Remdesivir Evidence Review

Summary:

- Remdesivir administered intravenously over 3 days to non-hospitalised patients within 7 days of COVID-19 symptom onset and had risk factors for disease progression , resulted in a relative risk reduction of 87% in hospitalisation or death at day 28
- Non statistically significant impact on mortality in meta-analysis. Mortality reduction up to day 14 is not statistically significant at day 28. Meta-analysis remains consistent with 20% or less impact on mortality on those not initially on ventilation. There is no statistically significant impact in those requiring oxygen and suitable for mechanical ventilation in reducing need for mechanical ventilation.
- There is no statistical evidence of benefit once patient is on mechanical ventilation. Meta-analysis of all randomised clinical trials to date does not exclude the possibility of a modest increase in mortality
- On ACTT-1 trial subgroup analysis patients treated in first 10 days after symptoms and younger than 40 and on oxygen (not high flow or non invasive ventilation) have significant benefit. An un-prespecified secondary analysis of the raw NIAID ACTT-1 trial data showed a mortality reduction of 8.5% at the 0.05 significance level in those requiring low-flow oxygen at recruitment and no benefit on high flow oxygen or NIV. Results from SOLIDARITY, a larger trial, did not address the early treatment issue and did not confirm any younger age benefit.
- The mean age of the patients studied was less than 60 up to mid September. This contrasts with the mean age of patients treated in real practice. There have been no safety incidents in the Trust.
- Remdesivir is commissioned for treatment by the NHS on criteria subsequently inserted into the SPC in January 2021. It is available for treatment in most 1st world countries. WHO regards it as an ineffectual treatment on resource effectiveness grounds.
- The NHS interim commission criteria from June 2021 now allow use in severely immunocompromised patients without meeting the former criteria for a COVID-19 pneumonia (Patients with a significant impairment of humoral immune response (antibody production) and/or cellular immune competence) and in haemodialysis patients previously excluded by eGFR criteria.

Please note: As at time of preparation of this paper all COVID-19 resources are free to access on internet and can be accessed by clicking on the in line link . The references and additions to this review are done at the end except for summary above so most recent(and convincing) paper will be cited towards the end. The standard reference for UK practice is the relevant NICE Guideline but this document may be updated faster than this. The main source for this briefing is from The Centre for Evidence-Based Medicine, Oxford: Drug vignettes: Remdesivir updated as of 23rd September 2020. The studies are labelled as to whether data included therein is likely to have been known at time of

licensing (see review of the abbreviated fast track process) and NHS commissioning decision (3rd July)

Studies in patients

Holshue et al [available to licensing authorities]

This reported the first patient to be treated for COVID-19 in the USA . He was a 35-year-old American who presented with cough and fever for four days, having returned from Wuhan on the first day of his illness. Viral PCR confirmed SARS-CoV-2 infection. The chest X-ray was clear 7 days after the start of the illness, but in view of fears of deterioration, remdesivir was infused. Radiology showed left lower lobe pneumonia on day 9, and a fall in oxygen saturation. He was given supplementary oxygen and vancomycin and cefepime for possible hospital-acquired pneumonia. His condition improved by day 12 and his symptoms gradually abated [1]. ***This case adds no useful information about the possible therapeutic value of remdesivir.***

Bhatraju et al [available to licensing authorities]

This is an early report of 24 patients with confirmed COVID-19, of whom 18 required mechanical ventilation, stated that seven patients had received compassionate-use remdesivir, but noted that "***we have insufficient information to report associated outcomes***." Twelve of the 24 patients died [2].

Grein et al [available to licensing authorities]

Short-term outcomes were reported in 53 of 61 patients who received at least one dose of remdesivir, 200 mg on day 1 followed by 100 mg/day for the next nine days [3]. At the start of remdesivir treatment 30 patients were being ventilated, and four were having extracorporeal membrane oxygenation (ECMO). The patients were recruited from three continents. Follow-up was planned for day 28 or until discharge or death. The authors used a "cumulative index of clinical improvement", but its validity is unclear. A more robust measure of outcome was death or discharge. By a median of 18 days after treatment had started, 25/53 patients had been discharged from hospital, and 7 (13%) had died. Among patients who received no mechanical ventilation, mortality was 5%. Sixty percent of patients suffered one or more adverse event, serious in 23%. The most common adverse events were abnormal liver function, diarrhoea, rash, renal impairment, and hypotension.

