.52, 1.32**
Baseline pulmonary category*						
Not on supplemental O2	**47**	**4 (9%)**	**48**	**7 (15%)**	**0.57**	**0.17, 1.92**
Sup O2, flow rate < 4 L/min	**68**	**16 (24%)**	**77**	**13 (17%)**	**1.41**	**0.68, 2.91**
Sup O2, flow rate ≥ 4 L/min	**82**	**34 (41%)**	**65**	**22 (34%)**	**1.21**	**0.72, 2.05**
HF or NIV	**50**	**24 (48%)**	**48**	**28 (58%)**	**0.83**	**0.48, 1.41**
BMI kg/m^{2*}						
≤ 30	**135**	**43 (32%)**	**122**	**40 (33%)**	**0.96**	**0.63, 1.46**
> 30	**112**	**35 (31%)**	**116**	**30 (26%)**	**1.25**	**0.77, 2.02**
History of chronic condition**						
Yes	**142**	**54 (38%)**	**133**	**45 (34%)**	**1.14**	**0.77, 1.69**
No	**105**	**24 (23%)**	**105**	**25 (24%)**	**0.97**	**0.56, 1.69**
Covid-19 vaccination status**						
Fully vaccinated	**62**	**19 (31%)**	**62**	**18 (29%)**	**1.06**	**0.56, 2.00**
Partially vaccinated	**12**	**2 (17%)**	**17**	**5 (29%)**	**0.57**	**0.12, 2.78**
Not vaccinated	**173**	**57 (33%)**	**159**	**47 (30%)**	**1.12**	**0.77, 1.64**
Immunosuppressed**						
Yes	**18**	**7 (39%)**	**12**	**6 (50%)**	**0.68**	**0.24, 1.95**
No	**229**	**71 (31%)**	**226**	**64 (28%)**	**1.11**	**0.80, 1.55**

*** Hazard ratio by Cox proportional hazards model.**

Supplement Table 31 : Subgroup Analysis for Mortality through Day 90

	Ensovibep		Placebo		Hazard Ratio*	
Baseline Subgroup	**Pts**	**N (%)**	**Pts**	**N (%)**	**HR**	**95% CI**
Age* (years)						
< 50	**79**	**4 (5%)**	**83**	**4 (5%)**	**1.03**	**0.26, 4.12**
50-59	**53**	**3 (6%)**	**50**	**6 (12%)**	**0.48**	**0.12, 1.93**
60-69	**56**	**9 (16%)**	**55**	**14 (25%)**	**0.59**	**0.26, 1.37**
70-79	**49**	**12 (24%)**	**27**	**4 (15%)**	**1.74**	**0.56, 5.38**
80 +	**10**	**2 (20%)**	**23**	**7 (30%)**	**0.59**	**0.12, 2.82**
Gender						
Male	**147**	**20 (14%)**	**128**	**22 (17%)**	**0.77**	**0.42, 1.42**
Female	**100**	**10 (10%)**	**110**	**13 (12%)**	**0.84**	**0.37, 1.92**
Race						
Black	**60**	**9 (15%)**	**60**	**6 (10%)**	**1.49**	**0.53, 4.19**
Hispanic	**40**	**4 (10%)**	**38**	**10 (26%)**	**0.35**	**0.11, 1.12**
White/other	**147**	**17 (12%)**	**140**	**19 (14%)**	**0.83**	**0.43, 1.61**
Region						
Africa	**22**	**6 (27%)**	**23**	**3 (13%)**	**2.08**	**0.52, 8.33**
Asia	**12**	**0 (0%)**	**11**	**2 (18%)**	**0.00**	**0.00, .**
Europe	**41**	**3 (7%)**	**45**	**4 (9%)**	**0.79**	**0.18, 3.55**
N. America	**172**	**21 (12%)**	**159**	**26 (16%)**	**0.73**	**0.41, 1.30**
Days since symptom onset*						
≤ 5	**62**	**6 (10%)**	**59**	**6 (10%)**	**0.94**	**0.30, 2.93**
6-8	**77**	**12 (16%)**	**96**	**14 (15%)**	**1.04**	**0.48, 2.25**
9 +	**108**	**12 (11%)**	**83**	**15 (18%)**	**0.61**	**0.29, 1.30**
Baseline pulmonary category*						
Not on supplemental O2	**47**	**1 (2%)**	**48**	**3 (6%)**	**0.34**	**0.04, 3.24**
Sup O2, flow rate < 4 L/min	**68**	**3 (4%)**	**77**	**5 (6%)**	**0.66**	**0.16, 2.76**
Sup O2, flow rate ≥ 4 L/min	**82**	**13 (16%)**	**65**	**6 (9%)**	**1.75**	**0.66, 4.59**
HF or NIV	**50**	**13 (26%)**	**48**	**21 (44%)**	**0.54**	**0.27, 1.07**
BMI kg/m^2*						
≤ 30	**135**	**18 (13%)**	**122**	**21 (17%)**	**0.73**	**0.39, 1.37**
> 30	**112**	**12 (11%)**	**116**	**14 (12%)**	**0.92**	**0.42, 1.98**
History of chronic condition						
Yes	**142**	**23 (16%)**	**133**	**22 (17%)**	**1.00**	**0.56, 1.79**
No	**105**	**7 (7%)**	**105**	**13 (12%)**	**0.51**	**0.20, 1.28**
Covid-19 vaccination status						
Fully vaccinated	**62**	**9 (15%)**	**62**	**8 (13%)**	**1.07**	**0.41, 2.78**
Partially vaccinated	**12**	**0 (0%)**	**17**	**3 (18%)**	**0.00**	**0.00, .**
Not vaccinated	**173**	**21 (12%)**	**159**	**24 (15%)**	**0.80**	**0.44, 1.43**
Immunosuppressed						
Yes	**18**	**2 (11%)**	**12**	**3 (25%)**	**0.38**	**0.06, 2.26**
No	**229**	**28 (12%)**	**226**	**32 (14%)**	**0.86**	**0.52, 1.43**

