ACTIV-6:
1-year Later and Trial Results for Ivermectin 400 & Inhaled Fluticasone Results

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On behalf of Adrian Hernandez, MD, MHS, Chris Lindsell, PhD, Tom Stewart, PhD and the ACTIV-6 Study Team

ACTIV-6

Key clinical questions

How to help someone *feel better faster* with newly diagnosed mild-moderate COVID-19?

How to *prevent hospitalizations or death* in someone with newly diagnosed mild-moderate COVID-19?

What is ACTIV-6?

A STUDY TO HELP PEOPLE WITH MILD-TO-MODERATE COVID-19 FEEL BETTER FASTER

@ACTIV6study

ACTIV-6 is part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership, which was created to speed the development of effective treatments and vaccines for COVID-19.

What are we trying to find out together?

How can we help people with COVID-19 feel better faster?

How can we prevent people with COVID-19 from going to the hospital?

How do we share what we are learning?

Visit activ6study.org for study results and the latest news.

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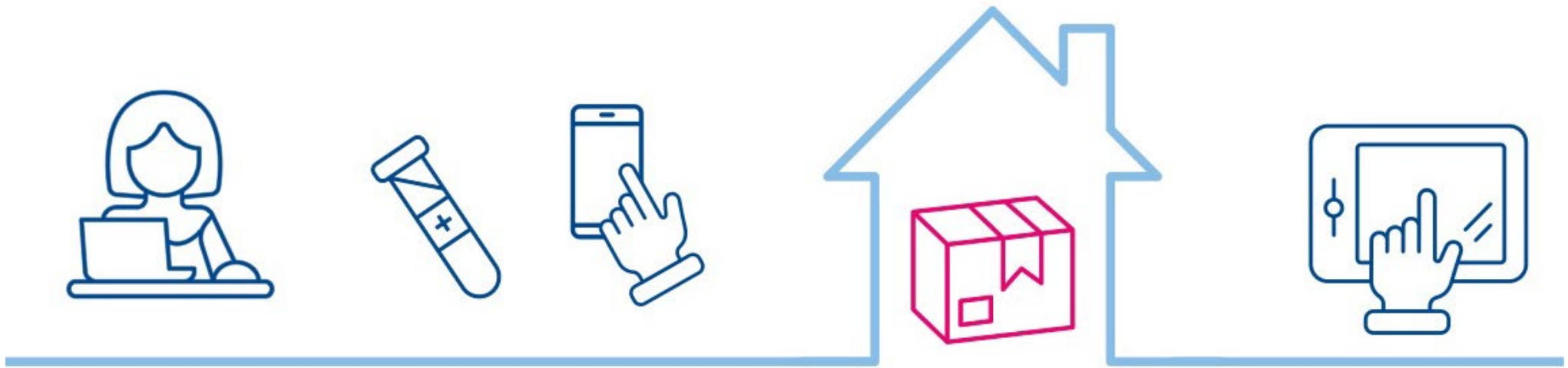
What makes ACTIV-6 different?

ACTIV-6 is testing several medications that are approved to treat conditions other than COVID-19 and can be found at your local pharmacy. This provides options to participants and helps generate results faster.

Participate from home — study medication is mailed directly to participants who can sign up and complete surveys online or over the phone.

How does the study work?



Learn about ACTIV-6 online, on the radio, or from health systems, pharmacies, testing centers, or community partners.

Test positive for COVID-19.

Enroll online or over the phone. activ6study.org

Receive assigned study medication and directions at home. **Take** the study medication as directed.

Complete surveys about how you feel online or over the phone.

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WHAT ARE THE STEPS IN THIS STUDY?

1 SIGN UP ONLINE

People can participate from anywhere in the US. After signing up online, by web or phone, you will get an email or text message within a day with a link. That link will take you to the registration survey.

2 ABOUT THE MEDICINES

This study is testing several different medicines. You will be selected by chance to get either a medicine you are eligible for or a placebo. Learn about the medicines here.

CLINICAL STUDIES AND PLACEBOS

Participants in this study take either a study medicine or a placebo. A placebo is a medication that has no active ingredients and will have no effect on you. When some people take medicines and others take placebos, that lets researchers figure out if a medicine is useful or not.

3 CHOOSE THE MEDICINES YOU WOULD WANT TO TRY

Participating in this study involves: **1)** choosing which medicines you'd be willing to take, **2)** taking the medication assigned to you, and **3)** keeping track of your symptoms by using online surveys. No one, including you, will know if you're taking a medicine or a placebo.

Your chance of taking a medicine instead of a placebo depends on how many medicines you are willing to try and are eligible for:

Choose 1, your chance is 50% (1 out of 2)

Choose 2, your chance is 67% (2 out of 3)

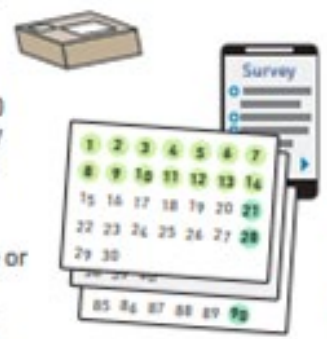
Choose 3, your chance is 75% (3 out of 4)

4 RECEIVE AND TAKE YOUR MEDICATION, COMPLETE DAILY SURVEYS

Your medication will be mailed to your home at no cost, and then you will start taking it according to its instructions.

You will be asked to answer a short (5 to 10 minutes) survey on a secure website every day for 14 days, and follow-up surveys on days 21, 28 and 90.

If you still have symptoms after 14 days, you'll take a daily survey until they're gone or you reach day 28. If you feel worse at any time, you should seek medical care as you normally would and notify the study team during the next survey.



There are no in-person visits involved with this study. You can stop participating in the study at any time.

5 GET YOUR REWARD

You will receive gift cards on the 28th and 90th day that total $100.

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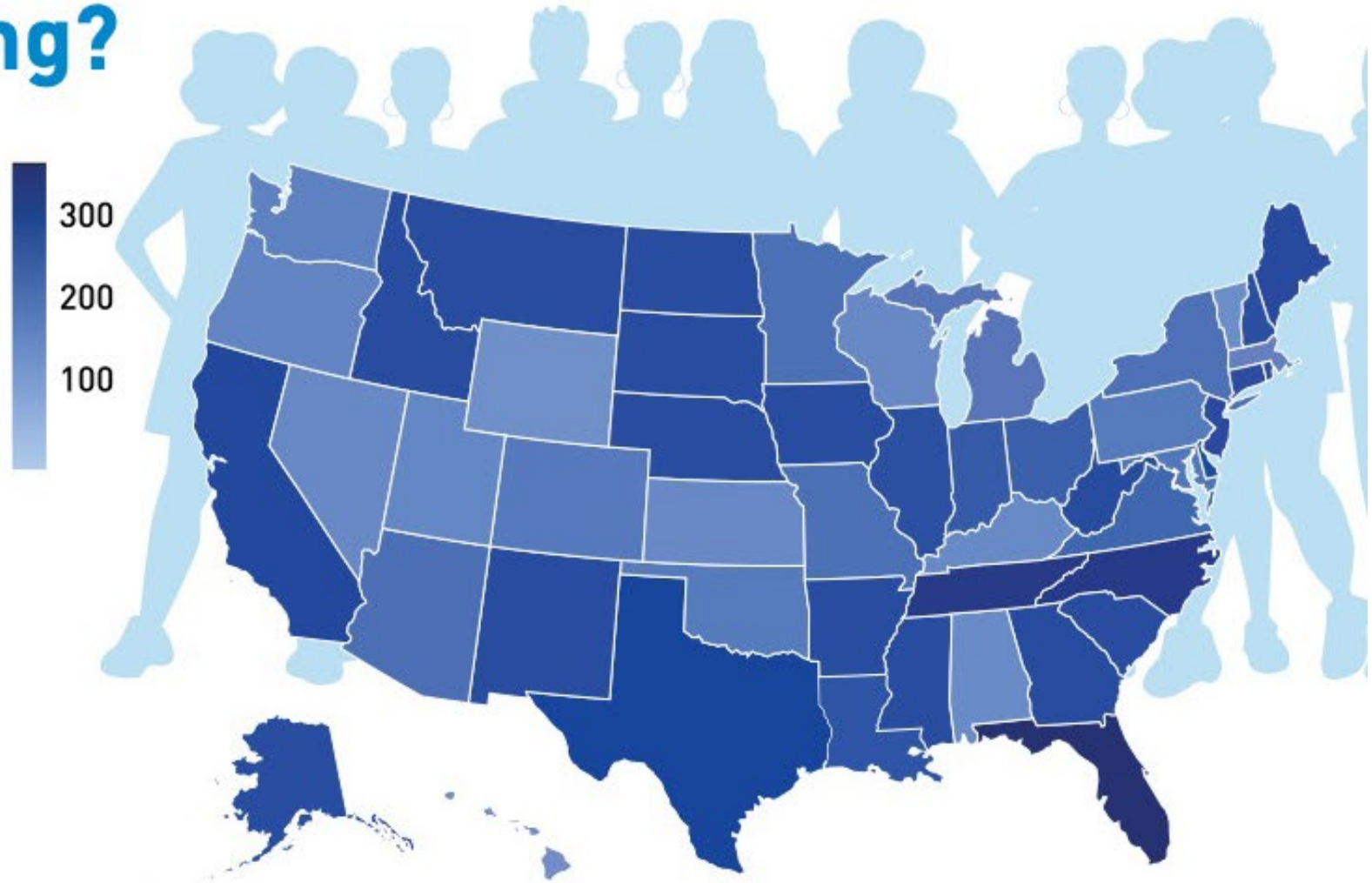
Who is participating?