The authors noted that mortality in patients admitted to hospital in Wuhan was 22% overall and 66% in mechanically ventilated patients. As they stated, "***Interpretation of the results of this study is limited by the small size of the cohort, the relatively short duration of follow-up, potential missing data owing to the nature of the program, the lack of information on 8 of the patients initially treated, and the lack of a randomized control group***."

Wang et al [available to licensing authorities]

This was a multi-site, randomized, masked, placebo-controlled trial of remdesivir + standard care versus standard care in patients with PCR positive SARS-CoV-2 infection, pneumonia on chest radiography, and hypoxyaemia (O_2 saturation below 95% or a reduced P_aO_2:FiO_2 ratio), recruited within 12 days of symptoms [4]. Recruitment stopped after 158 patients had been enrolled in the remdesivir arm and 78 in the placebo arm; a further patient, enrolled in the placebo arm, did not take part in the trial. The groups were somewhat mismatched, with more men in the placebo group (56% -v- 65%), but more patients with hypertension, diabetes, and coronary heart disease, and more

patients who required high-flow oxygen or non-invasive ventilation in the remdesivir group. Rates of additional treatments—interferon alfa, lopinavir-ritonavir, antibacterial agents, and corticosteroids—were similar in the two groups. The primary end-point was defined as time to clinical improvement of two grades or more on a six-point scale, or discharge from hospital, within 28 days after randomization. The primary outcome was a non-significant difference in clinical improvement, which fell from 23 days in the placebo arm to 21 days in the remdesivir arm (hazard ratio 1.23, 0.87 to 1.75). Mortality by day 28 was 14% in the remdesivir arm and 13% in the placebo arm. The authors concluded that "***Our trial found that intravenous remdesivir did not significantly improve the time to clinical improvement, mortality, or time to clearance of virus in patients with serious COVID-19 compared with placebo***." Note that the mortality rate was very similar to the rate reported by Grein et al in the case series of patients treated with remdesivir published in the *New England Journal of Medicine* [3].

Beigel et al [available to licensing authorities]
The preliminary results of the first stage of ACTT-1, an adaptive trial of treatments for COVID-19, were published on 22 May 2020 [5]. The interim results of the trial, in which 538 patients were randomized to remdesivir and 521 to placebo, were analysed early, at the request of the data monitoring committee. Financial support came from the National Institute of Allergy and Infectious Diseases, but Gilead Sciences provided remdesivir for the trial. On the 8th October 2020 the final results of the trial[6] were published allowing benefit to be better understood (see later).

The specified primary outcome was time to recovery up to day 29, recovery having been defined in the protocol as "the first day on which the subject satisfies one of the following three categories from the ordinal scale: 1) Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Not hospitalized, no limitations on activities." Mortality at 28 days and duration of hospital stay were two of 28 secondary outcomes [7]. Selected baseline and outcome data are shown in Table 1.

Table 1. Selected data from the study of Beigel et al

	Remdesivir	**Placebo**	**Rate ratio (95% CI)**	**P value**
At baseline				
N	541	522		
Aged 65+ years	187 (34.6%)	198 (37.9%)		
Supplemental O_2 only	222 (41%)	199 (38.1%)		
Invasive ventilation/ECMO	125 (23.1%)	147 (28.2%)		
Days from onset	9 (6–12)	9 (7–13)		
Outcomes				
Median time to recovery (days)	11 (9–12)	15 (13–19)	1.32 (1.12–1.55)	<0.001
Mortality at day 14	32 (7.1%)	54 (11.9%)	0.70 (0.47–1.04)	NS
Discharged by day 15	257 (59.2%)	203 (49.5%)		

Based on these results, the European Medicines Agency granted a Conditional Marketing Authorization to remdesivir [8].