*** Hazard ratio (E/P), from a Cox proportional hazards model. .**

Supplement Table 32 : Sustained Recovery by Baseline Antibody/Antigen Subgroups

	Ensovibep		Placebo		sHR [a]	
Baseline Subgroup	Pts	N (%)	Pts	N (%)	sHR	95% CI
GenScript Antibody (nAb)						
Positive	154	123 (80%)	118	98 (83%)	0.98	0.76, 1.25
Negative	86	75 (87%)	109	86 (79%)	1.13	0.84, 1.51
BioRad (Anti-N Ab)						
Positive	154	121 (79%)	134	109 (81%)	0.92	0.72, 1.18
Negative	86	77 (90%)	93	75 (81%)	1.28	0.95, 1.73
Quanterix Antibody						
Positive	142	114 (80%)	114	97 (85%)	0.97	0.76, 1.25
Negative	98	84 (86%)	113	87 (77%)	1.11	0.83, 1.48
Quanterix Antigen						
< 1374 pg/mL	119	101 (85%)	114	103 (90%)	1.01	0.78, 1.30
1374+ pg/mL	121	97 (80%)	112	80 (71%)	1.12	0.84, 1.50
Antigen x GenScript						
Ag 1374+, nAb neg	62	51 (82%)	74	54 (73%)	1.13	0.78, 1.63
Ag 1374+, nAb pos	59	46 (78%)	38	26 (68%)	1.11	0.70, 1.77
Ag < 1374, nAb neg	24	24 (100%)	35	32 (91%)	1.45	0.95, 2.24
Ag < 1374, nAb pos	95	77 (81%)	79	71 (90%)	0.96	0.71, 1.29
Antigen x BioRad						
Ag 1374+, anti-N Ab neg	58	50 (86%)	55	40 (73%)	1.32	0.88, 1.97
Ag 1374+, anti-N Ab pos	63	47 (75%)	57	40 (70%)	0.95	0.63, 1.43
Ag < 1374, anti-N Ab neg	28	27 (96%)	37	34 (92%)	1.72	1.11, 2.66
Ag < 1374, anti-N Ab pos	91	74 (81%)	77	69 (90%)	0.90	0.66, 1.21
Antigen x Quanterix Ab						
Ag 1374+, Ab neg	72	58 (81%)	77	55 (71%)	1.13	0.79, 1.61
Ag 1374+, Ab pos	49	39 (80%)	35	25 (71%)	1.09	0.68, 1.76
Ag < 1374, Ab neg	26	26 (100%)	36	32 (89%)	1.30	0.84, 2.02
Ag < 1374, Ab pos	93	75 (81%)	78	71 (91%)	0.95	0.70, 1.28

[a] subhazard ratio (E/Ps) from a Fine-Gray model

Supplement Table 33 : Day 28 Composite Safety Outcome by Baseline Antibody/Antigen Subgroups

