Supplemental Online Content

Self WH, Shotwell MS, Gibbs KW, et al; ACTIV-4 Host Tissue Investigators. Renin-angiotensin system modulation with synthetic angiotensin (1-7) and angiotensin II type 1 receptor–biased ligand in adults with COVID-19: two randomized clinical trials. *JAMA*. Published April 11, 2023. doi:10.1001/jama.2023.3546

eAppendix. ACTIV-4 Host Tissue Platform Collaborators
eFigure 1. Schematic of the renin-angiotensin system (RAS) and trial agent targets
eFigure 2. Distribution of oxygen-free days in TXA-127 trial
eFigure 3. Distribution of oxygen-free days in TRV-027 trial
eFigure 4. TXA-127 trial WHO COVID-19 ordinal scale results over time
eFigure 5. TRV-027 trial WHO COVID-19 ordinal scale results over time
eTable 1. Enrolling sites
eTable 2. Eligibility criteria
eTable 3. Trial outcomes
eTable 4. Protocol-specified exempt serious events (PSESEs)
eTable 5. Results at the first interim analyses
eTable 6. Details of placebo groups
eTable 7. Additional baseline patient characteristics
eTable 8. Usual care in-hospital medications before randomization
eTable 9. Study drug delivery in the TXA-127 trial
eTable 10. Study drug delivery in the TRV-027 trial
eTable 11. Summaries of oxygen-free days for subgroup analyses in TXA-127 trial
eTable 12. Summaries of oxygen-free days for subgroup analyses in TRV-027 trial
eTable 13. Additional outcome results in TXA-127 trial
eTable 14. Additional outcome results in TRV-027 trial
eTable 15. PSESEs results in TXA-127 trial
eTable 16. PSESEs results in TRV-027 trial
eTable 17. Adverse events (AEs) in TXA-127 trial
eTable 18. Adverse events (AEs) in TRV-027 trial

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

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eAppendix. ACTIV-4 Host Tissue Platform Collaborators

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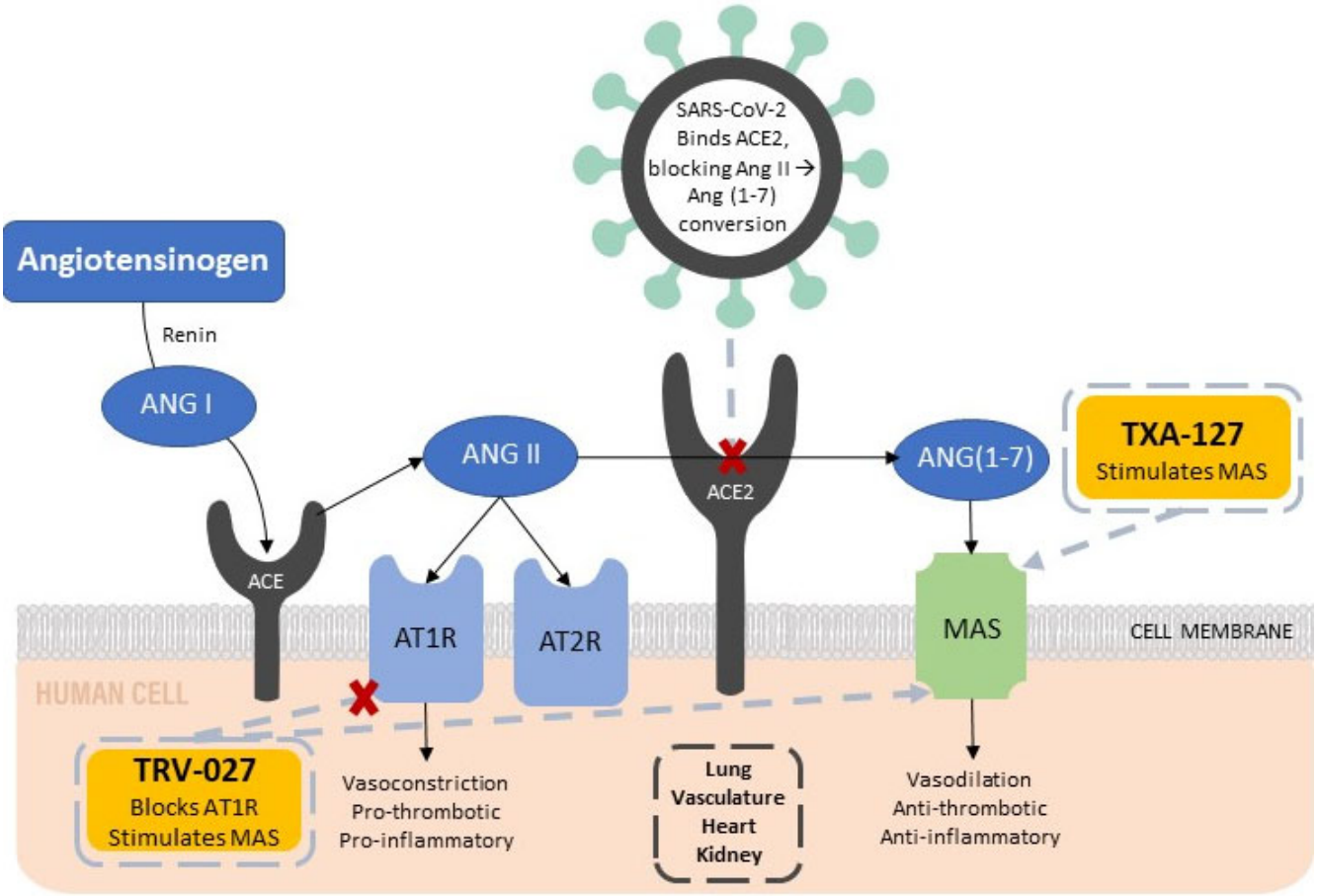
eFigure 1. Schematic of the renin-angiotensin system (RAS) and trial agent targets

The renin-angiotensin system (RAS) involves a series of sequential steps that convers angiotensinogen to angiotensin (1-7) [Ang (1-7)]. SARS-CoV-2 binds the angiotensin converting enzyme 2 (ACE2), which results in cellular entry for the virus and decreased conversion of angiotensin II (Ang II) to Ang (1-7) for the human host. It is hypothesized that viral binding to ACE2 leads to higher relative activity of Ang II compared to Ang (1-7). Ang II activates the angiotensin II type 1 receptor (AT1R), which leads to inflammatory, vasoconstrictor, thrombotic, and fibrotic actions. Alternatively, Ang (1-7) activates MAS receptors, which leads to anti-inflammatory, vasodilatory, anti-thrombotic, and anti-fibrotic actions. Thus, SARS-CoV-2 infection may cause a pathological RAS imbalance with relatively high Ang II compared to Ang (1-7) activity, which could lead to organ injury, particularly in the lungs. TXA-127 is a synthetic Ang (1-7) analogue. We hypothesized that TXA-127 would improve outcomes for patients with COVID-19 by restoring Ang II-to-Ang (1-7) balance through exogenous administration of Ang (1-7). TRV-027 is a biased ligand at the AT1R that blocks the activity of Ang II and stimulates a beta-arrestin pathway that activates MAS receptors [mimicking the action of Ang (1-7)]. We hypothesized that TRV-027 would improve outcomes for patients with COVID-19 by restoring the balance of AT1R and MAS receptor activation.



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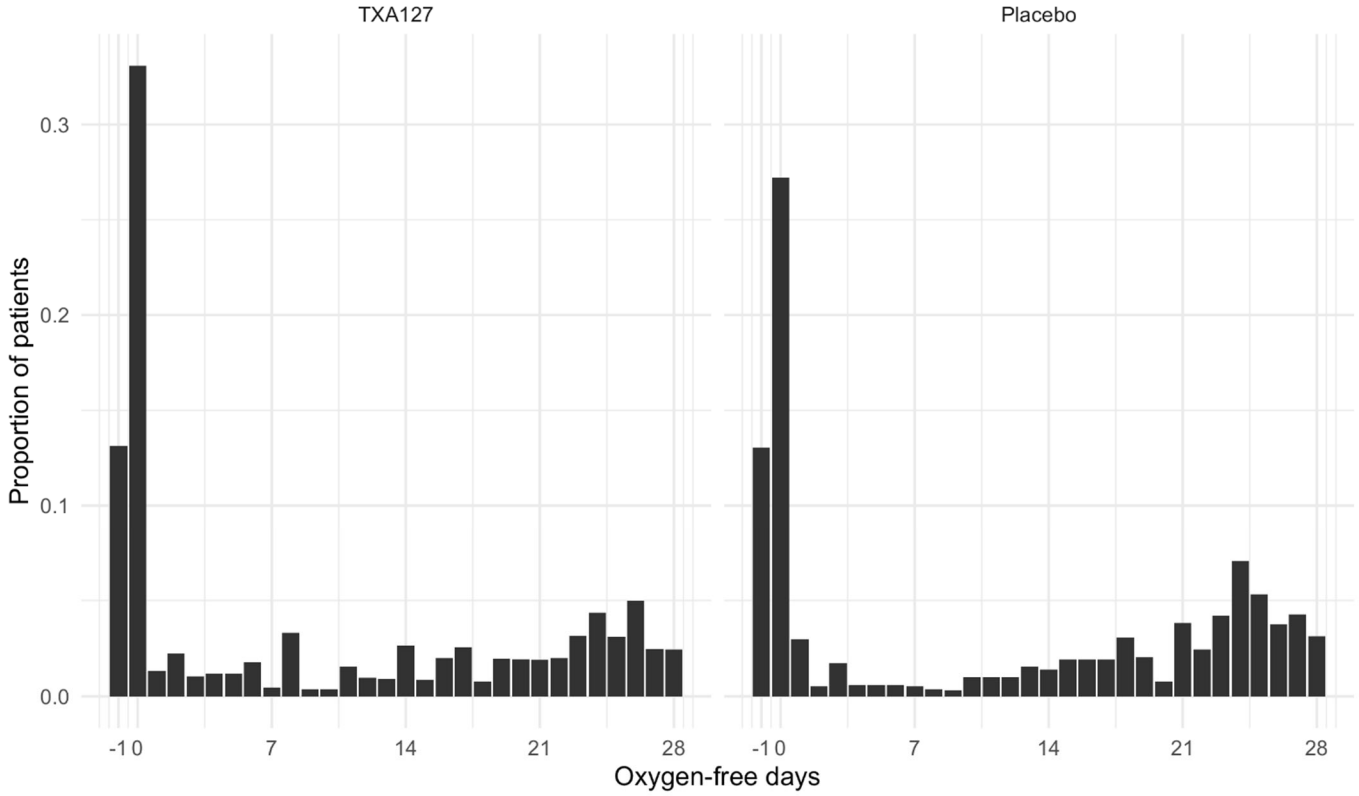
eFigure 2. Distribution of oxygen-free days in TXA-127 trial

The histograms display the proportion of patients at day 28 in each of the 30 categories of the oxygen-free days ordinal outcome, stratified by TXA-127 study drug vs placebo. The table below the histograms displays summary statistics for the oxygen-free days outcome.