Olender et al [assumed available to licensing authorities and was available NHS commissioners]
The manuscript of a paper accepted for publication in the journal *Clinical Infectious Diseases* was posted online on 24 July 2020 [9]. The title was "Remdesivir for Severe COVID-19 versus a Cohort Receiving Standard of Care". The corresponding author, who was not the first author, and a further 14 of the 33 named authors were from Gilead Sciences, the manufacturer of remdesivir, who provided funding for the study.

This was an analysis of observational data on the outcomes in patients with COVID-19, some of whom received treatment with remdesivir. The analysis included results from a study whose protocol was titled "Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19)" [10]. This was described as a randomized Phase III study. According to the clinicaltrials.gov website, it had recruited 4891 patients by the time the study closed on 30 June 2020.

The study reported in *Clinical Infectious Diseases* combined the results of a randomized trial of two different doses of remdesivir and a retrospective cohort study of clinical outcomes in patients receiving "standard of care". All the patients had tested positive for SARS-CoV-2, had been admitted to hospital, and required oxygen for an oxygen saturation of 94% or less.

The primary endpoint was the proportion of patients who had recovered at 14 days, judged by rather complex criteria related to a 7-point clinical scale, on which "recovery was defined as having a score of 5–7 points for patients with a baseline score of 2–4, or a score of 6–7 for patients with a baseline score of 5, or a score of 7 for patients with a baseline score of 6".

The authors adjusted for differences in baseline characteristics by "the inverse probability of treatment weighting procedure", which involved propensity scores, and produced 312 patients (out of 397 patients assessed) treated with remdesivir and a control group of 818 patients (out of 1268 patients assessed) who received standard care. The number of remdesivir-treated subjects was 298 before statistical adjustment and 312 after adjustment. Notes stated that "The weighted patient number was 312 after applying the IPTW weighting method", and "Based on IPTW, the number of patients in remdesivir and non-remdesivir cohorts were modestly different from the original sample size (some patients weighted more, and some patients weighted less based on the patients' propensity scores)".

Supplementary tables listed the factors for which correction was made. Supplemental Digital Content 6 was a table containing a list of potential medications for COVID-19 treatment; dexamethasone was not listed and was therefore presumably not included in the propensity scoring, despite the fact that it reduces mortality in those with severe disease.

A cohort of Italian patients was omitted because they had a higher mortality rate than expected.

The authors concluded that "In this comparative analysis, by day 14, remdesivir was associated with significantly greater recovery and 62% reduced odds of death versus standard-of-care treatment in patients with severe COVID-19."

This is another company-sponsored interim analysis of observational data on remdesivir, when what we need is a proper, large, masked, randomized, controlled trial.

Spinner et al [post license and commissioning decision]

The results of an unmasked, three-arm, randomized trial of remdesivir for 10 days, remdesivir for 5 days, or standard care alone, were published online on 21 August 2020 [11] and in print on 15 September [12].

Patients were chosen to have "moderate COVID-19 pneumonia" and a positive PCR test for SARS-CoV-2. "Moderate COVID-19 pneumonia" was defined as the presence of any radiographic evidence of pulmonary infiltrates and an oxygen saturation above 94% on room air, with adequate liver and kidney function.

The treatments were randomly assigned in equal proportions to each of the three groups. The protocol specified "up to approximately 160 centers globally" and the number of subjects planned was "approximately 1600" [13]. However, in the published data 584 patients were described, recruited from 105 hospitals in the USA, Europe, and Asia; that is, fewer than six patients per hospital on average. A third of the hospitals enrolled 1 or 2 patients each.

Patients in the active treatment arms were given an intravenous infusion of remdesivir 200 mg on day 1 and 100 mg intravenously on subsequent days for 5 or 10 days.

The original primary objective (24 February 2020) was "To evaluate the efficacy of 2 remdesivir regimens compared to standard of care, with respect to the proportion of participants discharged on or before Day 14"; this was changed on 15 March to "To evaluate the efficacy of 2 remdesivir regimens compared to standard of care, with respect to clinical status assessed by a 7-point ordinal scale Day 11".

