Supplemental Online Content

Naggie S, Boulware DR, Lindsell CJ, et al; Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-6) Study Group and Investigators. Effect of ivermectin vs placebo on time to sustained recovery in outpatients with mild to moderate COVID-19: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2022.18590

This supplemental material has been provided by the authors to give readers additional information about their work.

© 2022 American Medical Association. All rights reserved.

eAppendix. ACTIV-6 Group Members

ACTIV-6 Executive Committee

Adrian F. Hernandez, Duke Clinical Research Institute (Clinical Coordinating Center PI)
Susanna Naggie, Duke Clinical Research Institute (Clinical Coordinating Center Co-PI)
G. Michael Felker, Duke Clinical Research Institute (Medical Monitor, blinded)
Sybil Wilson, Duke Clinical Research Institute
Allison DeLong, Duke Clinical Research Institute
April Remaly, Duke Clinical Research Institute
Rhonda Wilder, Duke Clinical Research Institute
Christopher J. Lindsell, Vanderbilt University Medical Center (Data Coordinating Center PI)
Thomas G. Stewart, Vanderbilt University Medical Center
Sean Collins, Vanderbilt University Medical Center
Sarah Dunsmore, National Center for Advancing Translational Sciences
Sam Bozzette, National Center for Advancing Translational Sciences
Gene Passamani, National Center for Advancing Translational Sciences
Stacey Adam, Foundation for the National Institutes of Health
David Boulware, University of Minnesota
Elizabeth Shenkman, University of Florida
Florence Thicklin, Stakeholder Advisory Committee
Matthew William McCarthy, Weill Cornell Medicine, Stakeholder Advisory Committee
George Hanna, Biomedical Advanced Research and Development Authority

ACTIV-6 Protocol Oversight Committee

David Boulware, University of Minnesota, POC Co-Chair
Elizabeth Shenkman, University of Florida, POC Co-Chair
Adrian F. Hernandez, Duke Clinical Research Institute (Clinical Coordinating Center PI)
Susanna Naggie, Duke Clinical Research Institute (Clinical Coordinating Center co-PI)
G. Michael Felker, Duke Clinical Research Institute (Medical Monitor, blinded)
Sybil Wilson, Duke Clinical Research Institute
Allison DeLong, Duke Clinical Research Institute
April Remaly, Duke Clinical Research Institute
Rhonda Wilder, Duke Clinical Research Institute
Christopher J. Lindsell, Vanderbilt University Medical Center (Data Coordinating Center PI)
Thomas G. Stewart, Vanderbilt University Medical Center

© 2022 American Medical Association. All rights reserved.

Sean Collins, Vanderbilt University Medical Center
Sarah Dunsmore, National Center for Advancing Translational Sciences
Sam Bozzette, National Center for Advancing Translational Sciences
Gene Passamani, National Center for Advancing Translational Sciences
Stacey Adam, Foundation for the National Institutes of Health
Florence Thicklin, Stakeholder Advisory Committee
Matthew William McCarthy, Weill Cornell Medicine, Stakeholder Advisory Committee
George Hanna, Biomedical Advanced Research and Development Authority
Adit Ginde, University of Colorado Denver – Anschutz
Mario Castro, University of Kansas Medical Center
Dushyantha Jayaweera, University of Miami
Mark Sulkowski, John Hopkins University
Nina Gentile, Lewis Katz School of Medicine at Temple University
Kathleen McTigue, University of Pittsburgh Medical Center
Kim Marschhauser, PCORI
Julia Garcia-Diaz, Ochsner Health

ACTIV-6 Clinical Trial Team

Adrian F. Hernandez, Duke Clinical Research Institute (Clinical Coordinating Center PI)
Susanna Naggie, Duke Clinical Research Institute (Clinical Coordinating Center Co-PI)
G. Michael Felker, Duke Clinical Research Institute (Medical Monitor, blinded)
Sybil Wilson, Duke Clinical Research Institute
Allison DeLong, Duke Clinical Research Institute
April Remaly, Duke Clinical Research Institute
Rhonda Wilder, Duke Clinical Research Institute
Christopher J. Lindsell, Vanderbilt University Medical Center (Data Coordinating Center PI)
Thomas G. Stewart, Vanderbilt University Medical Center

ACTIV-6 Independent Data Monitoring Committee

Voting Members:

Clyde Yancy, Northwestern University Feinberg School of Medicine (Chair)
Adaora Adimora, University of North Carolina, Chapel Hill (Vice-chair)
Susan Ellenberg, University of Pennsylvania

© 2022 American Medical Association. All rights reserved.