Adjusted Odds Ratio comparing distribution of oxygen-free days in TXA-127 group vs placebo:

aOR: 0.88; 95% CI: 0.59 to 1.30

(aOR <1.0 is in the direction of inferiority for TXA-127 compared to placebo)



	TXA-127 (n=170)	Placebo (n=173)	Adjusted absolute difference (95% CI)
Mean oxygen-free days	9.0	11.3	-0.80 (-3.21 to 1.62)
Median (IQR) oxygen-free days	0 (0 – 21)	13 (0 – 24)	-1 (-8 to 3)
-1 oxygen-free days (dead), no. (%)	22 (12.9)	22 (12.7)	Difference in percentage: 0.7 (-1.5, 2.9)
0 OFDs (oxygen use for 28 days), no. (%)	55 (32.4)	46 (26.6)	Difference in percentage: 2.1 (-4.3, 8.5)
Patients with partially observed oxygen-free days, no (%)	17 (10.0)	18 (10.4)	N/A

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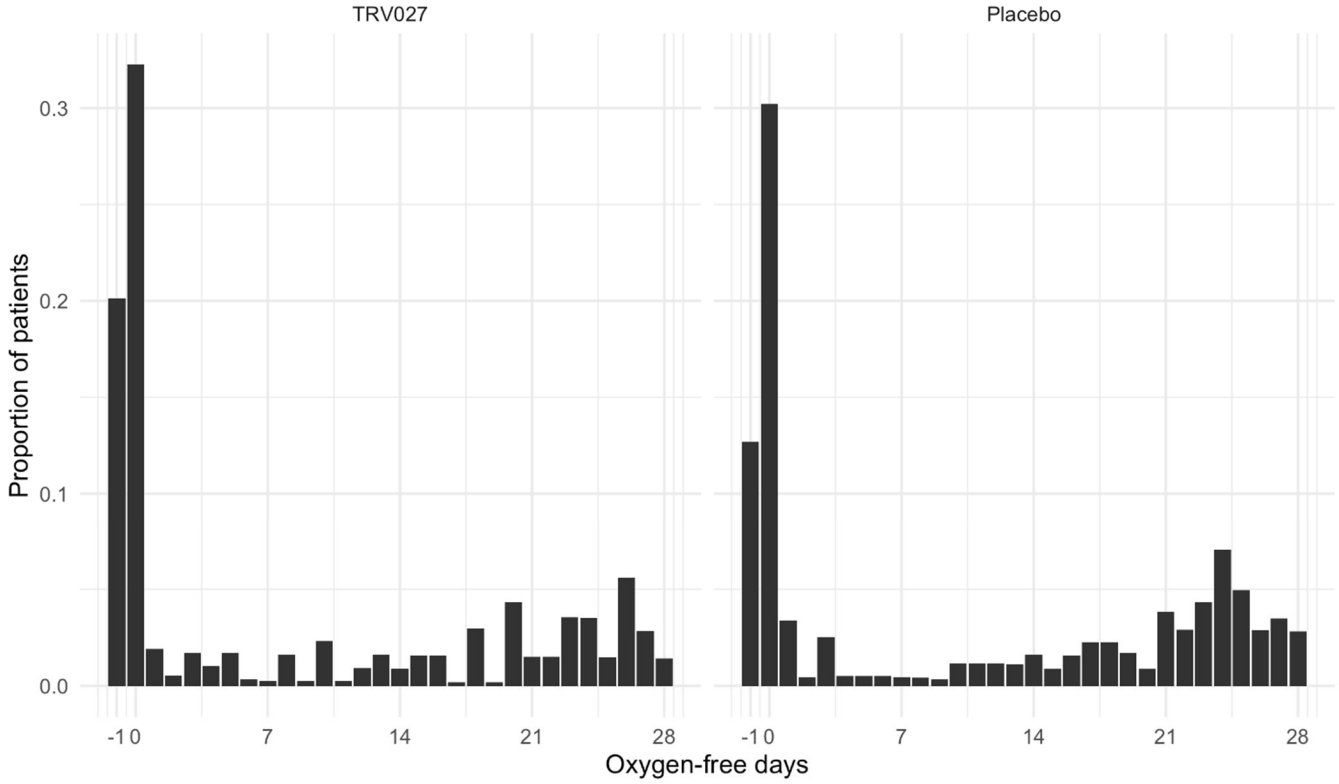
eFigure 3. Distribution of oxygen-free days in TRV-027 trial

The histograms display the proportion of patients at day 28 in each of the 30 categories of the oxygen-free days ordinal outcome, stratified by TRV-027 study drug vs placebo. The table below the histograms displays summary statistics for the oxygen-free days outcome.

Adjusted Odds Ratio comparing distribution of oxygen-free days in TRV-027 group vs placebo:

aOR: 0.74; 95% CI: 0.48 to 1.13

(aOR <1.0 is in the direction of inferiority for TRV-027 compared to placebo)



	TRV-027 (n=145)	Placebo (n=145)	Adjusted absolute difference (95% CI)
Mean oxygen-free days	8.1	10.5	-1.86 (-4.50 to -0.70)
Median (IQR) oxygen-free days	0 (0 – 20)	3 (0 – 23)	-5 (-15 to 2)
-1 oxygen-free days (dead), no. (%)	29 (20.0)	18 (12.4)	Difference in percentage: 2.0 (-0.9 to 5.0)
0 OFDs (oxygen use for 28 days), no. (%)	46 (31.7)	43 (29.7)	Difference in percentage: 4.8 (-2.0 to 11.6)
Patients with partially observed oxygen-free days, no (%)	10 (6.9)	14 (9.7)	N/A

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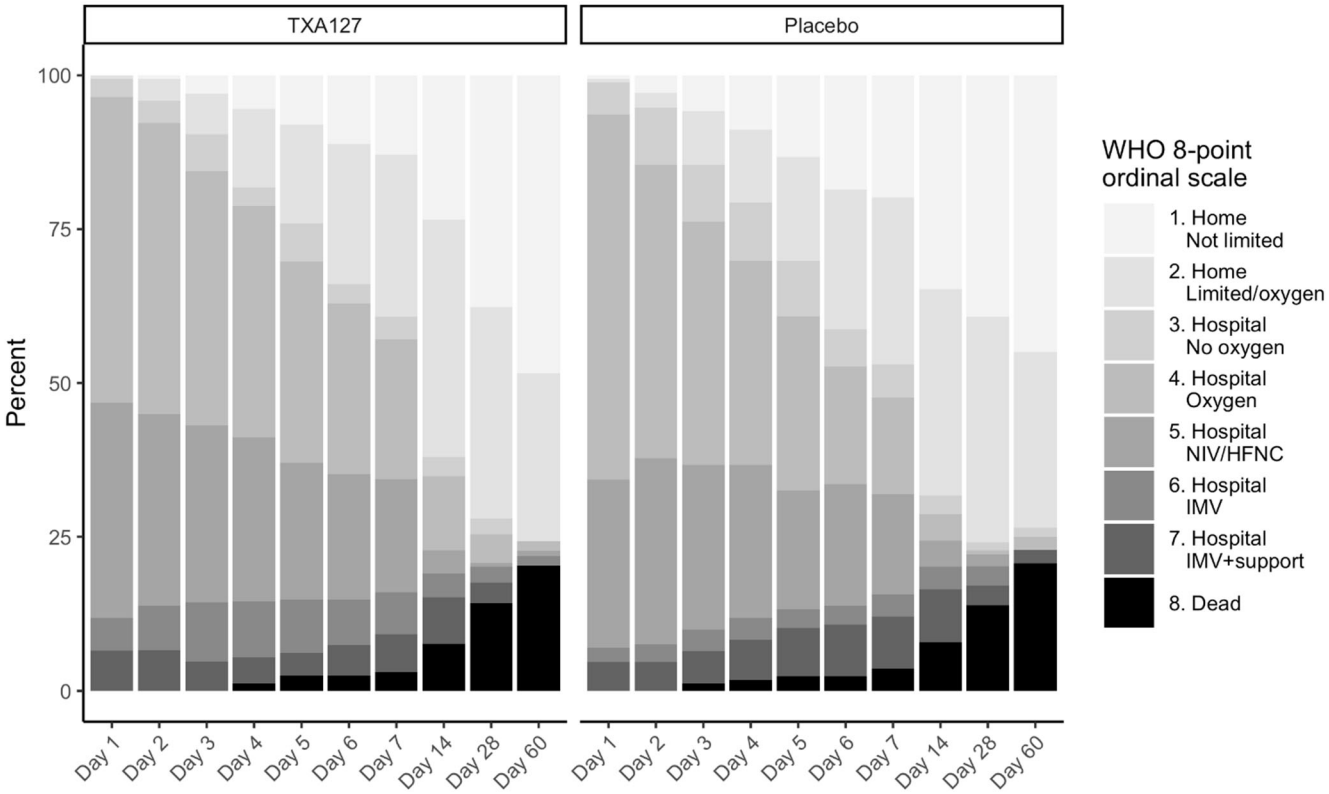
eFigure 4. TXA-127 trial WHO COVID-19 ordinal scale results over time

Distribution of the WHO COVID-19 clinical progression ordinal scale on Days 1-7, 14, 28, and 60 by treatment group in the TXA-127 trial.

