Supplemental Online Content

Stewart TG, Rebolledo PA, Mourad A, et al; for the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group and Investigators. Higher-Dose Fluvoxamine and Time to Sustained Recovery in Outpatients With COVID-19. *JAMA*. Published online November 17, 2023. doi:10.1001/jama.2023.23363

eMethods, eTables, and eFigures

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

Supplemental Online Content

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Supplemental Methods

Participant Monitoring

The daily and follow-up assessments were monitored, and sites were actively notified of events requiring review, including serious adverse events (SAEs). In addition, participants were invited during assessments to request contact from the study team or to report any unusual circumstances. Failure to complete daily assessments also triggered a review for any possible SAEs. 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 a notification to the site 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

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. Due to extremely rapid enrollment, the last planned interim analysis was not conducted. The independent data monitoring committee reviewed interim data when approximately 300 and 600 participants with primary endpoint data, 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 small. Approximately 5–7% of participants did not report activity level for the COVID clinical progression score endpoint at each time point, 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.

Proportional Hazards

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.

Heterogeneity of Treatment Effect 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).

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, renal replacement therapy, extracorporeal membrane oxygenation
8. Death

eTable 1. Baseline symptom prevalence and severity

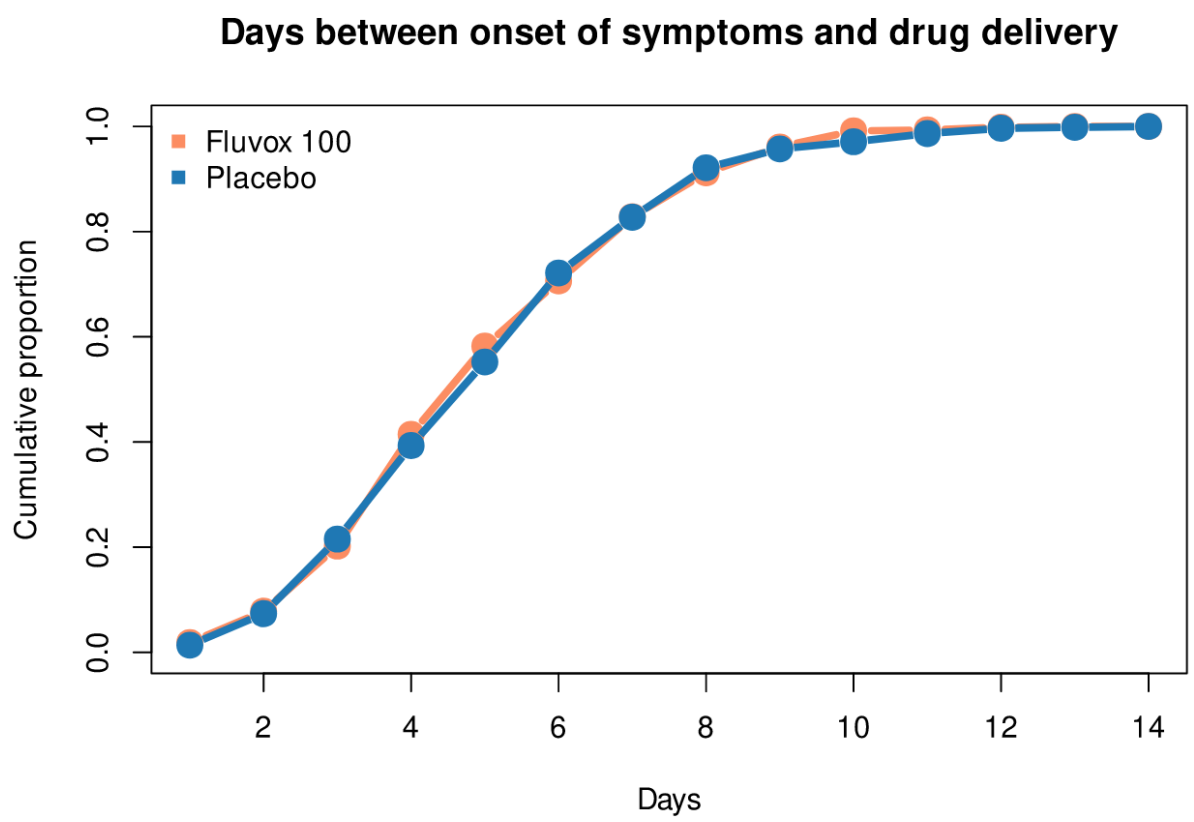
Variable	Fluvoxamine (n=589)	Placebo (n=586)	Overall (n=1175)
Overall symptom burden on study day 1, No./total (%)			
None	54/542 (9.96)	46/542 (8.49)	100/1084 (9.23)
Mild	289/542 (53.32)	291/542 (53.69)	580/1084 (53.51)
Moderate	197/542 (36.35)	198/542 (36.53)	395/1084 (36.44)
Severe	2/542 (0.37)	7/542 (1.29)	9/1084 (0.83)
Symptoms on study day 1			
Fatigue, No./total (%)			
None	80/488 (16.39)	105/496 (21.17)	185/984 (18.80)
Mild	230/488 (47.13)	212/496 (42.74)	442/984 (44.92)
Moderate	166/488 (34.02)	162/496 (32.66)	328/984 (33.33)
Severe	12/488 (2.46)	17/496 (3.43)	29/984 (2.95)
Dyspnea, No./total (%)			
None	322/487 (66.12)	315/496 (63.51)	637/983 (64.80)
Mild	131/487 (26.90)	139/496 (28.02)	270/983 (27.47)
Moderate	33/487 (6.78)	35/496 (7.06)	68/983 (6.92)
