Supplementary Material*

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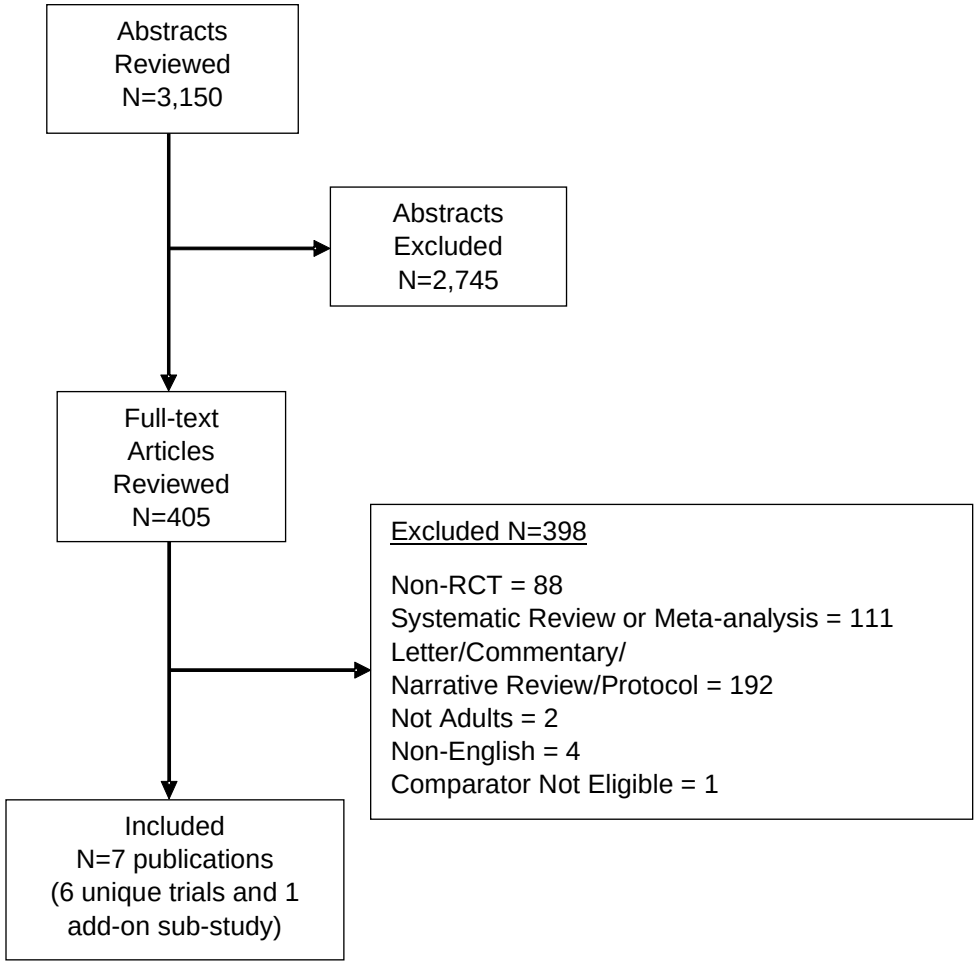
* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

Supplement Figure. Literature Flow Diagram



Supplement Table 1. Study Characteristics of the Included Trials

Author, Year Country **Funding** **Risk of Bias**	**Intervention** **Comparator** **Inclusion/exclusion criteria** **Study Period/Length of Follow-up**	**Demographics**
Beigel 2020 (1) Adaptive Covid-19 Treatment Trial (ACTT-1) Multinational (60 sites and 13 subsites, 45 in the US) Design: RCT Funding: Primarily government, other Risk of Bias: Low	Intervention: Remdesivir (n=541) 200 mg on day 1 followed by 100 mg on days 2–10 (or until hospital discharge or death) in single daily infusions Comparator: Placebo (n=521) Inclusion criteria: 18 years or older and meeting one of the following criteria suggestive of lower respiratory tract infection at enrollment: radiographic infiltrates by imaging study, peripheral oxygen saturation (SpO2) ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or ECMO; no limit to duration of symptoms prior to enrollment; laboratory-confirmed SARS-CoV-2 infection as determined by a positive RT-PCR assay result from any respiratory specimen collected <72 hours prior to randomization (during the study, this criterion was modified due to limitations in testing capacity to also allow a RT-PCR positive specimen that was collected ≥72 hours prior to randomization if the site was unable to obtain a repeat sample and if the participant had progressive disease consistent with ongoing SARS-CoV-2 infection) Exclusion criteria: ALT or AST >5 times the upper limit of the normal range, impaired renal function as determined by calculating an eGFR or need for hemodialysis or hemofiltration, allergy to study product, pregnancy or breast-feeding, and anticipated discharge from hospital or transfer to another hospital within 72 hours of enrollment **Study Period/Length of Follow-up:** 29 days	N=1062 **Age (years, mean):** 59 **Gender (male):** 64% **Race/Ethnicity:** White 53% Black/African American 21% Asian 13% Latino (of any race) 23% **Time from symptom onset to randomization** Overall, median [IQR] 9 days [6-12] Remdesivir median [IQR] 9 days [6-12] Placebo median [IQR] 9 days [7-13] **Oxygen status on admission:** Percent on no oxygen 13% Percent on supplemental oxygen 41% Percent on non-invasive ventilation 18% Percent on invasive ventilation 27%
Wang 2020 (2) China Design: RCT Funding: Government, other	Intervention: Remdesivir (n=158; 2:1 ratio) 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions Comparator: Placebo (n=79)	N=237 **Age (years, median):** Remdesivir 66 Placebo 64 **Gender (male):** Remdesivir 56%

Author, Year Country **Funding** **Risk of Bias**	**Intervention** **Comparator** **Inclusion/exclusion criteria** **Study Period/Length of Follow-up**	**Demographics**
Risk of Bias: Low	Inclusion criteria: men and non-pregnant women with COVID-19, age at least 18 years, RT-PCR positive for SARS-CoV-2, pneumonia confirmed by chest imaging, oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, within 12 days of symptom onset Exclusion criteria: pregnancy or breast feeding; hepatic cirrhosis; ALT or AST >5 times the upper limit of the normal range; known severe renal impairment (estimated eGFR<30 mL/min per 1·73 m^2) or receipt of continuous renal replacement therapy, hemodialysis, or peritoneal dialysis; enrolment into an investigational treatment study for COVID-19 in the 30 days before screening **Study Period/Length of Follow-up:** 28 days	Placebo 65% **Race:** East Asian **Time from symptom onset to drug** Remdesivir median [IQR] 11 days [9-12] Placebo median [IQR] 10 days [9-12] **Oxygen status on admission:** Percent on no oxygen Remdesivir 0% Placebo 4% Percent on supplemental O_2 Remdesivir 82% Placebo 83% Percent on non-invasive ventilation Remdesivir 18% Placebo 12% Percent on invasive ventilation Remdesivir 0% Placebo 1%
Goldman 2020 (3) GS-US-540-5773 SIMPLE 1 55 hospitals around the world, including sites in the US, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan. Design: Randomized, open-label, multi-center Phase 3 clinical trial Funding: Industry Risk of Bias: Moderate	Intervention 1: Remdesivir, 5-day course (n=200) 200 mg on day 1 followed by 100 mg on days 2–5 in single daily infusions Intervention 2: Remdesivir, 10-day course (n=197) 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions Inclusion criteria: patients ≥ 18 years (at all sites), or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law) currently hospitalized with SARS-CoV-2 infection confirmed by PCR test ≤ 4 days before randomization; radiographic evidence of pulmonary infiltrates and peripheral capillary oxygen saturation (SpO2) ≤ 94% or requiring supplemental oxygen at screening	N=397 **Age (years, median):** 5-day group 61 10-day group 62 **Gender (male):** 5-day group 60% 10-day group 68% **Race:** White 70% Black 11% Asian 11% Other 7% **Time from symptom onset to drug**