Adjusted odds ratio (aOR) comparing TXA-127 to placebo based on the WHO COVID-19 clinical progression ordinal scale at key time points; aOR <1.0 is the direction of superiority for the active agent.			
Day	14	28	60
aOR (95% CI)	1.12 (0.75, 1.67)	0.88 (0.58, 1.35)	0.68 (0.43, 1.07)



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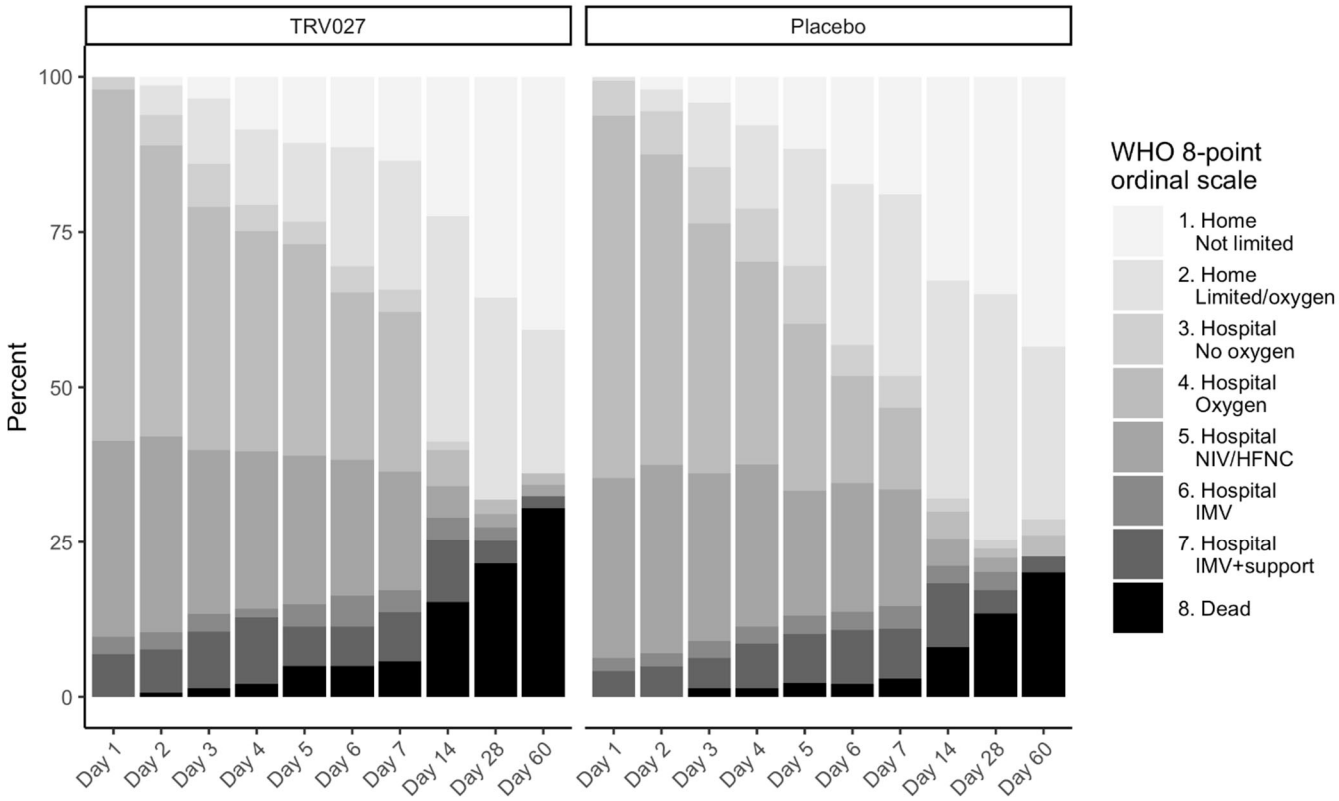
eFigure 5. TRV-027 trial WHO COVID-19 ordinal scale results over time

Distribution of the WHO COVID-19 clinical progression ordinal scale on Days 1-7, 14, 28, and 60 by treatment group in the TRV-027 trial.

Adjusted odds ratio (aOR) comparing TXA-127 to placebo based on the WHO COVID-19 clinical progression ordinal scale at key time points; aOR <1.0 is the direction of superiority for the active agent.			
Day	14	28	60
aOR (95% CI)	1.41 (0.91, 2.19)	0.97 (0.62, 1.53)	1.03 (0.63, 1.67)



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eTable 1. Enrolling sites

Enrolling Site Number	Hospital	Number of In-patient Hospital Beds	Type of Hospital	TXA-127 and TRV-027 Eligible Randomizations (combined)
1	Vanderbilt University Medical Center	1046	Teaching Hospital Affiliated with a University	63
2	Wake Forest University	886	Teaching Hospital Affiliated with a University	58
3	University of New Mexico Health Sciences Center	618	Teaching Hospital Affiliated with a University	55
4	University of Nebraska Medical Center	616	Teaching Hospital Affiliated with a University	37
5	Washington University	375	Teaching Hospital Affiliated with a University	33
6	Yale University	1541	Teaching Hospital Affiliated with a University	33
7	Dignity Health Research Institute		Community Hospital System	24
8	Virginia Commonwealth University	805	Teaching Hospital Affiliated with a University	23
9	University of Virginia	671	Teaching Hospital Affiliated with a University	23
10	University of Florida, Gainesville	1037	Teaching Hospital Affiliated with a University	21
11	Newton-Wellesley Hospital	273	Community Hospital Affiliated with a University	20
12	Stanford University	584	Teaching Hospital Affiliated with a University	16
13	Denver Health Medical Center	472	Public Hospital, academically affiliated	14
14	University of Colorado Denver	703	Teaching Hospital Affiliated with a University	11
15	Emory Johns Creek Hospital	173	Community Hospital, academically affiliated	11
16	Beth Israel Deaconess Medical Center	673	Teaching Hospital Affiliated with a University	11
17	Oregon Health and Science University	549	Teaching Hospital Affiliated with a University	10
18	Moses Hospital of Montefiore Medical Center	1530	Teaching Hospital Affiliated with a University	9
19	Johns Hopkins University	1162	Teaching Hospital Affiliated with a University	9
20	University of Cincinnati	726	Teaching Hospital Affiliated with a University	9
21	Cleveland Clinic Foundation	1300	Teaching Hospital Affiliated with a University	8

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Enrolling Site Number	Hospital	Number of In-patient Hospital Beds	Type of Hospital	TXA-127 and TRV-027 Eligible Randomizations (combined)
22	Cedars-Sinai Medical Center	886	Community Hospital, academically affiliated	6
23	Intermountain Healthcare	430	Community Hospital, academically affiliated	6
24	Hennepin County Medical Center	469	Public Hospital, academically affiliated	5
25	Jack D. Weiler Hospital of Montefiore Medical Center	369	Teaching Hospital Affiliated with a University	4
26	Ochsner Health/Louisiana State University	345	Teaching Hospital Affiliated with a University	3
27	Cleveland Clinic Akron General	454	Community Hospital, academically affiliated	2
28	Cleveland Clinic Fairview Hospital	488	Community Hospital, academically affiliated	2
29	Temple University	879	Teaching Hospital Affiliated with a University	2
30	University of Utah Health Sciences Center	806	Teaching Hospital Affiliated with a University	1
31	Alexian Brothers Medical Center		Community Hospital	1
32	Columbia University Medical Center	738	Teaching Hospital Affiliated with a University	1
33	University of Washington (Harborview)	413	Teaching Hospital Affiliated with a University	1
34	Johns Hopkins Bayview Medical Center	422	Teaching Hospital Affiliated with a University	1
35	Emory St. Joseph’s Hospital	410	Community Hospital, academically affiliated	1

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eTable 2. Eligibility criteria

To enter a trial, patients must have met all eligibility criteria for the ACTIV-4 Host Tissue Platform and the specific criteria for the individual trial. The platform level inclusion and exclusion criteria applied to both the TXA-127 and TRV-027 trials. Additionally, the TXA-127 and TRV-027 trials had trial-specific exclusion criteria based on the individual agent under study in that trial. Based on the trial-specific exclusion criteria, a patient could be eligible for one or both trials. Patients eligible for both trials were first randomized to active versus placebo and then to a trial. Patients eligible for both trials who randomized to placebo were included in the placebo group of both trials regardless of which placebo was received.