People who are 30 years old or older who have COVID-19 are taking part.

ACTIV-6 participants represent every state plus the District of Columbia.

ACTIV-6 participants are key partners in the research process. Their valuable contributions help generate results that may impact the care of people with COVID-19.



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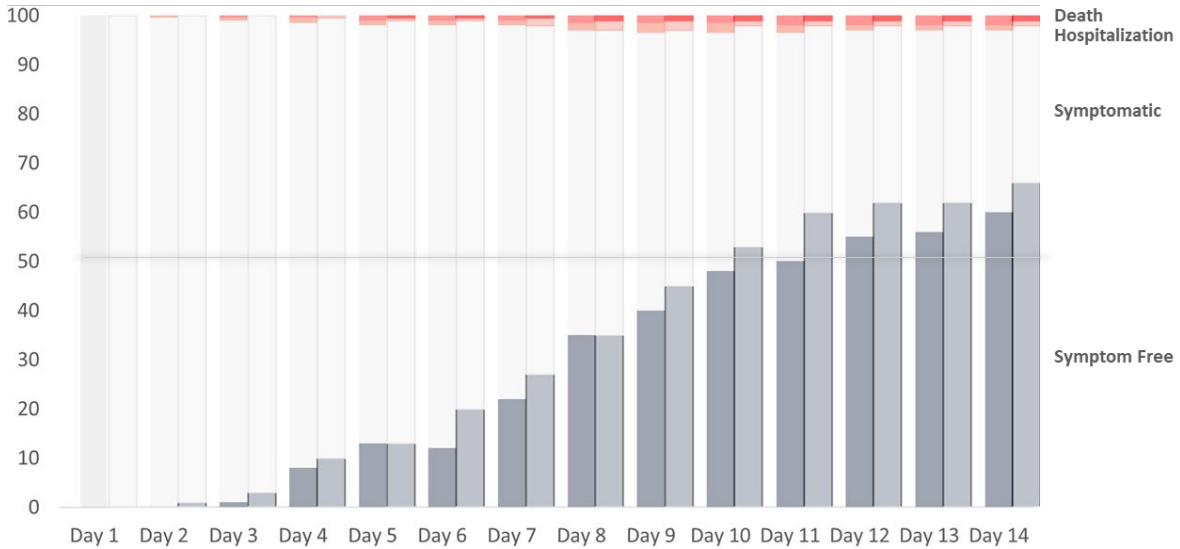
Measurements

No symptoms
Mild symptoms
Moderate symptoms
Severe symptoms
Hospitalization
Death

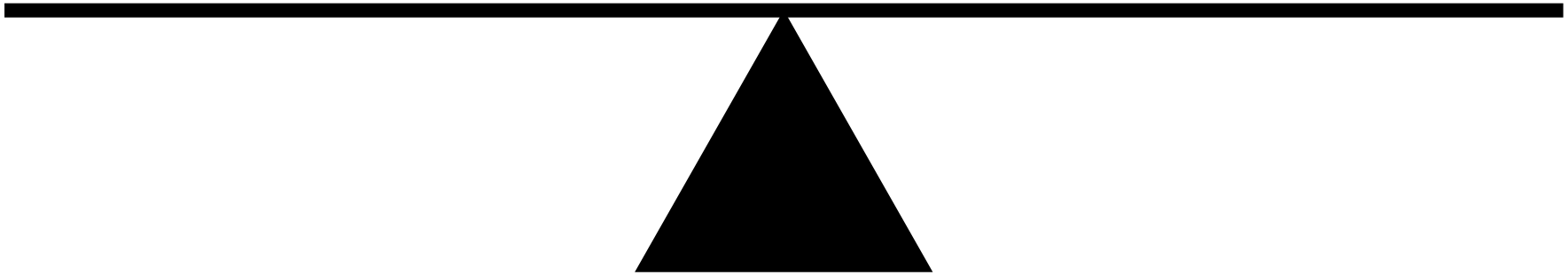
Outcomes



Time to recovery, clinical events
Days of benefit

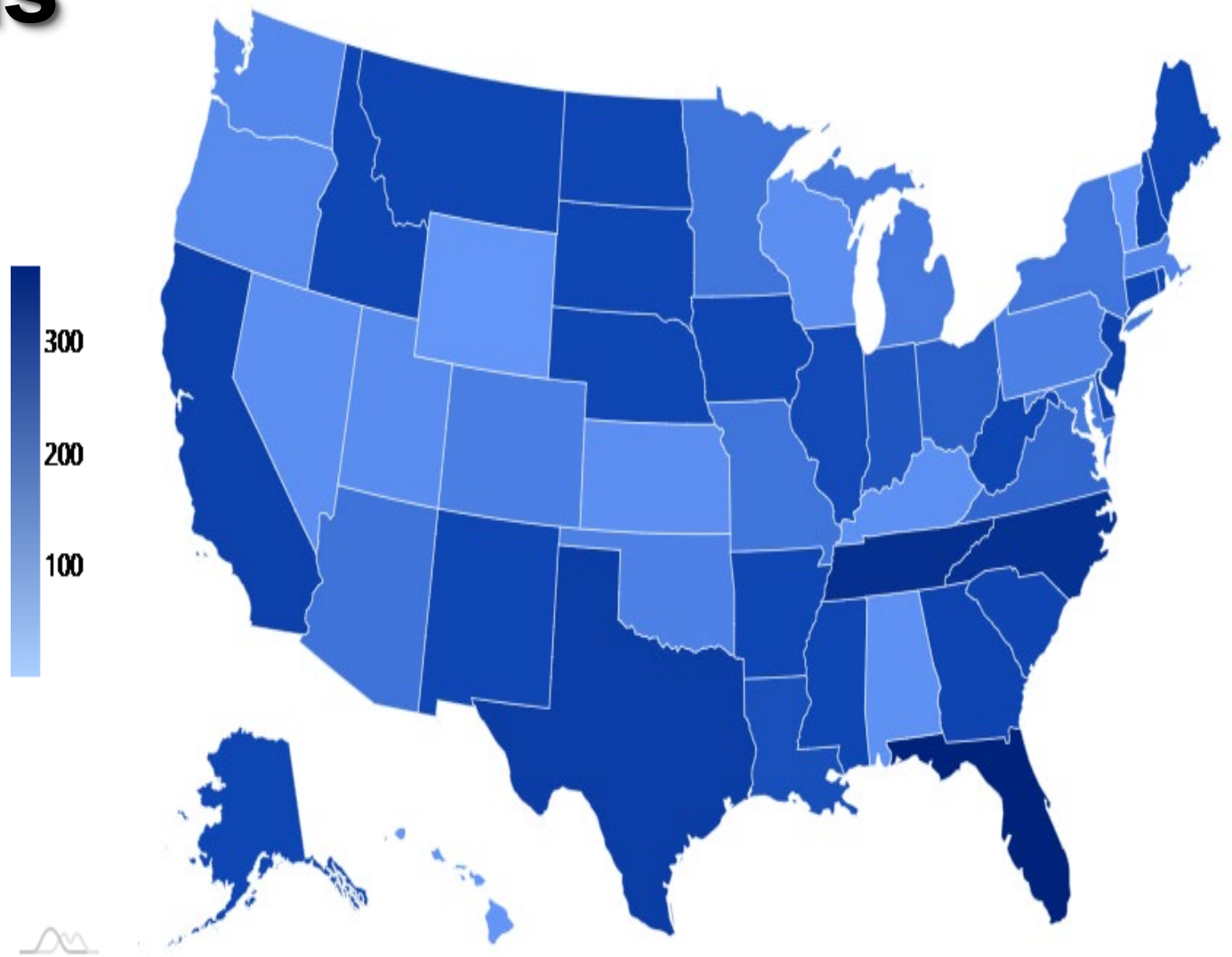
Days of benefit: for early looks in the data as a screening phase for the intervention

Time to recovery / hospitalization & death: for later looks at the data as a specific test of intervention effects



Current Study Status

- 93 sites activated
- 5034 randomized
- Ivermectin 400: 1537
- Fluticasone: 1127
- Fluvoxamine 50: 1021
- Ivermectin 600: 1349