Author, Year Country Funding Risk of Bias	Intervention Comparator Inclusion/exclusion criteria Study Period/Length of Follow-up	Demographics
	Exclusion criteria: Pregnant or women who were breast feeding infants, ALT or AST >5 times the upper limit of the normal range, creatinine clearance < 50 mL/min using the Cockcroft-Gault formula for participants ≥ 18 years of age and Schwartz Formula for participants < 18 years of age; mechanically ventilated (including V-V ECMO) ≥ 5 days, or any duration of V-A ECMO; evidence of multiorgan failure; concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 < 24 hours prior to study drug dosing; participant in any other clinical trial of an experimental treatment for COVID-19 **Study Period/Length of Follow-up:** 14 days (up to 30 days for adverse events)	Remdesivir 5-day median [IQR] 8 days [5-11] Remdesivir 10-day median [IQR] 9 days [6-12] **Oxygen status on admission:** Percent on no oxygen 14% Percent on supplemental oxygen 55% Percent on non-invasive ventilation 27% Percent on invasive ventilation 4%
Spinner 2020 (4) GS-US-540-5774 SIMPLE 2 105 sites in the US, France, Germany, Hong Kong, Italy, Republic of Korea, The Netherlands, Singapore, Spain, Switzerland, Taiwan and the United Kingdom Design: Randomized, open-label, multi-center Phase 3 clinical trial Funding: Industry Risk of Bias: Low	Intervention 1: Remdesivir, 5-day course (n=199) 200 mg on day 1 followed by 100 mg on days 2–5 in single daily infusions Intervention 2: Remdesivir, 10-day course (n=197) 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions Comparator: Standard care (n=200) Inclusion criteria: ≥ 18 years (at all sites), or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law and approved by relevant review boards) currently hospitalized and requiring medical care for COVID-19; SARS-CoV-2 infection confirmed by PCR test ≤ 4 days before randomization; moderate COVID-19 pneumonia (peripheral capillary oxygen saturation (SpO_2) >94% on room air radiographic evidence of pulmonary infiltrates) Exclusion criteria: Women who were pregnant or breast feeding infants, ALT or AST >5 times the upper limit of the normal range; creatinine clearance < 50 mL/min using the Cockcroft-Gault formula for participants ≥ 18 years of age and Schwartz Formula for participants < 18 years of age; mechanically ventilated at screening; concurrent treatment or planned concurrent treatment	**N=596 randomized (584 analyzed)** **Age (years, median):** 5-day group 58 10-day group 56 Standard care 57 **Gender (male):** 61% **Race:** White 58% Black 18% Asian 18% Other 7% Latino (of any race) 18% **Time from symptom onset to drug** Remdesivir 5-day median [IQR] 8 days [5-11] Remdesivir 10-day median [IQR] 8 days [5-11] **Oxygen status on admission:** Percent on no oxygen: 84% Percent on supplemental oxygen: 15% Percent on non-invasive ventilation: NA Percent on invasive ventilation: NA

Author, Year Country Funding Risk of Bias	Intervention Comparator Inclusion/exclusion criteria Study Period/Length of Follow-up	Demographics
	with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2; participation in any other clinical trial of an experimental treatment for COVID-19 **Study Period/Length of Follow-up:** 11 days (primary outcome); final assessment on day 28	
WHO Solidarity 2020 (5) 30 countries: Europe (13), Canada, Latin America (5), Asia (9), Africa (2) Design: Open-label randomized trial Funding: No funders for main Solidarity trial Risk of Bias: Moderate	Intervention: Remdesivir, intravenous, (n=2750), 200 mg on day 0 followed by 100 mg on days 1-9 (treatment stopped at discharge or death) Comparator: No study drug (local standard of care) (n=2725) Inclusion criteria: ≥ 18 years, hospitalized with a diagnosis of COVID-19, not known to have received any study drug, without anticipated transfer elsewhere within 72 hours, no contraindication to any study drug (physician's view) Exclusion criteria: none reported **Study Period/Length of Follow-up:** 28 days (Note: mortality only during initial hospitalization; follow-up ceased at discharge)	**N=5475 randomized (5451 analyzed)** **Age (years):** <50: 35% 50-69: 47% 70+: 18% **Gender (male):** 63% **Race: NR** **Geographic Location** Europe or Canada: 26% Latin America: 18% Asia or Africa: 56% **Time from symptom onset to drug: NR** **Oxygen status on admission:** Percent on no oxygen: 24% Percent on oxygen: 67% Percent on ventilation: 9%
NOR-Solidarity 2021 (6) * ***Sub-study of WHO Solidarity*** ***Norway*** ***Design: Open-label randomized trial*** ***Funding: National Clinical Therapy Research in the Specialist Health Services, Norway***	***Intervention: Remdesivir, intravenous, (n=43), 200 mg on day 0 followed by 100 mg on days 1-9 (treatment stopped at discharge or death)*** ***Comparator: No study drug (local standard of care) (n=58 allocated versus remdesivir, 87 total in full analysis set).*** ***Inclusion criteria: (see WHO Solidarity)*** ***Exclusion criteria: severe comorbid conditions with life expectancy <3 months, level of aspartate***	***N=101 randomized (83 completed 3-month follow-up).*** ***Age (years): 59*** ***Gender (male): 73%*** ***Race: NR*** ***Time from symptom onset to drug: mean 7 days*** ***Oxygen status on admission: NR*** ***Patients with respiratory failure (Po_2–FIo_2 <40 kPa): 44%***

Author, Year Country Funding Risk of Bias	Intervention Comparator Inclusion/exclusion criteria Study Period/Length of Follow-up	Demographics
	aminotransferase or ALT > 5 times the upper limit of normal, rate-corrected QT interval greater >470 ms, pregnancy, breastfeeding, acute occurrence of a comorbid condition in a 7-day period before inclusion, known intolerance to study drugs, ***participation in a potentially confounding trial, or concomitant medications interfering with the study drugs.***	
Mahajan 2021 (7) India Design: Open-label randomized trial Funding: No funders Risk of Bias: High	Intervention: Remdesivir, intravenous, (n=41) 200 mg on day 1 followed by 100 mg once daily on days 2-5. Both treatment groups continued supportive therapy Comparator: No study drug (local standard of care) (n=41) Inclusion criteria: 18 to 60 years of age hospitalized with a diagnosis of COVID-19 by PCR, radiographic evidence of pneumonia, respiratory rate >24/min, oxygen saturation ≤94%, creatine clearance >40 mL/min Exclusion criteria: receiving mechanical ventilation, multi organ failure, AST/ALT >3 times the upper limit of normal **Study Period/Length of Follow-up:** 24 days or until discharge or death	**N=82 randomized (70 analyzed)** **Age (years):** 58 **Gender (male):** 66% **Race: NR** **Time from symptom onset to drug:** mean 7 days **Oxygen status on admission:** Percent on no oxygen: 0% Percent on low-flow oxygen: 76% Percent on high-flow oxygen /non-invasive ventilation: 24% Percent on invasive mechanical ventilation: 0%

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; IQR = interquartile range; RT-PCR = reverse transcription, polymerase-chain-reaction; SARS-CoV = Severe Acute Respiratory Syndrome Coronavirus-2 infection

* Indicates newly identified sub-study

Supplement Table 2. Summary of Conclusions and Updated Findings for Randomized Trials of Remdesivir