	Ensovibep		Placebo		Hazard Ratio [a]	
Baseline Subgroup	Pts	N (%)	Pts	N (%)	HR	95% CI
GenScript Antibody (nAb)						
Positive	154	48 (31%)	118	43 (36%)	0.84	0.56, 1.27
Negative	86	33 (38%)	109	46 (42%)	0.90	0.57, 1.40
BioRad (Anti-N Ab)						
Positive	154	57 (37%)	134	50 (37%)	0.99	0.68, 1.45
Negative	86	24 (28%)	93	39 (42%)	0.62	0.37, 1.03
Quanterix Antibody						
Positive	142	47 (33%)	114	40 (35%)	0.96	0.63, 1.46
Negative	98	34 (35%)	113	49 (43%)	0.76	0.49, 1.18
Quanterix Antigen						
< 1374 pg/mL	119	29 (24%)	114	26 (23%)	1.10	0.65, 1.86
1374+ pg/mL	121	52 (43%)	112	63 (56%)	0.70	0.49, 1.02
Antigen x GenScript						
Ag 1374+, nAb neg	62	30 (48%)	74	41 (55%)	0.85	0.53, 1.37
Ag 1374+, nAb pos	59	22 (37%)	38	22 (58%)	0.57	0.31, 1.02
Ag < 1374, nAb neg	24	3 (13%)	35	5 (14%)	0.86	0.21, 3.61
Ag < 1374, nAb pos	95	26 (27%)	79	21 (27%)	1.06	0.60, 1.89
Antigen x BioRad						
Ag 1374+, anti-N Ab neg	58	22 (38%)	55	33 (60%)	0.55	0.32, 0.95
Ag 1374+, anti-N Ab pos	63	30 (48%)	57	30 (53%)	0.87	0.53, 1.45
Ag < 1374, anti-N Ab neg	28	2 (7%)	37	6 (16%)	0.43	0.09, 2.15
Ag < 1374, anti-N Ab pos	91	27 (30%)	77	20 (26%)	1.18	0.66, 2.10
Antigen x Quanterix Ab						
Ag 1374+, Ab neg	72	33 (46%)	77	43 (56%)	0.77	0.49, 1.22
Ag 1374+, Ab pos	49	19 (39%)	35	20 (57%)	0.61	0.33, 1.15
Ag < 1374, Ab neg	26	1 (4%)	36	6 (17%)	0.21	0.03, 1.78
Ag < 1374, Ab pos	93	28 (30%)	78	20 (26%)	1.24	0.70, 2.21

[a] Hazard ratio (E/P) for time to first grade 3/4 AE, SAE, death, organ failure or serious coinfection event by Day 28, by Cox proportional hazards model.

ss

Supplement Table 34 : Day 90 Composite Safety Outcome Antibody/Antigen Subgroups

	Ensovibep		Placebo		Hazard Ratio [a]	
Baseline Subgroup	**Pts**	**N (%)**	**Pts**	**N (%)**	**HR**	**95% CI**
GenScript Antibody (nAb)						
Positive	154	45 (29%)	118	34 (29%)	1.03	0.66, 1.61
Negative	86	30 (35%)	109	30 (28%)	1.28	0.77, 2.12
BioRad (Anti-N Ab)						
Positive	154	52 (34%)	134	37 (28%)	1.25	0.82, 1.90
Negative	86	23 (27%)	93	27 (29%)	0.92	0.53, 1.60
Quanterix Antibody						
Positive	142	43 (30%)	114	29 (25%)	1.24	0.77, 1.98
Negative	98	32 (33%)	113	35 (31%)	1.05	0.65, 1.70
Quanterix Antigen						
< 1374 pg/mL	119	26 (22%)	114	20 (18%)	1.30	0.73, 2.33
1374+ pg/mL	121	49 (40%)	112	44 (39%)	1.02	0.68, 1.53
Antigen x GenScript						
Ag 1374+, nAb neg	62	28 (45%)	74	26 (35%)	1.33	0.78, 2.26
Ag 1374+, nAb pos	59	21 (36%)	38	18 (47%)	0.70	0.37, 1.31
Ag < 1374, nAb neg	24	2 (8%)	35	4 (11%)	0.68	0.13, 3.74
Ag < 1374, nAb pos	95	24 (25%)	79	16 (20%)	1.33	0.70, 2.49
Antigen x BioRad						
Ag 1374+, anti-N Ab neg	58	22 (38%)	55	20 (36%)	1.04	0.57, 1.91
Ag 1374+, anti-N Ab pos	63	27 (43%)	57	24 (42%)	0.99	0.57, 1.72
Ag < 1374, anti-N Ab neg	28	1 (4%)	37	7 (19%)	0.18	0.02, 1.46
Ag < 1374, anti-N Ab pos	91	25 (27%)	77	13 (17%)	1.72	0.88, 3.37
Antigen x Quanterix Ab						
Ag 1374+, Ab neg	72	31 (43%)	77	31 (40%)	1.08	0.65, 1.77
Ag 1374+, Ab pos	49	18 (37%)	35	13 (37%)	0.95	0.46, 1.93
Ag < 1374, Ab neg	26	1 (4%)	36	4 (11%)	0.32	0.04, 2.89
Ag < 1374, Ab pos	93	25 (27%)	78	16 (21%)	1.41	0.75, 2.64

