Supplementary material

Szarpak Ł, Dzieciątkowski T, Jaguszewski MJ, et al. Is remdesivir important in clinical practice as a treatment of COVID-19? A study based on meta-analysis data. Pol Arch Intern Med. 2021; 131: 96-97. doi:10.20452/pamw.15686

REMDESIVIR AS A TREATMENT AGAINST COVID-19: A STUDY BASED ON META-ANALYSIS DATA

Supplementary Digital File

Characteristics of a meta-analysis conducting process

This trial was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.

Search strategy

A comprehensive literature search was performed with PubMed/Medline, Scopus, EMBASE, Web of Science, and Cochrane Central Register and Controlled Trials (CENTRAL) databases, from the inception of each database up to September 20, 2020. The following terms were used: “Remdesivir” OR “Veklury” OR “antiviral” AND “coronavirus” OR “2019 novel coronavirus disease” OR “COVID19” OR “COVID-19” OR “corona virus” OR “SARS-CoV-2” OR “2019 novel coronavirus infection”. The electronic database search was supplemented by searching Google Scholar and by back searching the reference lists of identified studies for suitable articles.

Selection criteria/eligibility

The references retrieved by electronic search were imported to and managed by EndNote X7 software. Two independent investigators (L.S. and K.J.F.) screened both the titles and abstracts to exclude non-permanent studies. Discrepancies were resolved by a third author (T.D.). Relevant full text articles were retrieved and analyzed for eligibility with the application of pre-defined inclusion criteria.

Data extraction

Two reviewers (L.S. and K.J.F.) reviewed the full text of the selected papers and extracted data in standardized and independent forms. The following items were extracted: author, year, study design, location, sample size, gender, intervention and control group treatment, inclusion and exclusion criteria. If the reported data is insufficient or ambiguous, we will contact the corresponding author for complete information. If we are unable to get in touch with the author, we will exclude the study because of missing important information.

Quality assessment

The methodological quality of the included RCTs was assessed by using the “risk of bias” tool in accordance with the Review Manager software, version 5.4 (RevMan; Cochrane Collaboration, Oxford, UK). The following domains were evaluated for RCTs: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. To assess the risk of bias, we only relied on the information presented in the publications. Two authors (L.S. and J.R.L) estimated the risk of bias in each domain as “yes”, “no”, or “unclear”, which reflected a high, low, and uncertain risk of bias, respectively.

Statistical analysis

The meta-analysis was carried out with the Review Manager (RevMan) software for Mac (version 5.3, Cochrane Collaboration, Oxford, UK). We used Mantel-Haenszel models for all dichotomous outcomes and the inverse-variance method for continuous outcomes. For continuous measures (procedure time), we calculated the mean differences (MD). A random effect model was applied to analyze the data. Results are presented as risk ratios (RR) with

95% confidence intervals (CI) for dichotomous measures. When the continuous outcome was reported in a study as median, range, and interquartile range, we estimated means and standard deviations using the formula described by Hozo et al. We quantified heterogeneity in each analysis by the tau-squared and I-squared statistics. Heterogeneity was detected with the chi-squared test with n – 1 degrees of freedom, which was expressed as I^2. Values of I^2 > 50% and > 75% were considered to indicate moderate and significant heterogeneity among studies, respectively [13]. All p-values were two-tailed and considered statistically significant if $p < 0.05$.

Comparison Remdesivir group vs. Placebo group

Characteristics of included studies

Study	Country	Study design	Intervention	Control	Remdesivir group			Non-Remdesivir group		
					No.	Age	Sex, male	No.	Age	Sex, male
Beigel et al. 2020	Multi-country	Double-blinded multicenter RCT	Intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death.	The same volume of placebo infusions.	541	58.6 (14.6)	352 (65.1)	522	59.2 (15.4)	332 (63.6)
Spinner et al. 2020	Multi-country	Open-label multicenter RCT	Remdesivir was dosed intravenously at 200 mg on day 1 followed by 100 mg/d.	Standard care.	384	56.6 (6.4)	232 (60.4)	200	56.3 (3.5)	125 (62.5)
Wang et al. 2020	China	Double-blinded multicenter RCT	Remdesivir was dosed intravenously at 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions	The same volume of placebo infusions.	158	65.5 (2.7)	89 (56.3)	78	62.8 (2.8)	51 (65.4)