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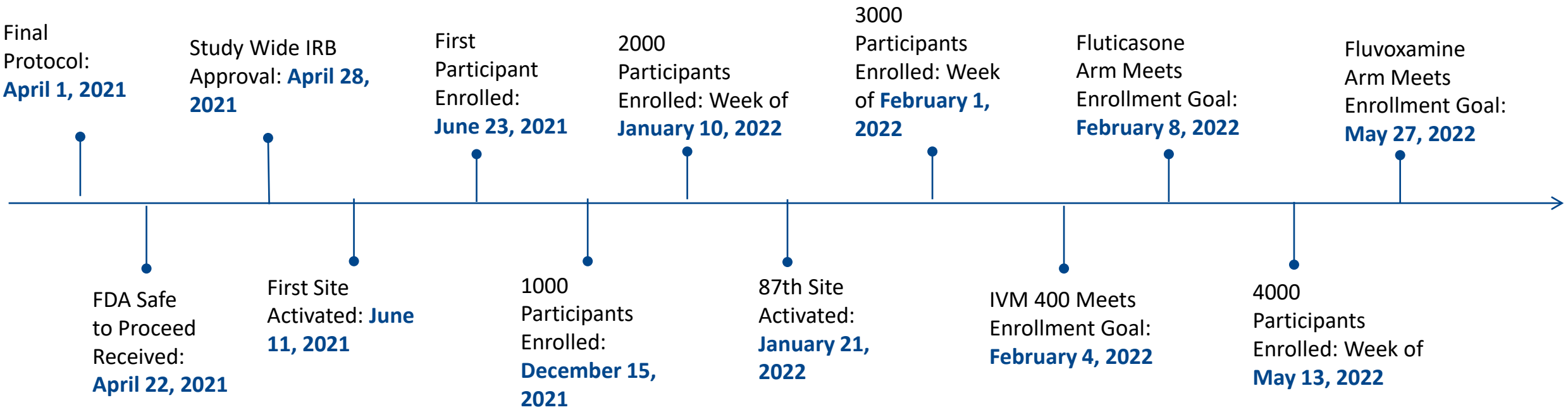
ACTIV-6 | MILESTONES



Summary Results
Ivermectin 400

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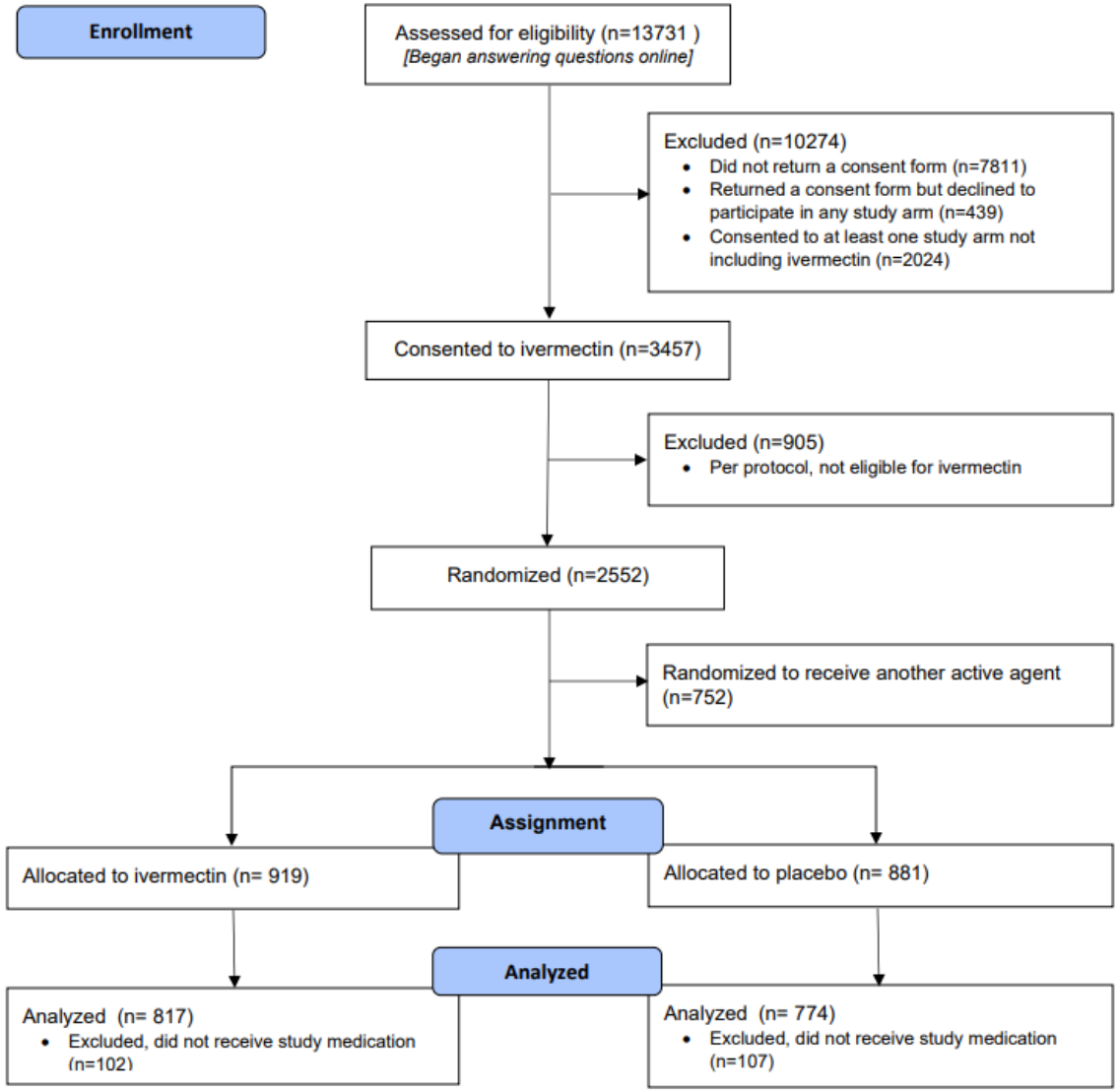
Enrollment



Ivermectin n=(817)

Placebo n=(774)

Participant characteristics (1)

	Placebo (n=774)	Active (n=817)	Overall (n=1591)
Age, median (IQR), y	48 (39-56)	47 (39-56)	47 (39-56)
Age < 50, No. (%)	435 (56.2)	476 (58.3)	911 (57.3)
Female, No. (%)	424 (54.8)	508 (62.2)	932 (58.6)
Race, not mutually exclusive:			
Black or African American, No. (%)	56 (7.2)	57 (7.0)	113 (7.1)
White, No. (%)	627 (81.0)	659 (80.7)	1286 (80.8)
Ethnicity: Latino, No. (%)	70 (9.0)	93 (11.4)	163 (10.3)
Region, No. (%)			
MW	166 (21.5)	157 (19.2)	323 (20.3)
NE	68 (8.8)	85 (10.4)	153 (9.6)
S	455 (58.8)	475 (58.1)	930 (58.5)
W	85 (11.0)	100 (12.2)	185 (11.6)
Call center, No. (%)	112 (14.5)	127 (15.5)	239 (15.0)

Participant characteristics (2)

	Placebo (n=774)		Active (n=817)		Overall (n=1591)	
BMI, median (IQR), kg/m^2	28.3	(24.9-33.3)	28.3	(24.9-33.2)	28.3	(24.9-33.3)
BMI > 30 kg/m^2, No./total (%)	314	(40.6)	334/816	(40.9)	648/1590	(40.8)
Heart disease, No./total (%)	36/756	(4.8)	34/804	(4.2)	70/1560	(4.5)
Diabetes, No./total (%)	88/756	(11.6)	96/804	(11.9)	184/1560	(11.8)
High blood pressure, No./total (%)	203/756	(26.9)	212/804	(26.4)	415/1560	(26.6)
COPD, No./total (%)	23/756	(3.0)	34/804	(4.2)	57/1560	(3.7)
Asthma, No./total (%)	120/756	(15.9)	121/804	(15.05)	241/1560	(15.5)
Chronic kidney disease, No./total (%)	6/756	(0.8)	6/804	(0.8)	12/1560	(0.8)
Smoker, past year, No./total (%)	103/756	(13.6)	134/804	(16.27)	237/1560	(15.2)
Malignant cancer, No. (%)	22	(2.8)	26	(3.2)	48	(3.0)
Vaccine status, No. (%)						
Not vaccinated	394	(50.9)	420	(51.4)	814	(51.2)
Vaccinated (1 dose)	12	(1.6)	12	(1.5)	24	(1.5)
Vaccinated (2+ doses)	368	(47.6)	385	(47.1)	753	(47.3)

Status on Day 1

	Placebo (n=774)	Active (n=817)
Days from onset to receipt of study drug (mean, SD)	6 (4-7)	6 (4-7)
Symptom burden on Day 1[a]		
None (%)	54 (7.0)	55 (6.7)
Mild (%)	434 (56.1)	490 (60.0)
Moderate (%)	247 (31.9)	221 (27.1)
Severe (%)	39 (5.0)	51 (6.2)
Unknown (%)	54 (7.0)	55 (6.7)

[a]Day 1 is the day the participant received their study drug. All participants were symptomatic at the time of enrollment

Safety events

	Active, not taken (n=41)	Active, taken (n=776)	Placebo, not taken (n=50)	Placebo, taken (n=724)	Overall (n=1591)
	41	776	50	724	1591
Experienced an adverse events, No. (%)	1 (2.4)	24 (3.1)	0 (0.0)	27 (3.7)	52 (3.3)
Experienced a serious adverse events, No. (%)	1 (2.4)	9 (1.2)	0 (0.0)	9 (1.2)	19 (1.2)
Serious adverse events, No. (not mutually exclusive)					
COVID-19 pneumonia	0	4	0	4	8
Pulmonary embolism	0	1	0	3	4
COVID-19 pneumonia aggravated	0	1	0	3	4
Venous thromboembolism	0	0	0	2	2
Bacteremia	0	0	0	1	1
Diplopia	0	0	0	1	1
Pneumonia due to Staphylococcus	0	1	0	0	1
Pneumonia due to Streptococcus, group b	0	1	0	0	1
Acute kidney injury	1	0	0	0	1
Hospitalization (shortness of breath)	0	1	0	0	1
Viral bronchopneumonia	0	1	0	0	1
COVID-19	0	1	0	0	1