Kaleab Abebe, University of Pittsburgh
Arthur Kim, Massachusetts General Hospital
John D. Lantos, Children's Mercy Hospital
Jennifer Silvey-Cason, Participant representative

Statistical Data Analysis Center:

Frank Rockhold, Duke Clinical Research Institute (Lead faculty statistician)
Sean O'Brien, Duke Clinical Research Institute (Faculty statistician)
Frank Harrell, Vanderbilt University Medical Center (DCC-SDAC Faculty Liaison)
Zhen Huang, Duke Clinical Research Institute (Lead statistician)

ACTIV-6 Clinical Events Classification Committee

Renato Lopes, (CEC PI)
Faculty Reviewers: W. Schuyler Jones, Antonio Gutierrez, Robert Harrison, David Kong, Robert McGarrah
Fellow Reviewers: Michelle Kelsey, Konstantin Krychtiuk, Vishal Rao

ACTIV-6 Data Coordinating Center

David Aamodt, Vanderbilt University Medical Center
JaMario Ayers, Vanderbilt University Medical Center
Jess Collins, Vanderbilt University Medical Center
John Graves, Vanderbilt University Medical Center
James Grindstaff, Vanderbilt University Medical Center
Frank Harrell, Vanderbilt University Medical Center (DCC-SDAC Faculty Liaison)
Jessica Lai, Vanderbilt University Medical Center
Christopher J. Lindsell, Vanderbilt University Medical Center (Data Coordinating Center PI)
Itzel Lopez, Vanderbilt University Medical Center
Jessica Marlin, Vanderbilt University Medical Center
Alyssa Merkel, Vanderbilt University Medical Center
Sam Nwosu, Vanderbilt University Medical Center
Savannah Obregon, Vanderbilt University Medical Center
Dirk Orozco, Vanderbilt University Medical Center
Yoli Perez-Torres, Vanderbilt University Medical Center

© 2022 American Medical Association. All rights reserved.

Nelson Prato, Vanderbilt University Medical Center
Colleen Ratcliff, Vanderbilt University Medical Center
Max Rohde, Vanderbilt University Medical Center
Russell Rothman, Vanderbilt University Medical Center
Jana Shirey-Rice, Vanderbilt University Medical Center
Krista Vermillion, Vanderbilt University Medical Center
Thomas Stewart, Vanderbilt University Medical Center (Lead statistician)
Hsi-nien Tan, Vanderbilt University Medical Center
Seibert Tregoning, Vanderbilt University Medical Center
Meghan Vance, Vanderbilt University Medical Center
Amber Vongsamphanh, Vanderbilt University Medical Center
Maria Weir, Vanderbilt University Medical Center
Nicole Zaleski, Vanderbilt University Medical Center

© 2022 American Medical Association. All rights reserved.

ACTIV-6 Primary Site Investigators / Study Coordinators

A New Start II, LLC: William (Kelly) Vincent / Raina Vincent. **Advanced Medical Care, Ltd:** Ray Bianchi / Jen Premas. **AMRON Vitality and Wellness Center, LLC:** Diana Cordero-Loperena / Evelyn Rivera. **Ananda Medical Clinic:** Madhu Gupta / Greg Karawan & Carey Ziomek. **Arena Medical Group:** Joseph Arena / Sonaly DeAlmeida. **Assuta Family Medical Group APMC:** Soroush Ramin / Jaya Nataraj. **Boston Medical Center:** Michael Paasche-Orlow / Lori Henault & Katie Waite. **Bucks County Clinical Research:** David Miller / Ginger Brounce. **Christ the King Health Care, P.C.:** Constance George-Adebayo / Adeolu Adebayo. **Clinical Trials Center of Middle Tennessee:** Alex Slandzicki / Jessica Wallan. **Comprehensive Pain Management and Endocrinology:** Claudia Vogel / Sebastian Munoz. **David Kavtaradze MD, Inc.:** David Kavtaradze / Cassandra Watson. **David Singleton MD, PA:** David Singleton / Maria Rivon & Amanda Sevier. **Del Pilar Medical and Urgent Care:** Arnold Del Pilar / Amber Spangler. **DHR Health Institute for Research:** Sohail Rao / Luis Cantu. **Diabetes and Endocrinology Assoc. of Stark County:** Arvind Krishna / Kathy Evans, Tylene Falkner & Brandi Kerr. **Doctors Medical Group of Colorado Springs, P.C.:** Robert Spees / Mailyn Marta. **Duke University:** G. Michael Felker / Amanda Harrington. **Duke University Hospital:** Rowena Dolor / Madison Frazier, Lorraine Vergara & Jessica Wilson. **Elite Family Practice:** Valencia Burruss / Terri Hurst. **Emory University:** Igho Ofotokun / Laurel Bristow. **Essentia Health:** Rajesh Prabhu / Krystal Klicka & Amber Lightfeather. **Essential Medical Care, Inc.:** Vicki James / Marcella Rogers. **Express Family Clinic:** Pradeep Parihar / De'Ambra Torress. **Family Practice Doctors P.A.:** Chukwuemeka Oragwu / Ngozi Oguego. **First Care Medical Clinic:** Rajesh Pillai / Mustafa Juma. **Focus Clinical Research Solutions:** Ahab Gabriel / Emad Ghaly. **Franciscan Health Michigan City:** Dafer Al-Haddadin / Courtney Ramirez. **G&S Medical Associates, LLC:** Gammal Hassanien / Samah Ismail. **George Washington University Hospital:** Andrew Meltzer / Seamus Moran. **Geriatrics and Medical Associates:** Scott Brehaut / Angelina Roche. **GFC of Southeastern Michigan, PC:** Manisha Mehta / Nicole Koppinger. **Health Quality Primary Care:** Jose Baez / Ivone Pagan. **Highlands Medical Associates, P.A.:** Dallal Abdelsayed / Mina Aziz. **Hoag Memorial Hospital Presbyterian:** Philip Robinson / Julie Nguyen. **Hugo Medical Clinic:** Victoria Pardue / Llisa Hammons. **Innovation Clinical Trials Inc.:** Juan Ruiz-Unger / Susan Gonzalez & Lionel Reyes. **Jackson Memorial Hospital:** John Cienki / Gisselle Jimenez. **Jadestone Clinical Research, LLC:** Jonathan Cohen / Matthew Wong & Ying Yuan. **Jeremy W. Szeto, D.O., P.A.:** Jeremy Szeto. **Johns Hopkins Hospital:** Mark Sulkowski / Lauren Stelmash. **Lakeland Regional Medical Center:** Arch Amon / Daniel Haight. **Lamb Health, LLC:** Deryl Lamb / Amron Harper.