	Inclusion Criteria	**Exclusion Criteria**
ACTIV-4 Host Tissue Platform	1. Hospitalized for COVID-19 2. ≥18 years of age 3. SARS-CoV-2 infection, documented by: a) a nucleic acid test (NAT) or equivalent testing within 3 days prior to randomization OR b) documented by NAT or equivalent testing more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator (For non-NAT tests, only those deemed with equivalent specificity to NAT by the protocol team will be allowed. A central list of allowed non-NAT tests is maintained in Appendix F.) 4. Hypoxemia, defined as SpO2 <92% on room air, new receipt of supplemental oxygen to maintain SpO2 ≥92%, or increased supplemental oxygen to maintain SpO2 ≥92% for a patient on chronic oxygen therapy 5. Symptoms or signs of acute COVID-19, defined as one or more of the following: a) cough b) reported or documented body temperature of 100.4° F or greater c) shortness of breath d) chest pain e) infiltrates on chest imaging (x-ray, CT scan, lung ultrasound)	1. COVID-19 symptom onset >14 days prior to randomization 2. Hospitalized for >72 hours prior to randomization 3. Pregnancy 4. Breastfeeding 5. Prisoners 6. End-stage renal disease (ESRD) on dialysis 7. Patient and/or clinical team is not pursuing full medical management (if a patient has a Do Not Resuscitate order that precludes chest compressions in the event of a cardiac arrest but is otherwise pursuing full medical management, he/she is eligible for this trial). 8. The treating clinician expects inability to participate in study procedures or participation would not be in the best interests of the patient

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	Inclusion Criteria	Exclusion Criteria
TXA-127 Trial	No additional inclusion criteria beyond the platform criteria.	1. Patient unable to participate or declines participation in the TXA127/Ang(1-7) arm. 2. History of sensitivity (including angioedema) or allergic reaction to medication targeting the RAAS system including study medications or other allergy in the opinion of the investigator that contraindicates participation (not applicable to fostamatinib arm) 3. Hemodynamic instability - defined as MAP < 65 mmHg at time of randomization confirmed on two measurements 5 minutes apart OR vasopressors at or above norepinephrine equivalent of 0.1 mcg/kg/min in prior 4 hours to maintain MAP > 65 mmHg. 4. Known severe renal artery stenosis. 5. Known significant left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or severe aortic or mitral stenosis. 6. Randomized in another trial evaluating RAAS modulation in the prior 30 days
TRV-027 Trial	No additional inclusion criteria beyond the platform criteria.	1. Participants on ARBs will be excluded from this study arm. 2. Patient unable to participate or declines participation in the TRV027 arm. 3. History of sensitivity (including angioedema) or allergic reaction to medication targeting the RAAS system including study medications or other allergy in the opinion of the investigator that contraindicates participation (not applicable to fostamatinib arm) 4. Hemodynamic instability - defined as MAP < 65 mmHg at time of randomization confirmed on two measurements 5 minutes apart OR vasopressors at or above norepinephrine equivalent of 0.1 mcg/kg/min in prior 4 hours to maintain MAP > 65 mmHg. 5. Known severe renal artery stenosis. 6. Known significant left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or severe aortic or mitral stenosis. 7. Randomized in another trial evaluating RAAS modulation in the prior 30 days

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eTable 3. Trial outcomes

Pre-specified clinical outcomes for the TXA-127 and TRV-027 trials are shown in this table. Exploratory biomarker-based outcomes will be reported separately in a different manuscript.

Outcome	Definition	Variable type	Analysis approach	Interpretation of OR <1.0
Primary efficacy outcome				
Oxygen-free days to day 28	28 minus the number of days between initiation and final liberation from new supplemental oxygen use during the 28 days following randomization. Patients who died before day 28 were coded as -1.	Ordinal scale with 30 levels	Multivariable proportional odds regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Inferiority of active agent
Key secondary efficacy outcomes				
All-cause all-location mortality at day 28	Alive vs dead at study day 28	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Superiority of active agent
Alive and respiratory failure free at day 28	Composite of alive and off respiratory support (no high flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation) vs either dead or on respiratory support at day 28	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Inferiority of active agent
WHO COVID-19 clinical progression ordinal scale at day 28	Patient's clinical status at day 28 classified based on the following 8 mutually exclusive categories: 1. Ambulatory – Not hospitalized, no limitation of activities 2. Ambulatory – Not hospitalized with limitation of activities or home oxygen therapy 3. Hospitalized Mild Disease – Hospitalized, no oxygen therapy 4. Hospitalized Mild Disease – Oxygen by mask or nasal prongs 5. Hospitalized Severe Disease – Non-invasive ventilation	Ordinal scale with 8 levels	Multivariable proportional odds regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Superiority of active agent

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Outcome	Definition	Variable type	Analysis approach	Interpretation of OR <1.0
	or high-flow oxygen 6. Hospitalized Severe Disease – Invasive mechanical ventilation 7. Hospitalized Severe Disease – Invasive mechanical ventilation plus additional organ support with vasopressors, renal replacement therapy or extracorporeal membrane oxygenation (ECMO) 8. Dead			
Other secondary efficacy outcomes				
Alive and oxygen free at 14 days	Composite of alive and off new supplemental oxygen therapy vs either dead or on new supplemental oxygen therapy at day 14	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Inferiority of active agent
Alive and oxygen free at 28 days	Composite of alive and off new supplemental oxygen therapy vs either dead or on new supplemental oxygen therapy at day 28	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Inferiority of active agent
Alive and respiratory failure free at 14 days	Composite of alive and off respiratory support (no high flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation) vs either dead or on respiratory support at day 14	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Inferiority of active agent
Alive and free of new invasive mechanical ventilation at day 14	Composite of alive and off new invasive mechanical ventilation vs either dead or on invasive mechanical ventilation at day 14	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Inferiority of active agent
Alive and free of new invasive mechanical ventilation at day 28	Composite of alive and off new invasive mechanical ventilation vs either dead or on invasive mechanical ventilation at day 28	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal	Inferiority of active agent

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Outcome	Definition	Variable type	Analysis approach	Interpretation of OR <1.0
			scale at baseline (level 4, 5, or 6-7)	
In-hospital mortality	Died prior to hospital discharge vs survived to hospital discharge based on the index hospitalization in which the patient was enrolled in the trial	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Superiority of active agent
60-day mortality	Dead vs alive at day 60	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Superiority of active agent
90-day mortality	Dead vs alive at day 90	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Superiority of active agent
WHO COVID-19 clinical progression ordinal scale at day 14	Patient's clinical status at day 14 classified based on the 8 mutually exclusive categories defined above.	Ordinal scale with 8 levels	Multivariable proportional odds regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Superiority of active agent
WHO COVID-19 clinical progression ordinal scale at day 60	Patient's clinical status at day 60 classified based on the 8 mutually exclusive categories defined above.	Ordinal scale with 8 levels	Multivariable proportional odds regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Superiority of active agent
Hospital-free days through day 28	28 minus the number of days between randomization and hospital discharge for the index hospital admission in which the patient was enrolled in the trial. Patients who died before day 28	Ordinal scale with 30 levels	Multivariable proportional odds regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and	Inferiority of active agent

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Outcome	Definition	Variable type	Analysis approach	Interpretation of OR <1.0
	were coded as -1. Patients who remained hospitalized after day 28 were coded as 0.		WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	
Respiratory-failure-free days through day 28	28 minus the number of days between initiation and final liberation from respiratory support (high flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation) during the 28 days following randomization. Patients who died before day 28 were coded as -1.	Ordinal scale with 30 levels	Multivariable proportional odds regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Inferiority of active agent
Ventilator-free days through day 28	28 minus the number of days between initiation and final liberation from invasive mechanical ventilation during the 28 days following randomization. Patients who died before day 28 were coded as -1.	Ordinal scale with 30 levels	Multivariable proportional odds regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Inferiority of active agent
Safety outcomes				
Allergic reaction through day 7	Angioedema or another acute reaction proximate to study drug administration that the site investigator judged to be possibly related to a study drug allergy. Patients were coded as no allergic reaction vs ≥1 allergic reaction.	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Fewer safety events with active agent
Allergic reaction through day 28	Same definition as above for allergic reaction through day 7	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Fewer safety events with active agent
New renal replacement therapy through day 7	Initiation of renal replacement therapy prior to day 28 in a patient not on renal replacement therapy at randomization.	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Fewer safety events with active agent

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Outcome	Definition	Variable type	Analysis approach	Interpretation of OR <1.0
New renal replacement therapy through day 28	Same definition as above for new renal replacement therapy through day 7	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Fewer safety events with active agent
Hypotension through day 7	A low blood pressure leading to initiation or increase in vasopressor therapy, administration of a fluid bolus of ≥500 ml, or discontinuation of the study drug. Patients were coded as no hypotensive events vs ≥1 hypotensive events.	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Fewer safety events with active agent
Hypotension through day 28	Same definition as above for hypotension through day 7	Binary	Multivariable logistic regression model adjusted for age group (18-30, 31-65, or >65 years), sex at birth, and WHO COVID ordinal scale at baseline (level 4, 5, or 6-7)	Fewer safety events with active agent

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eTable 4. Protocol-specified exempt serious events (PSESEs)

Protocol specified exempt serious events (PSESEs) were medical events that were systemically collected for all enrolled patients so that data on these events did not rely on *ad hoc* adverse event reporting. PSESEs were collected through day 60.

