Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

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, University of Virginia
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 R. 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

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David R. 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, University of Virginia

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
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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, University of Virginia

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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

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 D. 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

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, University of Virginia (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

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 / Paulina A. Rebolledo. **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.

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**

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.

ACTIV-6 Manuscript-specific Contributions

Trial Design: SN, AH, CL, TS, DB, and protocol oversight committee
Data Collection: All ACTIV-6 investigators, as above
Data Analysis: CL, TS
Trial Guarantors: DB, SN, AH, CL, TS
Wrote first draft: DB, SN
Contributed intellectual input: All authors
Decision to Publish: DB, SN, AH, CL, TS
TS has full access to the data.

Interim Analysis

Due to extremely rapid enrollment related to the omicron variant surge, 2000 participants were enrolled in ACTIV-6 from December 15, 2021 to February 1, 2022. This resulted in the rapid and full accrual of the fluticasone arm before the first planned interim analysis by the independent data monitoring committee.

Final Endpoint Selection

Immediately prior to the final analysis and still blinded to treatment assignment, the investigators proposed time to recovery as the primary endpoint based on low event rates precluding an informative statistical comparison on progression to hospitalization or death. The choice of endpoint was approved by the Data and Safety Monitoring Committee and study oversight committees.

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

Table S1. Demographics of ACTIV-6 and US populations

	COVID-19 Cases		U.S. General Population
	U.S. CDC Data	ACTIV-6 Participants	
Female %	53%	63%	51%
Age, years (median)	36-41	45	38.1
Race (%)			
Native American	1.1%	1.4%	0.7%
Asian	3.8%	5.1%	5.6%
Hawaiian, Pacific Islander	0.3%	0.2%	0.2%
Black	12.3%	7.1%	12.5%
White	54%	80.1%	60.1%
Ethnicity (%)			
Latino	25%	12.6%	18.5%

Table S2. Baseline prevalence and severity of symptoms on study day 1

Variable	Inhaled Fluticasone (n=656)	Placebo (n=621)	Total (N=1277)
Symptom burden on study day 1, No. (%)			
None	35/634 (5.52)	39/609 (6.40)	74/1243 (5.95)
Mild	402/634 (63.41)	371/609 (60.92)	773/1243 (62.19)
Moderate	186/634 (29.34)	174/609 (28.57)	360/1243 (28.96)
Severe	11/634 (1.74)	25/609 (4.11)	36/1243 (2.90)
Fatigue, No./total (%)			
None	41/628 (6.53)	30/592 (5.07)	71/1220 (5.82)
Mild	245/628 (39.01)	231/592 (39.02)	476/1220 (39.02)
Moderate	270/628 (42.99)	277/592 (46.79)	547/1220 (44.84)
Severe	72/628 (11.46)	54/592 (9.12)	126/1220 (10.33)
Dyspnea, No./total (%)			
None	318/628 (50.64)	313/592 (52.87)	631/1220 (51.72)
Mild	248/628 (39.49)	221/592 (37.33)	469/1220 (38.44)
Moderate	54/628 (8.60)	50/592 (8.45)	104/1220 (8.52)
Severe	8/628 (1.27)	8/592 (1.35)	16/1220 (1.31)
Fever, No./total (%)			
None	399/628 (63.54)	370/592 (62.50)	769/1220 (63.03)
Mild	158/628 (25.16)	160/592 (27.03)	318/1220 (26.07)
Moderate	56/628 (8.92)	56/592 (9.46)	112/1220 (9.18)
Severe	15/628 (2.39)	6/592 (1.01)	21/1220 (1.72)
Cough, No./total (%)			
None	62/628 (9.87)	50/592 (8.45)	112/1220 (9.18)
Mild	324/628 (51.59)	304/592 (51.35)	628/1220 (51.48)
Moderate	199/628 (31.69)	200/592 (33.78)	399/1220 (32.70)
Severe	43/628 (6.85)	38/592 (6.42)	81/1220 (6.64)
Nausea, No./total (%)			
None	435/627 (69.38)	415/592 (70.10)	850/1219 (69.73)
Mild	146/627 (23.29)	138/592 (23.31)	284/1219 (23.30)
Moderate	32/627 (5.10)	33/592 (5.57)	65/1219 (5.33)
Severe	14/627 (2.23)	6/592 (1.01)	20/1219 (1.64)
Vomiting, No./total (%)			
None	595/627 (94.90)	555/592 (93.75)	1150/1219 (94.34)
Mild	21/627 (3.35)	28/592 (4.73)	49/1219 (4.02)
Moderate	10/627 (1.59)	7/592 (1.18)	17/1219 (1.39)
Severe	1/627 (0.16)	2/592 (0.34)	3/1219 (0.25)
Diarrhea, No./total (%)			
None	440/627 (70.18)	416/592 (70.27)	856/1219 (70.22)
Mild	140/627 (22.33)	131/592 (22.13)	271/1219 (22.23)
Moderate	34/627 (5.42)	37/592 (6.25)	71/1219 (5.82)
Severe	13/627 (2.07)	8/592 (1.35)	21/1219 (1.72)
Body aches, No./total (%)			