Comparison	Outcome	Conclusions from Last Report Version	New Trial Results/Analyses	Updated Conclusions
Remdesivir 10-day course versus control (placebo or SC) for any severity of COVID-19 4 trials (n=7171 randomized) (1, 2, 4, 5)	Mortality	Remdesivir 10-day course probably results in little to no difference versus control (1, 2, 4, 5) *Subgroup analyses (post-hoc), based on initial respiratory support:* • *Not requiring supplemental O_2;* may result in little to no difference versus control (1, 4, 5) • *Requiring supplemental O_2 but not ventilated;* may result in a moderate reduction versus control (1, 2, 5) • *Requiring ventilation/ECMO*;* may result in a moderate increase versus control (1, 2, 5)	***Results from one small sub-study of WHO Solidarity found 28-day and 60-day mortality did not differ between remdesivir and SC (6) §***	No change in conclusions
	Proportion recovered†	Remdesivir 10-day course probably results in a moderate increase in percent recovered versus control (1, 2, 4)	No new evidence	No change in conclusions
	Proportion with clinical improvement‡	Remdesivir 10-day course may result in a moderate increase in percent with clinical improvement versus control (2, 4)	No new evidence	No change in conclusions
	Hospital length of stay	No pooled analysis	No new evidence	No change in conclusions
	Time to recovery/ Clinical improvement	Remdesivir 10-day course may result in up to a large reduction in median time to recovery or a moderate reduction in time to clinical improvement versus control (1, 2, 4)	No new evidence	No change in conclusions
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 10-day course may result in a small reduction versus control (1, 2, 4)	No new evidence	No change in conclusions
	Proportion with new need for ventilation	Remdesivir 10-day course probably results in little to no difference versus control (5)	***Results from one small sub-study of WHO Solidarity found no***	No change in conclusions

Comparison	Outcome	Conclusions from Last Report Version	New Trial Results/Analyses	Updated Conclusions
			differences between groups. (6) §	
	Serious adverse events	Remdesivir 10-day course probably results in a moderate reduction versus control (1, 2, 4)	***Results from one small sub-study of WHO Solidarity found no differences between groups. (6) §***	No change in conclusions
Remdesivir 10-day course versus placebo 2 trials, any severity COVID-19 (n=1299 randomized) (1, 2)	Mortality	Remdesivir 10-day course may result in a small reduction versus placebo (1, 2)	No new evidence	No change in conclusions
	Proportion recovered†	Remdesivir 10-day course probably results in a moderate increase versus placebo (1, 2)	No new evidence	No change in conclusions
	Proportion with clinical improvement‡	Remdesivir 10-day course may result in a moderate increase versus placebo (2)	No new evidence	No change in conclusions
	Hospital length of stay	Remdesivir 10-day course may result in a moderate reduction versus placebo (1, 2)	No new evidence	No change in conclusions
	Time to recovery or clinical improvement	Remdesivir 10-day course may result in a moderate to large reduction versus placebo (1, 2) *Subgroup analyses (prespecified):* (1) • Time to recovery did not vary by age, gender, symptom duration (≤10 days vs >10 days) or disease severity (mild/ moderate, or severe)	No new evidence	No change in conclusions
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 10-day course may result in a moderate reduction versus placebo (1, 2)	No new evidence	No change in conclusions
	Serious adverse events	Remdesivir 10-day course probably results in a moderate reduction versus placebo (1, 2)	No new evidence	No change in conclusions
Remdesivir 10-day course versus SC, any severity COVID-19	Mortality	Remdesivir 10-day course probably results in little to no difference versus SC (4, 5)	***Results from one small sub-study of WHO Solidarity found 28-day and 60-day mortality did not differ between groups (6) §***	No change in conclusions

Comparison	Outcome	Conclusions from Last Report Version	New Trial Results/Analyses	Updated Conclusions
2 trials (n=5872 randomized) (4, 5)	Proportion recovered†	Remdesivir 10-day course may result in a moderate increase in percent recovered versus SC (4)	No new evidence	No change in conclusions
	Proportion with clinical improvement‡	Remdesivir 10-day course may result in a moderate increase in percent recovered versus SC (4)	No new evidence	No change in conclusions
	Hospital length of stay	The percentage of individuals hospitalized at days 7-14 did not differ between the remdesivir 10-day course and SC groups (4, 5)	No new evidence	No change in conclusions
	Time to recovery or clinical improvement	Insufficient CoE (4)		
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 10-day course may result in a small reduction versus SC (4)	No new evidence	No change in conclusions
	Proportion with new need for ventilation	Remdesivir 10-day course probably results in little to no difference versus control (5)	***Results from one small sub-study of WHO Solidarity found no differences between groups. (6) §***	No change in conclusions
	Serious adverse events	Remdesivir 10-day course may result in a small reduction versus SC (4)	***Results from one small sub-study of WHO Solidarity found no differences between groups. (6) §***	No change in conclusions
Remdesivir 5-day course versus SC 2 trials (n=481 randomized), moderate (4) **and severe COVID-19** (7)	Mortality	Remdesivir 5-day course may result in a small reduction versus SC (4, 7)	No new evidence	No change in conclusions
	Proportion recovered†	Remdesivir 5-day course may result in a moderate increase versus SC (4)	No new evidence	No change in conclusions
	Proportion with clinical improvement‡	Remdesivir 5-day course may result in a moderate increase versus SC (4)	No new evidence	No change in conclusions
	Hospital length of stay	The percentage of individuals hospitalized at day 11 and 14 did not differ between the remdesivir 5-day and SC groups (4)	No new evidence	No change in conclusions
	Time to recovery or clinical improvement	Remdesivir 5-day course may result in a small reduction versus SC (4, 7)	No new evidence	No change in conclusions
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 5-day course may result in a small reduction versus SC (4)	No new evidence	No change in conclusions

Comparison	Outcome	Conclusions from Last Report Version	New Trial Results/Analyses	Updated Conclusions
	Proportion with new need for ventilation	Insufficient CoE, based on 1 RCT (7) assessed as high risk of bias	No new evidence	
	Serious adverse events	Remdesivir 5-day course may result in a small reduction versus SC (4)	No new evidence	No change in conclusions
Remdesivir 5-day course versus Remdesivir 10-day course, moderate (4) **and severe** (3) **COVID-19 (excludes critical COVID-19) 2 trials (n=798 randomized)**	Mortality	Remdesivir 5-day course may result in a small reduction versus 10-day course (3, 4)	No new evidence	No change in conclusions
	Proportion recovered†	Remdesivir 5-day course may result in a moderate increase versus 10-day course (3, 4)	No new evidence	No change in conclusions
	Proportion with clinical improvement‡	Remdesivir 5-day course may result in a moderate increase versus 10-day course (3, 4)	No new evidence	No change in conclusions
	Hospital length of stay	The percentage of individuals hospitalized at day 11 and 14 did not differ between the remdesivir 5-day and 10-day course groups (4)	No new evidence	No change in conclusions
	Time to recovery or clinical improvement	Remdesivir 5-day course may result in a small reduction versus 10-day course (3, 4)	No new evidence	No change in conclusions
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 5-day course may result in a small reduction versus 10-day course (3, 4)	No new evidence	No change in conclusions
	Serious adverse events	Remdesivir 5-day course may result in a moderate reduction versus 10-day course (3, 4)	No new evidence	No change in conclusions

Abbreviations
COE=certainty of evidence; ECMO=extracorporeal membrane oxygenation; NR=not reported; SC=standard of care

* Includes some patients receiving Hi-flow oxygen and non-invasive ventilation
† Recovery was defined as discharge from the hospital or hospitalization for infection control purposes only (1) or discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care (2-4)]
‡ Clinical improvement was defined as a two-point reduction in patients' admission status on a 6-point ordinal scale (1= live discharge to 6=death), or live discharge from the hospital, whichever came first (2) or as an improvement of at least 2 points from baseline on 7-point ordinal scale (1=death to 7=discharged from hospital) (3, 4)].
§ Indicates findings from newly identified sub-study