Concomitant treatments for Covid-19

	Placebo (n=774)	Active (n=817)
Remdesivir (%)	2 (0.3)	2 (0.2)
Monoclonal antibodies (%)	25 (3.2)	22 (2.7)
Paxlovid (%)	1 (0.1)	1 (0.1)

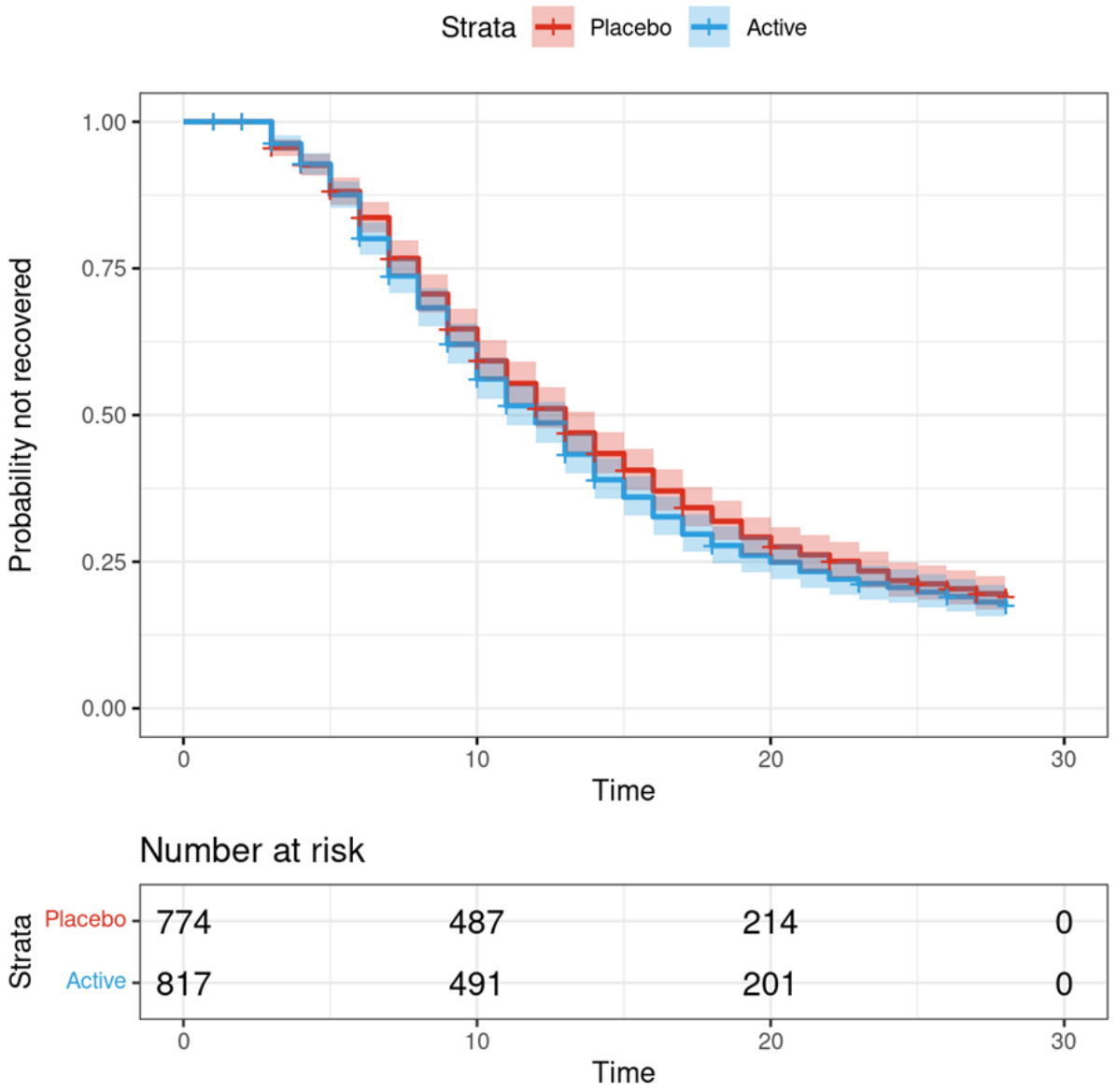
Time to recovery

Kaplan-Meier curve and 95% confidence intervals (point-wise) for time-to-recovery endpoint

Among participants that did not die during follow-up, recovery was defined as three consecutive days without COVID-19 symptoms, as affirmatively reported by the study participant

Participants that died, by definition, did not recover regardless of reported symptom freedom

Time to recovery was administratively censored at 28 days



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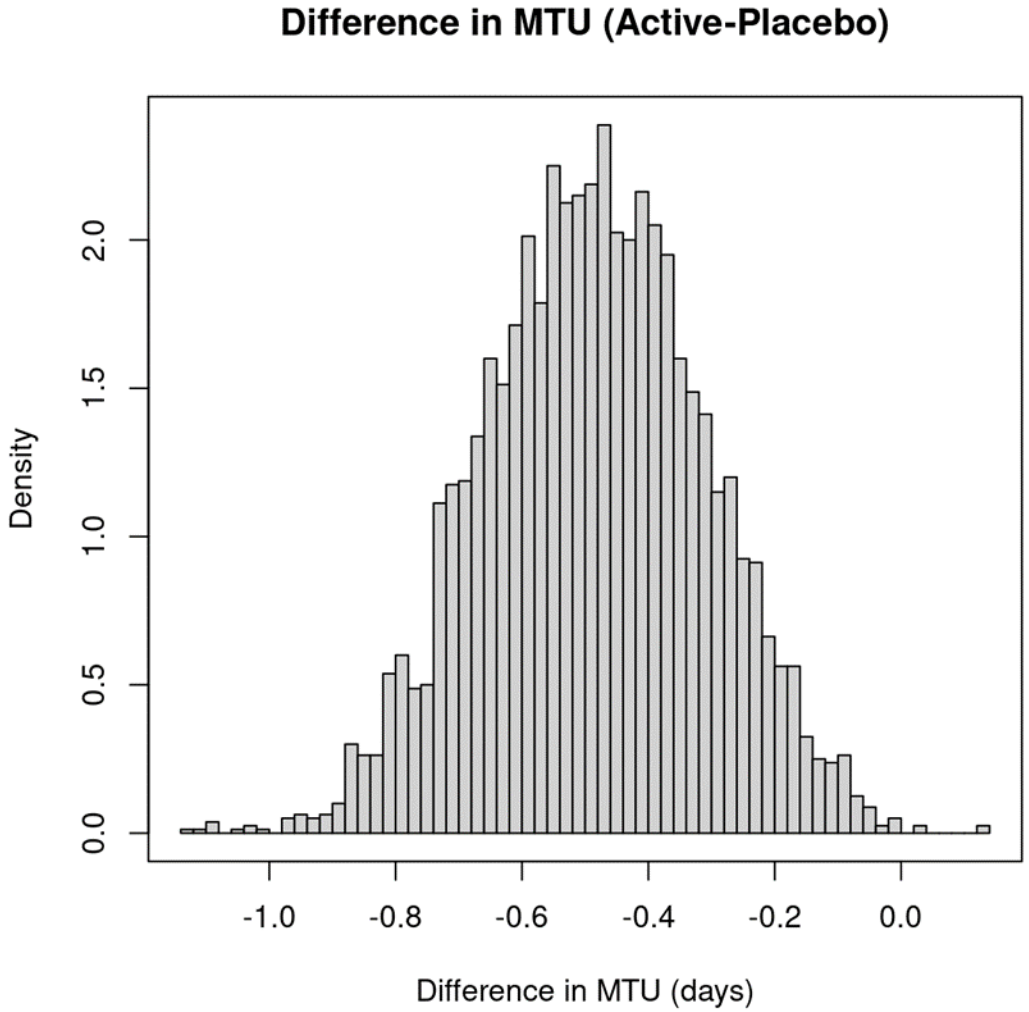
Time spent unwell

Posterior distribution of the difference in the mean time spent unwell (MTU) between those randomized to ivermectin and those randomized to placebo

The difference in the mean time spent unwell reflects the change in symptom duration when taking ivermectin compared with placebo; A negative number favors ivermectin

The probability that ivermectin decreases time spent unwell is 0.99

The probability ivermectin decreases the time spent unwell by more than one day is <0.01



