EVIDENCE SUMMARY

Should remdesivir be used in the management of COVID-19 patients?

Evidence Reviewers: Ian Theodore Cabaluna, RPh, MD, GDip (Epi) MSc (cand); Aldrich Ivan Lois D. Burog, MD, MSc (cand.), Howell Henrian G Bayona, MSc, CSP-PASP

Date of review: February 19, 2021

REMDESIVIR

RECOMMENDATION

We suggest against the use of remdesivir among COVID-19 patients who do not require oxygen supplementation and with O_2 saturation ≥94% *(Low quality of evidence; Conditional recommendation)*

We suggest adding remdesivir to dexamethasone among patients with COVID-19 infection who have O_2 saturation <94% and/or requiring oxygen supplementation. (*Low quality of evidence; Conditional recommendation)*

There is insufficient evidence for or against the use of remdesivir among patients with COVID-19 infection who are already on high flow oxygen, non invasive or invasive mechanical ventilation or ECMO. *(Low quality of evidence)*

Consensus Issues (may include Cost, Patient Values and Preferences, Feasibility, Acceptability, Affordability)

Early introduction of remdesivir in the treatment of COVID-19 is preferred because of its inhibitory action on the RNA-dependent polymerase resulting in halting of viral replication. Remdesivir is a relatively safe drug, however, its cost should be considered. Hence, routine use of the drug is not recommended. There are 26 ongoing trials pertaining on the efficacy and safety of remdesivir for the treatment of COVID-19.

Key Findings

Four randomized controlled trials on the use of remdesivir as treatment for COVI-19 were found. Low quality evidence shows that remdesivir has limited effect on all cause-mortality, clinical improvement, and initiation of mechanical ventilation among confirmed COVID-19 patients. However, remdesivir appears to be beneficial in the time to clinical improvement especially among cases needing supplemental oxygen but not high flow oxygen/ mechanical ventilation. Remdesivir did not show increased risk for serious adverse events. Availability and cost of intervention should be considered before making recommendation regarding its use locally.

Introduction

Remdesivir is an intravenously administered antiviral drug originally developed for the Ebola virus that is currently being evaluated as a potential treatment for COVID-19. It is a nucleotide analogue that inhibits RNA-dependent RNA polymerases.[1] Several in-vitro studies in cells, primates, and mice demonstrated its antiviral activities against an array of RNA viruses (e.g., MERS-COV, Ebola Virus, SARS-COV) [2-4]. An in-vitro study has shown that remdesivir can inhibit the growth of COVID-19 virus in infected Vero cells and inhibit infection in human cell line [5].

Review Methods

Trials found in the COVID-NMA living data (as of December 4, 2020) were included. Screening after their last search was done in Medline, Cochrane Library, MedRivx to check for newer trials. Randomized controlled trials on remdesivir compared to placebo or standard of care on COVID-19 patients, regardless of severity were included.

Results

There were 4 published randomized controlled clinical trials (RCTs) evaluating the effect of remdesivir compared to placebo and/or standard of care among confirmed COVID-19 patients (n=7,345). [6-10] All of these trials were included in the COVID-NMA Living Data which was last updated on December 4, 2020.[11] As of December 26, 2021, no new trials on remdesivir were found on MEDLINE. Meta-analysis from the COVID-NMA was adopted. Additional meta-analysis was done for the following outcomes: mechanical ventilation, duration of hospitalization, and duration of mechanical ventilation. Appendix 1 summarizes the characteristics of these included RCTs.

Three RCTs [6,7,10] were multi-national studies conducted in the United States, Europe, and parts of Asia, while one RCT [8] was conducted in China. Among the three multinational trials is the WHO Solidarity Trial that also looked at the effectiveness of hydroxychloroquine, lopinavir, and interferon beta-1a. Only one study [7] was conducted among moderate COVID-19 cases, which was diagnosed when patients demonstrated any radiographic evidence of pulmonary infiltrates and an oxygen saturation (SpO2) >94% on room air. Two studies [8,10] were conducted only among severe cases, which were characterized by radiographic infiltrates by imaging, an SpO2 ≤ 94% on room air requiring mechanical ventilation and/or supplemental oxygen, and other clinical signs. The WHO Solidarity trial included all hospitalized COVID-19 cases regardless of severity.