Supplement Table 3. Effect of Remdesivir in Randomized Controlled Studies

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
All-cause Mortality				
Remdesivir 10-day course versus placebo or standard of care; 4 trials (n=7142) (1, 2, 4, 5)	11-29 days Any severity - No O_2 at baseline 25%; Receiving O_2 or ventilation (non-invasive and invasive) at baseline 75%	10.6% (384/3635) vs. 11.2% (394/3507) Pooled ARD -0.8 (-2.2 to 0.7)	Moderate ‡	Remdesivir 10-day course probably results in little to no difference in mortality versus placebo or standard care
Remdesivir 10-day course versus placebo; 2 trials (n=1298)	Beigel (ACTT-1) 2020 (1); 29 days Severe - No O_2 13% Wang 2020 (2); 28 days Severe - No O_2 1%	10.9% (59/541) vs.14.8% (77/521) ARD -3.9% (-7.9 to 0.1) 13.9% (22/158) vs. 12.8% (10/78) ARD 1.1% (-8.1 to 10.3)	Low §	Remdesivir 10-day course may result in a small reduction in mortality versus placebo; Range of ARDs -3.9% to 1.1%
Remdesivir 10-day course versus standard of care; 2 trials (n=5844)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 84% Solidarity 2020 (5) ; 28 days (*reported only during initial hospitalization; follow-up ceased after discharge*) Severe - No O_2 24%	1.0% (2/193) vs. 2.0% (4/200) ARD-1.0% (-3.4 to 1.4) 11.0% (301/2743) vs. 11.2% (303/2708) ARD -0.2 (-1.9 to 1.5)	Moderate ‡	Remdesivir 10-day course probably results in little to no difference on mortality versus standard care; Range of ARDs -1.0% to -0.2%
Remdesivir 5-day course versus standard of care; 2 trials (n=461)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 82%	0% (0/191) vs. 2.0% (4/200) ARD -2.0% (-4.2 to 0.2)	Low ‖	Remdesivir 5-day course may result in a small reduction versus SC

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Mahajan 2021 (7) ; 24 days Severe - No O_2 0% Goldman (GS-US-540-5773: SIMPLE-1) 2020 (3); 14 days Severe - No O_2 14% Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 86%	Per protocol (day 12 to 24) 14.7% (5/34) vs. 8.3% (3/36) ARD 6.4% (-8.6 to 21.3) 8.0% (16/200) vs. 10.7% (21/197) ARD -2.7% (-8.4 to 3.1) 0% (0/191) vs. 1.0% (2/193) ARD -1.0% (-2.8 to 0.7)	Low ¶	Remdesivir 5-day course of may result in a small reduction in mortality versus 10-day course; Range of ARDs -2.7% to -1.0%
Proportion of patients recovered, defined as discharge from the hospital or hospitalization for infection control purposes only (1) or discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care (2-4)				
Remdesivir 10-day course versus placebo or standard of care; 3 trials (n=1682) (1, 2, 4)	28-29 days Any severity - No O_2 28%; Any O_2/Ventilation 72%	77.3% (683/884) vs. 71.6% (571/798) Pooled ARD 6.5% (2.4 to 10.7)	Moderate ‡	Remdesivir 10-day course probably results in a moderate increase in percent recovered versus placebo or standard care
Remdesivir 10-day course versus placebo; 2 trials (n=1289)	Beigel (ACTT-1) 2020 (1); 29 days Severe - No O_2 13% Wang 2020 (2); 28 days Severe - No O_2 1%	73.8% (399/541) vs. 67.6% (352/521) ARD 6.2% (0.7 to 11.7) 70.7% (106/150) vs. 63.6% (49/77) ARD 7.0% (-6.0 to 20.0)	Moderate ‡	Remdesivir 10-day course probably results in a moderate increase in percent recovered versus placebo; Range of ARDs 6.2% to 7.0%

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 10-day course versus standard of care; 1 trial (n=393)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 28 days Moderate - No O_2 84%	92.2% (178/193) vs. 85% (170/200) ARD 7.2% (1.0 to 13.5)	Low §	Remdesivir 10-day course may result in a moderate increase in percent recovered versus standard care
Remdesivir 5-day course versus standard of care; 1 trial (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 28 days Moderate - No O_2 82%	91.6% (175/191) vs. 85% (170/200) ARD 6.6% (0.3 to 12.9)	Low §	Remdesivir 5-day course may result in a moderate increase in percent recovered versus standard care
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (3); 14 days Severe - No O_2 14% Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 86%	64.5% (129/200) vs. 53.8% (106/197) Baseline-adjusted ARD 6.3% (-2.8 to 15.4) 73.8% (141/191) vs. 68.4% (132/193) ARD 5.4% (-3.6 to 14.5)	Low ¶	Remdesivir 5-day course may result in a moderate increase in percent recovered versus 10-day course; Range of ARDs 5.4% to 6.3%
Clinical improvement, defined as a two-point reduction in patients' admission status on a 6-point ordinal scale (1= live discharge to 6=death), or live discharge from the hospital, whichever came first (2) as an improvement of at least 2 points from baseline on 7-point ordinal scale (1=death to 7=discharged from hospital) (3, 4)				
Remdesivir 10-day course versus placebo (2) **or standard of care** (4)**;** 2 trials (n=629)	Wang 2020 (2); 28 days Severe - No O_2 1% Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 28 days Moderate - No O_2 84%	65.2% (103/158) vs. 57.7% (45/78) ARD 7.5% (-5.7 to 20.7) 90.2% (174/193) vs. 83% (166/200) ARD 7.2% (0.5 to 13.8)	Low §	Remdesivir 10-day course may result in a moderate increase in clinical improvement versus placebo or standard care Range of ARDs 7.2% to 7.5%

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 5-day course versus standard of care; 1 trial (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 28 days Moderate - No O_2 82%	89.5% (171/191) vs. 83% (166/200) ARD 6.5% (-0.3 to 13.3)	Low §	Remdesivir 5-day course may result in a moderate increase in clinical improvement versus standard care
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (3); 14 days Severe - No O_2 14%	64.5% (129/200) vs. 54.3% (107/197) Baseline-adjusted ARD 6.5% (-2.8 to 15.7)	Low ¶	Remdesivir 5-day course may result in a moderate increase in clinical improvement versus 10-day course Range of ARDs 4.9% to 6.5%
	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 86%	70.2% (134/191) vs. 65.3% (126/193) ARD 4.9% (-4.5 to 14.2)		
Hospital Length of Stay (LOS), Days (Median IQR)				
Remdesivir 10-day course versus placebo; 2 trials (n=1299)	Beigel (ACTT-1) 2020 (1); 29 days Severe - No O_2 13%	*Initial hospitalization* 12 (6 to 28) vs. 17 (8 to 28) MD -5 days [95% CI, -7.7 to -2.3]	Low **	Remdesivir 10-day course may result in a moderate reduction in median length of hospital stay versus placebo
	Wang 2020 (2); 28 days Severe - No O_2 1%	25 (16 to 38) vs. 24 (18 to 36) MD 0 days (-4.0 to 4.0)		
Remdesivir 10-day course versus standard of care	Hospital LOS: NR Solidarity (5), Severe - No O_2 24%; No differences in percent hospitalized at 7 (69% vs. 59%) and 14 days (22% vs. 19%) SIMPLE-2 (4), Moderate - No O_2 84%: No differences in percent hospitalized at 11 (34% vs. 38%) and 14 days (23% vs. 31%).			
Remdesivir 5-day course versus standard of care	Hospital LOS: NR SIMPLE-2 (4), Moderate - No O_2 82%: No differences in percent hospitalized at 11 (30% vs. 38%) and 14 days (23% vs. 31%),			