[a] Hazard ratio (E/P) of death, SAE, organ failure, or serious infection through Day 90 by Cox proportional hazards model

Supplement Table 35 : Death through Day 90 by Antibody/Antigen Subgroups

	Ensovibep		Placebo		Hazard Ratio [a]	
Baseline Subgroup	Pts	N (%)	Pts	N (%)	HR	95% CI
GenScript Antibody (nAb)						
Positive	154	21 (14%)	118	16 (14%)	1.03	0.54, 1.97
Negative	86	7 (8%)	109	15 (14%)	0.56	0.23, 1.37
BioRad (Anti-N Ab)						
Positive	154	21 (14%)	134	19 (14%)	0.96	0.52, 1.78
Negative	86	7 (8%)	93	12 (13%)	0.61	0.24, 1.55
Quanterix Antibody						
Positive	142	18 (13%)	114	13 (11%)	1.13	0.56, 2.32
Negative	98	10 (10%)	113	18 (16%)	0.62	0.28, 1.34
Quanterix Antigen						
< 1374 pg/mL	119	9 (8%)	114	8 (7%)	1.10	0.42, 2.86
1374+ pg/mL	121	19 (16%)	112	23 (21%)	0.73	0.40, 1.34
Antigen x GenScript						
Ag 1374+, nAb neg	62	7 (11%)	74	13 (18%)	0.60	0.24, 1.51
Ag 1374+, nAb pos	59	12 (20%)	38	10 (26%)	0.73	0.32, 1.70
Ag < 1374, nAb neg	24	0 (0%)	35	2 (6%)		. , .
Ag < 1374, nAb pos	95	9 (9%)	79	6 (8%)	1.30	0.46, 3.67
Antigen x BioRad						
Ag 1374+, anti-N Ab neg	58	7 (12%)	55	9 (16%)	0.70	0.26, 1.87
Ag 1374+, anti-N Ab pos	63	12 (19%)	57	14 (25%)	0.74	0.34, 1.61
Ag < 1374, anti-N Ab neg	28	0 (0%)	37	3 (8%)		. , .
Ag < 1374, anti-N Ab pos	91	9 (10%)	77	5 (6%)	1.56	0.52, 4.66
Antigen x Quanterix Ab						
Ag 1374+, Ab neg	72	10 (14%)	77	16 (21%)	0.64	0.29, 1.42
Ag 1374+, Ab pos	49	9 (18%)	35	7 (20%)	0.86	0.32, 2.32
Ag < 1374, Ab neg	26	0 (0%)	36	2 (6%)		. , .
Ag < 1374, Ab pos	93	9 (10%)	78	6 (8%)	1.32	0.47, 3.72

[a] Hazard ratio (E/P) by Cox proportional hazards model

Supplement Table 36 : Recovery and Death by Baseline Viral Load

Sustained Recovery

	Ensovibep		Placebo		sHR [a]	
Baseline VL Subgroup	Pts	N (%)	Pts	N (%)	sHR	95% CI
Viral RNA						
< 56,000 cp/mL (low)[c]	133	113 (85%)	125	106 (85%)	0.97	0.76, 1.25
≥ 56,000 cp/mL (high)	103	81 (79%)	102	74 (73%)	1.23	0.91, 1.66
Viral RNA by nAb						
RNA high, nAb neg	48	39 (81%)	59	45 (76%)	1.04	0.69, 1.57
RNA high, nAb pos	53	40 (75%)	35	26 (74%)	1.27	0.80, 2.00
RNA low, nAb neg	34	32 (94%)	44	36 (82%)	1.15	0.74, 1.77
RNA low, nAb pos	96	80 (83%)	78	67 (86%)	0.94	0.69, 1.28

Death through Day 90

	Ensovibep		Placebo		Hazard Ratio [d]	
Baseline VL Subgroup	Pts	N (%)	Pts	N (%)	HR	95% CI
Viral RNA						
< 56,000 cp/mL (low)[c]	133	13 (10%)	125	14 (11%)	0.88	0.41, 1.88
≥ 56,000 cp/mL (high)	103	17 (17%)	102	20 (20%)	0.81	0.42, 1.54
Viral RNA by nAb						
RNA high, nAb neg	48	5 (10%)	59	8 (14%)	0.71	0.23, 2.18
RNA high, nAb pos	53	12 (23%)	35	8 (23%)	1.01	0.41, 2.48
RNA low, nAb neg	34	2 (6%)	44	6 (14%)	0.41	0.08, 2.05
RNA low, nAb pos	96	9 (9%)	78	8 (10%)	0.93	0.36, 2.41

[a] Subhazard ratio (E/P) from a Fine-Gray model

[c] Viral RNA < 56,000 cp/mL (median), negative, or indeterminate

[d] Hazard ratio (E/P) by Cox proportional hazards model.