The baseline data and primary and selected secondary outcome data were as follows:

	Remdesivir for 5 days	**Standard care**	**Ratio (95% CI)**	**P**
At baseline				
N	191	200		
Age (median)	58	57		
Air or O_2 only	189	198		
NIVV or HFO	2	2		
Days from onset	8	9		
Steroids	33	38		
Outcomes				
Primary endpoint			OR 1.65 (1.09–2.48)	0.02
Median time to recovery (days)	6 (5–10)	7 (4–14)	RR 1.18 (0.96–1.45)	NS
Mortality at day 11	0	4		
Recovered by day 11	141	128		
Recovered by day 28	175	170		
Died by day 28	2	4	RR 0.51 (0.09–2.80)	NS
Kaplan–Meier estimate of survival	99%	98%		NS

OR = odds ratio, RR = rate ratio, NS = not significant at P=0.05

	Remdesivir for 10 days	Standard care	Rate ratio (95% CI)	P
At baseline				
N	193	200		
Age	56	57		
Air or O_2 only	192	198		
NIVV or HFO	1	2		
Days from onset	8	9		
Steroids	29	38		
Outcomes				
Primary endpoint			*	NS
Median time to recovery (days)	8 (4–13)	7 (4–15)	1.11 (0.90-1.37)	NS
Mortality at day 11	2	4		
Recovered by day 11	132	128		
Recovered by day 28	178	175		
Died by day 28	3	4	0.76 (0.17-3.40)	NS
Kaplan-Meier estimate of survival	98%	98%		NS

* "The proportional odds assumption was not met for the 10-day remdesivir group comparison, so no odds ratio is presented; the P value was calculated using the Wilcoxon rank sum test."

"**The 5-day or 10-day remdesivir groups and standard care did not differ significantly for time to clinical improvement, or time to recovery. The remdesivir and standard care groups did not differ significantly in duration of oxygen therapy or hospitalization, or in survival to 28 days**."

Eight of the thirty authors of the study were employees of Gilead, which markets remdesivir. A further nine authors had received financial or non-financial support from the company.

The authors interpreted their findings to mean that "Hospitalized patients with moderate COVID-19 randomized to a 5-day course of remdesivir had a statistically significantly better clinical status compared with those randomized to standard care at 11 days after initiation of treatment, but the difference was of uncertain clinical importance."

Beigel et als post license and commissioning on 8th October 2020 final analysis[6].

This had data on 1062 patients who underwent randomization (with 541 assigned to remdesivir

and 521 to placebo), which is 4 more than the initial report[6]. Those in the remdesivir arm had a