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 5-day course versus Remdesivir 10-day course	Hospital LOS: NR SIMPLE-2 (4), Moderate - No O_2 86%: No differences in percent hospitalized at 11 (30% vs. 34%) and 14 days (23% vs. 23%)			
Time to Recovery or Time to Clinical Improvement, Days, Median (IQR)				
Remdesivir 10-day course versus placebo or standard of care; 3 trials (n=1674) (1, 2, 4)	11-29 days Any severity - No O_2 28%; Any O_2/Ventilation 72%	Difference in medians ranged from -1 to 5 days)	Low ¶	Remdesivir 10-day course may result in an uncertain reduction in time to recovery in patients with moderate severity at day 11 and up to a large reduction in patients with severe disease at day 29 and a moderate reduction in median time to clinical improvement in patients with severe disease versus control
Remdesivir 10-day course versus placebo; 2 trials (n=1299)	Beigel (ACTT-1) 2020 (1); 29 days Severe - No O_2 13% *Recovery* Wang 2020 (2) 28 days Severe - No O_2 1% *Clinical Improvement*	10 (95% CI 9 to 11) vs. 15 (95% CI 13 to 18); P<.001 Rate ratio 1.29 (1.12 to 1.49) 21 (13 to 28) vs. 23 (18 to 36); HR 1.23 (0.87 to 1.75)	Low ††	Remdesivir 10-day course may result in large reduction in median time to recovery and a moderate reduction in median time to clinical improvement versus placebo *(time to recovery did not vary by age, sex, symptom duration (≤10 days vs >10 days) or disease severity*) (1)

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 10-day course versus standard of care; 1 trial (n=393)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 84% *Recovery*	8 (4 to 13) vs. 7 (4 to 15); HR 1.11 (0.90 to 1.37)	Insufficient ‡‡	
Remdesivir 5-day course versus standard of care; 2 trials (n=461)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 82%*Recovery*	6 (5 to 10) vs. 7 (4 to 15); HR 1.18 (0.96 to 1.45)	Low	Remdesivir 5-day course may result in a small reduction in median time to recovery versus standard care
	Mahajan 2021 (7); Day 10 through Day 20 Severe - No O_2 0% Recovery	Data NR Trialists noted patients in both groups "had an equal time to recovery (not defined) between 10 and 20 days."		
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (3); 14 days Severe - No O_2 14% *Recovery*	10 (6 to 18) vs. 11 (7 to not able to estimate); P NS HR 0.81 (0.64 to 1.04)	Low ¶	Remdesivir 5-day course may result in a small reduction in median time to recovery versus 10-day course
	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 86% *Recovery*	6 (5 to 10) vs. 8 (4 to 13); HR NR		
Proportion on invasive ventilation/ECMO at follow up (Spinner on day 11, Wang on day 14 and ACTT-1 on day 15)				

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 10-day course versus placebo or standard of care; 3 trials (n=1686) (1, 2, 4)	11-15 days Any severity - No O_2 28%; Any O_2/Ventilation 72%	11.3% (100/887) vs. 16.5% (132/799) Pooled ARD -4.8% (-8.0 to -1.5)	Low §	Remdesivir 10-day course may result in a small reduction in proportion on invasive ventilation or ECMO at follow-up versus placebo or standard care
Remdesivir 10-day course versus placebo; 2 trials (n=1299)	Beigel (ACTT-1) 2020 (1) Severe - No O_2 13%	17.6% (95/541) vs. 23.2% (121/521) ARD -5.7% (-10.5 to -0.8)	Low §	Remdesivir 10-day course may result in a moderate reduction in proportion on invasive ventilation or ECMO at follow-up versus placebo Range of ARDs -5.7% to -6.4%
	Wang 2020 (2) Severe - No O_2 1%	2.6% (4/153) vs. 9.0% (7/78) ARD -6.4 (-13.2 to 0.5)		
Remdesivir 10-day course versus standard of care; 1 trial (n=393)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4) Moderate - No O_2 84%	0.5% (1/193) vs. 2.0% (4/200) ARD -1.5% (-3.7 to 0.7)	Low §	Remdesivir 10-day course may result in a small reduction in proportion on invasive ventilation or ECMO at follow-up versus standard care
Remdesivir 5-day course versus standard of care; 1 trial (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4) Moderate - No O_2 82%	0% (0/191) vs. 2.0% (4/200) ARD -2.0% (-4.2 to 0.2)	Low §	Remdesivir 5-day course may result in a small reduction in proportion on invasive ventilation or ECMO at follow-up versus standard care
Remdesivir 5-day course versus Remdesivir 10-day course;	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (3) Severe - No O_2 14%	8.0% (16/200) vs. 16.8% (33/197) ARD -8.8% (-15.2 to -2.3)	Low §§	Remdesivir 5-day course may result in a small reduction in proportion on

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
2 trials (n=781)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4) Moderate - No O_2 86%	0% (0/191) vs. 0.5% (1/193) ARD -0.5% (-1.9 to 0.9)		invasive l ventilation or ECMO versus 10-day course at follow-up Range of ARDs -8.8% to -0.5% (*Observed effects may vary based on the baseline disease severity of the enrolled patients in each trial, i.e. severe disease in SIMPLE-1 and moderate disease in SIMPLE-2)*
Subsequent need for ventilation (invasive or non-invasive ventilation, or ECMO) in those not ventilated at baseline				
Remdesivir 10-day course versus standard of care; 1 trial (n=4964) (5)	Follow-up through day 28 Severe - No O_2 24%	11.9% (295/2489) vs. 11.5% (284/2475) ARD 0.4% (-1.4 to 2.2)	Moderate ‡	Remdesivir 10-day course probably results in little to no difference in new need for ventilation versus standard care
Remdesivir 5-day course versus standard of care; 1 trial (n=70) (7)	Day 12 through Day 24 Severe - No O_2 0%	11.8% (4/34) vs. 5.6% (2/36) ARD 6.2% (-7.0 to 19.4)	Insufficient ǁǁ	
Any Adverse Event (includes markers of COVID-19 progression and remdesivir toxicity)				
Remdesivir 10-day course versus placebo or standard of care; 3 trials (n=1674) (1, 2, 4)	11-29 days Any severity - No O_2 28%; Any O_2/Ventilation 72%	59.1% (520/880) vs. 58.7% (466/794) Pooled ARD -0.3 (-5.0 to 4.4)	Low §§	Remdesivir 10-day course may result in little to no difference in any adverse events versus control
Remdesivir 10-day course versus placebo;	Beigel (ACTT-1) 2020 (1); 29 days Severe - No O_2 13%	57.3% (305/532) vs. 62.6% (323/516) ARD -5.3% (-11.2 to 0.7)	Low §	Remdesivir 10-day course may result in a small reduction in any adverse events versus placebo

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
2 trials (n=1281)	Wang 2020 (2); 28 days Severe - No O_2 1%	65.8% (102/155) vs. 64.1% (50/78) ARD 1.7 (-11.3 to 14.7)		Range of ARDs -5.3% to 1.7%
Remdesivir 10-day course versus standard of care; 1 trial (n=393)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 84%	58.5% (113/193) vs. 47% (93/200) ARD 12.0% (2.2 to 21.9)	Low §	Remdesivir 10-day course may result in a moderate increase in any adverse events versus standard of care
Remdesivir 5-day course versus standard of care; 1 trial (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 82%	51.3% (98/191) vs. 46.5% (93/200) ARD 4.8% (-5.1 to 14.7)	Low §	Remdesivir 5-day course may result in a small increase in any adverse events versus standard care
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (3); 14 days Severe - No O_2 14%	70.5% (141/200) vs. 73.6% (145/197) ARD -3.1% (-11.9 to 5.7)	Low ¶	Remdesivir 5-day course may result in a moderate reduction in any adverse events versus 10-day course
	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 86%	51.3% (98/191) vs. 58.5% (113/193) ARD -7.2% (-17.2 to 2.7)		Range of ARDs -7.2% to -3.1%
Serious Adverse Events (includes markers of COVID-19 progression and remdesivir toxicity)				
Remdesivir 10-day course versus placebo or standard of care; 3 trials (n=1674) (1, 2, 4)	11-29 days Any severity - No O_2 28%; Any O_2/Ventilation 72%	19.2% (169/880) vs. 25.3% (201/794) Pooled ARD -6.3% (-10.2 to -2.4)	Moderate ‡	Remdesivir 10-day course probably results in a moderate reduction in serious adverse events versus control