Severe	1/487 (0.21)	7/496 (1.41)	8/983 (0.81)
Fever, No./total (%)			
None	373/488 (76.43)	374/496 (75.40)	747/984 (75.91)
Mild	85/488 (17.42)	81/496 (16.33)	166/984 (16.87)
Moderate	29/488 (5.94)	40/496 (8.06)	69/984 (7.01)
Severe	1/488 (0.20)	1/496 (0.20)	2/984 (0.20)
Cough, No./total (%)			
None	81/488 (16.60)	106/496 (21.37)	187/984 (19.00)
Mild	222/488 (45.49)	229/496 (46.17)	451/984 (45.83)
Moderate	171/488 (35.04)	147/496 (29.64)	318/984 (32.32)
Severe	14/488 (2.87)	14/496 (2.82)	28/984 (2.85)
Nausea, No./total (%)			
None	357/488 (73.16)	409/496 (82.46)	766/984 (77.85)
Mild	98/488 (20.08)	64/496 (12.90)	162/984 (16.46)
Moderate	28/488 (5.74)	22/496 (4.44)	50/984 (5.08)
Severe	5/488 (1.02)	1/496 (0.20)	6/984 (0.61)
Vomiting, No./total (%)			
None	460/487 (94.46)	476/496 (95.97)	936/983 (95.22)
Mild	21/487 (4.31)	14/496 (2.82)	35/983 (3.56)
Moderate	5/487 (1.03)	6/496 (1.21)	11/983 (1.12)
Severe	1/487 (0.21)	0/496 (0.00)	1/983 (0.10)
Diarrhea, No./total (%)			
None	390/488 (79.92)	399/496 (80.44)	789/984 (80.18)
Mild	72/488 (14.75)	80/496 (16.13)	152/984 (15.45)
Moderate	22/488 (4.51)	16/496 (3.23)	38/984 (3.86)
Severe	4/488 (0.82)	1/496 (0.20)	5/984 (0.51)
Body aches, No./total (%)			
None	147/488 (30.12)	162/496 (32.66)	309/984 (31.40)
Mild	221/488 (45.29)	187/496 (37.70)	408/984 (41.46)
Moderate	111/488 (22.75)	140/496 (28.23)	251/984 (25.51)
Severe	9/488 (1.84)	7/496 (1.41)	16/984 (1.63)
Sore throat, No./total (%)			
None	229/488 (46.93)	238/496 (47.98)	467/984 (47.46)
Mild	169/488 (34.63)	172/496 (34.68)	341/984 (34.65)
Moderate	80/488 (16.39)	78/496 (15.73)	158/984 (16.06)
Severe	10/488 (2.05)	8/496 (1.61)	18/984 (1.83)
Headache, No./total (%)			
None	213/488 (43.65)	232/496 (46.77)	445/984 (45.22)
Mild	188/488 (38.52)	165/496 (33.27)	353/984 (35.87)
Moderate	76/488 (15.57)	84/496 (16.94)	160/984 (16.26)
Severe	11/488 (2.25)	15/496 (3.02)	26/984 (2.64)

Variable	Fluvoxamine (n=589)	Placebo (n=586)	Overall (n=1175)
Chills, No./total (%)			
None	361/488 (73.98)	380/496 (76.61)	741/984 (75.30)
Mild	89/488 (18.24)	82/496 (16.53)	171/984 (17.38)
Moderate	35/488 (7.17)	33/496 (6.65)	68/984 (6.91)
Severe	3/488 (0.61)	1/496 (0.20)	4/984 (0.41)
Nasal symptoms, No./total (%)			
None	181/488 (37.09)	190/496 (38.31)	371/984 (37.70)
Mild	178/488 (36.48)	192/496 (38.71)	370/984 (37.60)
Moderate	119/488 (24.39)	102/496 (20.56)	221/984 (22.46)
Severe	10/488 (2.05)	12/496 (2.42)	22/984 (2.24)
New loss of sense of taste or smell, No./total (%)			
None	321/488 (65.78)	341/496 (68.75)	662/984 (67.28)
Mild	103/488 (21.11)	82/496 (16.53)	185/984 (18.80)
Moderate	43/488 (8.81)	42/496 (8.47)	85/984 (8.64)
Severe	21/488 (4.30)	31/496 (6.25)	52/984 (5.28)