Summary of inclusion and exclusion criteria of included studies

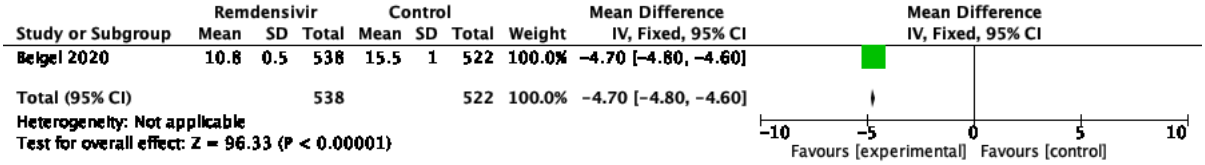
Study	Inclusion criteria	Exclusion criteria	Primary outcome
Beigel et al. 2020	Adults hospitalized with Covid-19	Ineligible owing to meeting exclusion criteria or not meeting inclusion criteria.	Time to recovery, defined as the first day, during the 28 days after enrollment, on which a patient satisfied categories 1, 2, or 3 on the eight-cate- gory ordinal scale.
Spinner et al. 2020	SARS-CoV-2 infection confirmed by polymerase chain reaction assay within 4 days of randomization and moderate COVID-19 pneumonia (defined as any radiographic evidence of pulmonary infiltrates and oxygen saturation >94% on room air)	Patients with alanine aminotransferase or aspartate amino- transferase greater than 5 times the upper limit of normal or creatinine clearance of less than 50 mL/min.	The distribution of clinical status assessed on the 7-point ordinal scale on study day 11.
Wang et al. 2020	Men and non-pregnant women with COVID-19 who were aged at least 18 years and were RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had oxygen saturation of 94% or lower on room air or a ratio of arterial oxy- gen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and were within 12 days of symptom onset.	Pregnancy or breast feeding; hepatic cirrhosis; alanine aminotransferase or aspartate amino- transferase more than five times the upper limit of normal; known severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1·73 m^2) or receipt of continuous renal replacement therapy, hemodialysis, or peritoneal dialysis; possibility of transfer to a non-study hospital within 72 h; and enrolment into an investigational treatment study for COVID-19 in the 30 days before screening.	Time to clinical improvement within 28 days after randomization.

Characteristic of patient's treatment

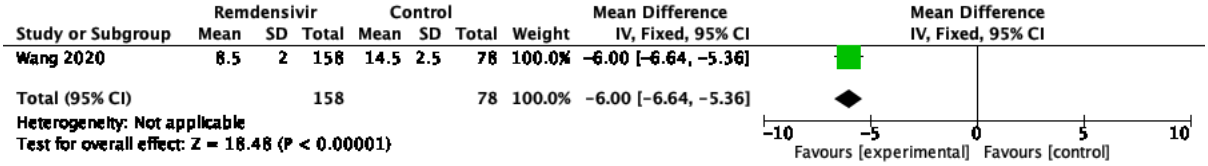
Parameter	No. of studies	Remdesivir group	Control group	OR (95%CI)	p-value	I^2 statistic
Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care	3	390/1083 (36.0)	223/800 (27.9)	1.12 (0.85, 1.49)	0.42	50%
Hospitalized, requiring supplemental oxygen	3	403/1083 (37.2)	300/800 (37.5)	1.01 (0.82, 1.25)	0.92	35%
Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	3	129/1083 (11.9)	110/800 (13.8)	1,01 (0.76, 1.35)	0.92	0%
Hospitalized, receiving invasive mechanical ventilation or ECMO	2	125/699 (17.9)	148/600 (24.7)	0.76 (0.57, 1.00)	0.05	0%

Outcomes

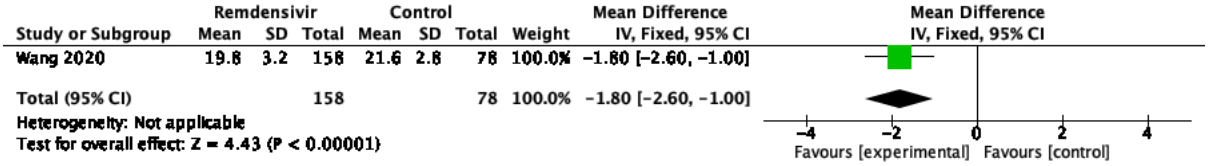
Time to recovery (days)