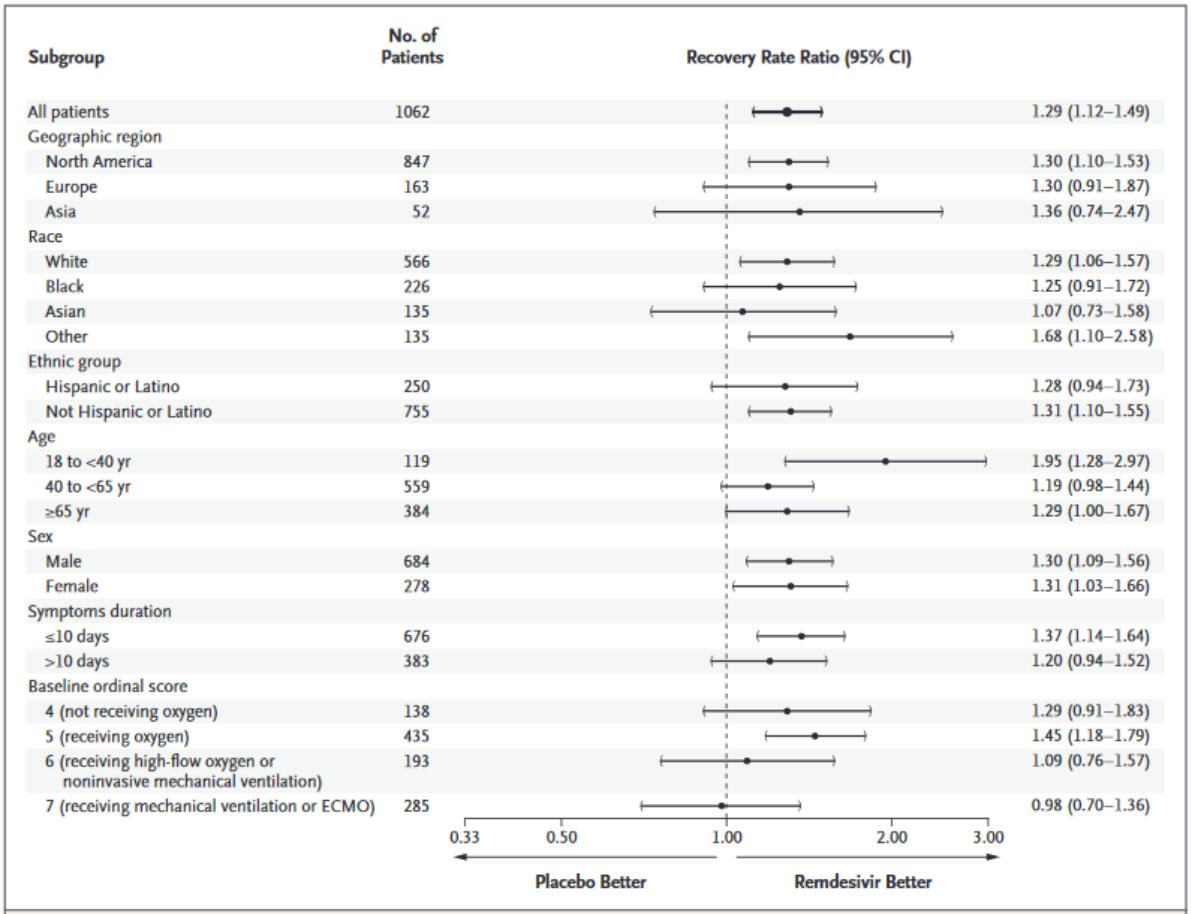


Figure 3. Time to Recovery According to Subgroup.
The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects. Race and ethnic group were reported by the patients.

median recovery time of 10 days compared with 15 days in the placebo arm and clinical improvement was more likely by day 15 in the remdesivir arm after adjustment for disease severity. Subgroup analysis showed benefit was selective and in particular most benefit occurred in those less than 40 years old and with symptom duration of less than 10 days. Escalation to high flow oxygen and non invasive ventilation reduced benefit and invasive ventilation or ECMO had no benefit. Mortality benefit at 28 days was not significant at 3.8%. Ad hoc subgroup analysis of 29 day mortality data was subsequently published by the marketing authorisation holder in January 2021.

> 29-day mortality in the overall population was 11.6% remdesivir vs 15.4% for placebo (hazard ratio, 0.73; [95% CI 0.52 to 1.03]; p=0.07). A post-hoc analysis of 29-day mortality by ordinal scale is reported.†1

29-Day mortality outcomes by ordinal scale at baseline—NIAID ACTT-1 Trial

ORDINAL SCORE AT BASELINE	
5	6

	Requiring low-flow oxygen		Requiring high-flow oxygen or non-invasive mechanical ventilation	
	Remdesivir (N=232)	Placebo (N=203)	Remdesivir (N=95)	Placebo (N=98)
29-day mortality	4.1	12.8	21.8	20.6
Hazard ratio[b] (95% CI)	0.30 (0.14, 0.64)		1.02 (0.54, 1.91)	

ECMO = Extracorporeal membrane oxygenation

a Not a pre-specified analysis.
b Hazard ratios for baseline ordinal score subgroups are from unstratified Cox proportional hazards models.