© 2022 American Medical Association. All rights reserved.

Lice Source Services Plantation: Nancy Pyram-Bernard / Arlen Quintero. **Lupus Foundation of Gainesville:** Eftim Adhami. **Maria Medical Center, PLLC:** Josette Maria / Diksha Paudel & Oksana Raymond. **Medical Specialists of Knoxville:** Jeffrey Summers / Tammy Turner. **Medical University of South Carolina:** Leslie Lenert / Sam Gallegos & Elizabeth Ann Szwast. **Mediversity Healthcare:** Ahsan Abdulghani / Pravin Vasoya. **Miller Family Practice, LLC:** Conrad Miller / Hawa Wiley. **North Shore University Health System/Evanston Hospital:** Nirav Shah / Tovah Klein. **Ochsner Clinic Foundation:** Julie Castex / Phillip Feliciano. **Olivo Wellness Medical Center:** Jacqueline Olivo / Marian Ghaly, Zainub Javed & Alexandra Nawrocki. **Pine Ridge Family Medicine Inc.:** Anthony Vecchiarelli / Nikki Vigil. **Premier Health:** Vijaya Cherukuri / Erica Burden. **Rapha Family Wellness:** Dawn Linn / Laura Fisher. **Raritan Bay Primary Care & Cardiology Associates:** Vijay Patel / Praksha Patel & Yuti Patel. **Romancare Health Services:** Leonard Ellison / Jeffrey Harrison. **Spinal Pain and Medical Rehab, PC:** Binod Shah / Sugata Shah. **Stanford University:** Upinder Singh / Julia Donahue & Yasmin Jazayeri. **Sunshine Walk In Clinic:** Anita Gupta / N Chandrasekar & Beth Moritz. **Tabitha B. Fortt, M.D., LLC:** Tabitha Fortt / Anisa Fortt. **Tallahassee Memorial Hospital:** Ingrid Jones-Ince / Alix McKee & Christy Schattinger. **Tampa General Hospital:** Jason Wilson / Brenda Farlow. **Temple University Hospital:** Nina Gentile / Lillian Finlaw. **Texas Health Physicians Group:** Randall Richwine & Tearani Williams / Penny Pazier & Lisa Carson. **Texas Tech University Health Sciences Center in El Paso:** Edward Michelson / Danielle Austin. **The Heart and Medical Center:** Sangeeta Khetpal / Tiffaney Cantrell, Drew Franklin & Karissa Marshall. **Trident Health Center:** Arvind Mahadevan / Madelyn Rosequist. **TriHealth, Inc:** Martin Gnoni / Crystal Daffner. **UF Health Precision Health Research:** Carla VandeWeerd / Mitchell Roberts. **University Diagnostics and Treatment Clinic:** Mark D'Andrea / Mina Aziz. **University Medical Center- New Orleans:** Stephen Lim / Wayne Swink. **University of Cincinnati:** Margaret Powers-Fletcher / Sylvere Mukunzi. **University of Florida Health:** Elizabeth Shenkman / Jamie Hensley & Brittney Manning. **University of Florida-JAX-ASCENT:** Carmen Isache / Jennifer Bowman, Angelique Callaghan-Brown & Taylor Scott. **University of Kansas – Wichita:** Tiffany Schwasinger-Schmidt / Ashlie Cornejo. **University of Miami:** Dushyantha Jayaweera / Maria Almanzar, Letty Ginsburg & Americo Hajaz. **University of Minnesota:** Carolyn Bramante. **University of Missouri – Columbia:** Matthew Robinson / Michelle Seithel. **University of Pittsburgh:** Akira Sekikawa / Emily Klawson. **University of Texas Health Science Center at Houston:** Luis Ostrosky / Virginia Umana. **University of Texas Health Science Center at San Antonio:** Thomas Patterson / Robin Tragus. **University of Virginia Health System:** Patrick Jackson / Caroline Hallowell & Heather Haughey. **Vaidya**

© 2022 American Medical Association. All rights reserved.

