Supplementary Material*

Kaka AS, MacDonald R, Greer N, et al. Major update: remdesivir for adults with COVID-19: a living systematic review and meta-analysis for the American College of Physicians Practice Points. Ann Intern Med. 9 February 2021. [Epub ahead of print]. doi:10.7326/M20-8148

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

SUPPLEMENT TABLE 1. SEARCH STRATEGIES

Source	Strategy
MEDLINE and CENTRAL (Cochrane Central Trials Register)	1. exp Coronavirus/ or exp Coronavirus Infections/ 2. (nCoV or 2019-nCoV or ((new or novel or wuhan) adj3 coronavirus) or covid19 or covid-19 or SARS-CoV-2 or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 3. 1 or 2 4. (remdesivir or Veklury or GS-5734).ti,ab,kw. 5. 3 and 4
WHO Database	1. remdesivir or Veklury or GS-5734
NIH COVID-19 iSearch Portfolio	1. remdesivir or Veklury or GS-5734 Title/Abstract fields only, medRxiv
Journal Tables of Contents (New England Journal of Medicine, JAMA Network, The Lancet)	Keyword search: (remdesivir or Veklury or GS-5734)
Gilead Sciences, Inc. https://www.gilead.com/science-and-medicine/research	

SUPPLEMENT TABLE 2. GRADE APPROACH TO RATING THE CERTAINTY OF EVIDENCE

The GRADE approach to rating the certainty of evidence for randomized controlled trials is based on five reasons to possibly rate down the quality of evidence.[1]	
Reason	**Consequence**
Limitations in study design or execution (risk of bias)	↓ 1 or 2 levels
Inconsistency of results	↓ 1 or 2 levels
Indirectness of evidence	↓ 1 or 2 levels
Imprecision	↓ 1 or 2 levels
Publication bias	↓ 1 or 2 levels

SUPPLEMENT TABLE 3. STUDY CHARACTERISTICS

Author, Year Country Funding Risk of Bias	**Intervention Comparator Inclusion/exclusion criteria Study Period/Length of Follow-up**	**Demographics**
Beigel 2020[2] 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[3] China Design: RCT	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

Author, Year Country **Funding** **Risk of Bias**	**Intervention** **Comparator** **Inclusion/exclusion criteria** **Study Period/Length of Follow-up**	**Demographics**
Funding: Government, other 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	**Gender (male):** Remdesivir 56% 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[4] 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	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;	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%

Author, Year Country **Funding** **Risk of Bias**	**Intervention** **Comparator** **Inclusion/exclusion criteria** **Study Period/Length of Follow-up**	**Demographics**
Funding: Industry Risk of Bias: Moderate	radiographic evidence of pulmonary infiltrates and peripheral capillary oxygen saturation (SpO2) ≤ 94% or requiring supplemental oxygen at screening 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)	Asian 11% Other 7% **Time from symptom onset to drug** 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[5] 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)	**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]

Author, Year Country Funding Risk of Bias	**Intervention Comparator Inclusion/exclusion criteria Study Period/Length of Follow-up**	**Demographics**
	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 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	**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
Pan 2020[6] WHO Solidarity 30 countries: Europe (13), Canada, Latin America (5), Asia (9), Africa (2) Design: Open-label randomized trial Funding: Support from WHO and other grants Risk of Bias Low for mortality. Some concern for hospital duration and adverse events (*publication presents interim results only*)	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: contraindication to any study drug (physician's view) because of patient characteristics, chronic liver or heart disease, or some concurrent medication. **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%

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

SUPPLEMENT TABLE 4. OUTCOMES A

Author, Year	Length of hospital stay		Time to recovery		Mortality		Recovery or Combined endpoint "Clinical Improvement"	
	Remdesivir	**Placebo**	**Remdesivir**	**Placebo**	**Remdesivir**	**Placebo**	**Remdesivir**	**Placebo**
Beigel 2020[2] 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[3]	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[4] GS-US-540-5773 SIMPLE 1	**Remdesivir 5-day**	**Remdesivir 10-day**	**Remdesivir 5-day**	**Remdesivir 10-day**	**Remdesivir 5-day**	**Remdesivir 10-day**	**Remdesivir 5-day**	**Remdesivir 10-day**
	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[5] 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)