Supplement Table 37 : Day 28 and Day 90 Composite Safety Outcome by Baseline Viral Load

Day 28 Composite Safety Outcome

	Ensovibep		Placebo		Hazard Ratio [a]			
Baseline VL Subgroup	**Pts**	**N (%)**	**Pts**	**N (%)**	**HR**	**95% CI**		
Viral RNA								
< 56,000 cp/mL (low)[c]	133	40 (30%)	125	43 (34%)	0.88	0.57, 1.35		.65
≥ 56,000 cp/mL (high)	103	42 (41%)	102	51 (50%)	0.76	0.51, 1.15		
Viral RNA by nAb								
RNA high, nAb neg	48	22 (46%)	59	28 (47%)	0.95	0.54, 1.65	dd	sss
RNA high, nAb pos	53	19 (36%)	35	17 (49%)	0.69	0.36, 1.34		
RNA low, nAb neg	34	10 (29%)	44	16 (36%)	0.81	0.37, 1.78		
sRNA low, nAb pos	96	28 (29%)	78	26 (33%)	0.87	0.51, 1.48		

Day 90 Composite Safety Outcome

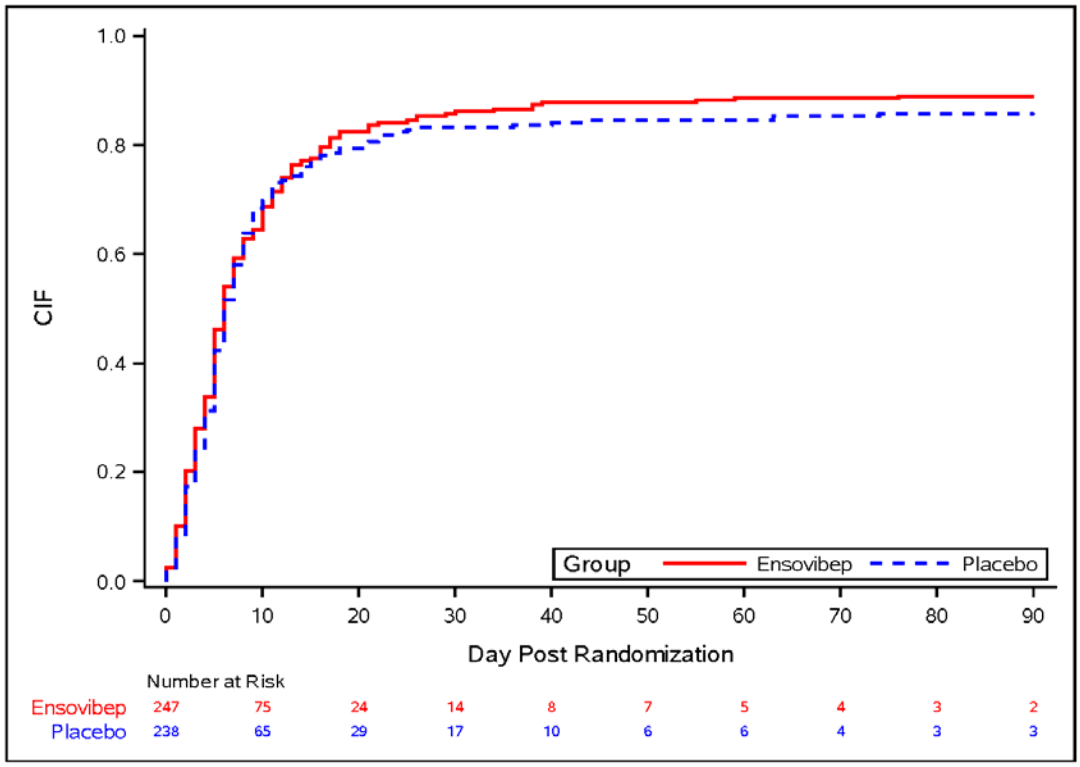
	Ensovibep		Placebo		Hazard Ratio [d]	
Baseline VL Subgroup	**Pts**	**N (%)**	**Pts**	**N (%)**	**HR**	**95% CI**
Viral RNA						
< 56,000 cp/mL (low)[c]	133	36 (27%)	125	31 (25%)	1.11	0.69, 1.79
≥ 56,000 cp/mL (high)	103	40 (39%)	102	37 (36%)	1.07	0.69, 1.68
Viral RNA by nAb						
RNA high, nAb neg	48	19 (40%)	59	18 (31%)	1.32	0.69, 2.51
RNA high, nAb pos	53	21 (40%)	35	14 (40%)	1.01	0.51, 1.98
RNA low, nAb neg	34	10 (29%)	44	10 (23%)	1.32	0.55, 3.17
RNA low, nAb pos	96	23 (24%)	78	20 (26%)	0.93	0.51, 1.70

[a] Hazard ratio (E/P) for time to first grade 3/4 AE, SAE, death, organ failure or serious coinfection event by Day 28, by Cox proportional hazards model.