eTable 2. Serious adverse events

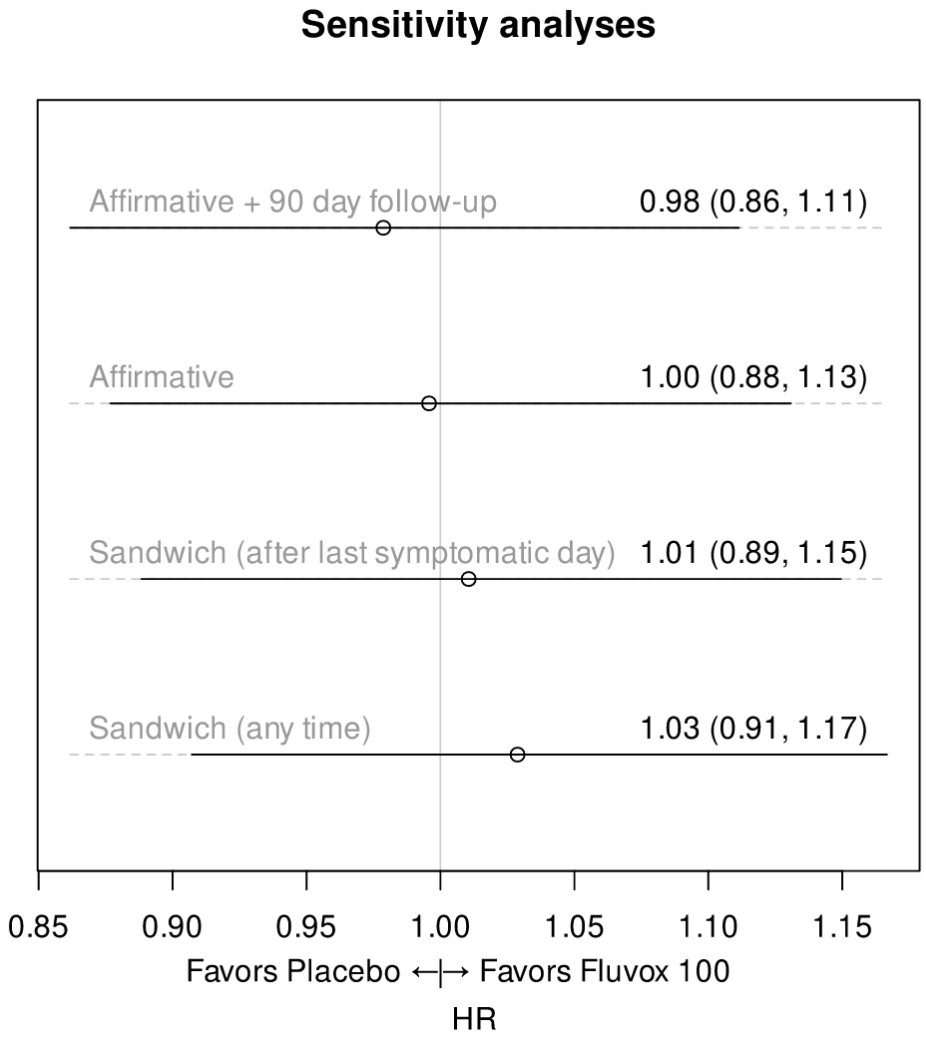
Variable	Measure	Fluvoxamine	Placebo	Overall
Serious adverse events	N			
Asthma aggravated		1	0	1
Community acquired pneumonia		1	0	1
Guillain-Barre syndrome		1	0	1
Ruptured appendix		0	1	1
Diabetic ulcer NOS		0	1	1
Partial bowel obstruction		0	1	1
Diverticulitis intestinal perforated		0	1	1

eFigure 1. 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**
Fluvoxamine	0.02	0.08	0.20	0.41	0.58	0.71	0.83	0.91	0.96	0.99	0.99	1	1	1
Placebo	0.01	0.07	0.22	0.39	0.55	0.72	0.83	0.92	0.96	0.97	0.99	1	1	1