Variable	Inhaled Fluticasone (n=656)	Placebo (n=621)	Total (N=1277)
None	158/627 (25.20)	127/592 (21.45)	285/1219 (23.38)
Mild	242/627 (38.60)	253/592 (42.74)	495/1219 (40.61)
Moderate	170/627 (27.11)	169/592 (28.55)	339/1219 (27.81)
Severe	57/627 (9.09)	43/592 (7.26)	100/1219 (8.20)
Sore throat, No./total (%)			
None	226/627 (36.04)	210/592 (35.47)	436/1219 (35.77)
Mild	259/627 (41.31)	235/592 (39.70)	494/1219 (40.53)
Moderate	107/627 (17.07)	113/592 (19.09)	220/1219 (18.05)
Severe	35/627 (5.58)	34/592 (5.74)	69/1219 (5.66)
Headache, No./total (%)			
None	191/627 (30.46)	170/592 (28.72)	361/1219 (29.61)
Mild	249/627 (39.71)	238/592 (40.20)	487/1219 (39.95)
Moderate	137/627 (21.85)	142/592 (23.99)	279/1219 (22.89)
Severe	50/627 (7.97)	42/592 (7.09)	92/1219 (7.55)
Chills, No./total (%)			
None	349/627 (55.66)	313/592 (52.87)	662/1219 (54.31)
Mild	177/627 (28.23)	194/592 (32.77)	371/1219 (30.43)
Moderate	77/627 (12.28)	73/592 (12.33)	150/1219 (12.31)
Severe	24/627 (3.83)	12/592 (2.03)	36/1219 (2.95)
Nasal symptoms, No./total (%)			
None	123/627 (19.62)	116/592 (19.59)	239/1219 (19.61)
Mild	293/627 (46.73)	281/592 (47.47)	574/1219 (47.09)
Moderate	174/627 (27.75)	153/592 (25.84)	327/1219 (26.83)
Severe	37/627 (5.90)	42/592 (7.09)	79/1219 (6.48)
New loss of sense of taste or smell, No./total (%)			
None	412/627 (65.71)	382/592 (64.53)	794/1219 (65.14)
Mild	102/627 (16.27)	93/592 (15.71)	195/1219 (16.00)
Moderate	51/627 (8.13)	57/592 (9.63)	108/1219 (8.86)
Severe	62/627 (9.89)	60/592 (10.14)	122/1219 (10.01)

Values are no. (%). Study day 1 was the day of receipt of study medication. Participants were required to have at least 2 symptoms at time of randomization.

Table S3. FDA-authorized therapeutics utilized by participants

COVID-19 Therapeutic	Inhaled Fluticasone (n=656)	Placebo (n=621)
Remdesivir	1 (0.2%)	0 (0.0%)
Monoclonal antibodies	17 (2.6%)	13 (2.1%)
Nirmatrelvir/ritonavir	0 (0.0%)	1 (0.2%)

Values are no. (%).

Table S4. Covid-19 clinical progression scale for inhaled fluticasone vs placebo

Clinical Progression Scale	Day 7		Day 14		Day 28	
	Fluticasone	Placebo	Fluticasone	Placebo	Fluticasone	Placebo
Not hospitalized, activity level not reported	6.4% (42)	4.35% (27)	9.8% (64)	6.6% (41)	7.9% (52)	4.7% (29)
Not hospitalized, no limitation of activities	86.4% (567)	87.9% (546)	86.3% (566)	88.1% (547)	88.3% (579)	92.4% (574)
Not hospitalized, limitation of activities	6.4% (42)	6.9% (43)	2.9% (19)	4.2% (26)	1.7% (11)	1.0% (6)
Hospitalized, no oxygen therapy	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Hospitalized, on oxygen therapy	0.0% (0)	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Hospitalized, on non-invasive ventilation or high-flow oxygen	0.15% (1)	0.0% (0)	0.15% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Hospitalized, on intubation and mechanical ventilation	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Hospitalized, on ventilation + additional organ support	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Death	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Missing Outcome	0.6% (4)	0.6% (4)	0.9% (6)	1.1% (7)	2.1% (14)	1.9% (12)

Covid-19 clinical progression outcome scale; values are % (n). Placebo reflects concurrently randomized placebo participants only within the platform trial.

Table S5. Serious adverse events experienced by participants

Variable	Fluticasone, Not Taken (n=16)	Fluticasone, Taken (n=640)	Placebo, Not Taken (n=16)	Placebo, Taken (n=605)	Total (N=1277)
Experienced an adverse event	0 (0%)	13 (2.03%)	0 (0%)	16 (2.6%)	29 (2.3%)
Experienced a serious adverse event	0 (0%)	3 (0.47%)	0 (0%)	6 (1.0%)	9 (0.7%)
Serious adverse events					
Covid-19 pneumonia		1		1	2
Covid-19 pneumonia aggravated		2		0	2
Coronary vasospasm		0		1	1
Diplopia		0		1	1
Nausea and vomiting symptoms		0		1	1
Urinary tract infection		0		1	1
Adverse drug reaction		0		1	1