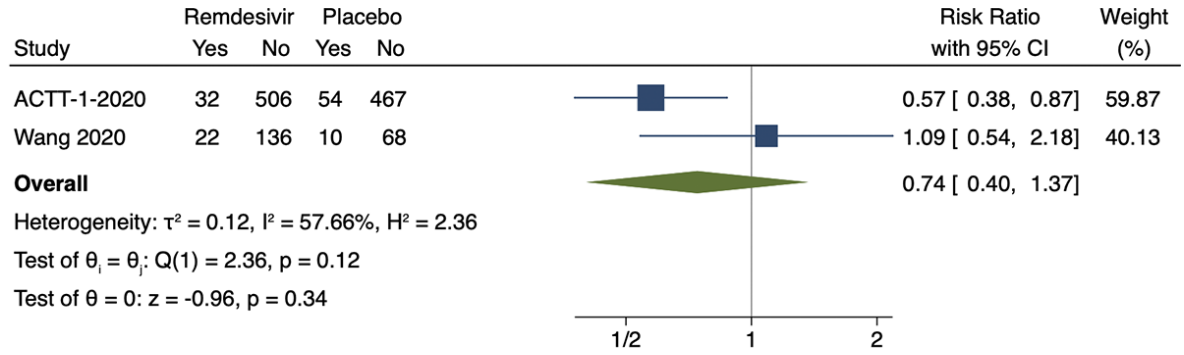
In other studies, VEKLURY was shown to have no benefit on mortality rates.

WHO SOLIDARITY interim results published 16th October 2020[14]

Remdesivir death rate ratios (with 95% CIs and numbers dead/randomized, drug vs its control) were: RR=0.95 (0.81-1.11, p=0.50; 301/2743 active vs 303/2708 control). So remdesivir did not definitely reduce mortality (in unventilated patients or any other subgroup of entry characteristics), initiation of ventilation or hospitalisation duration. Please see meta-analysis section below for trends with this data included.

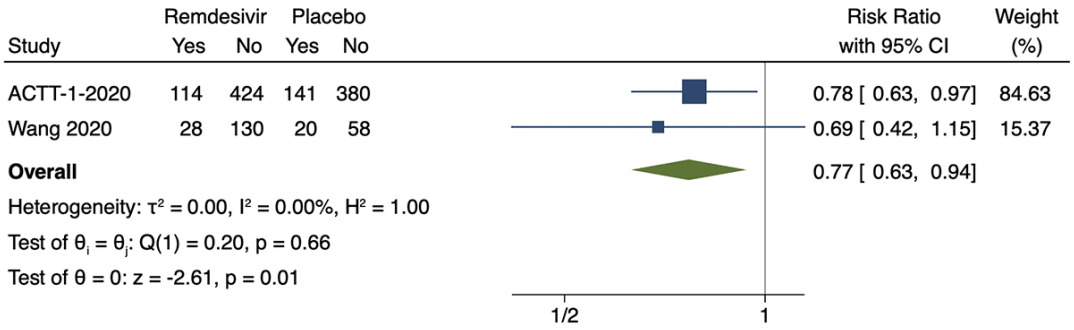
The LIVING Project is an ongoing meta-analysis of treatments in COVID-19. As of 17th September[15] it reported **there was no evidence of a difference between remdesivir versus placebo on all-cause mortality (RR 0.74; 95% CI 0.40–1.37; p = 0.34, I2 = 58%; 2 trials; very low certainty) or nonserious adverse events (RR 0.94; 95% CI 0.80–1.11; p = 0.48, I2 = 29%; 2 trials; low certainty). Meta-analysis showed evidence of a beneficial effect of remdesivir versus placebo on serious adverse events (RR 0.77; 95% CI 0.63–0.94; p = 0.009, I2 = 0%; 2 trials; very low certainty) mainly driven by respiratory failure in one trial.**