MD PLLC: Bhavna Vaidya-Tank / Cameron Gould. **Vanderbilt University Medical Center:** Parul Goyal / Carly Gatewood. **Wake Forest University Health Sciences:** John Williamson / Hannah Seagle. **Weill Cornell Medical College:** Matthew McCarthy / Elizabeth Salsgiver. **Well Pharma Medical Research:** Eddie Armas / Jhonsai Cheng & Priscilla Huerta.

© 2022 American Medical Association. All rights reserved.

eMethods

Participant Monitoring

The daily and follow-up assessments were monitored, and sites were actively notified of events requiring review, including serious adverse events. In addition, participants were invited during these assessments to request contact from the study team or to report any unusual circumstances that might be relevant. Failure to complete daily assessments was also a trigger for review of a possible serious adverse event. A missed assessment on the day after receiving the first dose of study medication (day 2) or any day of missed assessments up to day 14 prompted an investigator notification to contact the participant. All participants were instructed to self-report concerns either via an online event reporting system, by calling the site, or by calling a 24-hour hotline.

Hospitalizations, a record of seeking other healthcare, or serious adverse events were extracted by site personnel from the participant's medical record. Medical occurrences occurring before the receipt of study drug/placebo but after obtaining informed consent were not considered an adverse event.

Independent Data Monitoring Committee Oversight

Due to extremely rapid enrollment related to the omicron variant surge, 2000 participants were enrolled in the platform trial from December 15, 2021 to February 1, 2022. This resulted in the full accrual of the ivermectin group before the first planned interim analysis by the independent data monitoring committee review.

Interim analyses were planned at intervals of approximately 300 participants contributing to a study drug group, with an anticipated maximum of 1200 participants. There was also the potential to extend accrual for a study drug if there was potential to demonstrate benefit for hospitalization/death. Because the rate of enrollment was so rapid, it was not possible to complete the interim analyses, resulting in a planned primary analysis highly conservative of type 1 error. To provide additional context, the primary analysis was additionally performed with a non-informative prior and without a prior.

Handling of Missing Data

In both the primary and secondary endpoint analyses, missing data among covariates was addressed with conditional mean imputation because the amount of missing covariate data was

© 2022 American Medical Association. All rights reserved.

small (<4%). Approximately 7% of participants did not report activity level for the COVID clinical progression score endpoint, but the participants were known to be alive and at home. The missing activity level was a type of interval censored outcome, as the participants were known to be either a 1 or 2 on the scale. The ordinal regression models were fit accounting for the interval censoring. The proportional hazards assumption of the primary endpoint was evaluated by generating visual diagnostics such as the log-log plot and plots of time-dependent regression coefficients for each predictor in the model, a diagnostic which indicates deviations from proportionality if the time-dependent coefficients are not constant in time.

Subgroup Analysis

For each characteristic, a proportional hazards regression model was constructed using the same covariates as the primary endpoint model plus additional interaction terms between treatment assignment and the characteristic of interest. To allow the possibility of non-linear trends along continuous characteristics, like age or calendar time, continuous covariates were included in the model as restricted cubic splines. The hazard ratios and 95% confidence intervals were calculated from asymptotic, model-based estimates at specific values. The continuous variables were not discretized into bins (or groups).

© 2022 American Medical Association. All rights reserved.

COVID-19 Ordinal Outcome Scale

The COVID-19 outcomes for this trial are based on the World Health Organization's Ordinal Scale for Clinical Improvement and will be collected via the online system and from the medical record. The following outcomes will be assessed as part of the COVID Clinical Progression Scale:

0. No clinical or virological evidence of infection
1. No limitation of activities
2. Limitation of activities
3. Hospitalized, no oxygen therapy
4. Hospitalized, on oxygen by mask or nasal prongs
5. Hospitalized, on non-invasive ventilation or high-flow oxygen
6. Hospitalized, on intubation and mechanical ventilation
7. Hospitalized, on ventilation + additional organ support – pressors, RRT, ECMO
8. Death

© 2022 American Medical Association. All rights reserved.