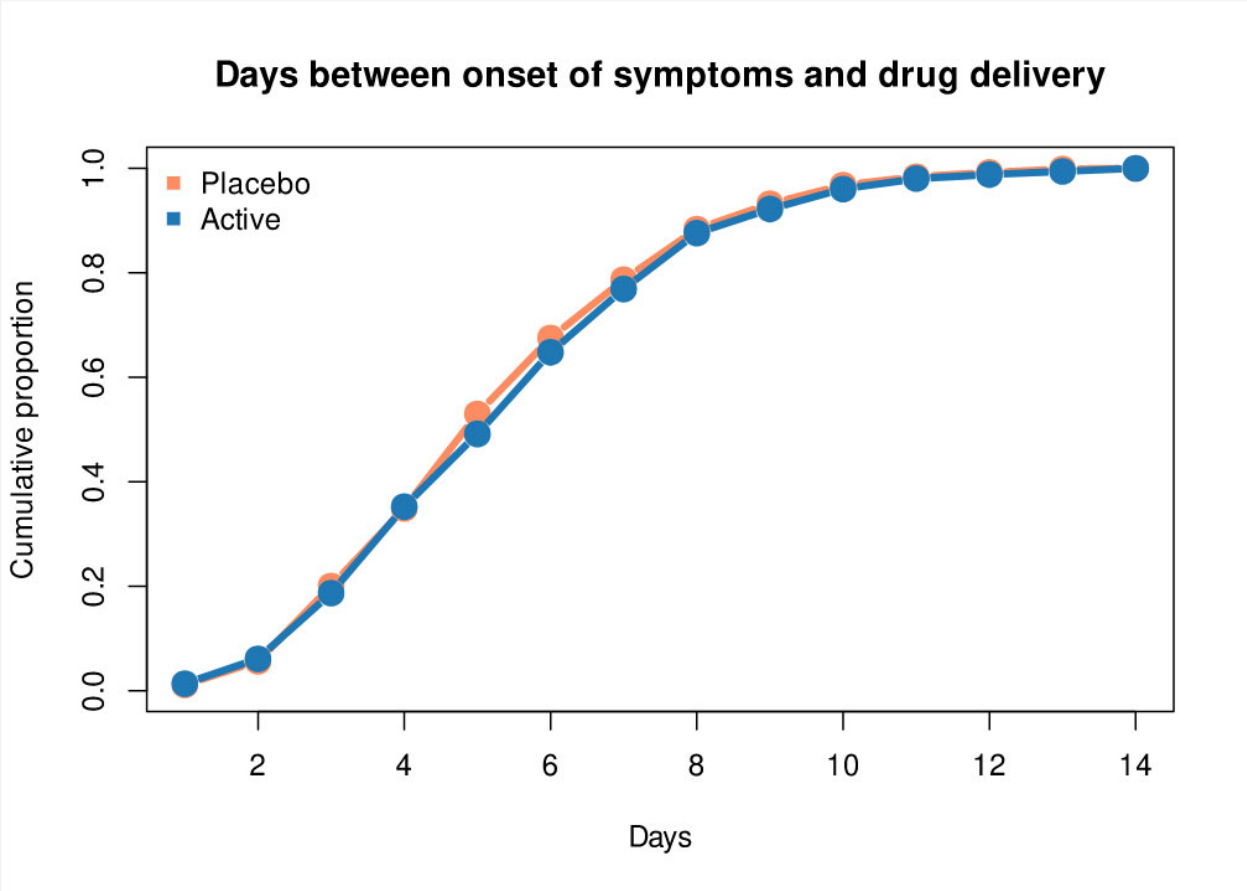
Values are N (%). Note: “Taken” refers to the participants who reported taking (or planning to take) the study drug at least once. “Not taken” refers to the participants (if any) who did not report taking the study drug. Adverse events reported from all available follow-up; some serious adverse events resulted in hospitalization, though not during the 28 day window of the secondary endpoint definition.
Covid-19 indicates coronavirus disease 2019.

Table S6. Adverse events experienced by participants

Adverse event list	Fluticasone Inhaled taken	Matched placebo inhaler, taken	Unmatched concurrent placebo, taken	Overall
COVID-19 pneumonia	3	0	1	4
Insomnia	0	1	2	3
Palpitations	0	2	0	2
COVID-19 pneumonia aggravated	2	0	0	2
Accelerated hair loss	0	0	1	1
Anxiety	0	1	0	1
Chest tightness	0	1	0	1
Coronary vasospasm	0	1	0	1
Cough	1	0	0	1
Coughing blood	1	0	0	1
Diarrhea	1	0	0	1
Diplopia	0	0	1	1
Facial swelling	0	1	0	1
Fever	1	0	0	1
Gastrointestinal reflux	0	1	0	1
Headache	1	0	0	1
Hypoxia	1	0	0	1
Insomnia NOS	0	1	0	1
Loss of smell	1	0	0	1
Loss of taste	1	0	0	1
Nausea and vomiting	0	1	0	1
Pneumonia, viral	1	0	0	1
Sinus infection	1	0	0	1
Sneezing	1	0	0	1
Swelling	1	0	0	1
Tachycardia	0	1	0	1
Urinary tract infection	0	1	0	1
Seasonal allergy	0	1	0	1
Sinusitis bacterial	1	0	0	1
Adverse drug reaction	0	1	0	1

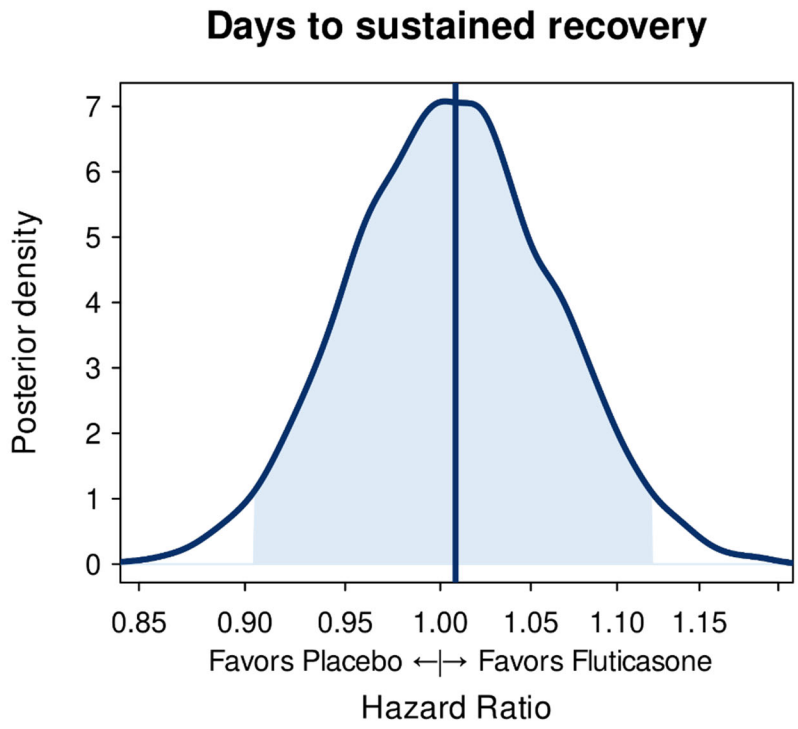
Values represent No. Note: `Taken' refers to the participants who reported taking (or planning to take) the study drug at least once.