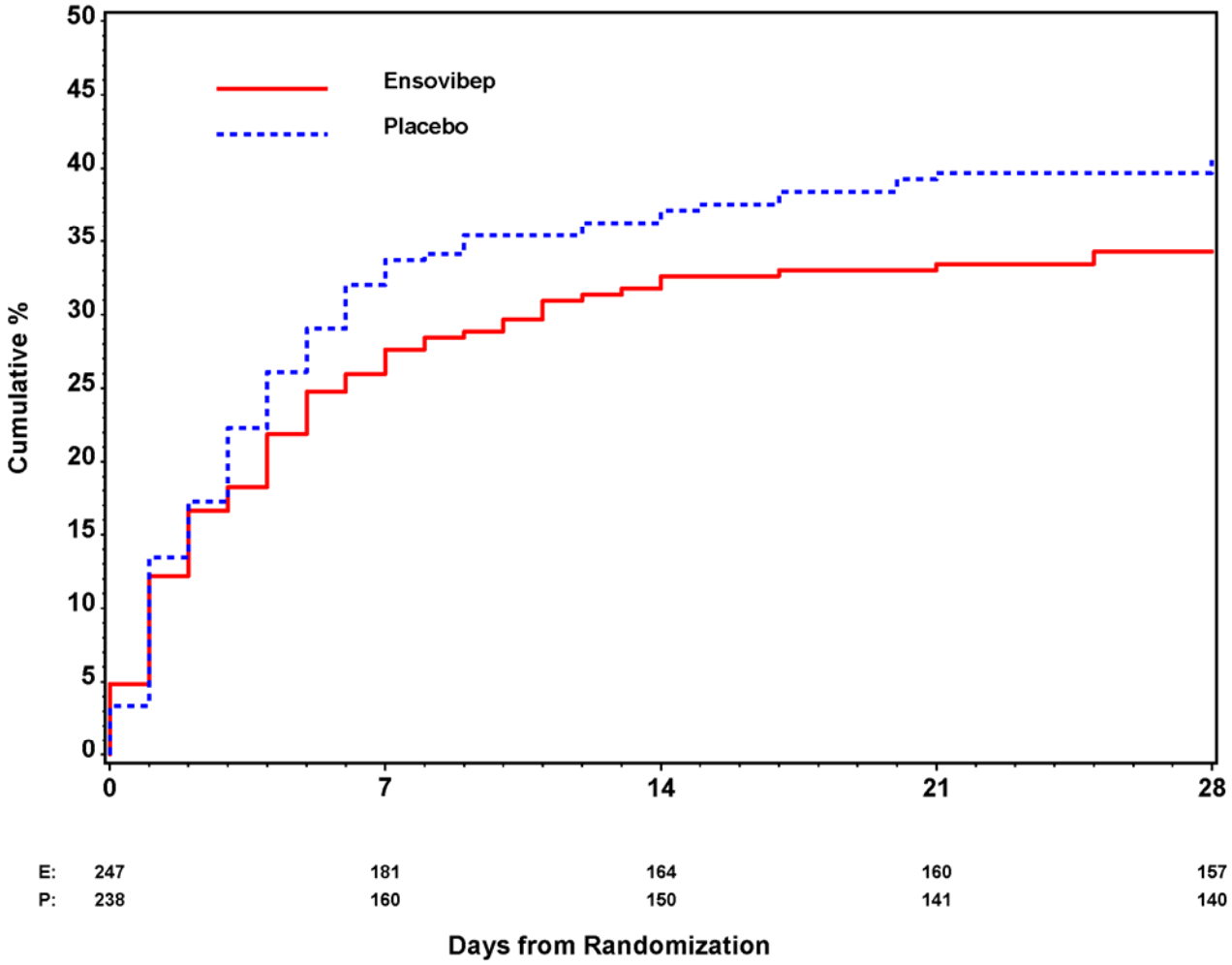
[c] Viral RNA < 56,000 cp/mL (median), negative, or indeterminate

[d] Hazard ratio (E/P) for time to first SAE, death, organ failure or serious coinfection event by Day 90, by Cox proportional hazards model.