PSESE (collected through day 60)	**Definition**	**Variable type**	**Analysis approach**
Seizure	Clinically identified seizure	Binary	Frequency counts and proportions
Stroke	Clinically identified ischemic or hemorrhagic stroke	Binary	Frequency counts and proportions
Arrythmia (atrial or ventricular)	Clinically identified atrial or ventricular arrythmia	Binary	Frequency counts and proportions
Cardiomyopathy	Clinically identified cardiomyopathy	Binary	Frequency counts and proportions
Cardiac arrest	Clinically identified cardiac arrest, regardless of cardiac rhythm	Binary	Frequency counts and proportions
Myocardial injury	Clinical identified myocardial injury that was judged not to be due to acute coronary syndrome	Binary	Frequency counts and proportions
Acute coronary syndrome	Clinically identified acute coronary syndrome	Binary	Frequency counts and proportions
Hypertension	Systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg plus clinical symptoms attributed to elevated blood pressure	Binary	Frequency counts and proportions
Hypoxemia requiring supplemental oxygen	New supplement oxygen treatment	Binary	Frequency counts and proportions
Acute respiratory distress syndrome	Clinically identified acute respiratory distress syndrome	Binary	Frequency counts and proportions
Receipt of non-invasive or invasive ventilation	New non-invasive or invasive ventilation	Binary	Frequency counts and proportions
Receipt of extracorporeal membrane oxygenation (ECMO)	New receipt of ECMO	Binary	Frequency counts and proportions
Elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	Clinically identified ALT or AST elevations, or ALT > 136U/L for Men, ALT > 96U/L for Women, or AST > 128U/L for Men, AST > 104U/L for Women	Binary	Frequency counts and proportions
Acute pancreatitis	Clinically identified acute pancreatitis	Binary	Frequency counts and proportions
Acute kidney injury	Clinically identified acute kidney injury or criteria for KDIGO AKI stage I or greater (serum creatinine criteria only)	Binary	Frequency counts and proportions
Receipt of renal replacement therapy	New receipt of renal replacement therapy	Binary	Frequency counts and proportions
Symptomatic hypoglycemia	Blood glucose level <60 mg/dl and clinically identified symptoms related to low blood glucose	Binary	Frequency counts and proportions
Neutropenia	Clinically identified neutropenia or ANC < 500 cells/mcl	Binary	Frequency counts and proportions

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PSESE (collected through day 60)	**Definition**	**Variable type**	**Analysis approach**
Lymphopenia	Clinically identified lymphopenia or ALC < 1000 cells/mcl	Binary	Frequency counts and proportions
Anemia	Clinically identified anemia or Hgb < 7g/dL for Men, Hgb < 6.5g/dL for Women	Binary	Frequency counts and proportions
Thrombocytopenia	Clinically identified thrombocytopenia or platelets < 100 thousand/L	Binary	Frequency counts and proportions
Venous thromboembolism	Clinically identified new deep vein thrombosis or pulmonary embolism	Binary	Frequency counts and proportions
Severe dermatologic reaction	New severe skin reaction (e.g., Stevens-Johnson Syndrome)	Binary	Frequency counts and proportions

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eTable 5. Results at the first interim analyses

Both the TXA-127 and TRV-027 trials halted at the first interim analysis on April 20, 2022 based on meeting the pre-specified stopping criterion for <5% probability of superiority (which is the same as >95% probability for inferiority) of the active agent compared with placebo. Results reviewed by the DSMB at the first interim analysis are shown here. The remainder of the manuscript and supplementary materials report the final results that include all patients, including those not part of the interim analysis. The first 200 patients in each trial were included in the interim analyses. All patients who were enrolled prior to the halting of enrollment were included in the final analyses.

	Interim Analysis	**Final Analysis**
TXA-127 Trial		
Sample size (active + placebo patients), no.	200	343
Oxygen-free days aOR (95% CI)	0.628 (0.373, 1.057)	0.879 (0.594, 1.300)
Probability of superiority for active vs placebo based on oxygen-free days	0.040	0.259
TRV-027 Trial		
Sample size (active + placebo patients), no.	200	290
Oxygen-free days aOR (95% CI)	0.611 (0.364, 1.025)	0.740 (0.483, 1.134)
Probability of superiority for active vs placebo based on oxygen-free days	0.031	0.083

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eTable 6. Details of placebo groups

(a) **TXA-127 trial**

The modified intention-to-treat population for efficacy analyses in the TXA-127 trial included 173 patients, including 135 patients included in both the TXA-127 trial and the TRV-027 trial and 38 patients included in the TXA-127 trial only. The type of placebo received is detailed in the table below.

TXA-127 trial: type of placebo received for the 173 patients in the placebo group	
Type of placebo	**no. (%)**
Placebo mimic of TXA-127	92 (53.2)
Placebo mimic of TRV-027	71 (41.0)
Placebo mimic of fostamatinib	10 (5.8)

(b) **TRV-027 trial**

The modified intention-to-treat population for efficacy analyses in the TRV-027 trial included 145 patients, including 135 patients included in both the TXA-127 trial and the TRV-027 trial and 10 patients included in the TRV-027 trial only. The type of placebo received is detailed in the table below.

TRV-027 trial: type of placebo received for the 145 patients in the placebo group	
Type of placebo	**no. (%)**
Placebo mimic of TXA-127	54 (37.2)
Placebo mimic of TRV-027	79 (54.5)
Placebo mimic of fostamatinib	12 (8.3)

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eTable 7. Additional baseline patient characteristics

Baseline patient characteristics for the modified intention-to-treat populations used for efficacy analyses not included in Table 1.

	TXA-127 Trial			TRV-027 Trial	
Characteristic	**TXA-127 (n=170)**	**Placebo (n=173)**		**TRV-027 (n=145)**	**Placebo (n=145)**
Age group, no (%)					
18 – 30 years	11 (6.5)	7 (4.0)		5 (3.4)	7 (4.8)
31 – 64 years	106 (62.4)	120 (69.4)		100 (69.0)	99 (68.3)
≥65 years	53 (31.2)	46 (26.6)		40 (27.6)	39 (26.9)
Patient location prior to presentation to the enrolling hospital, no. (%)					
Home	151 (88.8)	160 (92.5)		132 (91.0)	132 (91.0)
Nursing home	3 (1.8)	2 (1.2)		0 (0.0)	2 (1.4)
Rehabilitation facility	0 (0)	2 (1.2)		1 (0.7)	2 (1.4)
Skilled nursing facility	1 (0.6)	1 (0.6)		0 (0)	1 (0.7)
Long-term acute care facility	0 (0)	1 (0.6)		0 (0)	1 (0.7)
Outside hospital ward	9 (5.3)	5 (2.9)		7 (4.8)	6 (4.1)
Outside ICU	2 (1.2)	0 (0)		0 (0)	0 (0)
Other	4 (2.4)	2 (1.2)		5 (3.5)	1 (0.7)
Patient location at enrollment, no. (%)					
Emergency department	37 (21.8)	32 (18.5)		25 (17.2)	31 (21.4)
Inpatient ward	90 (52.9)	99 (57.2)		84 (57.9)	81 (55.9)
ICU	42 (24.7)	42 (24.3)		36 (24.8)	33 (22.8)
Other	1 (0.6)	0 (0)		0 (0)	0 (0)
Chronic medical conditions, no. (%)					
Asthma	17 (10.0)	29 (16.8)		18 (12.4)	24 (16.6)
Interstitial lung disease	4 (2.4)	4 (2.3)		6 (4.1)	4 (2.8)
Prior myocardial infarction or coronary artery disease	24 (14.1)	17 (9.8)		14 (9.7)	14 (9.7)
Atrial fibrillation or flutter	12 (7.1)	13 (7.5)		12 (8.3)	9 (6.2)
Stroke or transient ischemic attack	11 (6.5)	6 (3.5)		3 (2.1)	7 (4.8)
Peripheral vascular disease	3 (1.8)	6 (3.5)		2 (1.4)	4 (2.8)
Deep vein thrombosis or pulmonary embolism	7 (4.1)	12 (6.9)		7 (4.8)	9 (6.2)
Sickle cell disease	0 (0)	0 (0)		1 (0.7)	1 (0.7)
HIV infection without AIDS	0 (0)	0 (0)		0 (0)	0 (0)
AIDS	0 (0)	1 (0.6)		0 (0)	0 (0)
Connective tissue disease	10 (5.9)	6 (3.5)		5 (3.4)	5 (3.4)
Peptic ulcer disease	1 (0.6)	1 (0.6)		1 (0.7)	1 (0.7)
Current smoker	18 (10.6)	20 (11.6)		18 (12.4)	16 (11.0)
Former smoker	49 (28.8)	53 (30.6)		48 (33.1)	46 (31.7)
Alcohol abuse	5 (2.9)	3 (1.7)		1 (0.7)	2 (1.4)
Chronic medications (taken within 3 weeks prior to enrollment), no. (%)					
Antiplatelet medication	30 (17.6)	16 (9.25)		19 (13.1)	17 (11.7)
Anticoagulant medication	40 (23.5)	42 (24.3)		28 (19.3)	34 (23.4)
Renin-angiotensin blocking medication	25 (21.9)	25 (21.4)		12 (12.0)	11 (11.5)