Figure S1. Time from symptom onset to receipt of drug



	Cumulative proportion by day													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Placebo	0.01	0.06	0.20	0.35	0.53	0.68	0.79	0.88	0.93	0.97	0.98	0.99	1.00	1
Fluticasone	0.01	0.06	0.19	0.35	0.49	0.65	0.77	0.88	0.92	0.96	0.98	0.99	0.99	1

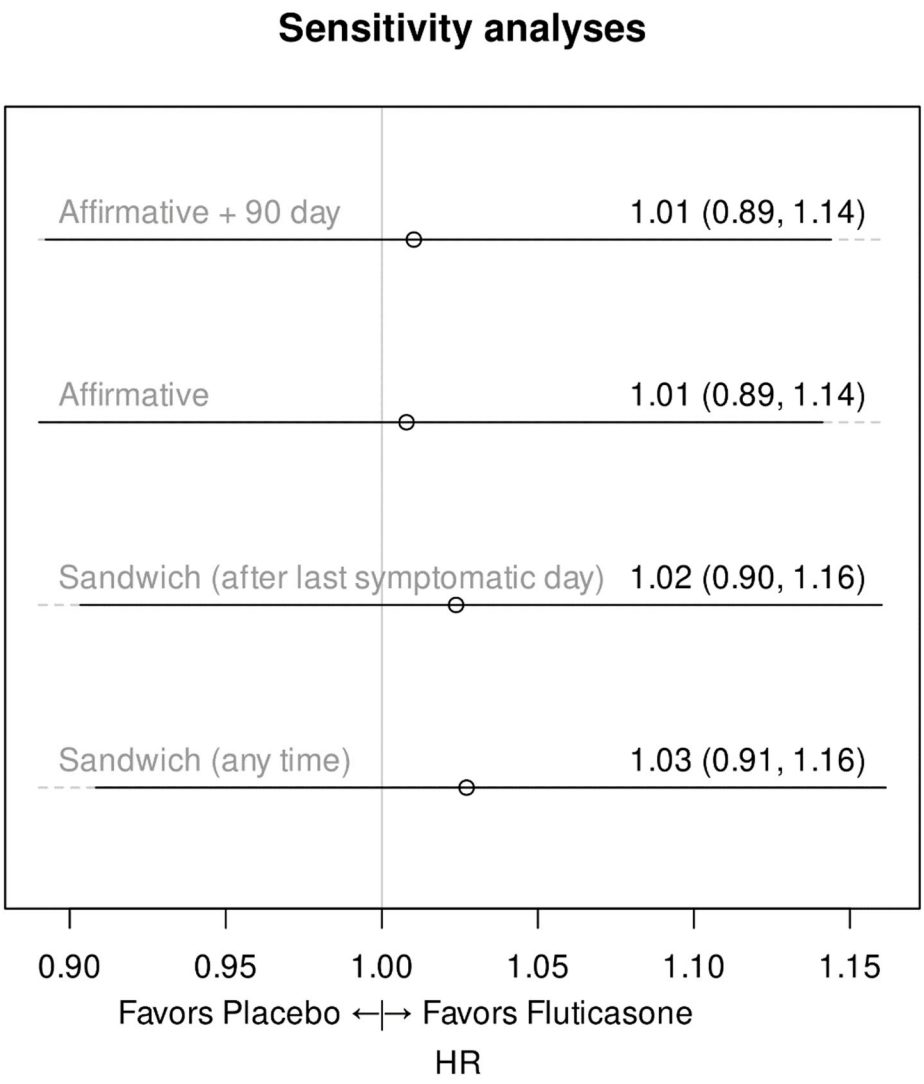
Figure S2. Posterior distribution of treatment effect hazard ratio for time to sustained recovery



Posterior distribution for the treatment effect hazard ratio for the time to sustained recovery. The posterior was based on a covariate adjusted Cox proportional hazards regression with skeptical prior. The baseline hazard was a degree 5 M-spline function. Covariates in the model included age (as restricted cubic spline), sex, duration of symptoms, vaccine status, geographic region, origination from call center, calendar time (as restricted cubic spline), and symptom burden on the day of drug receipt.