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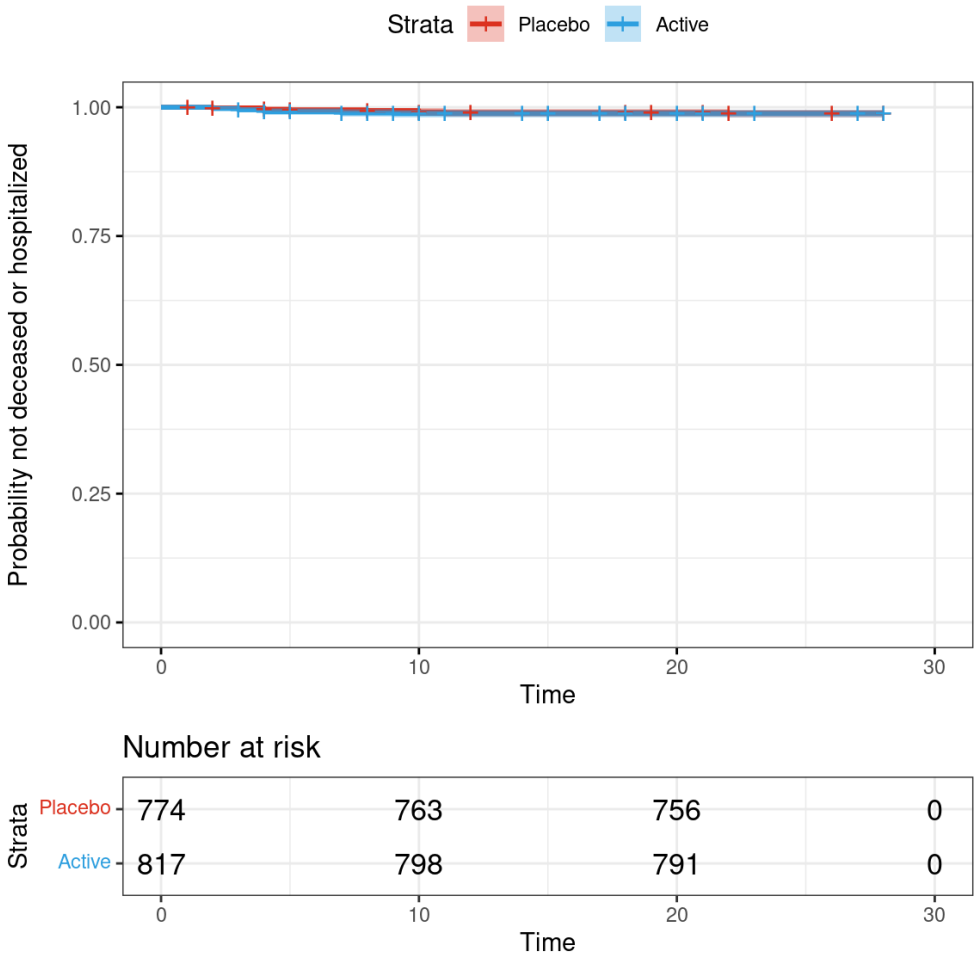
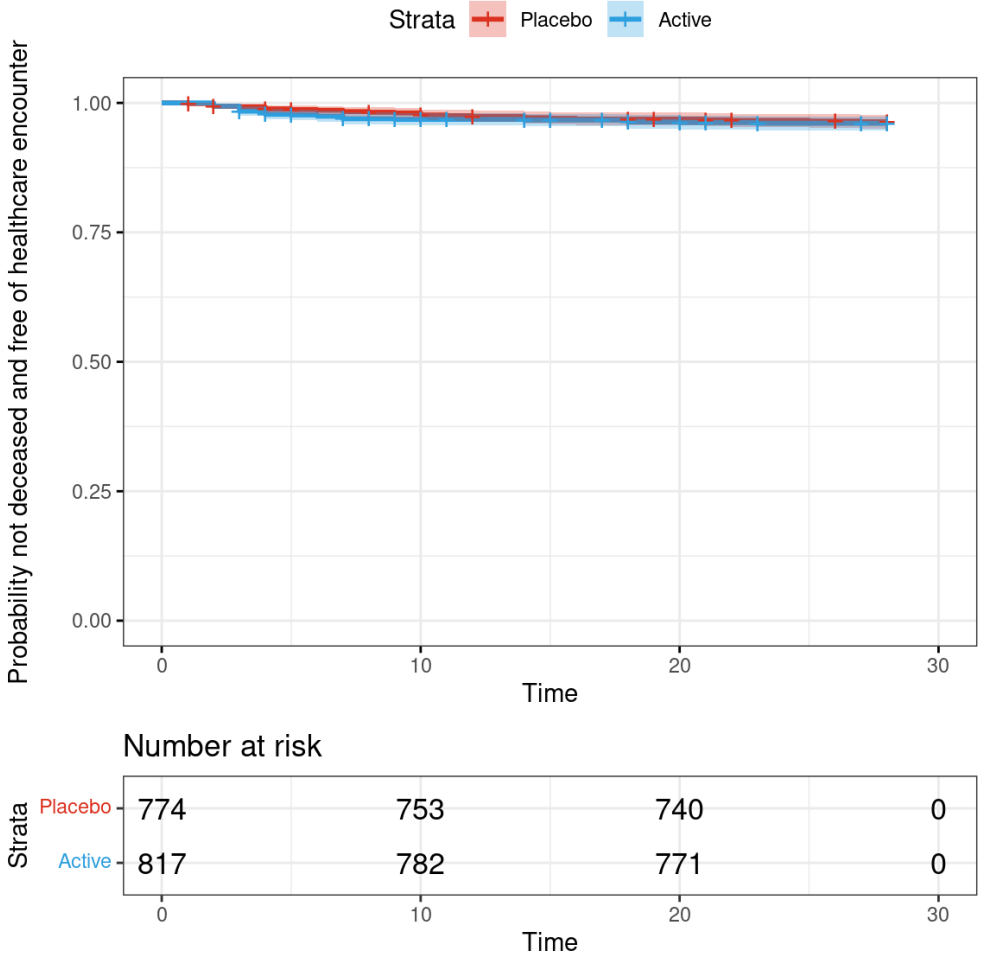
Secondary outcomes – 28 Day events



Hospitalization or death



Healthcare encounter or death

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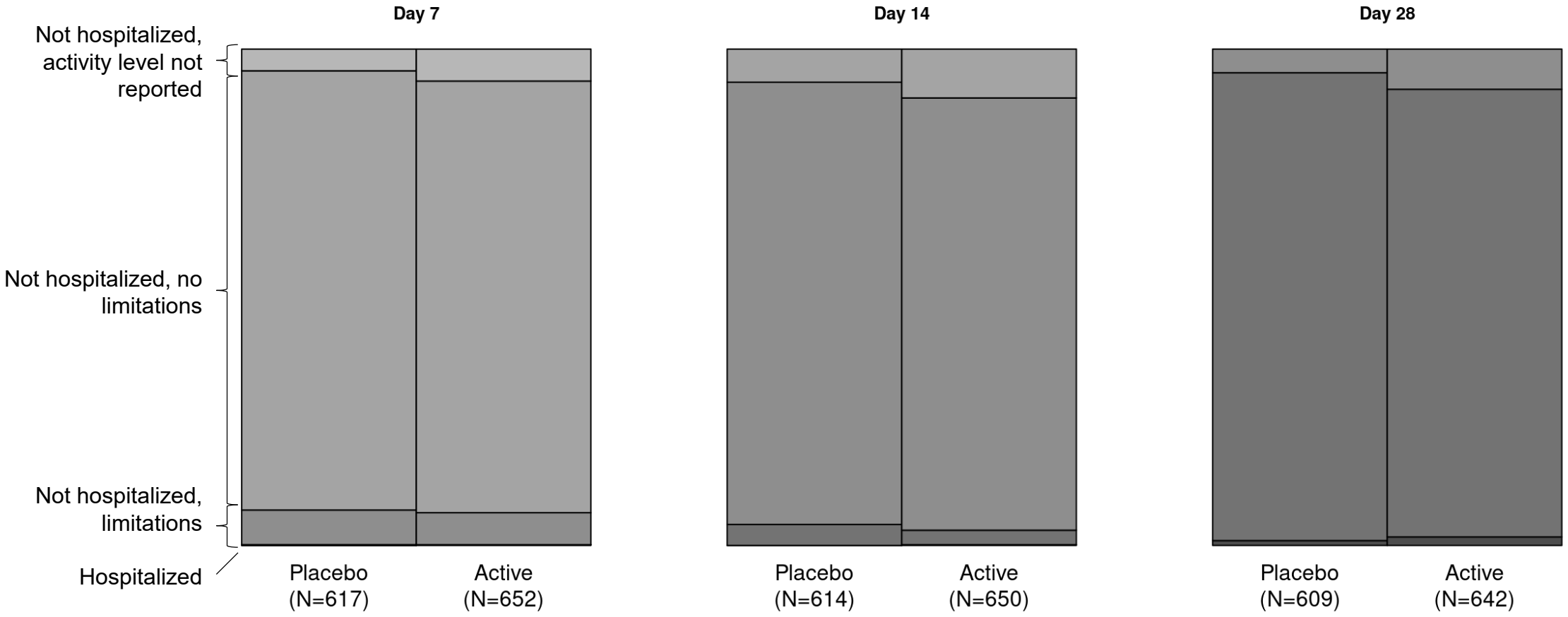
Secondary outcomes – 28 Day events