eTable 1. Baseline Symptom Prevalence and Severity

Variable	Ivermectin (N=817)	Placebo (N=774)
Symptom burden on study day 1, No. (%)		
None	55 (6.73)	54 (6.98)
Mild	490 (59.98)	434 (56.07)
Moderate	221 (27.05)	247 (31.91)
Severe	51 (6.24)	39 (5.04)
Symptoms on study day 1[a]		
Fatigue, No./total (%)		
None	61/730 (8.36)	65/700 (9.29)
Mild	365/730 (50.00)	317/700 (45.29)
Moderate	238/730 (32.60)	262/700 (37.43)
Severe	66/730 (9.04)	56/700 (8.00)
Dyspnea, No./total (%)		
None	371/729 (50.89)	358/700 (51.14)
Mild	271/729 (37.17)	255/700 (36.43)
Moderate	75/729 (10.29)	82/700 (11.71)
Severe	12/729 (1.65)	5/700 (0.71)
Fever, No./total (%)		
None	555/729 (76.13)	519/700 (74.14)
Mild	126/729 (17.28)	140/700 (20.00)
Moderate	40/729 (5.49)	36/700 (5.14)
Severe	8/729 (1.10)	5/700 (0.71)
Cough, No./total (%)		
None	98/729 (13.44)	85/700 (12.14)
Mild	407/729 (55.83)	385/700 (55.00)
Moderate	184/729 (25.24)	200/700 (28.57)
Severe	40/729 (5.49)	30/700 (4.29)
Nausea, No./total (%)		
None	544/729 (74.62)	504/700 (72.00)
Mild	136/729 (18.66)	143/700 (20.43)
Moderate	36/729 (4.94)	38/700 (5.43)
Severe	13/729 (1.78)	15/700 (2.14)
Vomiting, No./total (%)		
None	690/729 (94.65)	661/700 (94.43)
Mild	29/729 (3.98)	26/700 (3.71)
Moderate	8/729 (1.10)	11/700 (1.57)
Severe	2/729 (0.27)	2/700 (0.29)
Diarrhea, No./total (%)		
None	525/729 (72.02)	502/700 (71.71)
Mild	136/729 (18.66)	160/700 (22.86)
Moderate	57/729 (7.82)	31/700 (4.43)

© 2022 American Medical Association. All rights reserved.

Variable	Ivermectin (N=817)	Placebo (N=774)
Severe	11/729 (1.51)	7/700 (1.00)
Body aches, No./total (%)		
None	234/729 (32.10)	212/700 (30.29)
Mild	320/729 (43.90)	304/700 (43.43)
Moderate	140/729 (19.20)	148/700 (21.14)
Severe	35/729 (4.80)	36/700 (5.14)
Sore throat, No./total (%)		
None	392/729 (53.77)	331/700 (47.29)
Mild	247/729 (33.88)	258/700 (36.86)
Moderate	64/729 (8.78)	94/700 (13.43)
Severe	26/729 (3.57)	17/700 (2.43)
Headache, No./total (%)		
None	285/729 (39.09)	254/700 (36.29)
Mild	296/729 (40.60)	290/700 (41.43)
Moderate	108/729 (14.81)	123/700 (17.57)
Severe	40/729 (5.49)	33/700 (4.71)
Chills, No./total (%)		
None	513/729 (70.37)	471/700 (67.29)
Mild	162/729 (22.22)	165/700 (23.57)
Moderate	40/729 (5.49)	55/700 (7.86)
Severe	14/729 (1.92)	9/700 (1.29)
Nasal symptoms, No./total (%)		
None	210/729 (28.81)	194/700 (27.71)
Mild	377/729 (51.71)	356/700 (50.86)
Moderate	121/729 (16.60)	128/700 (18.29)
Severe	21/729 (2.88)	22/700 (3.14)
New loss of sense of taste or smell, No./total (%)		
None	366/729 (50.21)	358/700 (51.14)
Mild	160/729 (21.95)	158/700 (22.57)
Moderate	93/729 (12.76)	81/700 (11.57)
Severe	110/729 (15.09)	103/700 (14.71)
Concomitant Medications		
Remdesivir, No. (%)	2 (0.24)	2 (0.26)
Monoclonal antibodies, No. (%)	22 (2.69)	25 (3.23)
Nirmatrelvir + ritonavir, No. (%)	1 (0.12)	1 (0.13)

[a]Not all participants returned surveys on all days. The denominator reflects the participants who returned their survey on Day 1.

© 2022 American Medical Association. All rights reserved.