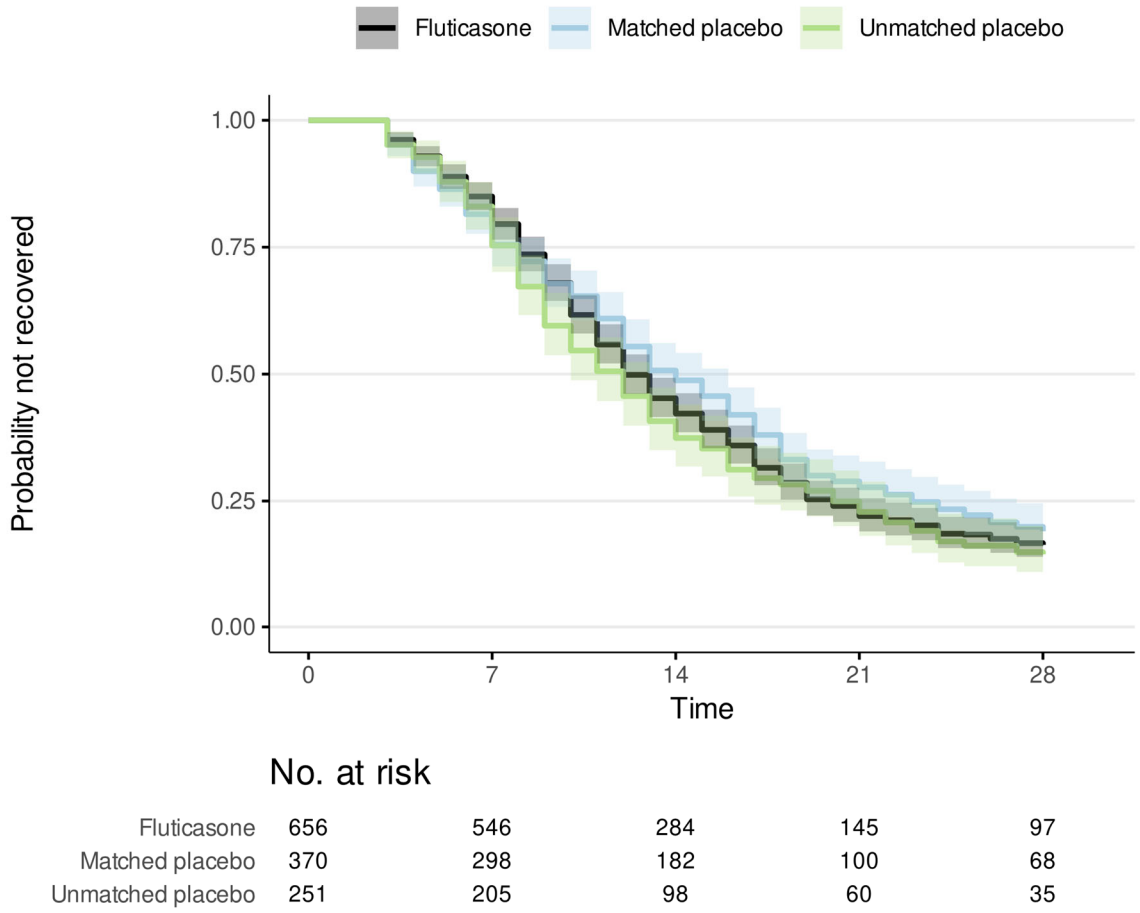
The posterior probability was 0.56 for hazard ratio >1.0. Hazard ratios greater than one favored the active intervention for a faster time to recovery.

Figure S3. Sensitivity analyses for missing daily symptom data on time to sustained recovery



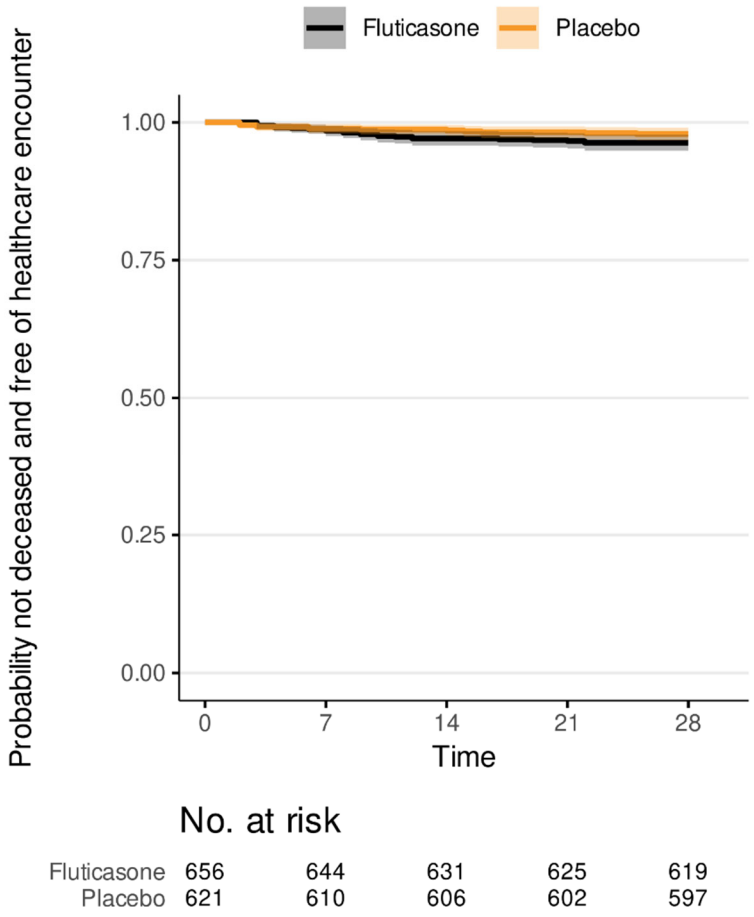
This figure shows the treatment effect for different definitions of sustained recovery. The "Affirmative + 90 day follow-up" is the primary definition. The first alternative, the "Affirmative" definition differs with respect to the definition of lost to follow-up, censoring participants that did not recover (per definition) and could not be contacted for day 28 responses. The second and third alternatives relax the primary definition by treating missing responses as days without symptoms if the days of missing responses are bookended or sandwiched by days without symptoms. For example, if a participant failed to provide a response on day two but reported no symptoms on day one and day three, the "Sandwich" definition would treat the day two missing response as "no symptoms". The "Sandwich after last symptomatic day" definition only applies the sandwich rule to missing responses that occurred after the last reported day of symptoms. The hazard ratios reported in the figure were estimated from the covariate-adjusted, proportional hazards regression model without prior. Note that regardless of how sustained recovery is defined, the treatment effect is relatively the same.