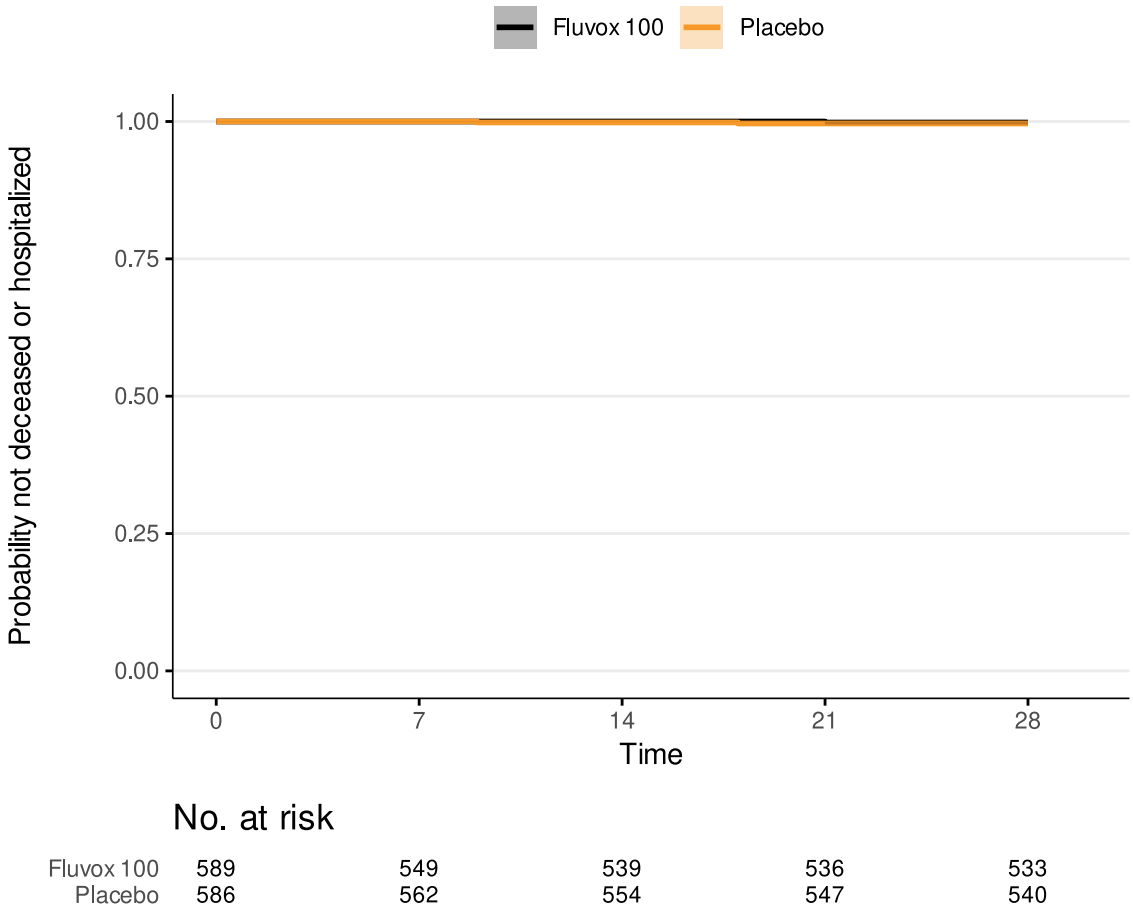
eFigure 2. Sensitivity analysis of time to sustained recovery