All-cause mortality



Random-effects DerSimonian-Laird model

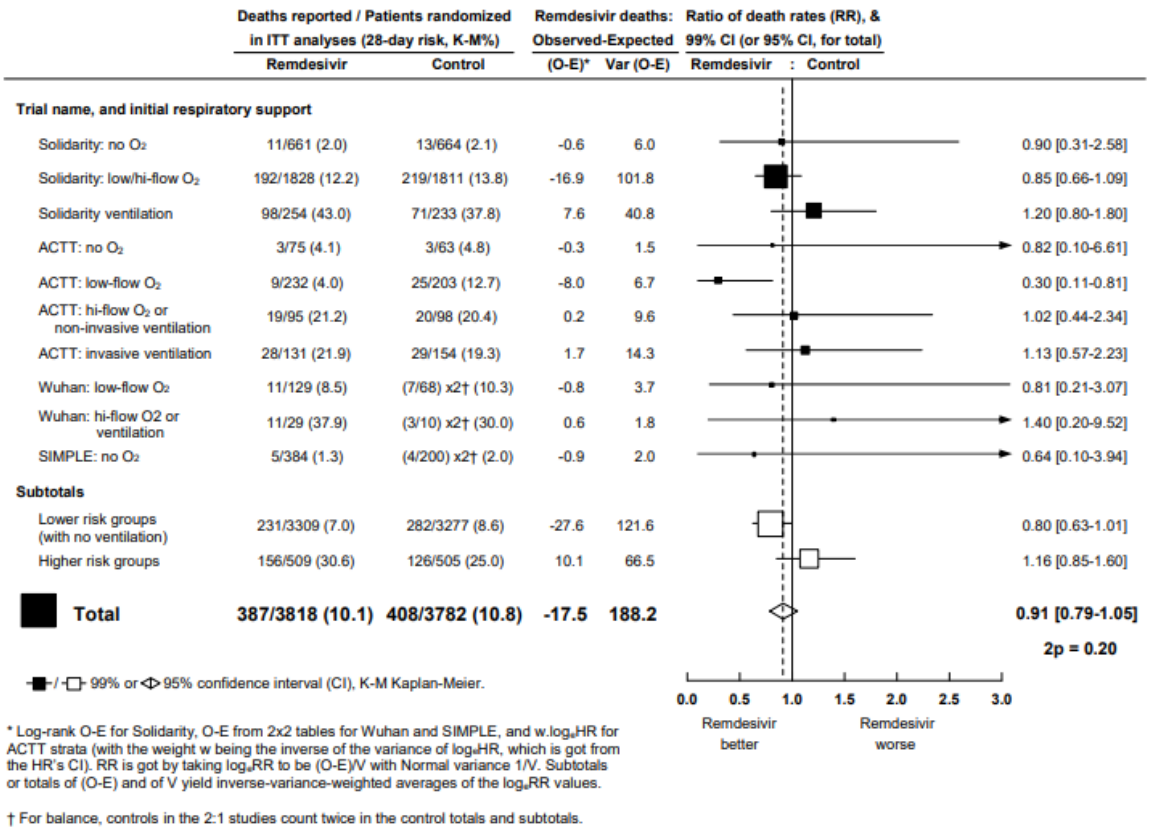
Serious Adverse effects driven by respiratory failure in one trial (ie need for ventilation)



Random-effects DerSimonian-Laird model

The before peer review meta-analysis done including Solarity trial data [14] suggests no significant impact on mortality. Please note that there are minor data inconsistencies wrt to final ACCT-1 published data detected by this reviewer. Including this trial result does not appear to exclude the possibility of a mortality reduction of up to 20% in those treated before ventilation.

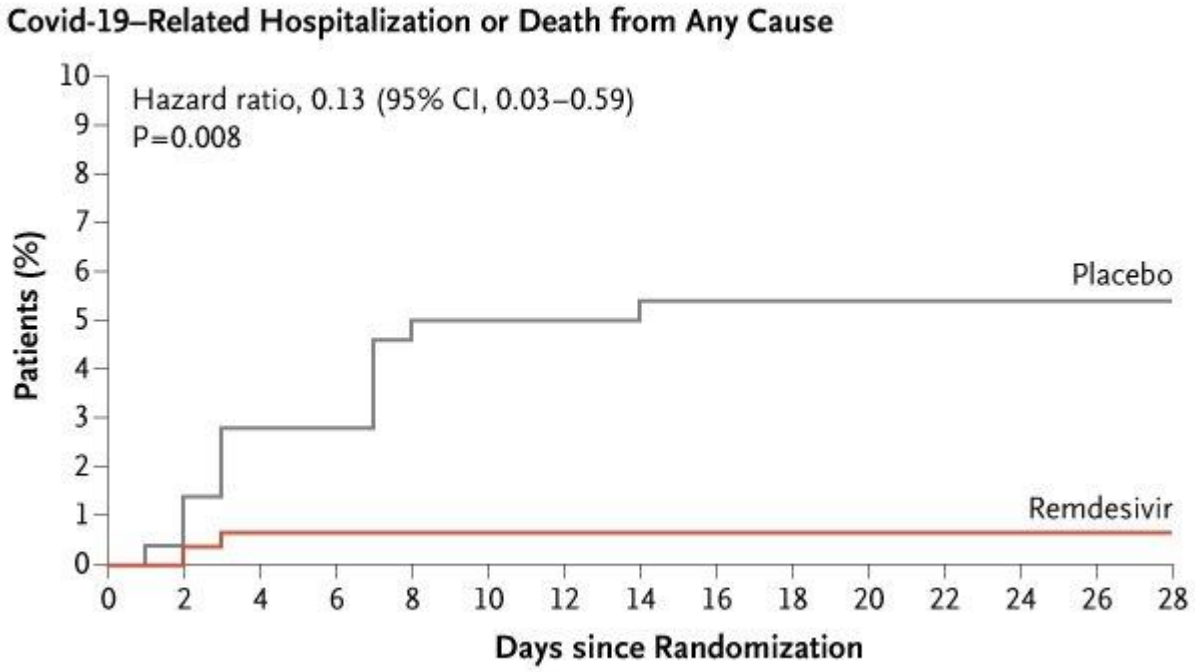
Figure 4. Remdesivir vs control – Meta-analysis of mortality in trials of random allocation of hospitalised COVID-19 patients to Remdesivir or the same treatment without it