Figure S4. Kaplan-Meier plot of time to recovery with matched and unmatched placebos



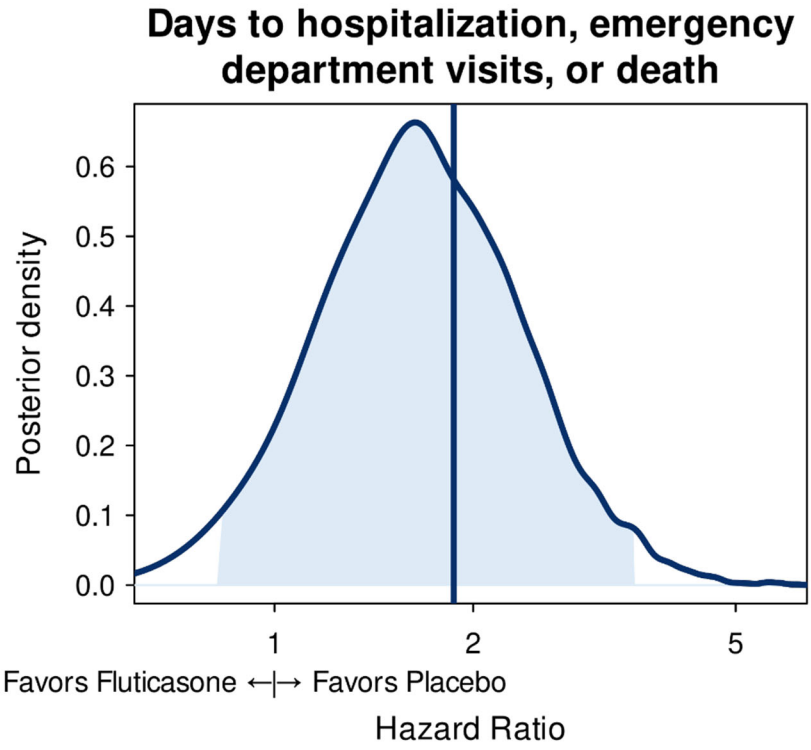
Kaplan-Meier curve for time-to-recovery primary endpoint stratified by treatment and type of placebo. This exploratory analysis used a 3-level treatment variable (active, matched placebo, unmatched placebo) in place of the pre-specified 2-level treatment variable (active versus placebo with matched and unmatched placebos combined). The unadjusted, log-rank test comparing the 3 groups resulted in a p-value of 0.1. Excluding the active group and comparing just the 2 placebo groups resulted in a p-value of 0.04. The covariate-adjusted Cox model with the 3-level treatment variable resulted in a 2 degree of freedom chunk test p-value of 0.01, suggesting possible heterogeneity between the placebo groups. The covariate-adjusted Cox model was consistent with the Kaplan-Meier curves in that the time to recovery for the active treatment group fell in between the time to recovery profiles of the two placebo groups. Specifically, the treatment effect hazard ratio when compared with matched placebo was 1.12 (95% CI: 0.97, 1.30). When compared with the unmatched placebo, the hazard ratio was 0.85 (95% CI: 0.72, 1.00). On the absolute scale, the unadjusted estimate of median time to recovery was 12 days (95% CI: 12, 13) for the active arm, 14 days (95% CI: 13, 16) for the matched placebo arm, and 12 days (95% CI: 10, 13) for the unmatched placebo arm.

Figure S5A. Time to composite endpoint of hospitalization, urgent care, emergency department visit, or death through day 28 for inhaled fluticasone furoate vs concurrent placebo



Kaplan-Meier curve for time-to-healthcare encounter/hospitalization/death endpoint. In the fluticasone furoate active group, 24 participants (3.7%) had a healthcare encounter of urgent care visit, emergency room visit, or hospitalization as compared with 13 (2.1%) in the pooled placebo group (Hazard Ratio 1.9, 95%CrI, 0.8-3.5, P(HR<1)=0.035). Overall, 13 fluticasone participants and 11 placebo participants were right-hand censored for lost to follow up. The Bayesian posterior distribution of treatment effect is presented in **Figure S5B**.

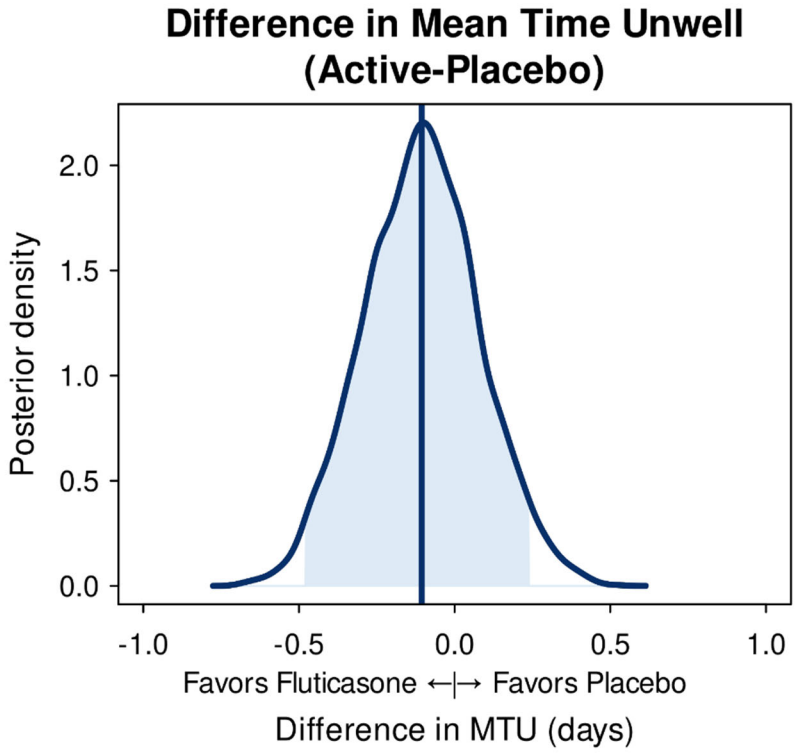
Figure S5B. Posterior distributions of treatment effect hazard ratio for time to the composite endpoint of hospitalization, urgent care, emergency department visit, or death through day 28



Posterior distribution for the treatment effect hazard ratio for the time to the composite endpoint of hospitalization, urgent care, emergency room visit, or death through day 28. The posterior was based on a covariate adjusted Cox proportional hazards regression with uninformative prior. The baseline hazard was a degree 5 M-spline function. Covariates in the model included age (as restricted cubic spline), sex, duration of symptoms, vaccine status, geographic region, origination from call center, calendar time (as restricted cubic spline), and symptom burden on the day of drug receipt.