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 10-day course versus placebo; 2 trials (n=1299)	Beigel (ACTT-1) 2020 (1); 29 days Severe - No O_2 13%	24.6% (131/532) vs. 31.6% (163/516) ARD -7.0% (-12.4 to -1.5)	Moderate ‡	Remdesivir 10-day course probably results in a moderate reduction in serious adverse events versus placebo Range of ARDs -7.6% to -7.0%
	Wang 2020 (2); 28 days Severe - No O_2 1%	18.1% (28/155) vs. 25.6% (20/78) ARD -7.6 (-19.0 to 3.9)]		
Remdesivir 10-day course versus standard of care; 1 trial (n=393)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 84%	5.2% (10/193) vs. 9.0% (18/200) ARD -3.8% (-8.9 to 1.2)	Low §	Remdesivir 10-day course may result in a small reduction in serious adverse events versus standard care
Remdesivir 5-day course versus standard of care; 1 trial (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 82%	4.7% (9/191) vs. 9.0% (18/200) ARD -4.3% (-9.3 to 0.7)	Low §	Remdesivir 5-day course may result in a small reduction in serious adverse events versus standard care
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (3); 14 days Severe - No O_2 14%	21.0% (42/200) vs. 34.5% (68/197) ARD -13.5% (-22.2 to -4.8)	Low §§	Remdesivir 5-day course may result in a moderate reduction in serious adverse events versus 10-day course Range of ARDs 13.5% to 0.5% (*Observed effects may vary based on the baseline disease severity of the enrolled patients in each trial, i.e. severe disease in SIMPLE-1 and moderate disease in SIMPLE-2)*
	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (4); 11 days Moderate - No O_2 86%	4.7% (9/191) vs. 5.2% (10/193) ARD -0.5% (-4.8 to 3.9)		

Abbreviations
ARD = Absolute risk difference; CI = Confidence intervals; HR=Hazard ratio; IQR = inter quartile range; MD=Mean difference; NR= Not reported; NS = Not statistically significant; RCT = Randomized controlled trial

*** GRADE Working Group grades of evidence**

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Explanations for Certainty of Evidence assessment

† Thresholds for determining magnitude by outcome are as follow:
All-cause mortality: Little or No effect <1%; Small effect 1-2.9%; Moderate effect 3-4.9%; Large effect ≥5%
Recovery: Little or No effect <2%; Small effect 2-4.9%; Moderate effect 5-9.9%; Large effect ≥10%
Clinical Improvement: Little or No effect <2% Small effect 2-4.9%; Moderate effect 5-9.9%; Large effect ≥10%
Length of Stay: Little or No effect <1 day; Small effect ≥1-2 days; Moderate effect >2 to < 3 days; Large effect ≥3 days
Time to Recovery or Clinical Improvement: Little or No effect <1 day; Small effect ≥1-2 days; Moderate effect >2 to < 3 days; Large effect ≥3 days
Invasive ventilation or ECMO: Little or No effect <1%; Small effect 1-4.9%; Moderate effect 5-9.9%; Large effect ≥10%
Any adverse event: Little or No effect <2%; Small effect 2-4.9%; Moderate effect 5-19.9%; Large effect ≥20%
Severe adverse event: Little or No effect <1%; Small effect 1-4.9%; Moderate effect 5-9.9%; Large effect ≥10%

‡ Downgraded for imprecision
§ Downgraded two levels for imprecision (very wide CIs) and/or sparse data.
‖ Downgraded two levels for imprecision (very wide CIs) and/or sparse data. The Mahajan trial (5), assessed as high risk of bias, did not impact the overall certainty of evidence or magnitude of effect
¶ Downgraded two levels for study limitations and imprecision (wide CIs)
** Downgraded two levels for imprecision and inconsistency
†† Downgraded two levels for difficulty in interpreting precision and inconsistency.
‡‡ Downgraded to insufficient for difficulty in interpreting results (HR not reported for 5-day vs.10 day) and higher median with 10-day vs standard of care but reduction in time to recovery favors 10-day based on HR
§§ Downgraded two levels for imprecision and inconsistency
‖‖ Downgraded to insufficient for study limitations and imprecision (very wide CIs)

Supplement Table 4. Study Outcomes A

Author, Year (ref)	Length of hospital stay		Time to recovery		Mortality		Recovery or Combined endpoint "Clinical Improvement"	
	Remdesivir	**Placebo**	**Remdesivir**	**Placebo**	**Remdesivir**	**Placebo**	**Remdesivir**	**Placebo**
Beigel 2020 (1) ACTT-1	Median [IQR] 12 [6 to 28] Difference -5.0 days [95% CI, -7.7 to -2.3] Median [IQR] for those who did not die 10 [5 to 21] Difference -4.0 days [95% CI, -6.0 to -2.0]	Median [IQR] 17 [8 to 28] Median [IQR] for those who did not die 14 [7 to 27]	Median [95% CI] 10 days [9 to 11]	Median [95% CI] 15 days [13 to 18]	14-day 6.5% (35/541) HR 0.55 [95% CI, 0.36 to 0.83] (through day 15) 29-day 10.9% (59/541) HR 0.73 [95% CI, 0.52 to 1.03]	14-day 11.7% (61/521) 29-day 14.8% (77/521)	Day 29 Recovery * 73.8% (399/541) Recovery Rate Ratio 1.29 [95% CI, 1.12 to 1.49] *Recovery Mild/mod. Disease* † *98.2% (54/55)* *Severe Disease* ‡ *71.0% (345/486*)	Day 29 Recovery * 67.6% (352/521) *Recovery Mild/mod. Disease* † *92.0% (46/50)* *Severe Disease* ‡ *65.0% (306/471)*
Wang 2020 (2)	Median [IQR] 25 days [16 to 38] Difference 0.0 days [95% CI, -4.0 to 4.0]	Median [IQR] 24 days [18 to 36]	Time to Clinical Improvement Median [IQR] 21 days [13 to 28]	Time to Clinical Improvement Median [IQR] 23 days [15 to 28]	28-day 13.9% (22/158) ARD 1.1% [95% CI, -8.1 to 10.3]	28-day 12.8% (10/78)	Day 28 Clinical improvement § 65.2% (103/158) ARD 7.5% [95% CI, -5.7 to 20.7] HR 1·23 [95% CI, 0·87 to 1·75]	Day 28 Clinical improvement § 57.7% (45/78)
Goldman 2020 (3)	**Remdesivir 5-day**	**Remdesivir 10-day**	**Remdesivir 5-day**	**Remdesivir 10-day**	**Remdesivir 5-day**	**Remdesivir 10-day**	**Remdesivir 5-day**	**Remdesivir 10-day**

GS-US-540-5773 SIMPLE 1	NR	NR	Median [IQR] 10 days [6 to 18] HR 0.81 [95% CI, 0.64 to 1.04]	Median [IQR] 11 days [7 to not possible to estimate]	14-day 8.0% (16/200) P=.70	14-day 10.7% (21/197)	Day 14 Clinical recovery ‖ 64.5% (129/200) Baseline-adjusted ARD and p-value -6.3% [95% CI, -15.4 to 2.8]; P=.17 Clinical (≥2-point) improvement ¶ 64.5% (129/200) Baseline-adjusted ARD and P-value -6.5% [95% CI, -15.7 to 2.8]; P=.16	Day 14 Clinical recovery ‖ 53.8% (106/197) Clinical (≥2-point) improvement ¶ 54.3% (107/197)
Spinner 2020 (4) GS-US-540-5774 SIMPLE 2 with standard care	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**