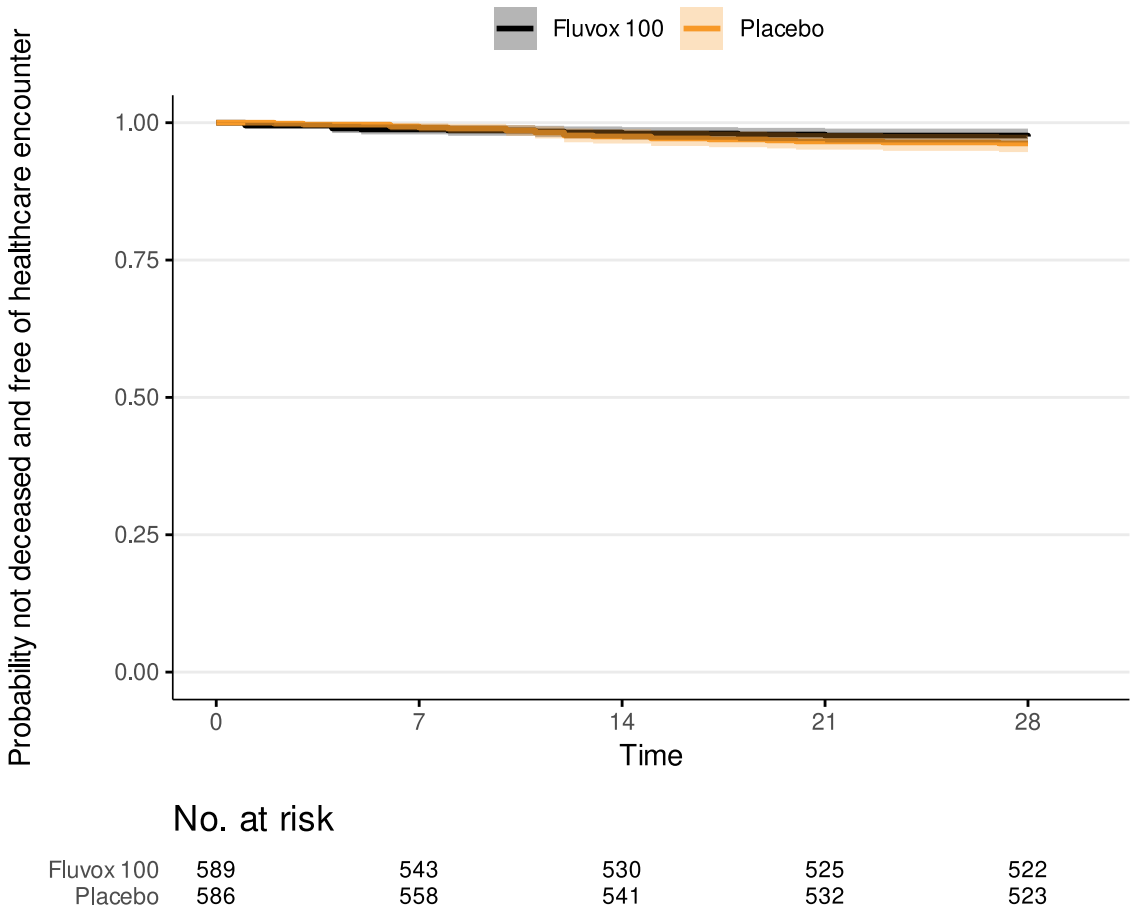
Sustained recovery is three consecutive symptom-free days. This figure illustrates the treatment effect estimate for different strategies of handling missing patient responses. The primary "Affirmative + 90 day follow-up" definition assumes that participants are symptomatic on the days without a response. The strategy does not censor recovery times earlier than day 28 if the day 90 survey is provided. The "Affirmative" assumes the same about days without a response. It differs for the primary definition in that follow-up is only based on responses during the first 28 days. A participant that fails to respond to surveys after day 14 is censored at day 14. The second and third alternatives are imputation strategies, treating missing responses as symptom-free days if surrounded by symptom-free days. For instance, if a participant lacked a day two response but reported no symptoms on days one and three, the "Sandwich" definition marks the missing day as "no symptoms." The "Sandwich after last symptomatic day" definition only applies this rule after the last reported symptomatic day.

The hazard ratios in the figure are from the covariate-adjusted, proportional hazards regression model without prior. Notably, irrespective of the sustained recovery definition, the treatment effect remains largely consistent.

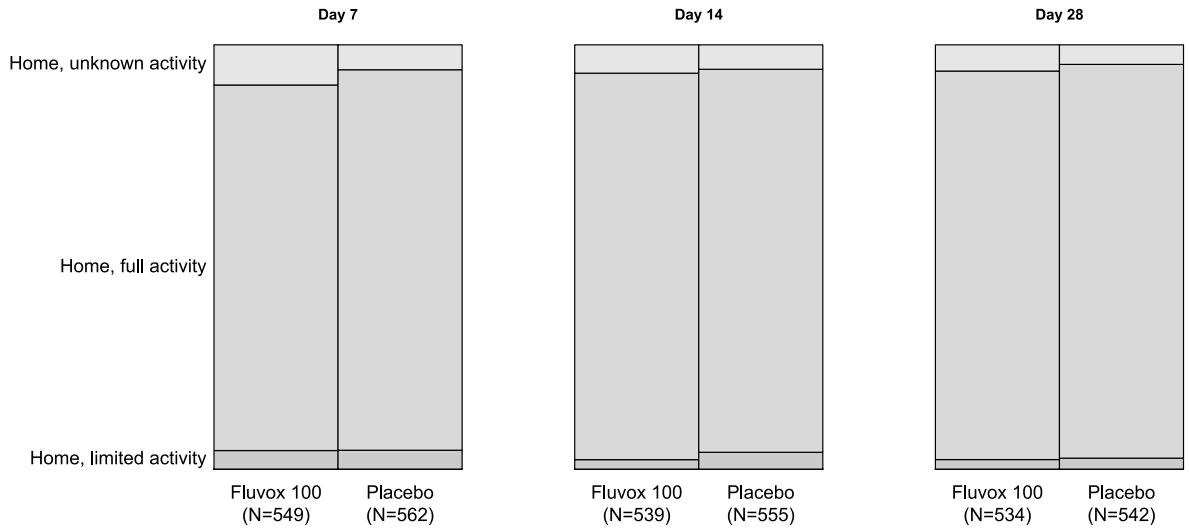
eFigure 3. All-cause hospitalization or death for fluvoxamine vs placebo