Pan 2020[6] WHO Solidarity *Interim results*	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**
	Still hospitalized among those reported as discharged On day 7 69% On day 14 22% On day 21 9% No appreciably accelerated recovery between remdesvir and standard of care was observed	Still hospitalized among those reported as discharged On day 7 59% On day 14 19% On day 21 8%	NR	NR	12.5% (301/2743) Rate Ratio: 0.95 [95% CI, 0.81 to 1.11]	12.7% (303/2708)	NR	NR

ARD = absolute risk difference; CI =confidence intervals; HR = Hazard ratio; IQR = interquartile range; NR = not reported

* 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.

SUPPLEMENT TABLE 5. OUTCOMES B

Author, Year	Required invasive mechanical ventilation; Duration of invasive mechanical ventilation, days		Required oxygen; Duration of oxygen support, days	
	Remdesivir	**Placebo**	**Remdesivir**	**Placebo**
Beigel 2020[2] 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[3]	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[4] GS-US-540-5773 SIMPLE 1	**Remdesivir 5-day**	**Remdesivir 10-day**	**Remdesivir 5-day**	**Remdesivir 10-day**
	8.0% (16/200); Duration NR	16.8% (33/197); Duration NR	NR	NR
Spinner 2020[5] GS-US-540-5774 SIMPLE 2 with standard care	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**
	5-day 0% (0/191) 10-day 0.5% (1/193)	2.0% (4/200)	Time to Room Air Median [IQR] 5-day 5 (3-7) 10-day 4 (2-6) 6.3% (12/191) and 6.7% (13/193) required oxygen support on Day 1	6 (4-14) 11% (22/200) required oxygen support on Day 1
Pan 2020[6] WHO Solidarity *Interim results*	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**
	Initiation of ventilation (including non-invasive) in those not already ventilated 11.9% (295/2489)	Initiation of ventilation (including non-invasive) in those not already ventilated 11.5% (284/2475)	NR	NR

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

SUPPLEMENT TABLE 6. VIRAL LOAD

Author, Year Viral load definition	Pre		Post	
	Remdesivir	**Placebo**	**Remdesivir**	**Placebo**
Beigel 2020[2] ACTT-1	NR	NR	NR	NR
Wang 2020[3] ***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[4] GS-US-540-5773 SIMPLE 1	**Remdesivir 5-day**	**Remdesivir 10-day**	**Remdesivir 5-day**	**Remdesivir 10-day**
	NR	NR	NR	NR
Spinner 2020[5] GS-US-540-5774 SIMPLE 2 with standard care	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**
	NR	NR	NR	NR
Pan 2020[6] WHO Solidarity *Interim results*	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**
	NR	NR	NR	NR

NR = not reported

SUPPLEMENT TABLE 7. HARMS A (BASED ON NUMBER OF SUBJECTS REPORTING AT LEAST ONE EVENT)

Author, Year	Serious AE		AE leading to drug withdrawal		Any AE	
	Remdesivir	**Placebo**	**Remdesivir**	**Placebo**	**Remdesivir**	**Placebo**
Beigel 2020[2] ACTT-1	24.6% (131/532) [a] *Study-related* 2 events Grade 3 or 4 51.3% (273/532)	31.6% (163/516) [a] *Study-related* 3 events Grade 3 or 4 57.2% (295/516)	10.7% (57/532) [a]	14.9% (77/516) [a]	57.3% (305/532) *	62.6% (323/516) *
Wang 2020[3]	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[4] 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[5] 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)	45.0% (90/200) Grade ≥3 12.0% (24/200)