	NR	NR	Median [IQR] 5 day 6 (5-10) 10 day 8 (4-13)	Median [IQR] 7 (4-14)	11-day 5-day 0% (0/191) 10-day 1.0% (2/193) HR for 5-day vs. standard care 0.51 [95% CI, 0.09 to 2.80] HR for 10-day vs. standard care 0.76 [95% CI, 0.17 to 3.40]	11-day 2.0% (4/200)	Day 11 Recovery ‖ 5-day 73.8% (141/191) 10-day 68.4% (132/193) HR for 5-day vs. standard care 1.18 [95% CI, 0.96 to 1.45] HR for 10-day vs. standard care 1.11 [95% CI, 0.90 to 1.36] Clinical (≥2-point) improvement ¶ 5-day 70.2% (134/191) 10-day 65.3% (126/193) HR for 5-day vs. standard care 1.15 [95% CI, 0.93 to 1.42] HR for 10-day vs. standard care 1.16 [95% CI, 0.93 to 1.43]	Day 11 Recovery ‖ 64.0% (128/200) Clinical (≥2-point) improvement ¶ 60.5% (121/200)
WHO Solidarity 2020 (5)	Still hospitalized at day 7 69%	Still hospitalized at day 7 59%	NR	NR	12.5% (301/2743) Rate Ratio: 0.95 [95% CI, 0.81 to 1.11]	12.7% (303/2708)	NR	NR

NOR-Solidarity 2021 (6) ** Sub-study of WHO Solidarity	***NR***	***NR***	***NR***	***NR***	***In-hospital 7.1% RR 1.0 [95% CI, 0.2 to 4.6] HR 1.0 [95% CI, 0.4 to 2.9] 28 day 2.4% Estimated Marginal Risk Difference vs. SC -2.9% [95% CI, -10.3 to 4.5] 60 day 7.1% Estimated Marginal Risk Difference vs. SC 1.9% [95% CI, -7.8 to 11.6]***	***In-hospital 7.0% 28 day 5.3% 60 day 5.3%***	***NR***	***NR***
Mahajan 2021 (7)	NR	NR	Patients in the remdesivir group and standard of care group had an equal time to recovery between 10 and 20 days (no other data reported)	All patients 14.6% (6/41) Per protocol Day 12-24 14.7% (5/34)	All patients 12.2% (5/41) Per Protocol Day 12-24 8.3% (3/36)	NR	NR

ARD = absolute risk difference; CI =confidence intervals; HR = Hazard ratio; IQR = interquartile range; NR = not reported; RR = relative risk; SC = standard care

* Defined by either discharge from the hospital or hospitalization extended for purposes of infection-control only with no medical needs.

† Mild/moderate disease was defined by a SpO2 >94% and respiratory rate <24 breaths per minute without supplemental oxygen requirement.

‡ Severe disease was defined as participants meeting one or more of the following criteria: requiring invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, an SpO2 ≤94% on room air, or respiratory rate ≥24 breaths per minute.

§ Defined as a two-point reduction in patients' admission status on a six-point ordinal scale, or live discharge from the hospital, whichever came first. The six-point scale was as follows: death=6; hospital admission for extracorporeal membrane oxygenation or mechanical ventilation=5; hospital admission for noninvasive ventilation or high-flow oxygen therapy=4; hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation)=3; hospital admission but not requiring oxygen therapy=2; and discharged or having reached discharge criteria (defined as clinical recovery—ie, normalization of pyrexia, respiratory rate <24 breaths per minute, saturation of peripheral oxygen >94% on room air, and relief of cough, all maintained for at least 72 h)=1 within 28 days after randomization

‖ Patients achieved clinical recovery if they no longer required oxygen support and medical care or were discharged from the hospital (improvement from a baseline score of 2 to 5 to a score of 6 or 7).

¶ Clinical improvement was defined as an improvement of two or more points from baseline on a predefined seven-point scale consisting of the following categories: 1, death; 2, hospitalized, receiving invasive mechanical ventilation or ECMO; 3, hospitalized, receiving noninvasive ventilation or high-flow oxygen devices; 4, hospitalized, requiring

low-flow supplemental oxygen; 5, hospitalized, not requiring supplemental 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.
** Indicates newly identified sub-study

Supplement Table 5. Study Outcomes B

Author, Year (ref)	Required invasive mechanical ventilation; Duration of invasive mechanical ventilation, days		Required oxygen; Duration of oxygen support, days	
	Remdesivir	**Placebo**	**Remdesivir**	**Placebo**
Beigel 2020 (1) ACTT-1	17.6% (95/541) at Day 15 visit; Length of use if receiving at baseline, Median [IQR] 17 days [9 to 28] Difference -3.0 days [95% CI, -9.3 to 3.3] Length of new use during study, Median [IQR] 21.5 days [9 to 28] Difference 1.0 days [95% CI, -6.0 to 8.0]	23.2% (121/521) at Day 15 visit; Length of use if receiving at baseline, Median [IQR] 20 days [8 to 28] Length of new use during study, Median [IQR] 23 days [12 to 28]	10.7% (58/541) at Day 15 visit: Length of use if receiving at baseline, Median [IQR] 13 days [5 to 28] Difference -8.0 days [95% CI, -11.8 to -4.2] Length of new use during study, Median [IQR] 4 days [2 to 12] Difference -1.0 days [95% CI, -7.6 to 5.6]	11.5% (60/521) at Day 15 visit; Length of use if receiving at baseline, Median [IQR] 21 days [8 to 28] Length of new use during study, Median [IQR] 5.5 days [1 to 15]
Wang 2020 (2)	8.2% (13/158) Median [IQR] 7.0 days [4 to 16] Difference -4.0 days [95% CI, -14.0 to 2.0]	12.8% (10/78) Median [IQR] 15.5 days [6 to 21]	Median [IQR] 19.0 days [11 to 30] Difference -2.0 days [95% CI, -6.0 to 1.0]	Median [IQR] 21.0 days [14 to 30.5]
Goldman 2020 (3) GS-US-540-5773 SIMPLE 1	**Remdesivir 5-day** 8.0% (16/200); Duration NR	**Remdesivir 10-day** 16.8% (33/197); Duration NR	**Remdesivir 5-day** NR	**Remdesivir 10-day** NR
Spinner 2020 (4) GS-US-540-5774 SIMPLE 2 with standard care	**Remdesivir** 5-day 0% (0/191) 10-day	**Standard Care** 2.0% (4/200)	**Remdesivir** Time to Room Air Median [IQR] 5-day 5 (3-7)	**Standard Care** 6 (4-14)

	0.5% (1/193)		10-day 4 (2-6) 6.3% (12/191) and 6.7% (13/193) required oxygen support on Day 1	11% (22/200) required oxygen support on Day 1
WHO Solidarity 2020 (5)	**Remdesivir** Initiation of ventilation in those not already ventilated 11.9% (295/2489)	**Standard Care** Initiation of ventilation in those not already ventilated 11.5% (284/2475)	**Remdesivir** NR	**Standard Care** NR
NOR-Solidarity 2021 (6)* *Sub-study of WHO Solidarity	***9.5% Estimated Marginal Risk Difference vs. SC 2.5% [95% CI, -8.6 to 13.6]***	***7.0%***	***NR***	***NR***
Mahajan 2021 (7)	Day 12-24 11.8% (4/34)	Day 12-24 5.6% (2/36)	Day 12-24 Supplemental O_2 11.8% (4/34) Day 12-24 High-flow O_2 or/ non-invasive ventilation 55.9% (19/34)	Day 12-24 Supplemental O_2 16.7% (6/36) Day 12-24 High-flow O_2 or/ non-invasive ventilation 61.1% (22/36)

ECMO = extracorporeal membrane oxygenation; IQR = interquartile range; NR = not reported; SC = standard care