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	TXA-127 Trial			TRV-027 Trial	
Characteristic	**TXA-127 (n=170)**	**Placebo (n=173)**		**TRV-027 (n=145)**	**Placebo (n=145)**
Antihypertensive medication other than renin-angiotensin blocking medication	43 (38.1)	40 (34.2)		30 (30.0)	29 (30.2)
Immunomodulator or biologic medication to treat autoimmune disease or cancer	34 (20.0)	35 (20.2)		29 (20.0)	26 (17.9)
Acute outpatient medications for COVID-19 (taken within 3 weeks prior to enrollment), no. (%)					
Small molecule antiviral medication	29 (17.1)	35 (20.2)		22 (15.2)	27 (18.6)
Anti-SARS-CoV-2 monoclonal antibody medication	10 (5.9)	10 (5.8)		6 (4.1)	4 (2.8)
Vital signs closest to randomization, median (IQR)					
Temperature, °C	36.7 (36.4 - 37.0) N=169	36.6 (36.4 - 36.9) N=171		36.7 (36.4 - 36.9) N=143	36.7 (36.4 - 36.9) N=143
Heart rate, beats/minute	78.5 (68.0 - 90.0)	81.0 (73.0 - 89.0)		79.0 (67.0 - 90.0)	80.0 (71.0 - 88.0)
Systolic blood pressure, mm HG	126 (114 – 140)	125 (114 – 138)		121 (110 - 134)	124 (114 - 138)
Diastolic blood pressure, mm HG	75.0 (68 - 82)	74 (67 - 82)		73 (67 - 82)	74 (66 - 82)
Respiratory rate	20 (18 – 25) N=169	21 (18 – 24)		20 (18 - 24) N=139	21 (18 - 24)
FiO2*	0.44 (0.32 – 0.75) N=169	0.40 (0.32 – 0.65) N=172		0.44 (0.32 – 0.80)	0.40 (0.32 – 0.65) N=144
PaO2: FiO2 ratio**	163 (95 - 225) N=168	183 (102 - 246) N=171		155 (96 - 228)	183 (111 - 246) N=143
Glasgow coma scale <15, no. (%)	25 (14.8)	12 (6.94)		19 (13.1)	10 (6.90)
Laboratory measurements closest to randomization, median (IQR)					
White blood cell count, thousand cells/ml	6.7 (4.8 - 9.6) N=155	6.9 (4.8 - 9.7) N=160		7.1 (5.1 - 10.6) N=136	7.0 (4.9 - 10.1) N=136
Platelet count, thousand/ml	228 (156 - 312) N=155	231 (161 - 284) N=160		208 (169 -282) N=136	230 (165 - 287) N=135
Hemoglobin, g/dL	13.2 (12.1 - 14.6) N=154	13.2 (12.0 - 14.5) N=160		13.4 (11.9 - 14.6) N=137	13.2 (12.1 - 14.5) N=136
Serum sodium, mmol/L	138 (135 - 139) N=164	137 (135 - 139) N=168		138 (135 - 140) N=144	137 (135 - 139) N=143
Serum potassium, mmol/L	4.2 (3.9 - 4.4) N=164	4.2 (3.8 - 4.6) N=165		4.1 (3.8 - 4.5) N=142	4.2 (3.8 - 4.5) N=140
Serum creatinine, mmol/L	0.8 (0.7 - 1.1) N=164	0.8 (0.7-1.0) N=168		0.9 (0.7 - 1.1) N=144	0.8 (0.7 - 1.0) N=143

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	TXA-127 Trial			TRV-027 Trial	
Characteristic	**TXA-127 (n=170)**	**Placebo (n=173)**		**TRV-027 (n=145)**	**Placebo (n=145)**
Serum aspartate aminotransferase (AST), U/L	45 (33 - 66) N=128	38 (25 - 52) N=138		53 (33 - 82) N=114	37 (25 - 52) N=116
Serum alanine aminotransferase (ALT), U/L	33 (18 - 53) N=129	31 (18 - 51) N=140		38 (22 - 70) N=115	31 (18 - 52) N=118
Serum total bilirubin, mg/dL	0.5 (0.4 - 0.7) N=131	0.5 (0.4 - 0.6) N=140		0.5 (0.3 - 0.7) N=117	0.4 (0.4 - 0.6) N=119

Abbreviations:
no.: number; IQR: interquartile range; ICU: intensive care unit; COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; C: Celsius

Footnotes:
*FiO2 was recorded directly from a respiratory support device if available. If not available, room air was recorded at 0.21 and for patients on supplemental oxygen, FiO2 was estimated based on supplemental oxygen flow rate.
** PaO2 was recorded directly from an arterial blood gas analysis if available. If not available, PaO2 was estimated from SpO2.

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eTable 8. Usual care in-hospital medications before randomization

Receipt of COVID-19 medications and renin angiotensin system (RAS) medications (any number of doses) in the hospital before trial randomization.

(a) TXA-127 trial

TXA-127 trial: in-hospital pre-randomization medications no. (%)		
Medication	**TXA-127 (n=170)**	**Placebo (n=173)**
Angiotensin converting enzyme (ACE) inhibitor	7 (4.1)	9 (5.2)
Angiotensin receptor blocker (ARB)	11 (6.5)	11 (6.4)
Beta-blockers	22 (12.9)	33 (19.1)
Antibiotics (systemic anti-bacterial medication)	43 (25.3)	37 (21.4)
Remdesivir	120 (70.6)	121 (69.9)
Anti-SARS-CoV-2 monoclonal antibody	0 (0.0)	1 (0.58)
COVID-19 convalescent plasma	0 (0.0)	0 (0.0)
Corticosteroids	149 (87.6)	136 (78.6)
Baricitinib	25 (14.7)	22 (12.7)
Tocilizumab	0 (0.0)	1 (0.6)
Other immunomodulator for COVID-19 treatment	3 (1.8)	1 (0.6)

(b) TRV-027 trial

TRV-027 trial: in-hospital pre-randomization medications no. (%)		
Medication	**TRV-027 (n=145)**	**Placebo (n=145)**
Angiotensin converting enzyme (ACE) inhibitor	7 (4.8)	9 (6.2)
Angiotensin receptor blocker (ARB) [exclusion criterion]	0 (0.0)	0 (0.0)
Beta-blockers	10 (6.9)	24 (16.6)
Antibiotics (systemic anti-bacterial medication)	28 (19.3)	29 (20.0)
Remdesivir	95 (65.5)	95 (65.5)
Anti-SARS-CoV-2 monoclonal antibody	0 (0.0)	1 (0.7)
COVID-19 convalescent plasma	0 (0.0)	0 (0.0)
Corticosteroids	113 (77.9)	112 (77.2)
Baricitinib	22 (15.2)	18 (12.4)
Tocilizumab	0 (0.0)	1 (0.7)
Other immunomodulator for COVID-19 treatment	4 (2.8)	0 (0.0)

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eTable 9. Study drug delivery in the TXA-127 trial

The TXA-127 study drug was scheduled to be dosed as 0.5 mg/kg intravenous over approximately 3 hours once daily for 5 days or until hospital discharge, whichever occurred first. To facilitate comparisons of study drug delivery, the table below shows patients in the modified intention-to-treat population who were randomized to the active TXA-127 agent and those randomized to the placebo mimic of the TXA-127 agent. The active TXA-127 group displayed in this table is the same group used in efficacy analyses. However, the placebo group presented in this table is not the same placebo group used in efficacy evaluations because some of the placebo patients in efficacy analyses in the TXA-127 trial received a placebo mimic of TRV-027 or fostamatinib, which used a different dosing schedule.

	TXA-127 Active Group	**Mimic TXA-127 Placebo Group**
All patients		
Patient sample size, no.	170	92
Number of complete study drug doses delivered, no. (%)		
5 study drug doses	107 (62.9)	57 (62.0)
4 study drug doses	24 (14.1)	12 (13.0)
3 study drug doses	19 (11.2)	11 (12.0)
2 study drug doses	12 (7.1)	4 (4.3)
1 study drug doses	8 (4.7)	8 (8.7)
Patients alive and hospitalized ≥5 days (available for all 5 doses of study drug)		
Patient sample size, no.	121	62
Number of complete study drug doses delivered, no. (%)		
5 study drug doses	107 (88.4)	57 (91.9)
4 study drug doses	10 (8.3)	3 (4.8)
3 study drug doses	2 (1.7)	1 (1.6)
2 study drug doses	0 (0.0)	1 (1.6)
1 study drug doses	2 (1.7)	0 (0.0)

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eTable 10. Study drug delivery in the TRV-027 trial

The TRV-027 study drug was scheduled to be dosed as a continuous intravenous infusion at 12 mg/hour for 5 days (120 hours) or until hospital discharge, whichever occurred first. To facilitate comparisons of study drug delivery, the table below shows patients in the modified intention-to-treat population who were randomized to the active TRV-027 agent and to the placebo mimic of the TRV-027 agent. The active TRV-027 group displayed in this table is the same group used in efficacy analyses. However, the placebo group presented in this table is not the same placebo group used in efficacy evaluations because some of the placebo patients in efficacy analyses in the TRV-027 trial received a placebo mimic of TXA-127 or fostamatinib, which used a different dosing schedule.

	TRV-027 Active Group	**Mimic TRV-027 Placebo Group**
All patients		
Patient sample size, no.	145	79
Full dose of study drug received (12mg/hr for 120 hours = 1440 mg), no. (%)	93 (64.1)	51 (64.6)
Patients who did not receive a full dose of 120 hours of study drug delivery		
Patient sample size, no.	52	28
Reasons that full dose was not administered, no. (%)		
Hospital discharge/death	21 (40.4)	19 (67.9)
Adverse event	14 (25.0)	1 (3.6)
Other clinical event	7 (13.5)	6 (21.4)
Logistical barrier	10 (19.2)	2 (7.1)
Total dose administered (mg) among participants who did not receive the full dose (1440mg), median (IQR)	575.6 (261.7 - 953.0)	814.0 (473.0 - 1089.0)

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eTable 11. Summaries of oxygen-free days for subgroup analyses in TXA-127 trial

These summaries of oxygen-free days do not include patients with partially observed data (patients for whom the number of oxygen-free days was not known precisely but was known to be within a certain range).