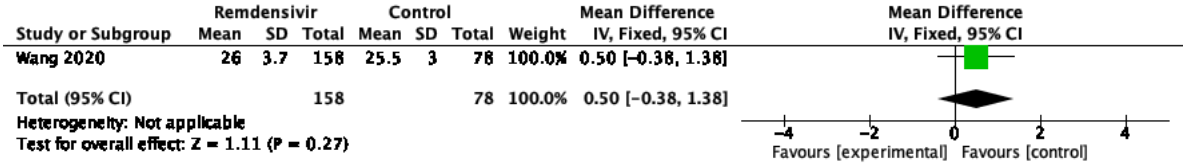
Duration of invasive mechanical ventilation, days



Duration of oxygen support, days



Duration of hospital stay, days



Parameter	No. of studies	Remdesivir group	Control group	OR (95%CI)	p-value	I^2 statistic
No. of recoveries	1	334/538 (62.1)	273/521 (52.4)	1.49 (1.16, 1.90)	0.001	NA
Mortality						
Day 7	1	10/154 (6.5)	4/77 (5.2)	1.27 (0.38, 4.18)	0.70	NA
Day 14	3	50/542 (9.2)	65/799 (8.1)	0.61 (0.41, 0.89)	0.01	4%
Day 28	2	27/542 (5.0)	14/278 (5.0)	0.96 (0.48, 1.90)	0.90	0%
Six-category scale at day 14						
1—discharge (alive)	2	55/537 (10.2)	29/278 (10.4)	0.97 (0.59, 1.59)	0.90	0%
2—hospital admission, not requiring supplemental oxygen	2	80/537 (14.9)	44/278 (15.8)	0.93 (0.62, 1.39)	0.73	0%
3—hospital	2	70/537	36/278	0.99 (0.61, 1.61)	0.98	37%

admission, requiring supplemental oxygen		(13.0)	(12.9)			
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	2	17/537 (3.2)	12/278 (4.3)	0.71 (0.33, 1.53)	0.38	0%
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	2	5/537 (0.6)	12/278 (4.3)	0.20 (0.07, 0.58)	0.003	0%
6—death	2	18/537 (3.4)	11/278 (3.9)	0.83 (0.38, 1.80)	0.63	25%
Six-category scale at day 28						
1—discharge (alive)	2	101/534 (18.9)	49/277 (17.7)	1.14 (0.69, 1.89)	0.62	0%
2—hospital admission, not requiring supplemental oxygen	2	33/534 (6.2)	21/277 (7.6)	0.80 (0.46, 1.41)	0.45	69%
3—hospital admission, requiring supplemental oxygen	2	22/534 (4.1)	18/277 (6.5)	0.59 (0.30, 1.15)	0.12	0%
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	2	4/534 (0.7)	2/277 (0.7)	0.93 (0.20, 3.30)	0.93	0%
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	2	3/534 (0.6)	7/277 (2.5)	0.22 (0.06, 0.84)	0.03	0%
6—death	2	27/534 (5.1)	14/277 (5.1)	0.99 (0.50, 1.97)	0.98	0%