	Placebo N=774	Active N=817	HR (CrI)[a]	Posterior P(efficacy)
Mortality	0 (0.0%)	1 (0.1%)	-	-
Death or hospitalization	8 (1.0%)	11 (1.4%)	1.1 (0.4, 2.6)	-
Hospitalization, urgent care, emergency room visit, or death	27 (3.5%)	32 (3.9%)	1.2 (0.6, 1.8)	0.32

[a]HR>1 favors placebo

Secondary outcomes - Clinical progression scale



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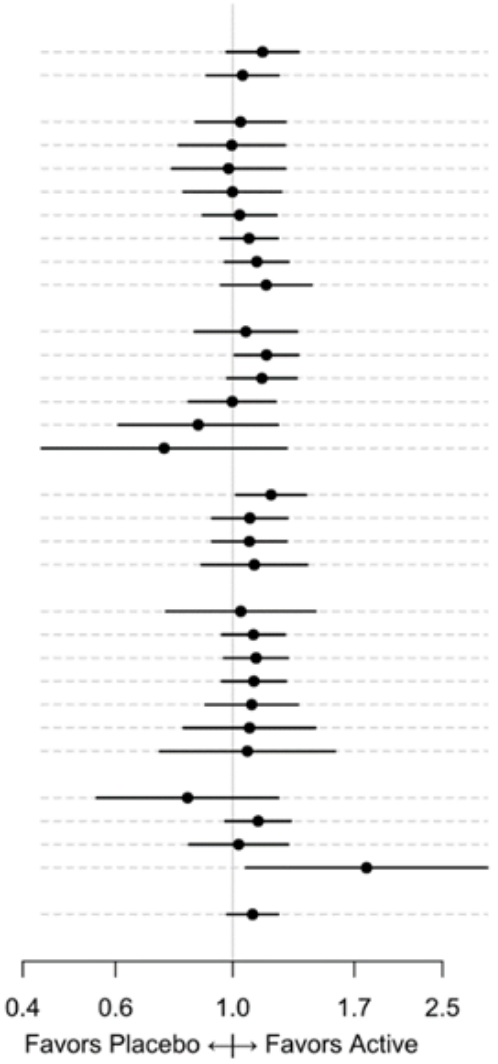
Secondary outcomes - Clinical progression scale

	OR (CrI)[a]	Posterior P(efficacy)
Day 7	0.76 (0.55, 1.00)	0.97
Day 14	0.73 (0.52, 0.98)	0.98
Day 28	0.90 (0.60, 1.21)	0.74

[a]OR<1 favors ivermectin

Heterogeneity of treatment effect

	Subgroup	Placebo N	Active N	HR (95% CI)	HTE p-value[a]
Vaccination status	Vaccinated	380	397	1.14 (0.97, 1.33)	0.442
	Not vaccinated	394	420	1.04 (0.89, 1.22)	
Calendar time	2021-10-15			1.04 (0.85, 1.26)	0.638
	2021-11-01			1.00 (0.79, 1.26)	
	2021-11-15			0.98 (0.77, 1.26)	
	2021-12-01			1.00 (0.81, 1.24)	
	2021-12-15			1.03 (0.88, 1.21)	
	2022-01-01			1.07 (0.95, 1.22)	
	2022-01-15			1.11 (0.97, 1.28)	
	2022-02-01			1.16 (0.95, 1.41)	
Symptom onset, days	3			1.06 (0.85, 1.33)	0.340
	5			1.16 (1.01, 1.33)	
	7			1.14 (0.98, 1.32)	
	9			1.00 (0.83, 1.21)	
	11			0.86 (0.61, 1.22)	
	13			0.74 (0.43, 1.27)	
Age, years	40			1.18 (1.02, 1.38)	0.984
	50			1.08 (0.91, 1.27)	
	60			1.08 (0.91, 1.27)	
	70			1.10 (0.87, 1.39)	
Body mass index, kg/m²	20			1.04 (0.75, 1.44)	0.940
	25			1.10 (0.95, 1.26)	
	30			1.11 (0.96, 1.27)	
	35			1.10 (0.95, 1.26)	
	40			1.09 (0.89, 1.33)	
	45			1.08 (0.81, 1.44)	
	50			1.07 (0.73, 1.56)	
Symptoms on study day 1	None	54	55	0.82 (0.55, 1.22)	0.123
	Mild	434	490	1.12 (0.97, 1.29)	
	Moderate	247	221	1.03 (0.83, 1.28)	
	Severe	39	51	1.79 (1.06, 3.04)	
mITT population		774	817	1.09 (0.98, 1.22)	



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[a]No subgrouping variable achieved significance

Key Messages

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Ivermectin 400 Key Messages

- No differences were observed in relief of mild-to-moderate COVID-19 symptoms between participants taking ivermectin and participants taking a placebo.
- There was also no difference observed in the number of hospitalizations or emergency room visits.
- No safety concerns at the studied dose (400 mcg/kg daily for three days) were identified, confirming that ivermectin is safe to take as part of a clinical research study.

Summary Results
Fluticasone Furoate

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Participant characteristics (1)

	Placebo (n=621)	Active (n=656)	Overall (n=1277)
Age, median (IQR), y	46.0 (38.0-56.0)	45.0 (37.0-55.0)	45.0 (37.0-55.0)
Female, No. (%)	376 (60.55)	431 (65.70)	807 (63.19)
Race, not mutually exclusive:			
Black or African American, No. (%)	44 (7.09)	47 (7.16)	91 (7.13)
White, No. (%)	500 (80.52)	523 (79.73)	1023 (80.11)
Ethnicity: Latino, No. (%)	83/620 (13.39)	78/655 (11.91)	161/1275 (12.63)
Region, No. (%)			
MW	115 (18.52)	141 (21.49)	256 (20.05)
NE	56 (9.02)	52 (7.93)	108 (8.46)
S	371 (59.74)	368 (56.10)	739 (57.87)
W	79 (12.72)	95 (14.48)	174 (13.63)
Call center	97 (15.62)	96 (14.63)	193 (15.11)

Participant characteristics (2)

	Placebo (n=621)	Active (n=656)	Overall (n=1277)
BMI, median (IQR), kg/m^2	28.1 (24.6-32.9)	28.1 (24.4-33.6)	28.1 (24.4-33.4)
BMI > 30 kg/m^2, No./total (%)	239/620 (38.5)	260 (39.6)	499/1276 (39.1)
Heart disease, No./total (%)	33/606 (5.45)	25/640 (3.91)	58/1246 (4.65)
Diabetes, No./total (%)	65/606 (10.73)	56/640 (8.75)	121/1246 (9.71)
High blood pressure, No./total (%)	169/606 (27.89)	156/640 (24.38)	325/1246 (26.08)
COPD, No./total (%)	11/606 (1.82)	7/640 (1.09)	18/1246 (1.44)
Asthma, No./total (%)	86/606 (14.19)	76/640 (11.88)	162/1246 (13.00)
Chronic kidney disease, No./total (%)	4/606 (0.66)	6/640 (0.94)	10/1246 (0.80)
Smoker, past year, No./total (%)	72/606 (11.88)	83/640 (12.97)	155/1246 (12.44)
Malignant cancer, No. (%)	23 (3.70)	20 (3.05)	43 (3.37)
Vaccine status, No. (%)			
Not vaccinated	211 (33.98)	221 (33.69)	432 (33.83)
Vaccinated (1 dose)	11 (1.77)	7 (1.07)	18 (1.41)
Vaccinated (2+ doses)	399 (64.25)	428 (65.24)	827 (64.76)

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Status on Day 1

	Placebo (n=621)	Active (n=656)
Days from onset to receipt of study drug (mean, SD)	5 (4-7)	6 (4-7)
Symptom burden on Day 1[a]		
None (%)	39 (6.3)	35 (5.3)
Mild (%)	371 (59.7)	402 (61.3)
Moderate (%)	174 (28.0)	2186 (28.4)
Severe (%)	25 (4.0)	11 (1.7)
Unknown (%)	12 (1.9)	22 (3.4)

[a]Day 1 is the day the participant received their study drug. All participants were symptomatic at the time of enrollment

Safety events

	Active, not taken (n=16)	Active, taken (n=640)	Placebo, not taken (n=16)	Placebo, taken (n=605)	Overall (n=1277)
Experienced an adverse events, No. (%)	0 (0.00)	13 (2.03)	0 (0.00)	16 (2.64)	29 (2.27)
Experienced a serious adverse events, No. (%)	0 (0.00)	3 (0.47)	0 (0.00)	6 (0.99)	9 (0.70)
Serious adverse events, No. (not mutually exclusive)					
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

Concomitant treatments for Covid-19

	Placebo (n=621)	Active (n=656)
Remdesivir (%)	0 (0.0)	1 (0.2)
Monoclonal antibodies (%)	13 (2.1)	17 (2.6)
Paxlovid (%)	1 (0.2)	0 (0.0)