Hazard ratios less than one favor the active intervention of inhaled fluticasone furoate.

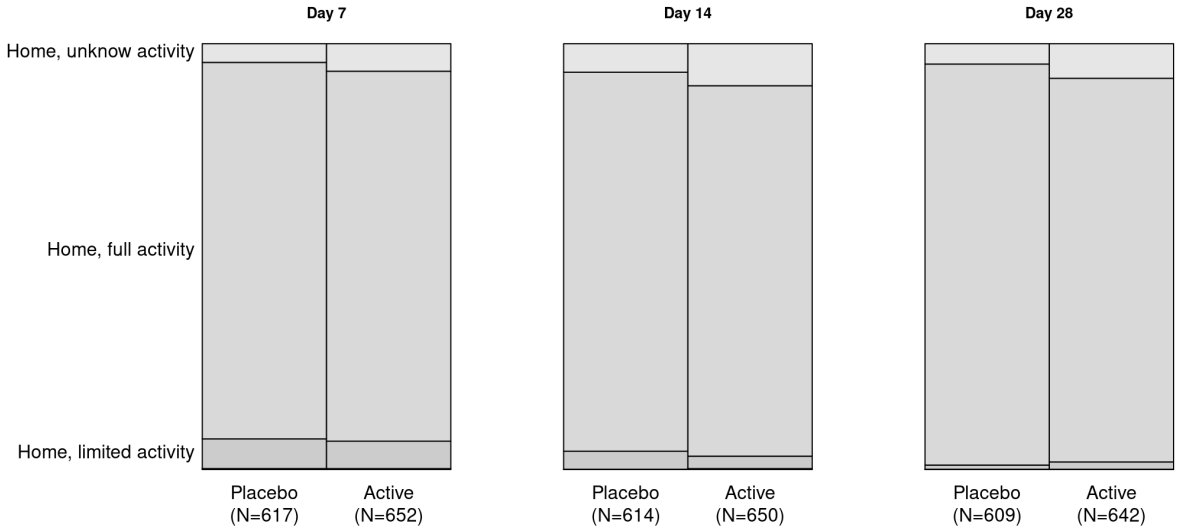
Figure S5C. Posterior distribution of the difference in mean time unwell



Posterior distribution of the difference in mean days unwell (Active-Placebo). Mean time unwell is a model-based estimate of the number of days with symptoms or hospitalized/deceased during the first 14 days of follow-up. Negative differences indicate that participants in the active arm were unwell shorter than participants in the placebo arm. The estimate of mean days unwell is calculated from a Bayesian, longitudinal, ordinal regression model with covariates age (as restricted cubic spline) and calendar time. The prior distribution was not informative.

The difference In mean days unwell was -0.10 (95% CrI, -0.46, 0.25) equating to an average of 2.4 hours faster recovery with inhaled fluticasone (95% CrI, 11 hours faster to +6 hours longer). The posterior probability that the difference was larger than 1 day was less than 0.001 probability.

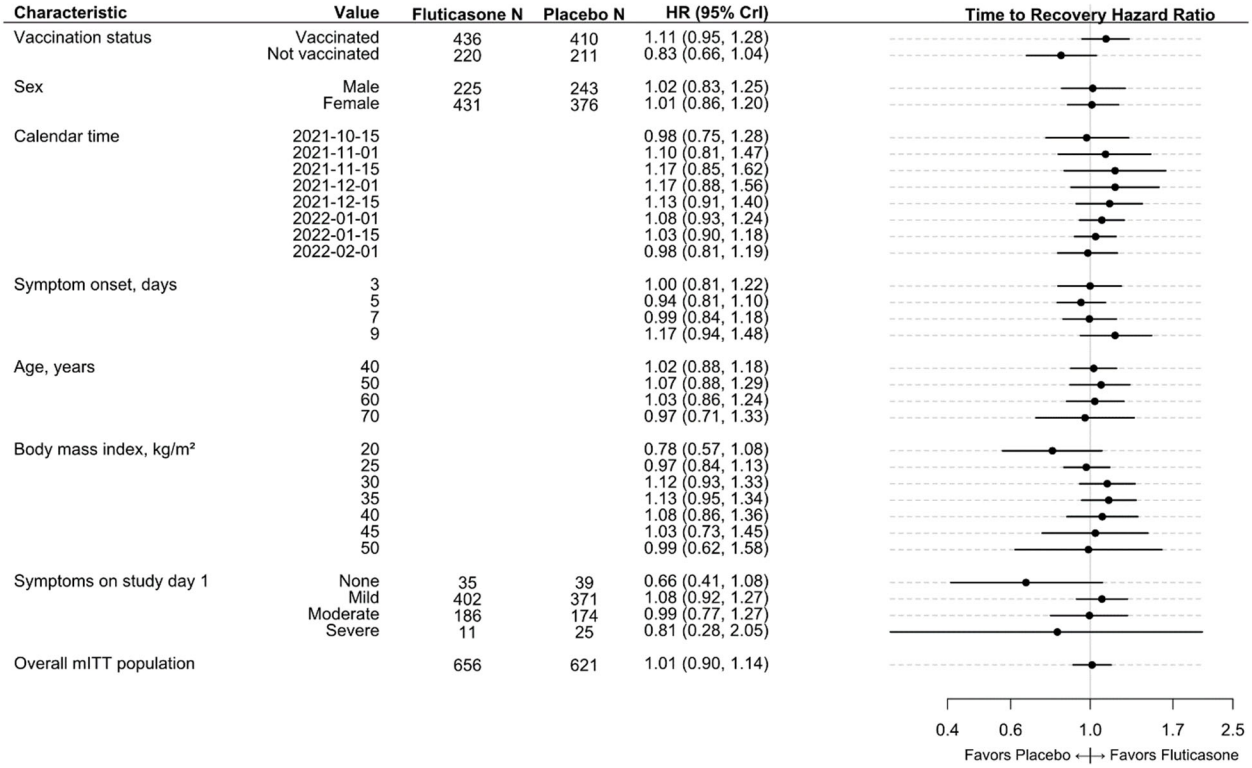
Figure S6. Covid-19 clinical progression scale for inhaled fluticasone vs placebo