Overall, trends for remdesivir pointed towards potential benefit on all patient-important outcomes but did not reach statistical significance for mortality, initiation of mechanical ventilation, time to recovery/clinical improvement, duration of hospitalization, and duration on mechanical ventilation. Pooled results from 4 RCTs (n=7,345) showed that remdesivir did not decrease all-cause mortality (RR 0.90, 95% CI 0.73-1.11). Based on 2 RCTs (n = 839), clinical improvement among patients on remdesivir was not significantly different (RR 1.06, 95%CI 0.99 to 1.13) from those treated with standard care. There was a trend towards benefit in preventing initiation of mechanical ventilation based on 4 RCTs (n= 6,549), but this did not reach statistical significance (RR 0.65, 95%CI 0.39 to 1.08). Effects of remdesivir on viral conversion, duration of hospitalization, and duration on mechanical ventilation were uncertain due to wide interval estimates.

Remdesivir demonstrated limited beneficial effect in the incidence of recovery and recovery rate. From 2 RCTs (n = 1,658), the rate of recovery was faster in the remdesivir group compared to the placebo/standard care group (Rate Ratio 1.23, 95%CI 1.11-1.37). The rate of clinical improvement was also faster in the remdesivir group (RR 1.22, 95%CI 1.11 to 1.35) based on 3 RCTs (n = 1,895).

The incidence of adverse events was similar among the remdesivir group compared to those on standard of care alone (RR 0.93, 95%CI 0.85-1.01). Common adverse events were decreased glomerular filtration rate, decreased hemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycemia, increased blood creatinine level, hypoalbuminemia, rash, increased neutrophil and increased blood glucose level. There were fewer serious adverse events in the remdesivir group (RR 0.60, 95% CI 0.38-0.96). Serious adverse events that were observed in both groups were respiratory failure and cardiopulmonary failure. Figures 1-8 (Appendix 3) illustrate the effect of remdesivir on various outcomes.

Subgroup analysis on mortality, incidence of clinical improvement/recovery, clinical improvement/ recovery rate and time to clinical improvement/recovery according to severity was done. Patients who had severe COVID-19 were more likely to benefit from remdesivir.

The use of remdesivir was associated with a trend towards benefit among severe patients (i.e. requiring oxygen) for mortality (RR 0.77, 95%CI 0.59 to 1.02). However, its effect remains uncertain for non-severe (RR 1.12, 95%CI 0.65 to 1.92) and critical COVID-19 cases (RR 0.94 0.50 to 1.75).

Incidence of recovery was significantly higher among severe COVID-19 on remdesivir (RR 1.09, 95%CI 1.01 to 1.18). Recovery rate was significantly better for the severe cases requiring oxygen (Rate Ratio 1.45, 95% CI 1.18 to 1.79) but still not on high-flow oxygen (Rate Ratio 1.09, 95%CI 0.76 to 1.57) and mechanical ventilation (Rate Ratio 0.98, 95% CI 0.70 to 1.37). This was noted from a significantly shorter time to recovery for severe/critical cases of 5 days (95%CI -4.93 days to -2.31 days) based on 2 RCTs (n=1,295).

Recommendations from Other Groups

There are varying recommendations regarding the use of remdesivir. The Infectious Disease Society of America (IDSA) and the US NIH recommend giving remdesivir to those with severe COVID-19 while WHO recommends against its use regardless of the severity.