Adverse events

Parameter	No. of studies	Remdesivir group	Control group	OR (95%CI)	p-value	I^2 statistic
ADVERSE EVENTS						
Any	2	313/539 (58.0)	143/278 (51.4)	1.31 (0.98, 1.75)	0.07	0%
Hypoalbuminemia	1	20/155 (12.9)	12/78 (15.4)	0.81 (0.38, 1.77)	0.60	NA
Hypokalemia	1	41/539 (7.6)	15/278 (5.4)	1.44 (0.78, 2.67)	0.24	75%
Increased blood glucose	1	11/155 (7.1)	6/78 (7.7)	0.92 (0.33, 2.58)	0.87	NA
Anemia	1	18/155 (11.6)	12/78 (15.4)	0.72 (0.33, 1.59)	0.42	NA
Rash	1	11/155 (7.1)	2/78 (2.6)	2.90 (0.63, 13.43)	0.17	NA
Thrombocytopenia	1	16/155 (10.3)	5/78 (6.4)	1.68 (0.59, 4.77)	0.33	NA
Increased blood bilirubin	1	15/155 (9.7)	7/78 (9.0)	1.09 (0.42, 2.79)	0.86	NA
Increased blood lipids	1	10/155 (6.5)	8/78 (10.3)	0.60 (0.23, 1.60)	0.31	NA
Increased white blood cell count	1	11/155 (7.1)	6/78 (7.7)	0.92 (0.33, 2.58)	0.87	NA
Hyperlipidemia	1	10/155 (6.5)	8/78 (10.3)	0.60 (0.23, 1.60)	0.31	NA
Increased blood urea nitrogen	1	10/155 (6.5)	5/78 (6.4)	1.01 (0.33, 3.05)	0.99	NA
Increased neutrophil	1	10/155 (6.5)	4/78 (5.1)	1.28 (0.39, 4.21)	0.69	NA
Aspartate aminotransferase increased	2	119/507 (23.5)	69/260 (26.5)	0.85 (0.59, 1.21)	0.36	66%
Constipation	1	21/155 (13.5)	12/78 (15.4)	0.86 (0.40, 1.86)	0.70	NA
Nausea	2	45/539 (8.3)	8/278 (2.9)	3.09 (1.43, 6.64)	0.004	0%
Diarrhea	2	27/539 (5.0)	16/278 (5.8)	0.87 (0.46, 1.64)	0.66	0%
Vomiting	1	4/155 (2.6)	2/78 (2.6)	1.01 (0.18, 5.62)	0.99	NA
Reduced serum sodium	1	4/155 (2.6)	2/78 (2.6)	1.01 (0.18, 5.62)	0.99	NA
Increased serum potassium	1	4/155 (2.6)	1/78 (1.3)	2.04 (0.22, 18.56)	0.53	NA
Headache	1	20/384 (5.2)	5/200 (2.5)	2.14 (0.79, 5.80)	0.13	NA
SERIOUS ADVERESE EVENTS						
Any	2	47/539 (7.4)	38/278 (13.7)	0.58 (0.36, 0.93)	0.02	0%
Respiratory distress	1	16/155 (10.3)	6/78 (7.7)	1.38 (0.52, 3.68)	0.52	NA
Cardiopulmonary failure	1	8/155 (5.2)	7/78 (9.0)	0.55 (0.19, 1.58)	0.27	NA

Pulmonary embolism	1	1/155 (0.6)	1/78 (1.3)	0.50 (0.03, 8.10)	0.63	NA
Recurrence of COVID-19	1	1/155 (0.6)	0/78 (0.0)	1.52 (0.06, 37.85)	0.80	NA
Cardiac arrest	1	1/155 (0.6)	0/78 (0.0)	1.52 (0.06, 37.85)	0.80	NA
Acute coronary syndrome	1	0/155 (0.6)	1/78 (1.3)	0.17 (0.01, 4.13)	0.27	NA
Tachycardia	1	0/155 (0.0)	1/78 (1.3)	0.17 (0.01, 4.13)	0.27	NA
Septic shock	1	1/155 (0.6)	1/78 (1.3)	0.50 (0.03, 8.10)	0.63	NA
Lung abscess	1	0/155 (0.0)	1/78 (1.3)	0.17 (0.01, 4.13)	0.27	NA
Sepsis	1	0/155 (0.0)	1/78 (1.3)	0.17 (0.01, 4.13)	0.27	NA
Bronchitis	1	0/155 (0.0)	1/78 (1.3)	0.17 (0.01, 4.13)	0.27	NA
Thrombocytopenia	1	1/155 (0.6)	0/78 (0.0)	1.52 (0.06, 37.85)	0.80	NA
Increased D-dimer	1	0/155 (0.0)	1/78 (1.3)	0.17 (0.01, 4.13)	0.27	NA
Hemorrhage of lower digestive tract	1	1/155 (0.6)	0/78 (0.0)	1.52 (0.06, 37.85)	0.80	NA
Ileus	1	0/155 (0.0)	1/78 (1.3)	0.17 (0.01, 4.13)	0.27	NA
Deep vein thrombosis	1	1/155 (0.6)	1/78 (1.3)	0.50 (0.03, 8.10)	0.63	NA
Acute kidney injury	1	1/155 (0.6)	0/78 (0.0)	1.52 (0.06, 37.85)	0.80	NA
Diabetic ketoacidosis	1	0/155 (0.0)	1/78 (1.3)	0.17 (0.01, 4.13)	0.27	NA
Multiple organ dysfunction syndrome	1	1/155 (0.6)	2/78 (2.6)	0.25 (0.02, 2.76)	0.26	NA
EVENTS LEADING TO DRUG DISCONTINUATION						
Any	2	30/539 (5.7)	3/78 (3.8)	3.28 (0.94, 11.51)	0.06	0%
Respiratory distress	1	7/155 (4.5)	1/78 (1.3)	3.64 (0.44, 30.14)	0.23	NA
Secondary infection	1	4/155 (2.6)	7/78 (9.0)	0.27 (0.08, 0.95)	0.04	NA
Cardiopulmonary failure	1	3/155 (1.9)	1/78 (1.3)	1.52 (0.16, 14.85)	0.72	NA
Nausea	1	1/155 (0.6)	0/78 (0.0)	1.52 (0.06, 37.85)	0.80	NA
Vomiting	1	1/155 (0.6)	0/78 (0.0)	1.52 (0.06, 37.85)	0.80	NA
Ileus	1	0/155 (0.0)	1/78 (1.3)	0.17 (0.01, 4.13)	0.27	NA
Increased alanine aminotransferase	1	2/155 (1.3)	0/78 (0.0)	2.56 (0.12, 53.91)	0.55	NA
Rash	1	2/155 (1.3)	0/78 (0.0)	2.56 (0.12, 53.91)	0.55	NA
Poor apetite	1	1/155	0/78	1.52 (0.06, 37.85)	0.80	NA