* Indicates newly identified sub-study

Supplement Table 6. Viral Load

Author, Year (ref) Viral load definition	Pre		Post	
	Remdesivir	**Placebo**	**Remdesivir**	**Placebo**
Beigel 2020 (1) ACTT-1	NR	NR	NR	NR
Wang 2020 (2) ***Mean baseline viral load of nasopharyngeal and oropharyngeal swabs***	4.7 log_{10} copies/mL	4.7 log_{10} copies per mL	NR	NR
Upper respiratory tract specimens	*Estimated from graph* 3.7 log_{10} copies/mL	*Estimated from graph* 3.6 log_{10} copies/mL	*Estimated from graph* 0.6 log_{10} copies/mL	*Estimated from graph* 0.1 log_{10} copies/mL
Lower respiratory tract specimens	*Estimated from graph* 7.3 log_{10} copies/mL	*Estimated from graph* 6.4 log_{10} copies/mL	*Estimated from graph* 1.4 log_{10} copies/mL	*Estimated from graph* 0.0 log_{10} copies/mL
Goldman 2020 (3) GS-US-540-5773 SIMPLE 1	**Remdesivir 5-day** NR	**Remdesivir 10-day** NR	**Remdesivir 5-day** NR	**Remdesivir 10-day** NR
Spinner 2020 (4) GS-US-540-5774 SIMPLE 2 with standard care	**Remdesivir** NR	**Standard Care** NR	**Remdesivir** NR	**Standard Care** NR
WHO Solidarity 2020 (5)	**Remdesivir** NR	**Standard Care** NR	**Remdesivir** NR	**Standard Care** NR
NOR-Solidarity 2021 (6) * Sub-study of WHO Solidarity oropharynx	***1.6 (1.6) log_{10} copies/1000 cells***	***2.3 (1.8) log_{10} copies/1000 cells***	***Difference in viral level at day 10, 0.203 log_{10} copies/1000 cells [95% CI, -0.348 to 0.754]*** ***Difference in daily viral decrease rate, 0.113 log_{10} copies/1000 cells [95% CI, -0.001 to 0.227]***	
Mahajan 2021 (7)	NR	NR	NR	NR

NR = not reported

* Indicates newly identified sub-study

Supplement Table 7. Harms A (Number of Subjects Reporting at Least One Event)

Author, Year (ref)	Serious AE		AE leading to drug withdrawal		Any AE	
	Remdesivir	**Placebo**	**Remdesivir**	**Placebo**	**Remdesivir**	**Placebo**
Beigel 2020 (1) ACTT-1	24.6% (131/532) * *Study-related* 2 events Grade 3 or 4 51.3% (273/532)	31.6% (163/516) * *Study-related* 3 events Grade 3 or 4 57.2% (295/516)	10.7% (57/532) *	14.9% (77/516) *	57.3% (305/532)[a]	62.6% (323/516)[a]
Wang 2020 (2)	18.1% (28/155) Grade 3 or 4 5.8% (9/155)	25.6% (20/78) Grade 3 or 4 12.8% (10/78)	11.6% (18/155)	5.1% (4/78)	65.8% (102/155) Grade 3 or 4 8.4% (13/155)	64.1% (50/78) Grade 3 or 4 14.1% (11/78)
Goldman 2020 (3) GS-US-540-5773 SIMPLE 1	**Remdesivir 5-day**	**Remdesivir 10-day**	**Remdesivir 5-day**	**Remdesivir 10-day**	**Remdesivir 5-day**	**Remdesivir 10-day**
	21.0% (42/200)	34.5% (68/197)	4.5% (9/200) P=.07	10.2% (20/197)	70.5% (141/200) P=.86 Grade ≥3 30% (60/200)	73.6% (145/197) Grade ≥3 43% (85/197)
Spinner 2020 (4) GS-US-540-5774 SIMPLE 2 with standard care	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**
	5-day 4.7% (9/191) 10-day 5.2% (10/193)	9.0% (18/200)	5-day 2.1% (4/191) 10-day 4.1% (8/193)	NA	5-day 51.3% (98/191) 10-day 58.5% (106/193) Grade ≥3 5-day 10.5% (20/191) 10-day	45.0% (90/200) Grade ≥3 12.0% (24/200)

					10.9% (21/193)	
WHO Solidarity 2020 (5)	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**
	NR	NR	NR	NR	NR	NR
NOR-Solidarity 2021 (6) ‡ Sub-study of WHO Solidarity	***19.0% (8/42) P=.56 †***	***14.9% (13/87)***	***0% (0/42)***	***0% (0/87)***	***38.5% (20/42)***	***25.3% (22/87)***
Mahajan 2021 (7)	NR	NR	7.3% (3/41) due to abnormal ALT and AST values	0/41	NR	NR

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NR = not reported
* Data for the treated population
† P-value calculated by review team
‡ Indicates newly identified sub-study

Supplement Table 8. Risk of Bias of studies

Author, Year (ref)	Random sequence generation	Allocation concealment	Blinding *	Incomplete outcome data †	Selective outcome reporting ‡	Overall Risk of Bias §
Beigel 2020 (1) ACTT-1	Low, adequate, permuted randomization sequence	Low, adequate, web-based	Low, patient, provider Follow-up safety and efficacy evaluations performed by blinded clinic staff	Low, 1 placebo patient and 3 remdesivir patients excluded due to no data after baseline.	No	Low
Wang 2020 (2) Note: trial stopped early	Low, adequate, permuted block randomization sequence	Low, adequate, centralized	Low, patient, provider	Low, 1 placebo patient withdrew consent, not in ITT analyses. Three remdesivir patients did not take drug and are not in the safety analyses.	No	Low
Goldman 2020 (3) GS-US-540-5773 SIMPLE 1	Low, adequate, computer generated	Low, adequate, web-based	Open-label Outcome assessors were not blinded.	Low,2 patients in the 5-day group and 3 in the 10-day group not included in analyses (withdrawn or randomized in error)	No	Moderate based on imbalance between groups (patients randomly assigned to the 10-day group had significantly worse clinical status than those assigned to the 5-day group (P = 0.02)) and open label nature of study.
Spinner 2020 (4) GS-US-540-5774	Low, adequate, computer generated	Low, adequate, web-based	Open-label	Low, 8 patients in the 5-day group and 4 in the 10-day group not	No	Low

Author, Year (ref)	Random sequence generation	Allocation concealment	Blinding *	Incomplete outcome data †	Selective outcome reporting ‡	Overall Risk of Bias §
SIMPLE 2 with standard care			Outcome assessors were not blinded.	included in analyses (did not start treatment)		
WHO Solidarity 2020 (5) ***(NOR-Solidarity – sub-study) (6)*** ǁ	WHO: Unclear, not reported; ***NOR-Solidarity: Low, computer randomization procedures***	WHO: Low, adequate, cloud-based; ***NOR-Solidarity: Low, allocation sequence was prepared by an independent statistician***	Open-label Blinded analyses of all relevant data	WHO: Low, 7 patients in remdesivir and 17 patients in control group not included in analyses (no or uncertain consent to follow-up) ***NOR-Solidarity: 2% patients not included in full analysis set, 18% did not complete 3-month follow-up***	WHO: Yes – limited reporting of hospitalization duration; no adverse event reporting	Moderate based on unclear sequence generation and selective outcomes reporting
Mahajan 2021 (7)	Low, adequate, computer generated	Unclear, not reported	Open-label	High, 8 patients in remdesivir and 5 patients in control group not included in analyses (Patients who were discharged when symptom-free, withdrawn from treatment, for had treatment stopped due to elevated ALT or AST levels were excluded). 16%	No	High based on not using ITT analysis, attrition, and absence of information on allocation concealment

Author, Year (ref)	Random sequence generation	Allocation concealment	Blinding *	Incomplete outcome data †	Selective outcome reporting ‡	Overall Risk of Bias §
				were excluded from analyses		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ITT = intent-to-treat

* For the open-label trial, blinding of study participants and study personnel was not feasible. This element was not considered in rating overall risk of bias.

† Incomplete outcome data was rated high if more than 10% of participants randomized were not included in the analyses.

‡ Selective reporting was determined by comparing reported outcomes with outcomes specified in the Methods section. If a protocol paper was available, reported outcomes were compared with outcomes specified in the protocol.

§ Studies were rated low risk of bias if at least 3 elements were rated low and no additional elements were rated high. Studies were rated High risk of bias if at least 2 elements were rated high risk of bias. All other studies were rated Moderate risk of bias.

ǁ Indicates newly identified sub-study.

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