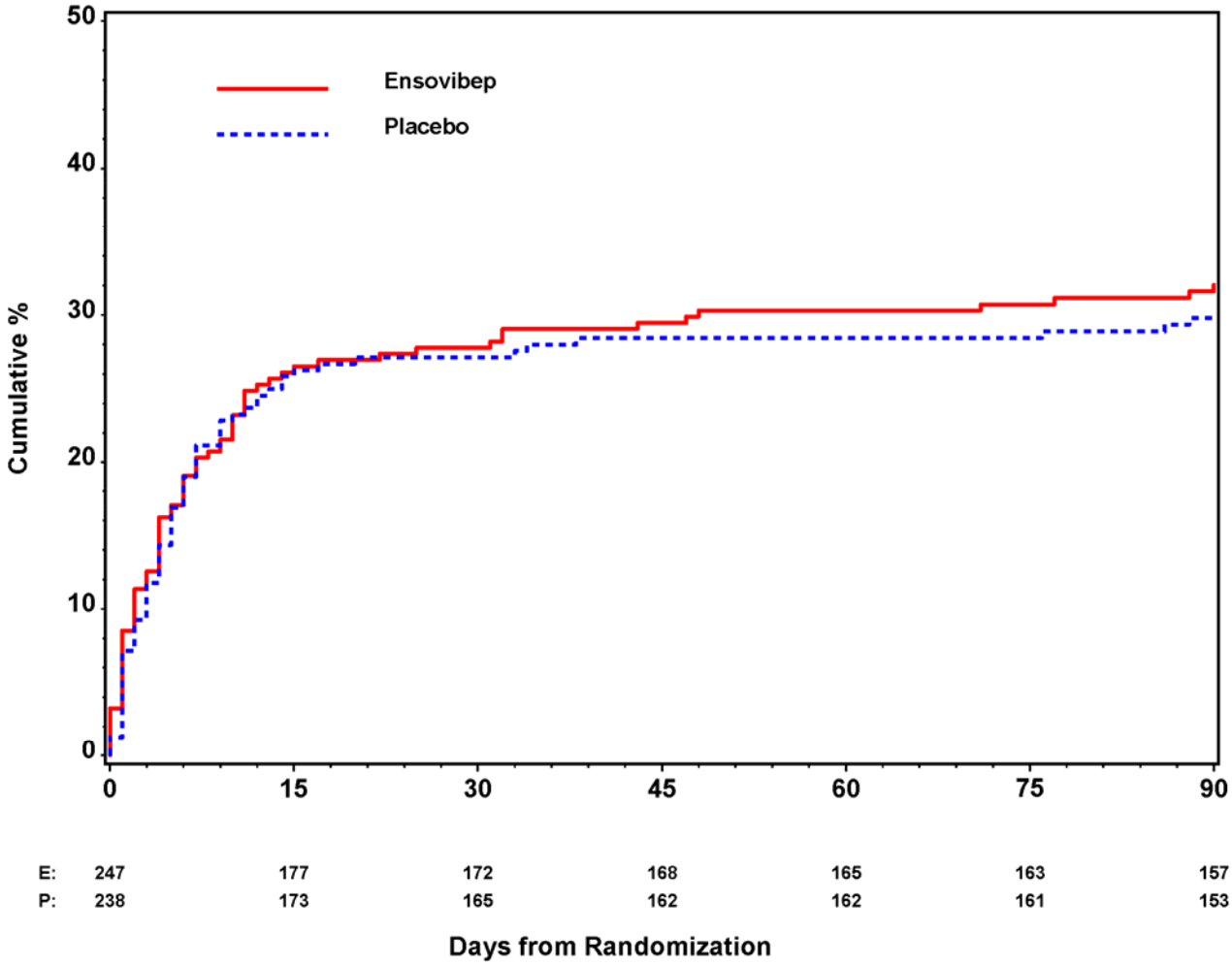
Supplement Figure 1: Time to Discharge from Index Hospitalization, Aalen-Johansen Cumulative Incidence Plot