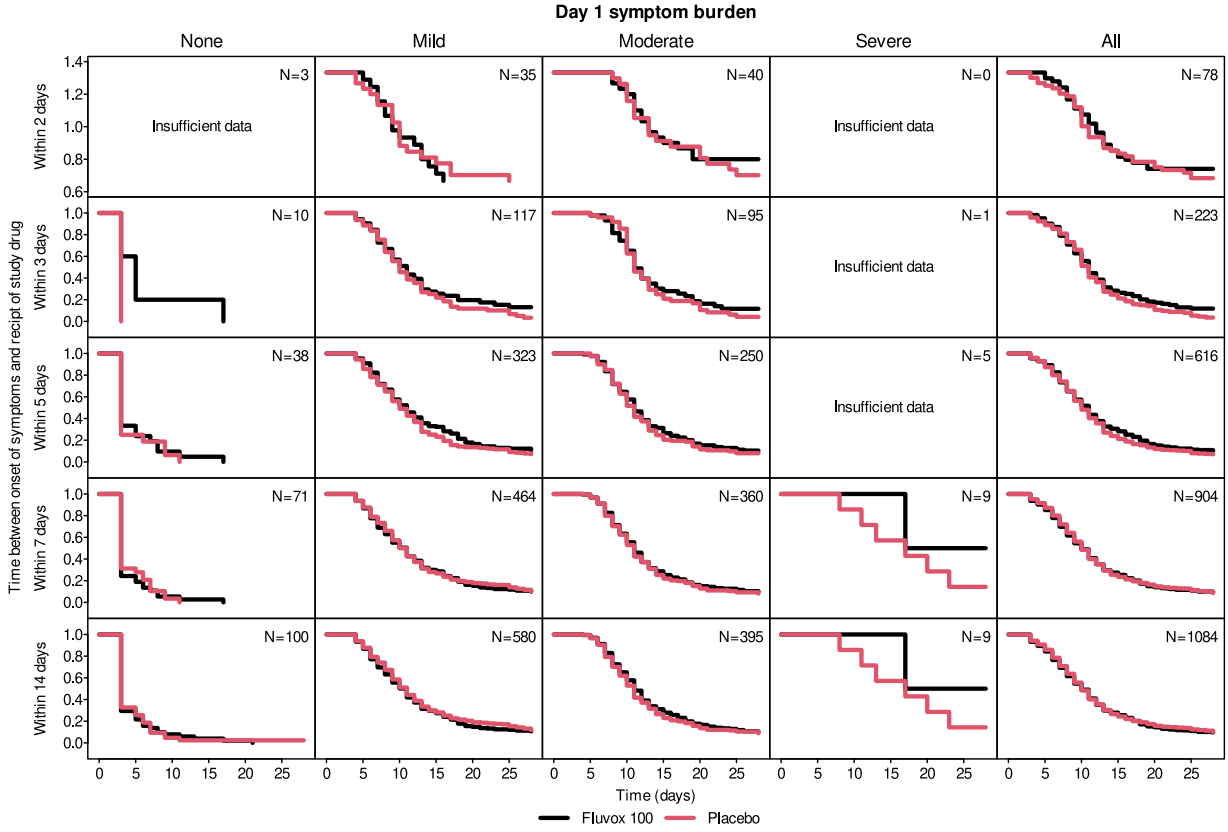
eFigure 4. All-cause hospitalization, urgent care, emergency department visit, or death for fluvoxamine versus placebo