As of December 17, 2020, WHO suggested against the use of remdesivir in addition to standard of care regardless of severity (conditional recommendation, low quality evidence) due to

insufficient evidence on its effectiveness on patient important outcomes such as mortality, need for mechanical ventilation and time to clinical improvement. The WHO panel raised concerns about *"opportunity costs and the importance of not drawing attention and resources away from best supportive care or the use of corticosteroids in severe COVID-19."* [12]

As of February 10, 2021, IDSA suggested against remdesivir for routine treatment of patients with oxygen saturation >94% and no supplemental oxygen and strongly urges for continued study. (Conditional recommendation, very low certainty of evidence) They also suggests the use of remdesivir for treatment of severe COVID-19 in hospitalized patients with $SpO_2 \leq 94\%$ on room air, including patients on supplemental oxygen, on mechanical ventilation and ECMO. (Conditional recommendation, moderate certainty of evidence). In patients on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, low certainty of evidence)

As of February 11, 2021, the US NIH COVID-19 treatment guidelines panel recommends one of the following options for hospitalized patients who require supplemental oxygen but not on high flow oxygen, non-invasive or invasive ventilation, or ECMO: a) remdesivir for patients who require minimal supplemental oxygen (BIIa recommendation), b) dexamethasone plus remdesivir for patients who require increasing amounts of oxygen (BIII recommendation) and c) dexamethasone when combination therapy with remdesivir cannot be used or is not available (BI recommendation). There are insufficient data to recommend either for or against the routine use of remdesivir in in hospitalized patients who do not require oxygen. The use of remdesivir may be appropriate in patients who have a high risk of disease progression. Remdesivir is also not recommended in patients with eGFR <30 mL/minute. Liver function tests and prothrombin time should be obtained on all patients before remdesivir is administered and during treatment as clinically indicated. The panel suggest discontinuing remdesivir if alanine transaminase (ALT) levels increase to >10 times the upper limit of normal and recommend discontinuing if an increase in ALT level and signs or symptoms of liver inflammation are observed.[13]

Research Gaps

As of January 7, 2021, 26 ongoing clinical trials on remdesivir are registered in ClinicalTrial.gov (Appendix 4).

References

[1] Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. *J Biol Chem* 2020.

[2] Ko WC, Rolain JM, Lee NY, et al. Arguments in favour of remdesivir for treating SARS-CoV-2 infections. *Int J Antimicrob Agents* 2020: 105933.

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[7] Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA* 2020; **324**(11): 1048-57.

[8] Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet* 2020; **395**(10236): 1569-78.

[9] Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. *New England Journal of Medicine* 2020.

[10] Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020; **383**(19): 1813-26.

[11] COVID-NMA. The COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials. 2020. https://covid-nma.com/living_data/index.php (accessed December 26,2020 2020).

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[13] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. (accessed February 2021).

Appendix 1: Characteristics of Included Studies

Title/ Author	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
Spinner, 2020	USA Europe UK Asia	596	Hospitalized patients with moderate COVID-19	5- day course 10-day course	Standard care	Clinical status day 11 (primary) Adverse events Time to recovery
Beigel, 2020	USA Denmark UK Greece, Germany Korea Mexico Spain Japan Singapore	1059	Severe COVID-19 patients	10-day course	Placebo	Time to recovery Mortality Adverse events
Wang, 2020	China	237	Severe COVID-19 patients	10-day course	Placebo	Time to clinical improvement Mortality Viral load Adverse events
WHO Solidarity Consortium, 2020	Europe Canada Latin America Asia Africa	11,330 (Total) 5451 (Remdesivir and its control)	All hospitalized patients diagnosed with COVID 19	Group 1: remdesivir, Group 2: hydroxychloroquine, Group 3: lopinavir, Group 4:interferon beta-1a	Standard care	Mortality (primary) Mechanical ventilation Hospital duration

Appendix 2: GRADE Evidence Profile

Author(s): Ian Theodore G. Cabaluna
Question: Remdesivir compared to standard of care in Covid-19
Bibliography: https://covid-nma.com/