					10-day 10.9% (21/193)	
Pan 2020[6] WHO Solidarity *Interim results*	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**
	NR	NR	NR	NR	NR	NR

AE = adverse event; NR = not reported

* Data for the treated population

SUPPLEMENT TABLE 8. HARMS B (BASED ON NUMBER OF SUBJECTS REPORTING AT LEAST ONE EVENT)

Author, Year	Respiratory failure or acute respiratory distress syndrome		Cardiopulmonary failure	
	Remdesivir	**Placebo**	**Remdesivir**	**Placebo**
Beigel 2020[2] ACTT-1	Serious respiratory failure 7.3% (39/532) * Respiratory distress 1.1% (6/532) *	Serious respiratory failure 8.0% (66/516) * Respiratory distress 2.1% (11/516) *	NR	NR
Wang 2020[3]	Respiratory failure or acute respiratory distress syndrome 10.3% (16/155) Grade 3 or 4 2.6% (4/155)	Respiratory failure or acute respiratory distress syndrome 7.7% (6/78) Grade 3 or 4 5.1% (4/78)	5.2% (8/155)	9.0% (7/78)
Goldman 2020[4] GS-US-540-5773 SIMPLE 1	**Remdesivir 5-day**	**Remdesivir 10-day**	**Remdesivir 5-day**	**Remdesivir 10-day**
	6.0% (12/200)	10.7% (21/197)	NR	NR
Spinner 2020[5] GS-US-540-5774 SIMPLE 2 with standard care	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**
	NR	NR	NR	NR
Pan 2020[6] WHO Solidarity *Interim results*	**Remdesivir**	**Standard Care**	**Remdesivir**	**Standard Care**
	NR	NR	NR	NR

AE = adverse event; NR = not reported
*Data for the treated population

SUPPLEMENT TABLE 9. RISK OF BIAS – RANDOMIZED CONTROLLED TRIALS

Author, Year	Random sequence generation	Allocation concealment	Blinding *	Incomplete outcome data†	Selective outcome reporting ‡	Overall Risk of Bias §
Beigel 2020[2] 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[3] 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[4] 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[5] GS-US-540-5774 SIMPLE 2 with standard care	Low, adequate, computer generated	Low, adequate, web-based	Open-label Outcome assessors were not blinded.	Low, 8 patients in the 5-day group and 4 in the 10-day group not included in analyses (did not start treatment)	No	Low

Author, Year	Random sequence generation	Allocation concealment	Blinding *	Incomplete outcome data†	Selective outcome reporting ‡	Overall Risk of Bias §
Pan 2020[6] WHO Solidarity	Low, adequate, computer generated through study website	Low, adequate, cloud-based	Open-label. External statisticians (independent data and safety monitoring committee) were utilized	Low, 7 patients in remdesivir and 17 patients in control group not included in analyses (no or uncertain consent to follow-up)	Yes – limited reporting of hospitalization duration; no adverse event reporting	Low for mortality. Publication presents interim results only

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.

SUPPLEMENT TABLE 10. COVID-19 DISEASE SEVERITY

COVID-19 Disease Severity	NIH COVID-19 Treatment Guidelines[7]	WHO Clinical Management of COVID-19[8]	Food and Drug Administration (FDA)[9]	Included Studies in Evidence Report
Asymptomatic or Presymptomatic	Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (*eg*, polymerase chain reaction) or antigen test, but have no symptoms.	**NA**	Positive testing by standard reverse transcription polymerase chain reaction (RT-PCR) assay or equivalent test; no symptoms.	**NA**
Mild	Individuals who have any of the various signs and symptoms of COVID 19 (*eg*, fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging.	Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.	Positive testing by standard RT-PCR assay or equivalent test; symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea; no clinical signs indicative of Moderate, Severe, or Critical Severity	**ACTT-1[2]:** Mild/Moderate disease: confirmed COVID-19 positive and hospitalized with radiographic infiltrates by imaging, SpO_2 >94% and respiratory rate <24 breaths per minute without supplemental oxygen. Mild not defined. Results for Mild not provided.