Day	Day 7	Day 14	Day 28
Odds ratio	1.10	0.91	2.74
95% Credible Interval	0.62, 1.63	0.42, 1.50	0.50, 5.94
Posterior P(efficacy)	0.407	0.673	0.065

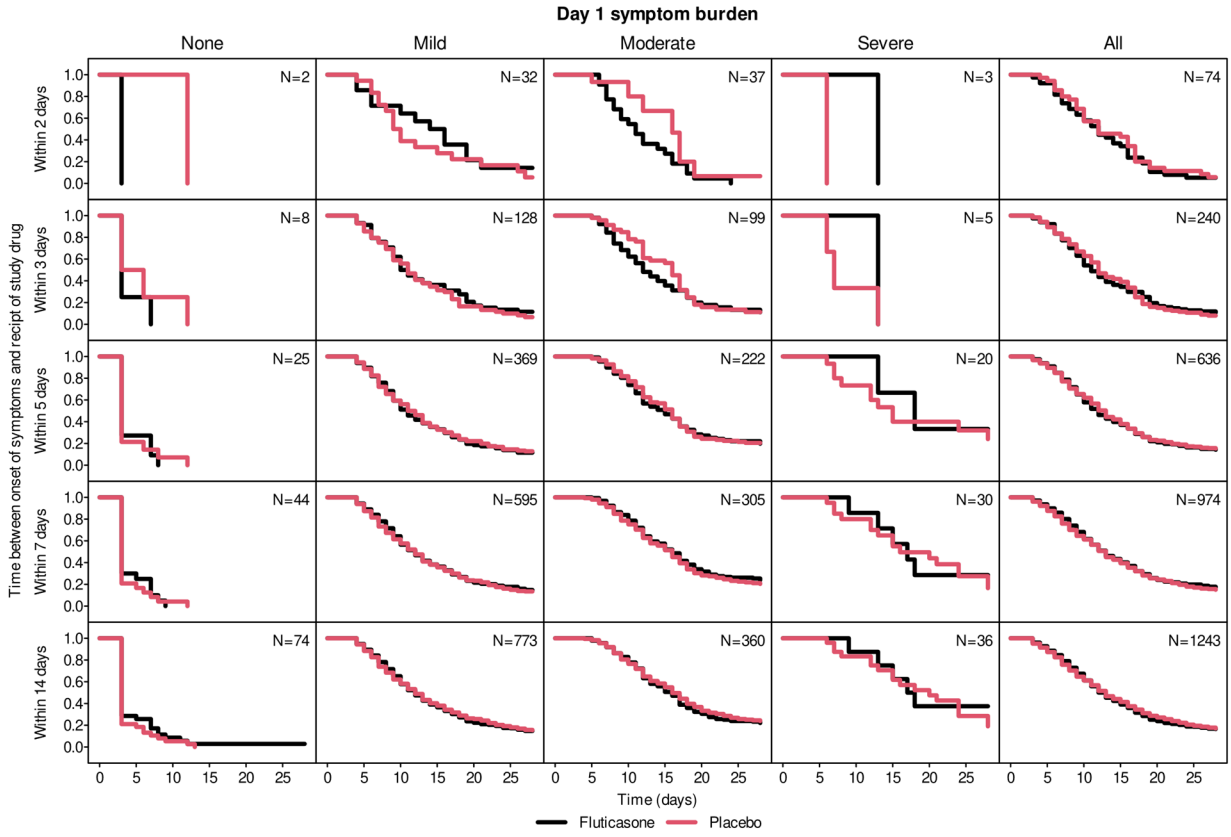
Odds ratio >1.0 favors placebo. Refer to Table S3 for numerical data. Posterior P(efficacy) is the probability for efficacy, P(OR<1)..

Figure S7. Heterogeneity of treatment effect between inhaled fluticasone furoate and concurrent placebo for time to recovery (Bayesian Method)



A hazard ratio greater than 1.0 indicates a faster time to recovery. Study day 1 was the day of starting the study medication. The 'mITT population' reflects a modified intent-to-treat analysis of participants randomized who enrolled within 7 days of symptom onset and received study drug. The figure reports the covariate-adjusted and model-based estimates of the treatment effect for selected subgroups. The estimates were generated from the Bayesian proportional hazard survival model with weakly informative prior. 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, such as 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 called 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% credible intervals were calculated from the posterior distribution. The hazard ratio for the full study population was generated from the primary endpoint model with weakly informative prior.

Figure S8. Kaplan-Meier curves of sustained recovery by onset of symptoms and symptom severity



34 participants were excluded from the figure for missing day 1 symptom burden.