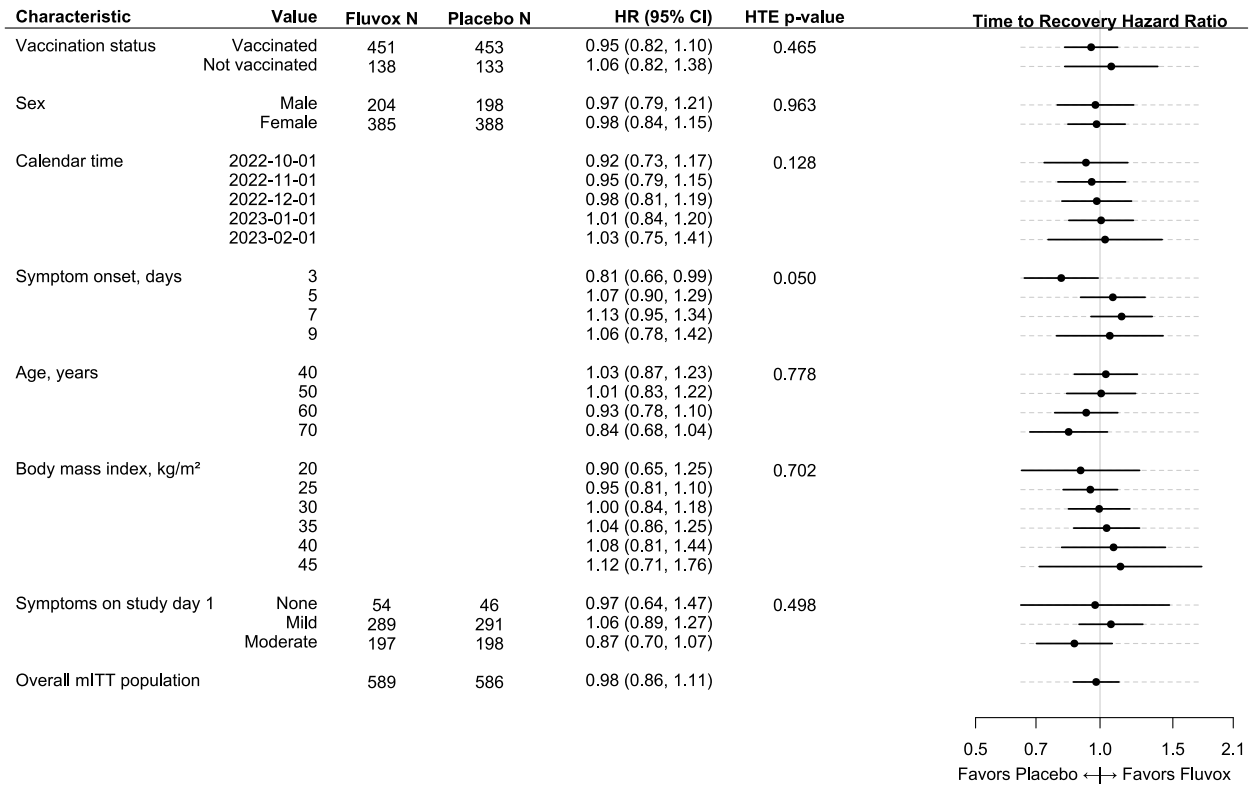
eFigure 5. Participants' COVID clinical progression scale at day 7, 14, and 28



eFigure 6. Kaplan-Meier curves of sustained recovery by onset of symptoms and symptom severity



eFigure 7. Heterogeneity of treatment effect between fluvoxamine and placebo for time to recovery



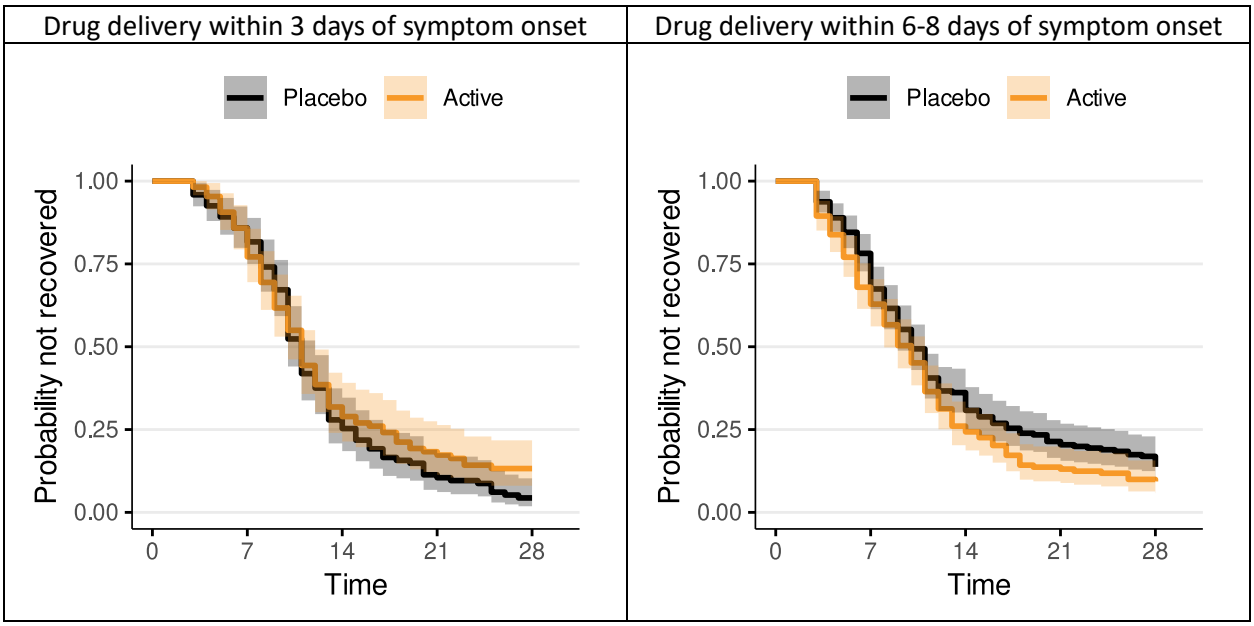
This figure presents the analyses exploring heterogeneity of treatment effect derived from the primary endpoint—time to sustained recovery. These exploratory analyses, outlined in the statistical analysis plan, did not undergo multiplicity adjustment. A hazard ratio larger than 1 signifies an accelerated recovery. Study day 1 corresponds to the participant's drug delivery day.