* Log-rank O-E for Solidarity, O-E from 2x2 tables for Wuhan and SIMPLE, and w.$\log_e$HR for ACTT strata (with the weight w being the inverse of the variance of $\log_e$HR, which is got from the HR's CI). RR is got by taking $\log_e$RR to be (O-E)/V with Normal variance 1/V. Subtotals or totals of (O-E) and of V yield inverse-variance-weighted averages of the $\log_e$RR values.

† For balance, controls in the 2:1 studies count twice in the control totals and subtotals.

The results of the PINETREE trial were published on 22nd December 2021 and showed major benefit early remdesivir to prevent progression to severe Covid-19 in outpatients [19}. A 3 day iv course was used and this produced a 87% lower risk of hospitalization or death than placebo. Covid-19–related hospitalization or death from any cause occurred in 2 patients (0.7%) in the remdesivir group and in 15 (5.3%) in the placebo group (hazard ratio, 0.13; 95% confidence interval [CI], 0.03 to 0.59; P=0.008). A total of 4 of 246 patients (1.6%) in the remdesivir group and 21 of 252 (8.3%) in the placebo group had a Covid-19–related medically attended visit by day 28 (hazard ratio, 0.19; 95% CI, 0.07 to 0.56). No patients had died by day 28. Adverse events occurred in 42.3% of the patients in the remdesivir group and in 46.3% of those in the placebo group



Registered clinical trials

There appear to be 11 trials of remdesivir in COVID-19, of which one is single-masked and three double-masked. The number of patients to be studied in masked trials is 2061 out of 22,437 in all (9.2%).

Safety Reports [after licensing and commissioning]

The overall safety of remdesivir for those meeting oxygen treatment criteria appears to be good. In the ACTT-1 trial serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%). By day ten 52 in the remdesivir arm and 70 in the placebo arm had with drawn [6]. Acute liver failure assigned to the remdesivir has been reported in two patients with a 50% mortality[15]. Single case reports appear to exist for side effects such as nephrotoxicity. On 5th October the EMEA announced that the Pharmacovigilance Risk Assessment Committee (PRAC) was commencing a review of its nephrotoxicity due to a safety signal[16].

Guidelines

WHO published its interim Guideline recommended against the use of Remdesivir on 20th November 2020 [16] on resource effectiveness grounds and this has not changed on 17th December 2020 update.

In January 2021 the SPC was updated and is now more consistent with the November 2020 NHS commissioning criteria. The Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 were last updated on 8/01/2021[17] and also remains consistent with the NHS interim commissioned criteria of 12th November based on NICE evidence review[18]. The NHS interim commissioning policy criteria were updated on 14th June [19] based on further evidence of subgroup safety and effectiveness.

The NICE guideline https://www.nice.org.uk/guidance/ng191 was last reviewed on 16th December 2021 for this document.