		(0.6)	(0.0)			
Increase total bilirubin	1	1/155 (0.6)	0/78 (0.0)	1.52 (0.06, 37.85)	0.80	NA
Acute kidney injury	1	1/155 (0.6)	0/78 (0.0)	1.52 (0.06, 37.85)	0.80	NA
Seizure	1	0/155 (0.0)	1/78 (1.3)	0.17 (0.01, 4.13)	0.27	NA
Aggravated schizophrenia	1	0/155 (0.0)	1/78 (1.3)	0.17 (0.01, 4.13)	0.27	NA
Aggravated depression	1	0/155 (0.0)	1/78 (1.3)	0.17 (0.01, 4.13)	0.27	NA

NA = Not applicable

Comparison Remdesivir 5-days vs. 10-days therapy

Characteristics of included studies

Study	Country	Study design	Intervention	Control	5-days Remdesivir group			10 days - Remdesivir group		
					No.	Age	Sex, male	No.	Age	Sex, male
Goldman et al. 2020	Multi-country	Open-label multicenter RCT	5-days treatment with Remdesivir	10-days treatment with Remdesivir	200	61(50-69)	120 (60.0)	197	62 (50-71)	133 (67.5)
Spinner et al. 2020	Multi-country	Open-label multicenter RCT	5-days treatment with Remdesivir	10-days treatment with Remdesivir	191	58 (48-66)	114 (59.7)	193	57 (45-66)	125 (62.5)

Summary of inclusion and exclusion criteria of included studies

Study	Inclusion criteria	Exclusion criteria	Primary outcome
Goldman et al. 2020	Hospitalized patients who were at least 12 years of age who had SARS-CoV-2 infection confirmed by polymerase-chain-reaction as- say within 4 days before randomization	Patients who were receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening were excluded, as were patients with signs of multiorgan failure. Exclusion criteria included alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 5 times the upper limit of the normal range or estimated creatinine clearance of less than 50 ml per minute (by the Cockcroft–Gault formula). Patients receiving concurrent treatment (within 24 hours before the start of trial treatment) with other agents with putative activity against Covid-19 were excluded.	Clinical status assessed on day 14 on a 7-point ordinal scale consisting of the following categories: 1, death; 2, hospitalized, receiving invasive mechanical ventilation or ECMO; 3, hospitalized, receiving noninvasive ventilation or high-f low oxygen devices; 4, hospitalized, requiring low-flow supplemental oxygen; 5, hospitalized, not requiring supple- mental oxygen but receiving ongoing medical care (related or not related to Covid-19); 6, hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for remdesivir administration); and 7, not hospitalized
Spinner et al. 2020	SARS-CoV-2 infection confirmed by polymerase chain reaction assay within 4 days of randomization and moderate COVID-19 pneumonia (defined as any radiographic evidence of pulmonary infiltrates and oxygen saturation >94% on room air)	Patients with alanine aminotransferase or aspartate amino- transferase greater than 5 times the upper limit of normal or creatinine clearance of less than 50 mL/min.	The distribution of clinical status assessed on the 7-point ordinal scale on study day 11.