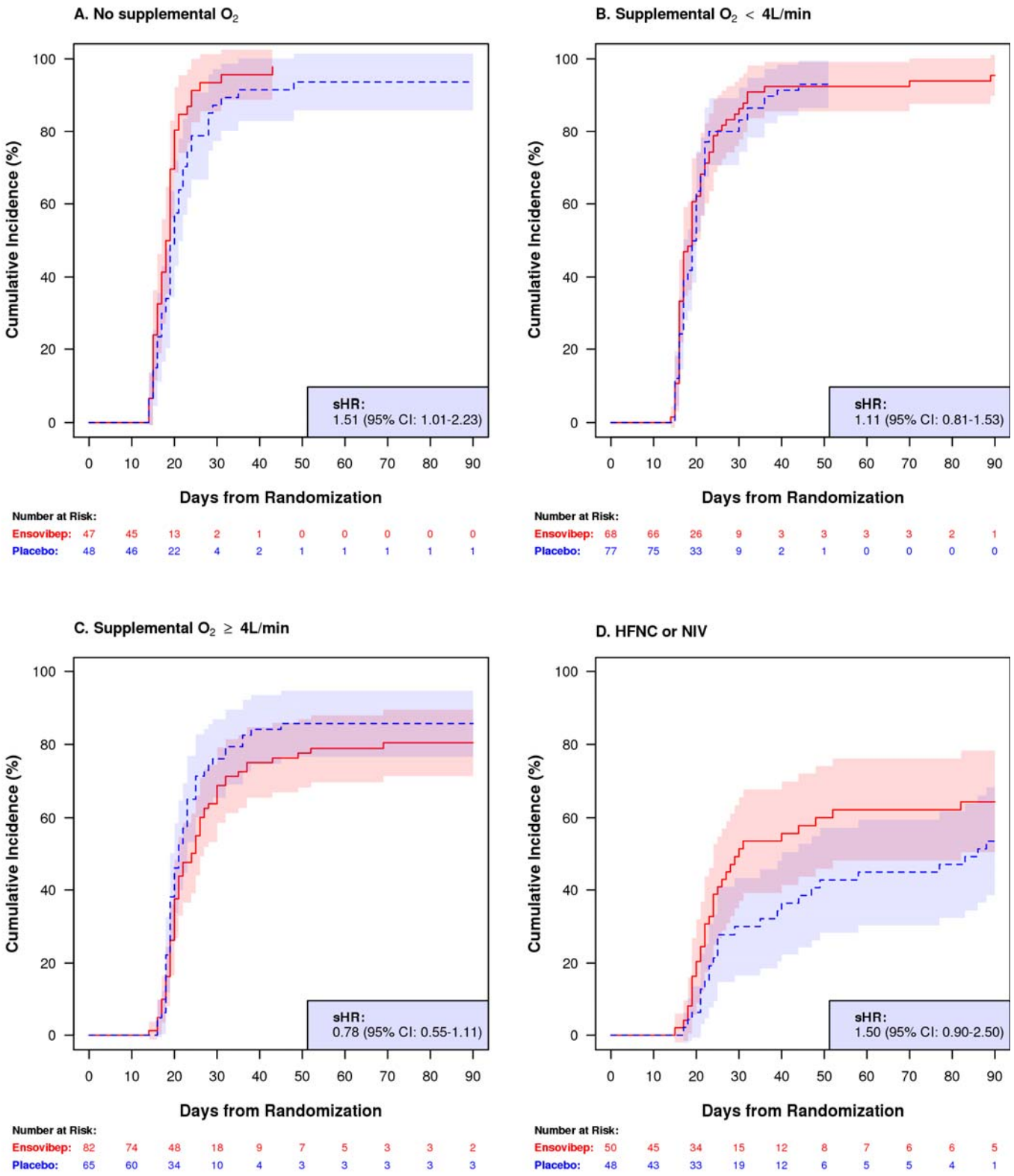
Supplement Figure 2: Kaplan Meier for Composite Safety Outcome through Day 28



Supplement Figure 3: Kaplan Meier for Composite Safety Outcome through Day 90



Supplement Figure 4 Time to sustained recovery through day 90 by O2 subgroup. Abbreviations: CI, confidence interval; HFNC, high flow nasal cannula; NIV, non-invasive ventilation


A. No supplemental O_2
Cumulative Incidence (%)
Days from Randomization
sHR:
1.51 (95% CI: 1.01-2.23)
Number at Risk:
Ensovibep: 47 45 13 2 1 0 0 0 0 0
Placebo: 48 46 22 4 2 1 1 1 1 1
B. Supplemental O_2 < 4L/min
Cumulative Incidence (%)
Days from Randomization
sHR:
1.11 (95% CI: 0.81-1.53)
Number at Risk:
Ensovibep: 68 66 26 9 3 3 3 3 2 1
Placebo: 77 75 33 9 2 1 0 0 0 0
C. Supplemental O_2 ≥ 4L/min
Cumulative Incidence (%)
Days from Randomization
sHR:
0.78 (95% CI: 0.55-1.11)
Number at Risk:
Ensovibep: 82 74 48 18 9 7 5 3 3 2
Placebo: 65 60 34 10 4 3 3 3 3 3
D. HFNC or NIV
Cumulative Incidence (%)
Days from Randomization
sHR:
1.50 (95% CI: 0.90-2.50)
Number at Risk:
Ensovibep: 50 45 34 15 12 8 7 6 6 5
Placebo: 48 43 33 19 12 6 5 5 4 1