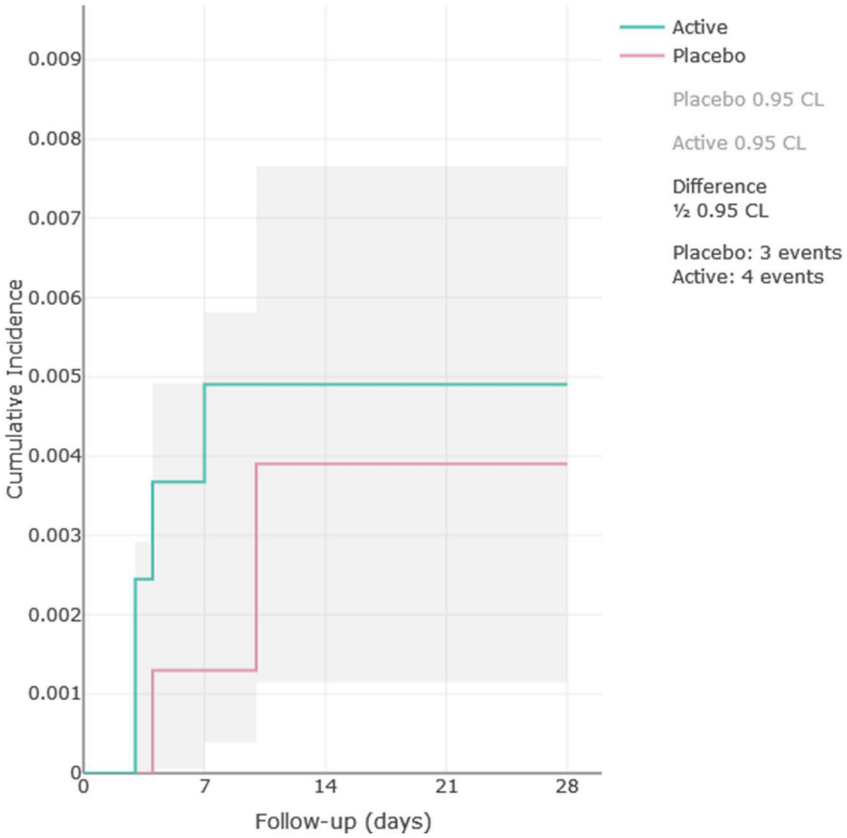
eTable 2. Adverse Events

Adverse Events	Ivermectin, Not Taken (N=41)	Ivermectin, Taken (N=776)	Placebo, Not Taken (N=50)	Placebo, Taken (N=724)
Experienced any adverse event, No. (%)	1 (2.44)	24 (3.09)	0 (0.00)	27 (3.73)
Experienced a serious adverse event, No. (%)	1 (2.44)	9 (1.16)	0 (0.00)	9 (1.24)
Serious adverse events, No. (not mutually exclusive)				
COVID-19 pneumonia	0	4		4
Pulmonary embolism	0	1		3
COVID-19 pneumonia aggravated	0	1		3
Venous thromboembolism	0	0		2
Bacteremia	0	0		1
Diplopia	0	0		1
Pneumonia due to *Staphylococcus*	0	1		0
Pneumonia due to *Streptococcus*, group b	0	1		0
Acute kidney injury	1	0		0
Hospitalization with dyspnea	0	1		0
Viral bronchopneumonia	0	1		0
COVID-19	0	1		0

“Taken” refers to the participants who reported taking (or planning to take) the study drug at least once. “Not taken” refers to the participants (if any) who did not report taking the study drug.

© 2022 American Medical Association. All rights reserved.

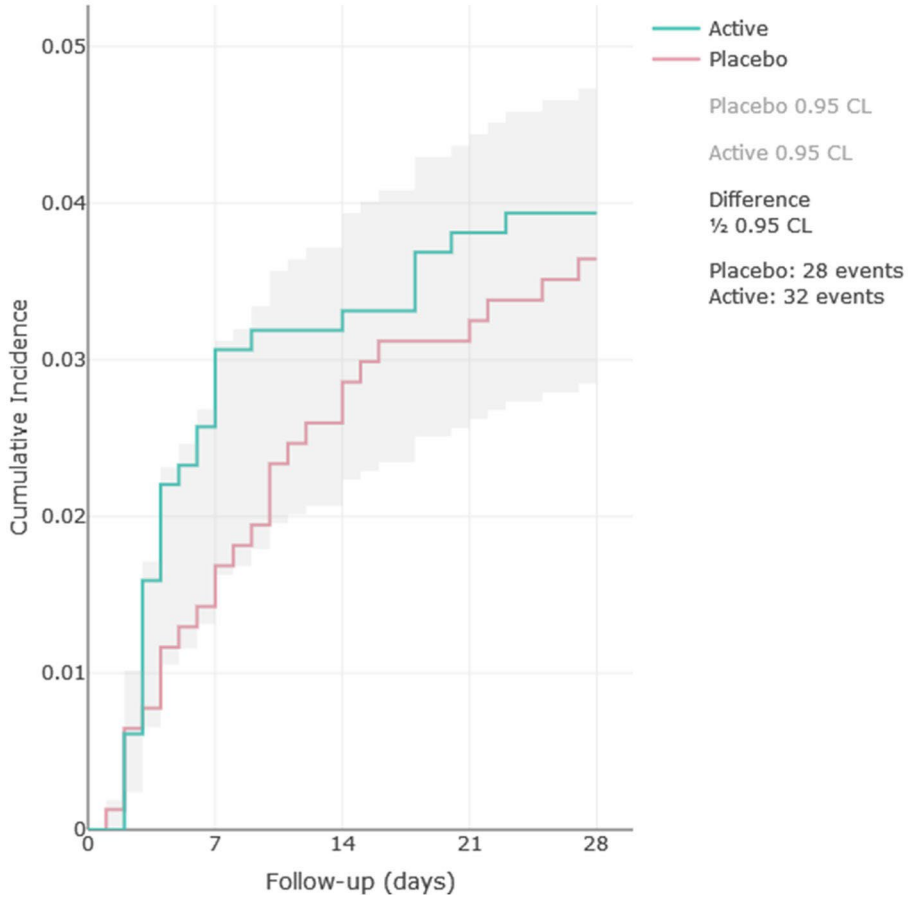
eFigure 1A. All-Cause Hospitalization or Death for Ivermectin Versus Placebo