	Sample sizes			Oxygen-free days		
Subgroup	TXA-127, n	Placebo, n	Partially observed, n	TXA-127, mean (SD)	Placebo, mean (SD)	Unadjusted absolute difference (95% CI)[1]
Age group, years						
18-30	9	7	2	8 (12.1)	16.3 (11.2)	-8.3 (-19.7, 3.2)
31-64	95	107	24	9.8 (11.1)	11.5 (11.6)	-1.7 (-4.8, 1.4)
65+	49	41	9	7.8 (10.3)	10.1 (11.4)	-2.3 (-6.8, 2.2)
Sex						
Female	60	72	11	9.6 (11.1)	12.1 (11.7)	-2.5 (-6.4, 1.4)
Male	93	83	24	8.7 (10.8)	10.7 (11.4)	-2.0 (-5.3, 1.3)
WHO ordinal scale level						
4: Standard supplemental O2	90	104	24	12.4 (11.4)	14.3 (11.4)	-1.9 (-5.1, 1.3)
5: HFNC or NIV	47	43	10	4.7 (8.5)	5.9 (9.6)	-1.2 (-5, 2.6)
6/7: Invasive mechanical ventilation	16	8	1	2.7 (6.9)	2.1 (7.6)	0.6 (-5.6, 6.9)
COVID-19 vaccination status						
Unvaccinated	96	102	18	8.8 (10.6)	10.6 (11.3)	-1.8 (-4.9, 1.3)
At least 1 vaccine dose	46	48	16	9.4 (11.4)	12.9 (12.2)	-3.5 (-8.3, 1.3)
Pre-COVID-19 ACE inhibitor or ARB use						
No	111	109	26	9.5 (10.9)	11.3 (11.5)	-1.8 (-4.8, 1.2)
Yes	40	44	9	7.6 (11.1)	11.3 (11.7)	-3.7 (-8.6, 1.2)

Footnote:
1. Unadjusted absolute differences and 95% credible intervals (CI) for oxygen-free days were calculated using the normal distribution with flat prior for both the mean and variance, excluding partially observed values.

Abbreviations:
WHO: World Health Organization; COVID-19: coronavirus disease 2019; SD: standard deviation; O2: oxygen; HFNC: high flow nasal cannula; NIV: non-invasive ventilation; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker

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eTable 12. Summaries of oxygen-free days for subgroup analyses in TRV-027 trial

These summaries of oxygen-free days do not include patients with partially observed data (patients for whom the number of oxygen-free days was not known precisely but was known to be within a certain range).

	Samples Sizes			Oxygen-free days		
Subgroup	TRV-027, n	Placebo, n	Partially observed, n	TRV-027, mean (SD)	Placebo, mean (SD)	Unadjusted absolute difference (95% CI)[1]
Age group, years						
18-30	5	7	0	16.6 (10.3)	16.3 (11.2)	0.3 (-12, 12.6)
31-64	91	90	18	8.7 (11)	10.6 (11.7)	-1.9 (-5.2, 1.4)
65+	39	34	6	5.5 (9.8)	9.1 (11)	-3.6 (-8.4, 1.2)
Sex						
Female	51	66	5	6.6 (10.4)	10.7 (11.8)	-4.1 (-8.1, -0.1)
Male	84	65	19	8.9 (11)	10.3 (11.3)	-1.4 (-5, 2.2)
WHO ordinal scale level						
4: Standard supplemental O2	74	88	20	11.7 (11.5)	13.4 (11.5)	-1.7 (-5.3, 1.9)
5: HFNC or NIV	48	37	3	3.9 (8.5)	5.4 (9.6)	-1.5 (-5.4, 2.4)
6/7: Invasive mechanical ventilation	13	6	1	2.3 (5.5)	-0.5 (0.5)	2.8 (-0.2, 5.8)
COVID-19 vaccination status						
Unvaccinated	90	85	15	6.4 (10)	10.1 (11.4)	-3.7 (-6.9, -0.5)
At least 1 vaccine dose	39	42	9	10.5 (11.7)	11.3 (11.9)	-0.8 (-5.9, 4.4)
Pre-COVID-19 ACE inhibitor or ARB use						
No	108	104	19	7.5 (10.5)	10.4 (11.4)	-2.9 (-5.9, 0.1)
Yes	26	26	5	10.7 (12)	11.2 (12.2)	-0.5 (-7.1, 6.1)

Footnote:
1. Unadjusted absolute differences and 95% credible intervals (CI) for oxygen-free days were calculated using the normal distribution with flat prior for both the mean and variance, excluding partially observed values.

Abbreviations:
WHO: World Health Organization; COVID-19: coronavirus disease 2019; SD: standard deviation; O2: oxygen; HFNC: high flow nasal cannula; NIV: non-invasive ventilation; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker

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eTable 13. Additional outcome results in TXA-127 trial

Secondary efficacy and safety outcomes in TXA-127 trial not presented in Table 2.

Outcome	TXA-127 (n=170)	Placebo (n=173)	Odds Ratio* (95% CI)
Secondary efficacy outcomes			
Alive and oxygen free at 14 days, no. (%)	60 (38.0) [n=158]	86 (52.4) [n=164]	0.61 (0.38, 0.98)
Alive and oxygen free at 28 days, no. (%)	78 (50.3) [n=155]	87 (55.1) [n=158]	0.94 (0.58, 1.51)
Alive and respiratory failure free at 14 days, no. (%)	123 (77.4) [n=159]	126 (75.9) [n=166]	1.46 (0.82, 2.6)
Alive and free of new invasive mechanical ventilation at day 14, no. (%)	129 (81.1) [n=159]	133 (80.1) [n=166]	1.43 (0.77, 2.64)
Alive and free of new invasive mechanical ventilation at day 28, no. (%)	124 (80.0) [n=155]	128 (80.0) [n=160]	1.3 (0.70, 2.42)
In-hospital mortality, no. (%)	23 (13.8) [n=167]	24 (14.0) [n=172]	0.78 (0.40, 1.55)
60-day mortality, no. (%)	26 (16.1) [n=161]	29 (17.5) [n=166]	0.71 (0.38, 1.35)
90-day mortality, no. (%)	28 (17.7) [n=158]	31 (19.3) [n=161]	0.71 (0.38, 1.32)
WHO COVID-19 clinical progression ordinal scale level at day 14, no. (%)	1: 37 (23.4) 2: 61 (38.6) 3: 5 (3.16) 4: 19 (12.0) 5: 6 (3.80) 6: 6 (3.80) 7: 12 (7.59) 8: 12 (7.59) Missing: 12	1: 57 (34.8) 2: 55 (33.5) 3: 5 (3.05) 4: 7 (4.27) 5: 7 (4.27) 6: 6 (3.66) 7: 14 (8.54) 8: 13 (7.93) Missing: 9	1.12 (0.75, 1.67)
WHO COVID-19 clinical progression ordinal scale level at day 60, no. (%)	1: 62 (48.4) 2: 35 (27.3) 3: 0 (0) 4: 2 (1.56) 5: 1 (0.78) 6: 2 (1.56) 7: 0 (0) 8: 26 (20.3) Missing: 42	1: 63 (45.0) 2: 40 (28.6) 3: 2 (1.43) 4: 3 (2.14) 5: 0 (0) 6: 0 (0) 7: 3 (2.14) 8: 29 (20.7) Missing: 33	0.68 (0.43, 1.07)
Hospital-free days through day 28, mean (sd), [median (IQR)]	14.2 (10.5) [18.0 (0.0 - 23.0)] n=154	15.6 (10.5) [21.0 (1.8 - 24.0)] n=160	0.91 (0.61, 1.33)
Respiratory-failure-free days through day 28, mean (sd), [median (IQR)]	19.5 (11.1) [25.0 (15.0 - 28.0)] n=150	20.1 (11.4) [28.0 (14.5 - 28.0)] n=160	1.01 (0.66, 1.57)
Ventilator-free days through day 28, mean (sd), [median (IQR)]	21.8 (11.1) [28.0 (21.5 - 28.0)] n=150	22.3 (10.9) [28.0 (28.0 - 28.0)] n=159	1.31 (0.75, 2.30)
Safety Outcomes			
Allergic reaction through day 28, no. (%)	3 (0.0)	0 (0.0)	NE
New renal replacement therapy through day 7, no (%)	11 (6.5)	12 (6.9)	0.75 (0.31, 1.84)
Hypotension through day 28, no. (%)	31 (18.2)	31 (17.9)	0.81 (0.45, 1.48)

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Abbreviations:
CI: credible interval; no: number; IQR: interquartile range; WHO: World Health Organization; COVID-19: coronavirus disease 2019; SD: standard deviation; NE: not estimable

Footnotes:
* See Table S3 for descriptions of how the odds ratios were calculated and the interpretation of the odds ratios.

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eTable 14. Additional outcome results in TRV-027 trial

Secondary efficacy and safety outcomes in TRV-027 trial not presented in Table 2.