Patient's clinical status at day 14

Parameter	No. of studies	5 days group	10 days group	OR (95%CI)	p-value	I^2 statistic
Clinical status at day 14						
Death	2	17/391 (4.3)	23/390 (5.9)	0.71 (0.37, 1.36)	0.30	0%
Hospitalized, on intensive mechanical ventilation or ECMO	2	16/391 (4.1)	34/390 (8.7)	0.43 (0.23, 0.80)	0.007	0%
Hospitalized, on noninvasive ventilation or high-flow oxygen devices	2	13/391 (3.3)	10/390 (2.6)	1.29 (0.56, 2.92)	0.55	58%
Hospitalized, requiring low-flow supplemental oxygen	2	24/391 (6.1)	18/390 (4.6)	1.35 (0.72, 2.54)	0.35	0%
Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care	2	39/391 (10.0)	44/390 (11.3)	0.87 (0.55, 1.39)	0.57	0%
Hospitalized, not requiring supplemental oxygen or medical care	2	16/391 (4.1)	12/390 (3.1)	1.35 (0.63, 2.89)	0.44	62%
Not hospitalized	2	266/391 (68.0)	249/390 (63.8)	1.22 (0.90, 1.65)	0.19	0%

Adverse events

Parameter	No. of studies	5 days group	10 days group	OR (95%CI)	p-value	I^2 statistic
Adverse events						
Any	2	239/391 (61.1)	258/390 (66.2)	0.79 (0.59, 1.07)	0.13	0%
Nausea	2	39/391 (10.0)	35/390 (9.0)	1.12 (0.70, 1.82)	0.63	0%
Acute respiratory failure	1	12/200 (6.0)	21/197 (10.7)	0.53 (0.26, 1.12)	0.10	NA
Alanine aminotransferase increased	1	11/200 (5.5)	15/197 (7.6)	0.71 (0.32, 1.58)	0.40	NA
Constipation	1	13/200 (6.5)	13/197 (6.6)	0.98 (0.44, 2.18)	0.97	NA
Aspirate aminotransferase increased	1	10/200 (5.0)	13/197 (6.6)	0.74 (0.32, 1.74)	0.50	NA
Hypokalemia	2	20/391 (5.1)	25/390 (6.4)	0.79 (0.43, 1.44)	0.44	0%
Hypotension	1	9/200 (4.5)	12/197 (6.1)	0.73 (0.30, 1.76)	0.48	NA
Respiratory failure	1	7/200 (3.5)	14/197 (7.1)	0.47 (0.19, 1.20)	0.12	NA
Insomia	1	10/200 (5.0)	11/197 (5.6)	0.89 (0.37, 2.15)	0.80	NA
Acute kidney injury	1	4/200 (2.0)	15/197 (7.6)	0.25 (0.08, 0.76)	0.01	NA
Diarrhea	1	12/191 (6.3)	10/193 (5.2)	1.23 (0.52, 2.91)	0.64	NA
Headache	1	10/191 (5.3)	10/193 (5.2)	1.01 (0.41, 2.49)	0.98	NA
Serious adverse events						
Any	2	51/391 (13.0)	78/390 (20.0)	0.56 (0.38, 0.84)	0.005	20%
Acute respiratory failure	1	10/200 (5.0)	18/197 (9.1)	0.52 (0.24, 1.16)	0.11	NA
Respiratory failure	1	5/200 (2.5)	10/197 (5.1)	0.48 (0.16, 1.43)	0.19	NA
Septic shock	1	2/200 (1.0)	5/197 (2.5)	0.39 (0.07, 2.02)	0.26	NA
ARDS	1	1/200 (0.5)	5/197 (2.5)	0.19 (0.02, 1.67)	0.13	NA
Hypoxia	1	2/200 (1.0)	4/197 (2.0)	0.49 (0.09, 2.69)	0.41	NA
Respiratory distress	1	3/200 (1.5)	4/197 (2.0)	0.73 (0.16, 3.33)	0.69	NA
Dyspnea	1	4/200 (2.0)	1/197 (0.5)	4.00 (0.44,36.11)	0.22	NA
Pneumothorax	1	2/200 (1.0)	3/197 (1.5)	0.65 (0.11, 3.95)	0.64	NA
Viral pneumonia	1	3/200 (1.5)	2/197 (1.0)	1.48 (0.25, 8.98)	0.67	NA
Aminotransferease	1	3/200	2/197	1.48 (0.25, 8.98)	0.67	NA

levels increased		(1.5)	(1.0)			
Adverse event leading to discontinuation of treatment						
Adverse event leading to discontinuation of treatment	2	13/391 (3.3)	28/390 (7.2)	0.44 (0.22, 0.86)	0.02	0%