Cumulative incidence curves and 95% confidence interval for hospitalization or death endpoint. Hospitalization or death was a composite endpoint. Ten hospitalizations occurred with ivermectin (1.22%) as compared to nine hospitalizations with placebo (1.16%). Hospitalization was defined as source documented confirmed hospital admission exceeding 24 hours, as measured from presentation (potentially in the emergency department) to discharge. Time to hospitalization or death was defined as the number of days between receipt of study drug and hospitalization or death (whichever occurred first). The endpoint was administratively censored at 28 days.

© 2022 American Medical Association. All rights reserved.

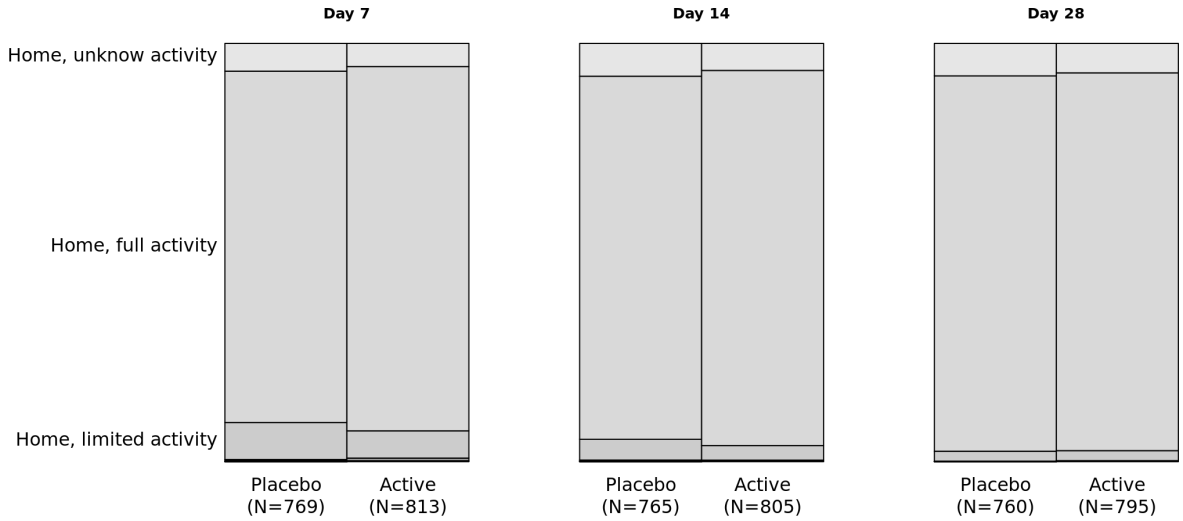
eFigure 1B. All-Cause Hospitalization, Urgent Care, Emergency Room Visit, or Death for Ivermectin Versus Placebo



Cumulative incidence curves and 95% confidence interval (point-wise) for healthcare encounter or death endpoint, which was a composite endpoint. Healthcare encounter was defined as a patient-reported hospitalization, urgent care visit, or emergency department visit of any duration. Healthcare encounters occurred in 32 (3.9%) ivermectin participants and 28 (3.6%) placebo participants. Time to healthcare encounter or death was defined as the number of days between receipt of study drug and the first occurrence of the composite endpoint.