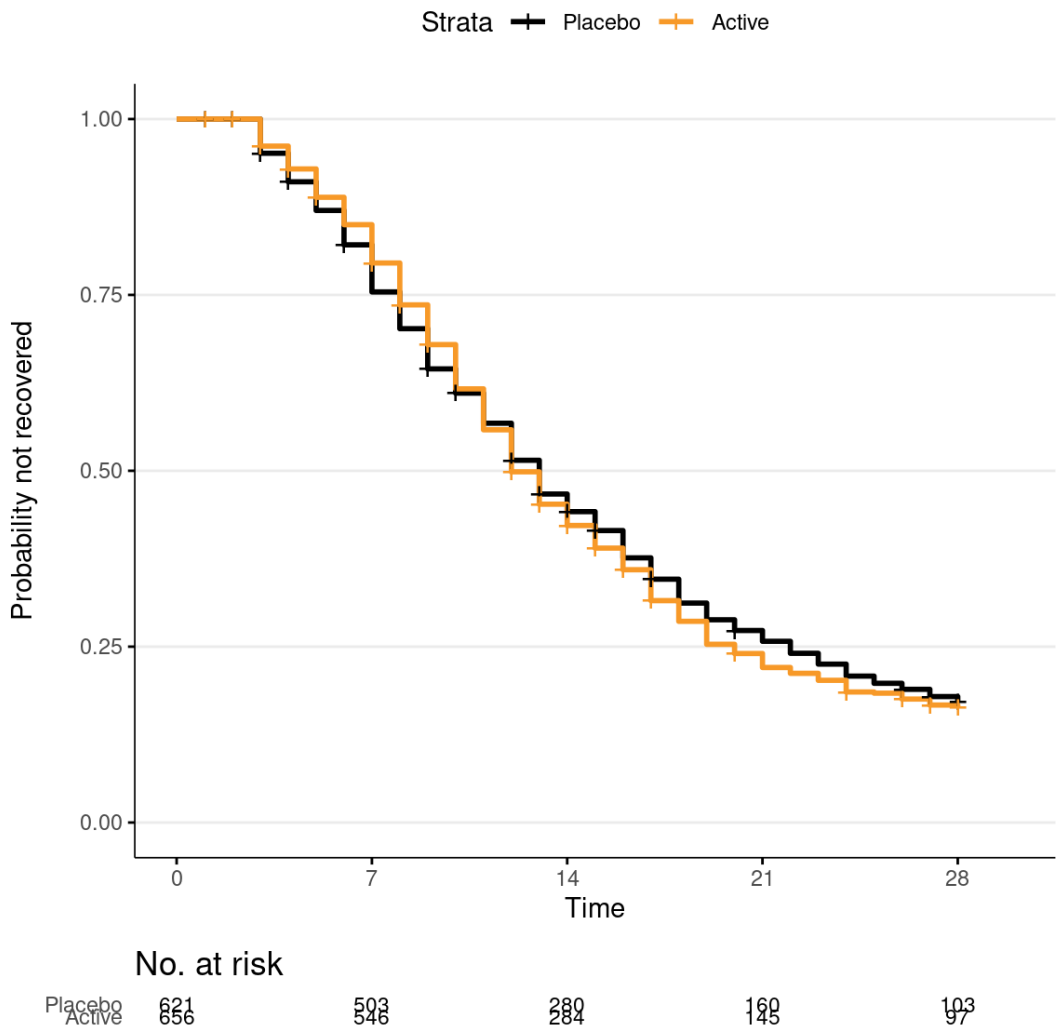
Time to recovery

Kaplan-Meier curve and 95% confidence intervals (point-wise) for time-to-recovery endpoint

Among participants that did not die during follow-up, recovery was defined as three consecutive days without COVID-19 symptoms, as affirmatively reported by the study participant

Participants that died, by definition, did not recover regardless of reported symptom freedom

Time to recovery was administratively censored at 28 days



ACTIV-6

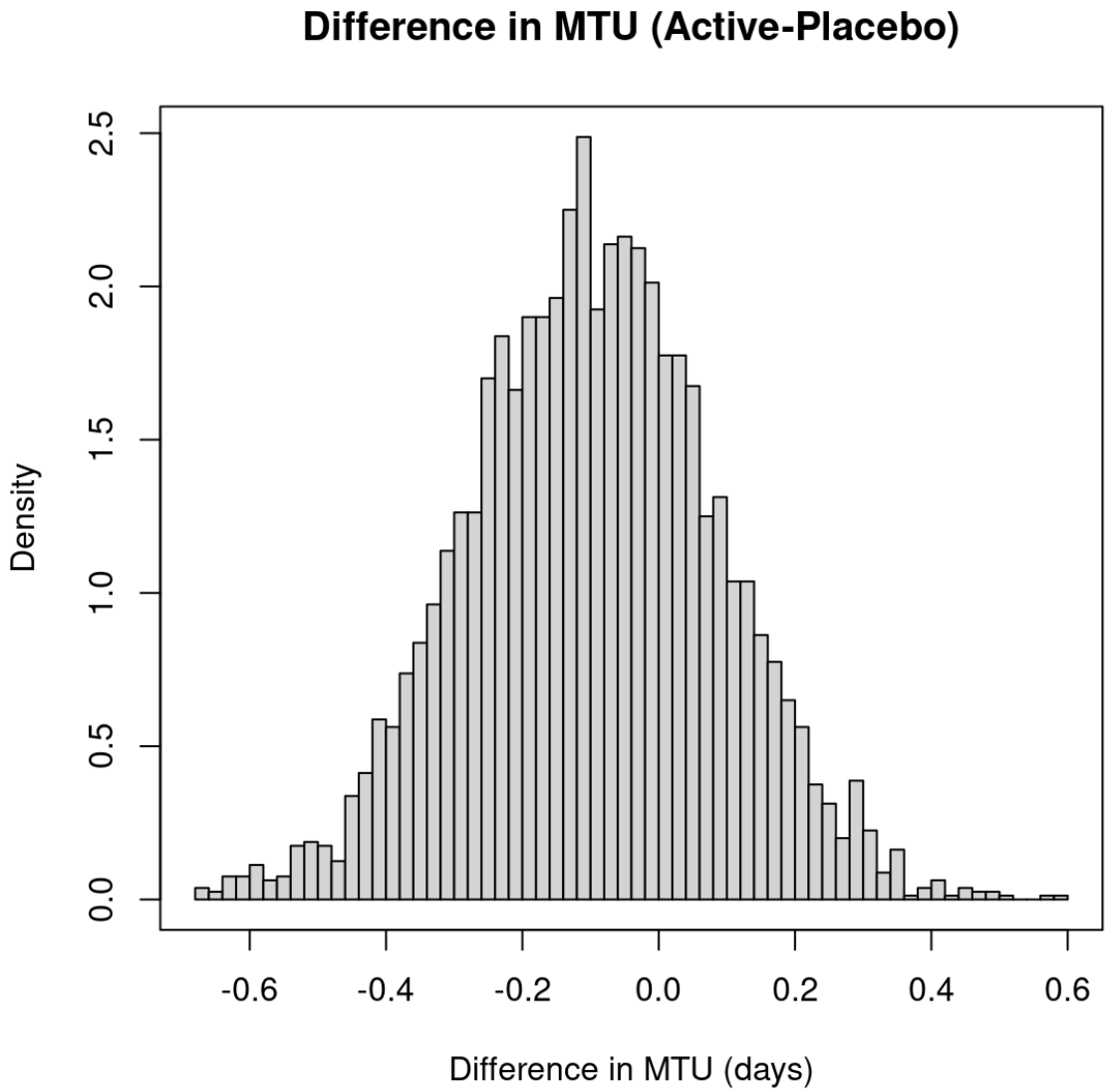
Time spent unwell

Posterior distribution of the difference in the mean time spent unwell (MTU) between those randomized to fluticasone furoate and those randomized to placebo

The difference in the mean time spent unwell reflects the change in symptom duration when taking fluticasone furoate compared with placebo; A negative number favors fluticasone

The probability that fluticasone furoate decreases time spent unwell is 0.70

The probability fluticasone furoate decreases the time spent unwell by more than one day is <0.001