Outcome	TRV-027 (n=145)	Placebo (n=145)	Odds Ratio* (95% CI)
Secondary efficacy outcomes			
Alive and oxygen free at 14 days, no. (%)	48 (34.8) [n=138]	66 (48.2) [n=137]	0.64 (0.38, 1.08)
Alive and oxygen free at 28 days, no. (%)	60 (44.4%) [n=135]	69 (51.5) [n=134]	0.84 (0.50, 1.41)
Alive and respiratory failure free at 14 days, no. (%)	91 (65.9) [n=138]	105 (75.0) [n=140]	0.8 (0.43, 1.49)
Alive and free of new invasive mechanical ventilation at day 14, no. (%)	98 (71.0) [n=138]	111 (79.3) [n=140]	0.8 (0.42, 1.52)
Alive and free of new invasive mechanical ventilation at day 28, no. (%)	99 (72.8) [n=136]	109 (80.1) [n=136]	0.85 (0.45, 1.61)
In-hospital mortality, no. (%)	31 (21.4) [n=145]	20 (13.9) [n=144]	1.49 (0.75, 2.96)
60-day mortality, no. (%)	33 (23.7) [n=139]	23 (16.4) [n=140]	1.36 (0.71, 2.62)
90-day mortality, no. (%)	34 (25.2) [n=135]	25 (18.1) [n=138]	1.31 (0.69, 2.5)
WHO COVID-19 clinical progression ordinal scale level at day 14, median (IQR)	1: 31 (22.5) 2: 50 (36.2) 3: 2 (1.5) 4: 8 (5.8) 5: 7 (5.1) 6: 5 (3.6) 7: 14 (10.1) 8: 21 (15.2) Missing: 7	1: 45 (32.8) 2: 48 (35.0) 3: 3 (2.2) 4: 6 (4.4) 5: 6 (4.4) 6: 4 (2.9) 7: 14 (10.2) 8: 11 (8.0) Missing: 8	1.42 (0.91, 2.19)
WHO COVID-19 clinical progression ordinal scale level at day 60, median (IQR)	1: 44 (40.7) 2: 25 (23.1) 3: 0 (0) 4: 2 (1.85) 5: 2 (1.85) 6: 0 (0) 7: 2 (1.85) 8: 33 (30.6) Missing: 37	1: 50 (43.5) 2: 32 (27.8) 3: 3 (2.61) 4: 4 (3.48) 5: 0 (0) 6: 0 (0) 7: 3 (2.61) 8: 23 (20.0) Missing: 30	1.03 (0.63, 1.67)
Hospital-free days through day 28, mean (SD) [median (IQR)]	13.5 (10.8) [18.0 (0.0 - 23.0)] n=136	15.4 (10.6) [21.0 (0.8 - 24.0)] n=136	0.80 (0.52, 1.21)
Respiratory-failure-free days through day 28, mean (SD) [median (IQR)]	17.4 (12.8) [26.0 (0.0 - 28.0)] n=135	20.0 (11.5) [28.0 (12.0 - 28.0)] n=136	0.91 (0.56, 1.47)
Ventilator-free days through day 28, mean (SD) [median (IQR)]	19.5 (12.5) [28.0 (3.5 - 28.0)] n=135	22.4 (10.9) [28.0 (28.0 - 28.0)] n=135	0.76 (0.43, 1.38)
Safety Outcomes			
Allergic reaction through day 28, no. (%)	0 (0.0)	3 (2.1)	NE
New renal replacement therapy through day 28, no (%)	9 (6.2)	11 (7.6)	0.59 (0.22, 1.55)
Hypotension through day 28, no. (%)	32 (22.1)	25 (17.2)	1.07 (0.55, 2.08)

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Abbreviations:
CI: credible interval; no: number; IQR: interquartile range; WHO: World Health Organization; COVID-19: coronavirus disease 2019; NE: not estimable

Footnotes:
* See Table S3 for descriptions of how the odds ratios were calculated and the interpretation of the odds ratios.

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eTable 15. PSESEs results in TXA-127 trial

PSESE = protocol-specified exempt serious events, which were systematically collected events captured through day 60

PSESE, no. (%)	TXA-127 (n=170)	Placebo (n=173)
Seizure	1 (0.59)	1 (0.58)
Stroke	5 (2.94)	0 (0)
Arrythmia (atrial or ventricular)	16 (9.41)	9 (5.20)
Cardiomyopathy	0 (0)	0 (0)
Cardiac arrest	6 (3.53)	6 (3.47)
Myocardial injury	1 (0.59)	3 (1.73)
Acute coronary syndrome	0 (0)	0 (0)
Hypertension	0 (0)	0 (0)
Hypotension	31 (18.2)	31 (17.9)
Hypoxemia requiring supplemental oxygen	8 (4.71)	8 (4.62)
Acute respiratory distress syndrome	15 (8.82)	20 (11.6)
Receipt of non-invasive ventilation	26 (15.3)	27 (15.6)
Receipt of invasive ventilation	39 (22.9)	38 (22.0)
Receipt of extracorporeal membrane oxygenation (ECMO)	2 (1.18)	3 (1.73)
Elevation of aspartate aminotransferase (AST)	0 (0)	5 (2.89)
Elevation of alanine aminotransferase (ALT)	5 (2.94)	5 (2.89)
Acute pancreatitis	0 (0)	1 (0.58)
Acute kidney injury	1 (0.59)	3 (1.73)
Receipt of renal replacement therapy (through day 28 only)	11 (6.47)	12 (6.94)
Symptomatic hypoglycemia	1 (0.59)	0 (0)
Neutropenia	0 (0)	1 (0.58)
Lymphopenia	2 (1.18)	2 (1.16)
Anemia	1 (0.59)	3 (1.73)
Thrombocytopenia	0 (0)	2 (1.16)
Venous thromboembolism	13 (7.65)	13 (7.51)
Severe dermatologic reaction	0 (0)	0 (0)

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eTable 16. PSESEs results in TRV-027 trial

PSESE = protocol-specified exempt serious events, which were systematically collected events captured through day 60

PSESE, no. (%)	TRV-027 (n=145)	Placebo (n=145)
Seizure	2 (1.38)	1 (0.69)
Stroke	0 (0)	0 (0)
Arrythmia (atrial or ventricular)	8 (5.52)	6 (4.14)
Cardiomyopathy	1 (0.69)	0 (0)
Cardiac arrest	7 (4.83)	5 (3.45)
Myocardial injury	0 (0)	2 (1.38)
Acute coronary syndrome	0 (0)	0 (0)
Hypertension	0 (0)	0 (0)
Hypotension	32 (22.1)	25 (17.2)
Hypoxemia requiring supplemental oxygen	4 (2.76)	8 (5.52)
Acute respiratory distress syndrome	14 (9.66)	16 (11.0)
Receipt of non-invasive ventilation	24 (16.6)	21 (14.5)
Receipt of invasive ventilation	38 (26.2)	31 (21.4)
Receipt of extracorporeal membrane oxygenation (ECMO)	3 (2.07)	3 (2.07)
Elevation of aspartate aminotransferase (AST)	5 (3.45)	5 (3.45)
Elevation of alanine aminotransferase (ALT)	7 (4.83)	5 (3.45)
Acute pancreatitis	1 (0.69)	1 (0.69)
Acute kidney injury	4 (2.76)	3 (2.07)
Receipt of renal replacement therapy (through day 28 only)	9 (6.21)	11 (7.59)
Symptomatic hypoglycemia	1 (0.69)	0 (0)
Neutropenia	0 (0)	1 (0.69)
Lymphopenia	5 (3.45)	2 (1.38)
Anemia	4 (2.76)	3 (2.07)
Thrombocytopenia	5 (3.45)	3 (2.07)
Venous thromboembolism	5 (3.45)	12 (8.28)
Severe dermatologic reaction	0 (0)	0 (0)

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eTable 17. Adverse events (AEs) in TXA-127 trial

The trial protocol instructed investigators to record adverse events (AEs) that met any of the following criteria: (1) serious and definitely or possibly related (regardless of PSESE status); (2) unexpected and definitely or possibly related (regardless of PSESE status); (3) serious and not a PSESE; (4) definitely or possibly related or of uncertain relationship and not a PSESE; (4) severity grade 3 or 4 clinical adverse event and not a PSESE.

A serious adverse event (SAE) was defined as an adverse event leading to death, a life-threatening experience, prolongation of inpatient hospitalization or re-hospitalization, or persistent or significant disability or incapacity.

Site investigators reported the suspected relatedness of each adverse event to study procedures using the following 5 options: definitely related; probably related; possibly related; probably not related; definitely not related; uncertain relationship.

In the TXA-127 active agent group, 41 total adverse events were reported. In the placebo group of the TXA-127 trial, 34 total adverse events were reported.

Patients with Adverse Events (AEs) in the TXA-127 trial intention-to-treat population.		
	TXA-127 (n=177)	**Placebo (n=174)**
Grade 1: patients with ≥1 grade 1 AE, no. (%)	4 (2.3)	1 (0.6)
Grade 2: patients with ≥1 grade 2 AE, no. (%)	5 (2.8)	3 (1.7)
Grade 3: patients with ≥1 grade 3 AE, no. (%)	13 (7.3)	11 (6.3)
Grade 4: patients with ≥1 grade 4 AE, no. (%)	3 (1.7)	5 (2.9)
Grade 5: patients with ≥1 grade 5 AE, no. (%)	3 (1.7)	3 (1.7)
Serious AE: patients with ≥1 SAE, no. (%)	7 (4.0)	10 (5.7)

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eTable 18. Adverse events (AEs) in TRV-027 trial

The trial protocol instructed investigators to record adverse events (AEs) that met any of the following criteria: (1) serious and definitely or possibly related (regardless of PSESE status); (2) unexpected and definitely or possibly related (regardless of PSESE status); (3) serious and not a PSESE; (4) definitely or possibly related or of uncertain relationship and not a PSESE; (4) severity grade 3 or 4 clinical adverse event and not a PSESE.

A serious adverse event (SAE) was defined as an adverse event leading to death, a life-threatening experience, prolongation of inpatient hospitalization or re-hospitalization, or persistent or significant disability or incapacity.

Site investigators reported the suspected relatedness of each adverse event to study procedures using the following 5 options: definitely related; probably related; possibly related; probably not related; definitely not related; uncertain relationship.

In the TRV-027 active agent group, 30 total adverse events were reported. In the placebo group of the TRV-027 trial, 22 total adverse events were reported.

Patients with Adverse Events (AEs) in the TRV-027 trial intention-to-treat population.		
	TRV-027 (n=149)	**Placebo (n=146)**
Grade 1: patients with ≥1 grade 1 AE, no. (%)	2 (1.3)	1 (0.7)
Grade 2: patients with ≥1 grade 2 AE, no. (%)	1 (0.7)	3 (2.1)
Grade 3: patients with ≥1 grade 3 AE, no. (%)	7 (4.7)	8 (5.5)
Grade 4: patients with ≥1 grade 4 AE, no. (%)	11 (7.4)	4 (2.7)
Grade 5: patients with ≥1 grade 5 AE, no. (%)	5 (3.4)	2 (1.4)
Serious AE: patients with ≥1 SAE, no. (%)	12 (8.1)	8 (5.5)

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