COVID-19 Disease Severity	NIH COVID-19 Treatment Guidelines[7]	WHO Clinical Management of COVID-19[8]	Food and Drug Administration (FDA)[9]	Included Studies in Evidence Report
Moderate	Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level.	Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥90% on room air OR Child with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia.	Positive testing by standard RT-PCR assay or equivalent testing; symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion; clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥20 breaths per minute, saturation of oxygen (SpO_2) >93% on room air at sea level, heart rate ≥90 beats per minute; no clinical signs indicative of Severe or Critical Illness	**ACTT-1[2]:** Mild/Moderate disease: confirmed COVID-19 positive and hospitalized with radiographic infiltrates by imaging, SpO_2 >94% and respiratory rate <24 breaths per minute without supplemental oxygen. Moderate not further defined. Results for Moderate not provided. **SIMPLE 2[5]:** Moderate disease: confirmed COVID-19 positive and hospitalized with radiographic evidence of pulmonary infiltrates and oxygen saturation >94% on room air. **WHO[6]:** Not defined as "moderate" but SOLIDARITY included and provided mortality data for hospitalized patients without supplemental oxygen on study entry.

COVID-19 Disease Severity	NIH COVID-19 Treatment Guidelines[7]	WHO Clinical Management of COVID-19[8]	Food and Drug Administration (FDA)[9]	Included Studies in Evidence Report
Severe	Individuals who have respiratory frequency >30 breaths per minute, SpO_2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, or lung infiltrates >50%.	Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO_2 <90% on room air OR Child with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following: 1) Central cyanosis or SpO_2 <90%; severe respiratory distress (*eg* fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. 2) Fast breathing (in breaths/min): <2 months: ≥60; 2–11 months: ≥50; 1–5 years: ≥40.	Positive testing by standard RT-PCR assay or an equivalent test; symptoms suggestive of severe systemic illness with COVID-19, which could include: any symptom of moderate illness or shortness of breath at rest, or respiratory distress; clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥30 per minute, heart rate ≥125 per minute, SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2 <300; no criteria for Critical Severity. Remdesivir Emergency Use Authorization Criteria: Hospitalized with severe disease defined as patients with an oxygen saturation ≤94% on room air or requiring supplemental oxygen or mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).	**Wang[3], ACTT-1[2], SIMPLE-1[4]:** Hospitalized patients meeting one of more of the following criteria: radiographic infiltrates by imaging or clinical assessment and an oxygen saturation ≤94% on room air or tachypnea (respiratory rate >24 breaths per minute without supplemental oxygen) or requiring supplemental oxygen or mechanical ventilation **WHO[6]**: Not defined as "severe" but SOLIDARITY included and provided mortality data for hospitalized patients with supplemental oxygen on study entry.

COVID-19 Disease Severity	NIH COVID-19 Treatment Guidelines[7]	WHO Clinical Management of COVID-19[8]	Food and Drug Administration (FDA)[9]	Included Studies in Evidence Report
Critical	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction	Positive testing by standard RT-PCR assay or equivalent test; evidence of critical illness, defined by at least one of the following: respiratory failure defined based on resource utilization requiring at least one of the following: endotracheal intubation and mechanical ventilation, oxygen delivered by high flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation); shock (defined by systolic blood pressure <90 mm Hg, or diastolic blood pressure <60 mm Hg or requiring vasopressors); multi-organ dysfunction/failure.	**ACTT-1**[2]: Not defined as "critical" but ACTT-1 included and provided recovery outcomes for patients requiring invasive mechanical ventilation or ECMO. **WHO**[6]**:** Not defined as "critical" but SOLIDARITY included and provided mortality data for hospitalized patients requiring invasive mechanical ventilation or ECMO on study entry.

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