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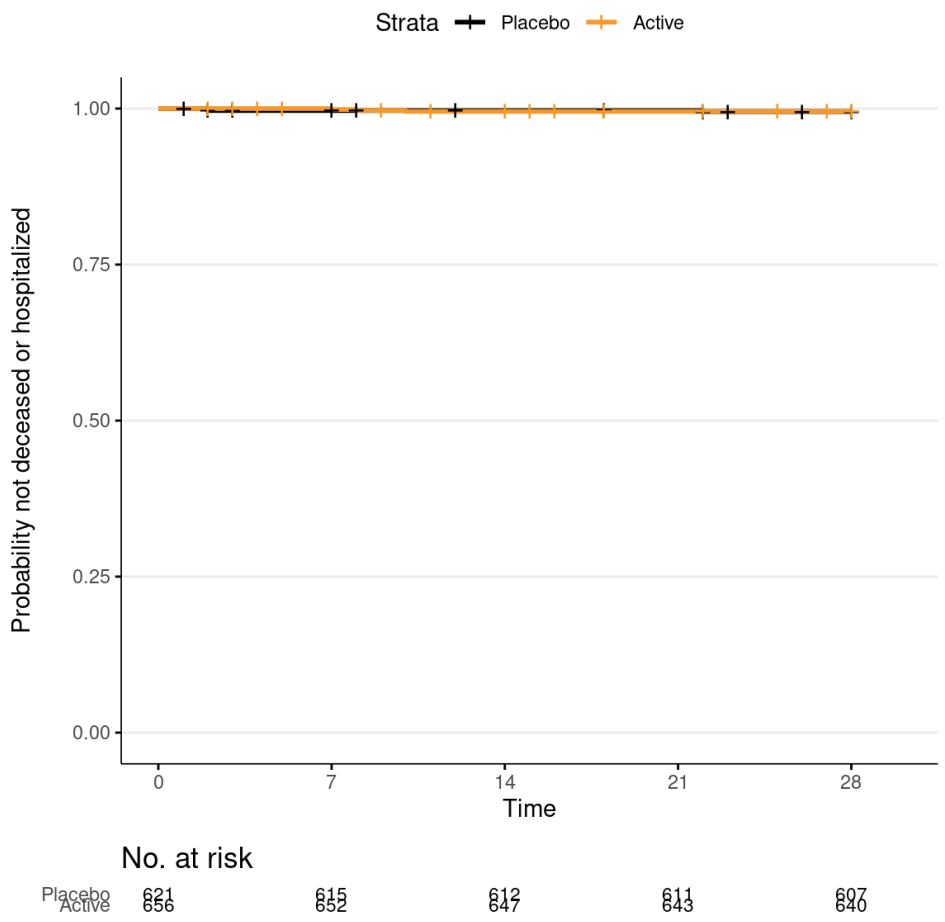
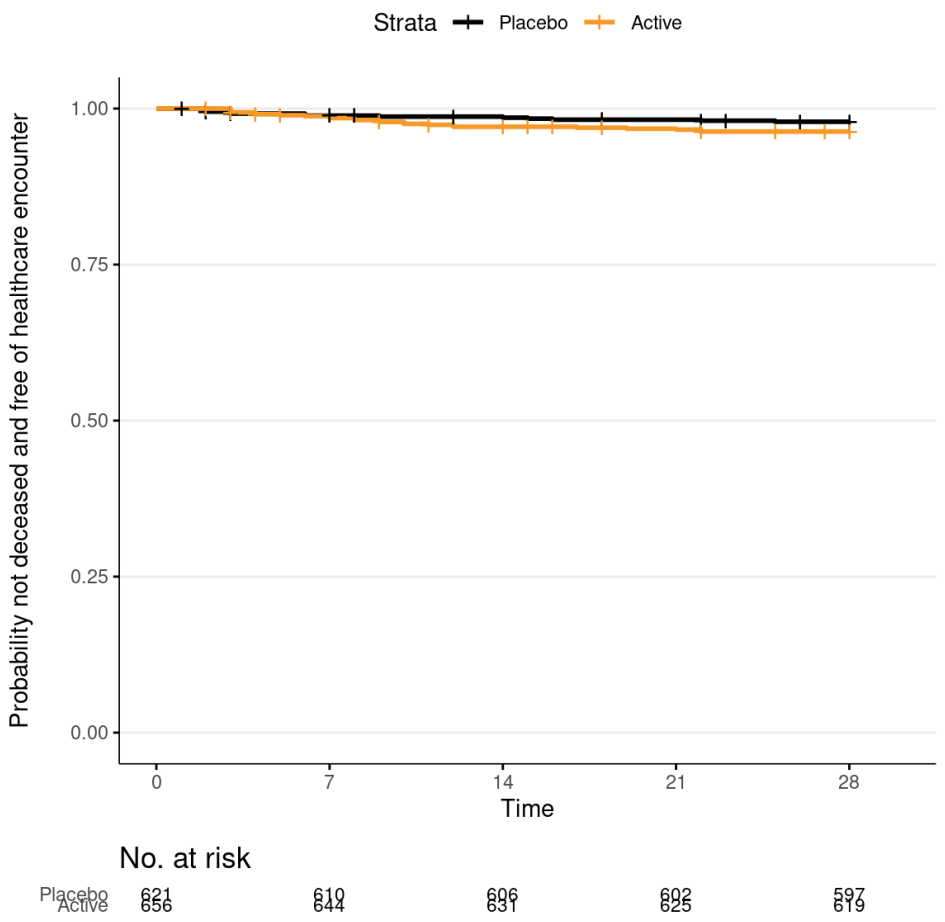
Secondary outcomes – 28 Day events



Hospitalization or death



Healthcare encounter or death

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Secondary outcomes – 28 Day events

	Placebo N=774	Active N=817	HR (CrI)[a]	Posterior P(efficacy)
Mortality	0 (0.0%)	0 (0.0%)	-	-
Death or hospitalization	3 (0.5%)	3 (0.5%)	0.94 (0.2, 4.7)	-
Hospitalization, urgent care, emergency room visit, or death	13 (2.1%)	24 (3.7%)	1.9 (0.8, 3.5)	0.034

[a]HR>1 favors placebo

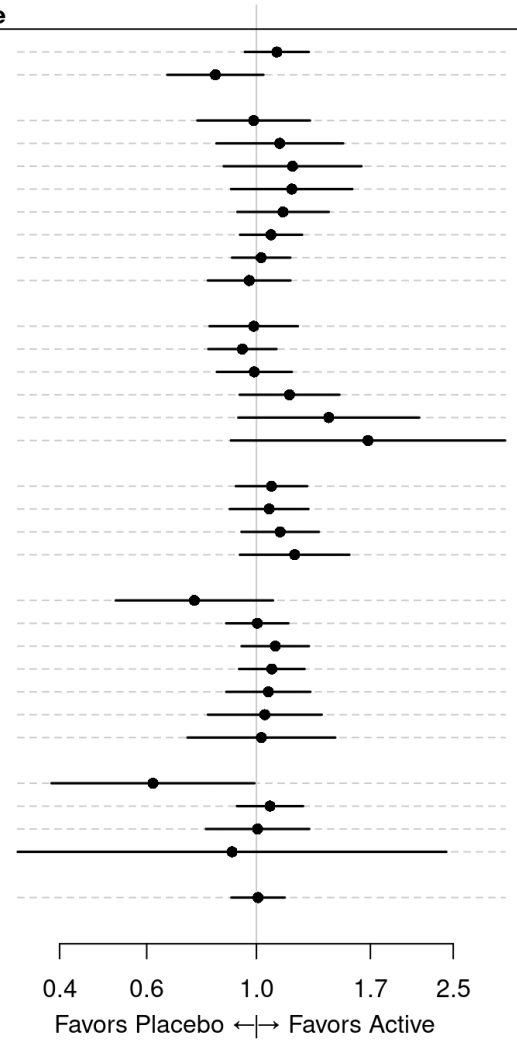
Secondary outcomes - Clinical progression scale

	OR (CrI)[a]	Posterior P(efficacy)
Day 7	1.28 (0.85, 1.70)	0.091
Day 14	1.33 (0.88, 1.84)	0.071
Day 28	2.06 (1.21, 3.05)	0.001

[a]OR>1 favors placebo

Heterogeneity of treatment effect

Characteristic	Subgroup	Placebo N	Active N	HR (95% CI)	HTE p-value
Vaccination status	Vaccinated	410	435	1.10 (0.95, 1.28)	0.036
	Not vaccinated	211	221	0.83 (0.66, 1.03)	
Calendar time	2021-10-15			0.99 (0.76, 1.28)	0.259
	2021-11-01			1.11 (0.83, 1.50)	
	2021-11-15			1.18 (0.86, 1.63)	
	2021-12-01			1.18 (0.89, 1.56)	
	2021-12-15			1.13 (0.91, 1.40)	
	2022-01-01			1.07 (0.93, 1.24)	
	2022-01-15			1.02 (0.89, 1.17)	
	2022-02-01			0.97 (0.80, 1.17)	
Symptom onset, days	3			0.99 (0.80, 1.21)	0.276
	5			0.94 (0.80, 1.10)	
	7			0.99 (0.83, 1.18)	
	9			1.17 (0.92, 1.47)	
	11			1.40 (0.92, 2.13)	
	13			1.68 (0.89, 3.18)	
Age, years	40			1.07 (0.91, 1.27)	0.718
	50			1.06 (0.88, 1.27)	
	60			1.12 (0.93, 1.34)	
	70			1.19 (0.93, 1.54)	
Body mass index, kg/m²	20			0.75 (0.52, 1.08)	0.234
	25			1.00 (0.87, 1.16)	
	30			1.09 (0.93, 1.28)	
	35			1.07 (0.92, 1.25)	
	40			1.06 (0.87, 1.29)	
	45			1.04 (0.80, 1.36)	
	50			1.02 (0.73, 1.44)	
Symptoms on study day 1	None	41	35	0.62 (0.39, 0.99)	0.196
	Mild	380	423	1.07 (0.91, 1.24)	
	Moderate	175	187	1.01 (0.79, 1.28)	
	Severe	25	11	0.89 (0.33, 2.42)	
mITT population		621	656	1.01 (0.89, 1.14)	



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Key Messages

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Fluticasone Key Messages

- We observed no major symptomatic or clinical benefit of this medication at this dose or duration.
- There was no evidence of improvement in time to recovery or reduction in hospitalizations.
- There was some evidence of increased acute care needs (urgent care, emergency room visit) in the fluticasone furoate arm.
- No safety concerns were identified, confirming that fluticasone furoate is safe to take at the dose and duration studied (200 mcg per day for 14 days).

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Questions

Additional questions can be sent to the ACTIV-6 inbox: DCRI-ACTIV6@dm.duke.edu