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.

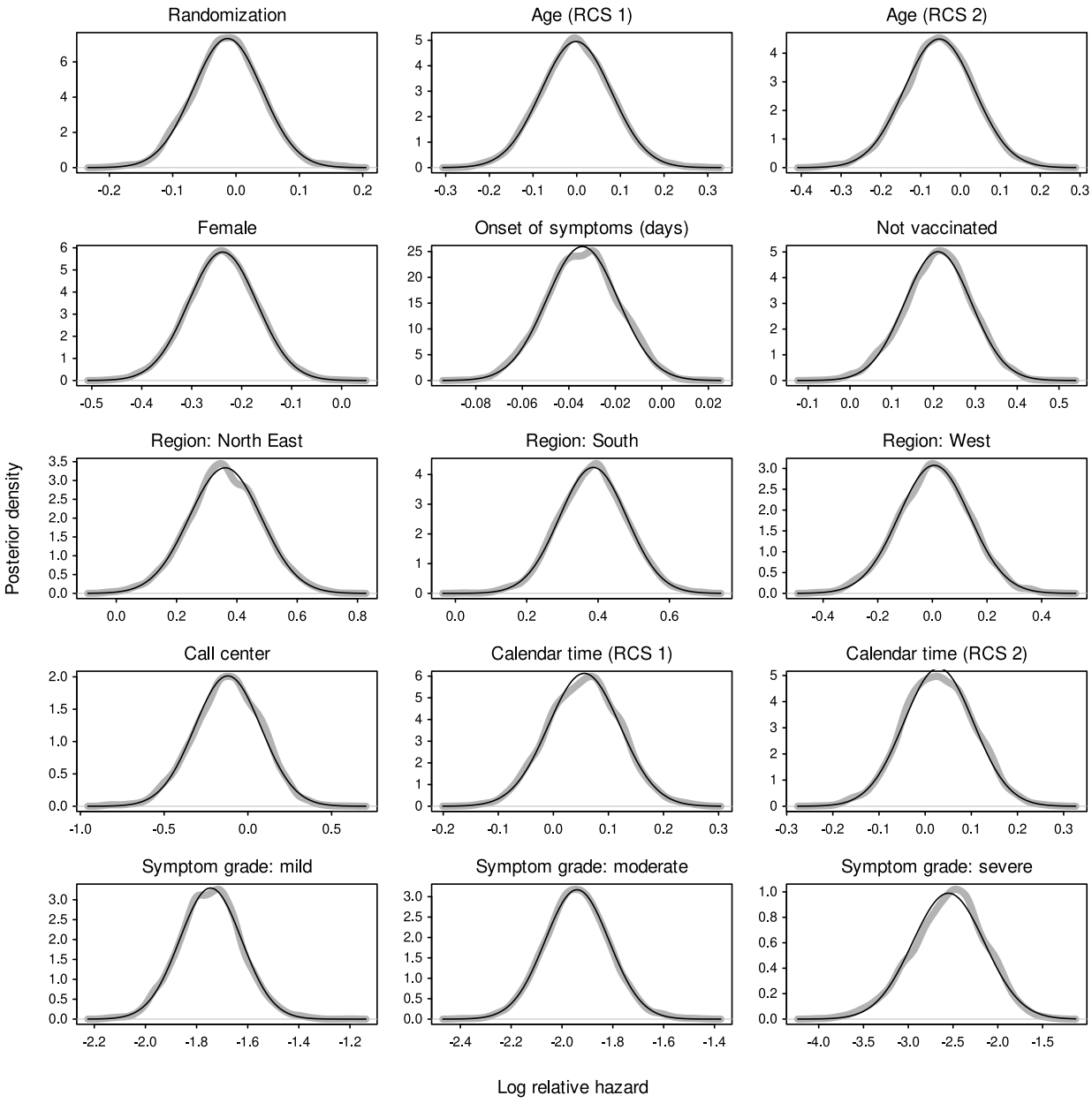
To allow the possibility of non-linear trends along continuous characteristics, like age or calendar time, the additional terms were interactions between treatment assignment and restricted cubic splines. Because the primary endpoint model did not include body mass index (BMI), the restricted cubic spline 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 adjustments. The estimates shown in the HTE plot are estimates calculated from the smooth, modeled relationship. For the continuous characteristics, there are no discrete categories or ranges or bins over which to tabulate the number of participants.

eFigure 8. Kaplan-Meier curves of time to recovery stratified by symptom onset



eFigure 9. Posterior densities of primary endpoint model



This figure provides the posterior densities of each regression coefficient in the primary endpoint model. The x-axis is the log relative hazard; the x-axis is density. The thick, grey lines are the kernel density estimates; thin, black lines represent parametric normal density estimates of the same.