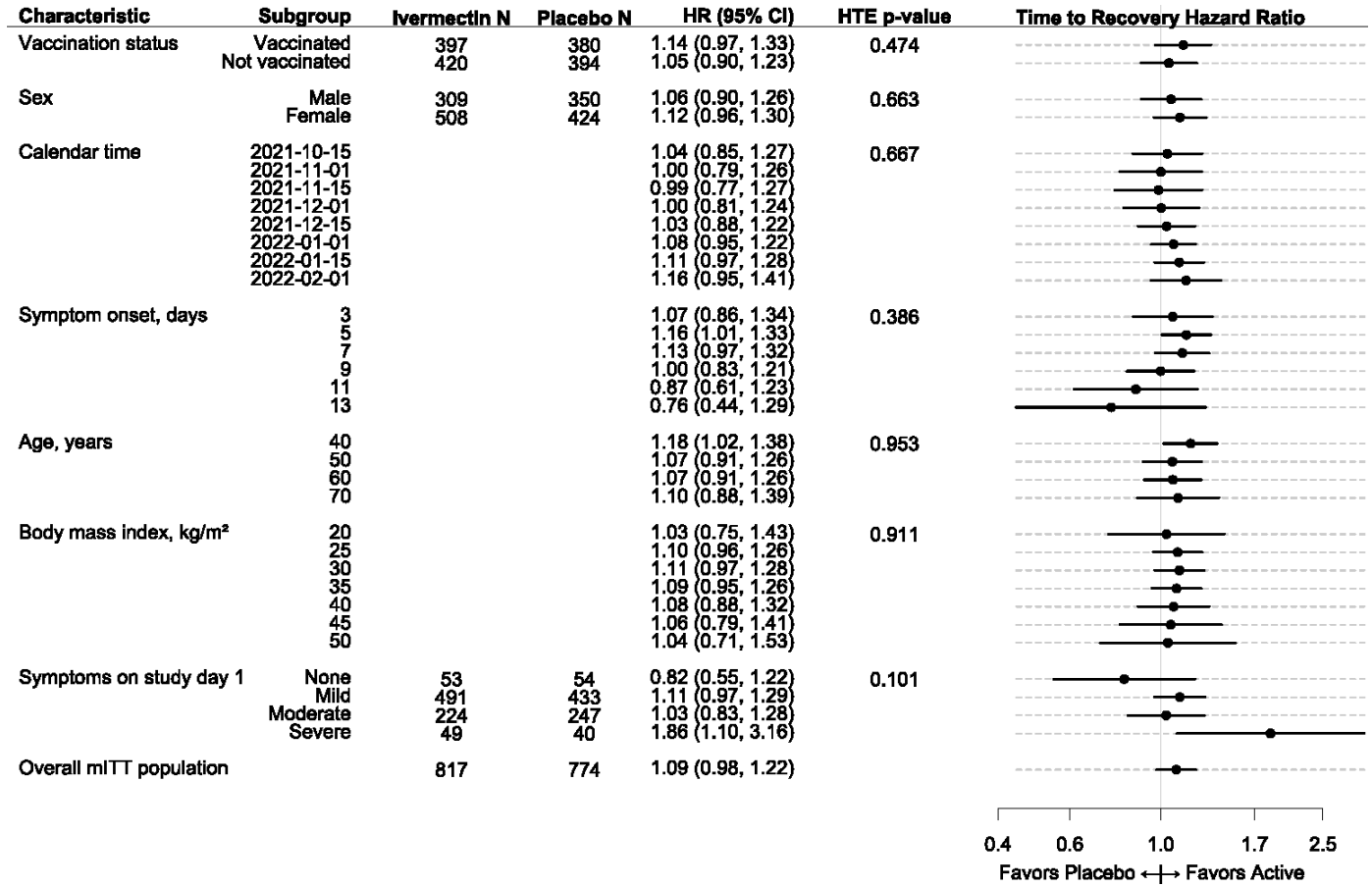
© 2022 American Medical Association. All rights reserved.

eFigure 2. Participants' Clinical Status at Days 7, 14, and 28



© 2022 American Medical Association. All rights reserved.

eFigure 3. Covariate-Adjusted and Model-Based Estimates of the Treatment Effect for Selected Characteristics for Ivermectin Versus Placebo



This figure reports the analyses of heterogeneity of treatment effect from the primary endpoint, time to sustained recovery. The analyses for heterogeneity of treatment effect were specified in the statistical analysis plan. As the analyses were deemed exploratory, no multiplicity adjustment was implemented. A hazard

© 2022 American Medical Association. All rights reserved.

ratio greater than 1.0 indicates a faster time to recovery. Study day 1 was the day of drug delivery to the participant. The ‘mITT population’ reflects a modified intent-to-treat analysis of participants randomized who received study medicine within 7 days.
Covariate-adjusted and model-based estimates of the treatment effect for selected subgroups. For each characteristic, a proportional hazards regression model was constructed using the same covariates as the primary endpoint model plus additional interaction terms between treatment assignment and the characteristic of interest. For example, the interaction of vaccination status and treatment assignment was added to the primary endpoint regression model to calculate a treatment effect for the vaccinated and unvaccinated subgroups. To allow the possibility of non-linear trends along continuous characteristics, like age or calendar time, the additional terms were interactions between treatment assignment and restricted cubic splines. Because the primary endpoint model did not include body mass index (BMI), the restricted cubic spline terms for BMI were also added to the model (sometimes call main effects) in addition to the interaction terms. Because the primary endpoint model only included a single linear term for symptom onset, the nonlinear terms of the restricted cubic spline were also added to the model in addition to the interaction terms. The hazard ratios and 95% confidence intervals were calculated from asymptotic, model-based contrasts. The hazard ratio for the full study population was generated from the primary endpoint model without prior.

The estimates shown in the HTE plot are estimates calculated from the smooth, modeled relationship. There are no discrete categories over which to tabulate the number of participants.

© 2022 American Medical Association. All rights reserved.