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	standard of care	Relative (95% CI)	Absolute (95% CI)		
All cause mortality at Day 14-28 (follow up: mean 28 days)												
4	randomised trials	not serious	not serious	not serious	serious	none	387/3838 (10.1%)	394/3507 (11.2%)	**RR 0.90** (0.73 to 1.11)	**11 fewer per 1,000** (from 30 fewer to 12 more)	⨁⨁⨁◯ MODERATE	
Incidence of recovery (follow up: 28 days)												
2	randomised trials	not serious	not serious	not serious	not serious [a]	none	752/937 (80.3%)	522/721 (72.4%)	**RR 1.08** (1.02 to 1.14)	**58 more per 1,000** (from 14 more to 101 more)	⨁⨁⨁⨁ HIGH	
Mechanical Ventilation												
4	randomised trials	not serious	serious [b]	not serious	serious [a]	none	363/3433 (10.6%)	384/3116 (12.3%)	**RR 0.90** (0.78 to 1.03)	**12 fewer per 1,000** (from 27 fewer to 4 more)	⨁⨁◯◯ LOW	
Duration of hospitalization (assessed with: days)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	699	599	-	MD **1.64 days lower** (4.02 lower to 0.75 higher)	⨁⨁⨁◯ MODERATE	
Duration on mechanical ventilation (assessed with: days)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	standard of care	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	serious [c]	not serious	serious [a]	none	699	599	-	MD **2.75 days lower** (7.05 lower to 1.55 higher)	⨁⨁◯◯ LOW	

Viral negative conversion (follow up: 7 days)

1	randomised trials	serious [d]	not serious	not serious	serious [a]	none	66/131 (50.4%)	32/65 (49.2%)	**RR 1.02** (0.76 to 1.38)	**10 more per 1,000** (from 118 fewer to 187 more)	⨁⨁◯◯ LOW	

Adverse events

2	randomised trials	not serious	not serious	not serious	not serious	none	618/1095 (56.4%)	466/799 (58.3%)	**RR 0.93** (0.85 to 1.01)	**41 fewer per 1,000** (from 87 fewer to 6 more)	⨁⨁⨁⨁ HIGH	

Serious adverse events

3	randomised trials	not serious	not serious	not serious	serious [a]	none	33/1095 (3.0%)	32/799 (4.0%)	**RR 0.60** (0.38 to 0.96)	**16 fewer per 1,000** (from 25 fewer to 2 fewer)	⨁⨁⨁◯ MODERATE	

Recovery rate

3	randomised trials	not serious	not serious	not serious	not serious	none	721 participants	937 participants	**Rate ratio 1.22** (1.06 to 1.41) [Recovery / Clinical Improvement]	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁⨁ HIGH	
							-	92.1%		**-- per 1000 patient(s) per years** (from -- to --)		

Time to recovery (follow up: 28 days)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	standard of care	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	not serious	serious [e]	not serious	serious [a]	none	889	799	-	MD **1.89 days lower** (7.77 lower to 3.99 higher)	⨁⨁◯◯ LOW	
Incidence of clinical improvement (follow up: 28 days)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	166/278 (59.7%)	448/554 (80.9%)	**RR 1.06** (0.99 to 1.13)	**49 more per 1,000** (from 8 fewer to 105 more)	⨁⨁⨁◯ MODERATE	
Clinical improvement rate (follow up: 28 days)												
2	randomised trials	not serious	not serious	not serious	not serious	none	554 participants	278 participants	**RR 1.22** (1.11 to 1.35) [clinical improvement]	**203 more per 1,000** (from 101 more to 322 more)	⨁⨁⨁⨁ HIGH	
							-	92.1%		**203 more per 1,000** (from 101 more to 322 more)		
Time to clinical improvement												
2	randomised trials	not serious	serious [f]	not serious	serious [a]	none	896	800	-	MD **1.87 days lower** (4.24 lower to 0.5 higher)	⨁⨁◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Downgraded by 1 level due to imprecision: wide confidence interval with possible benefit or harm
b. Downgraded by 1 due to inconstinency: I2=82%
c. Downgraded by 1 level due to inconsistency: result was heterogenous (I2=95)
d. Risk of bias downgraded by 1: some concern with missing data
e. Downgraded by 1 due to inconsistency: I2 - 93%
f. Downgraded by 1 due to inconsistency: I2=64%

Appendix 3: Forest Plots

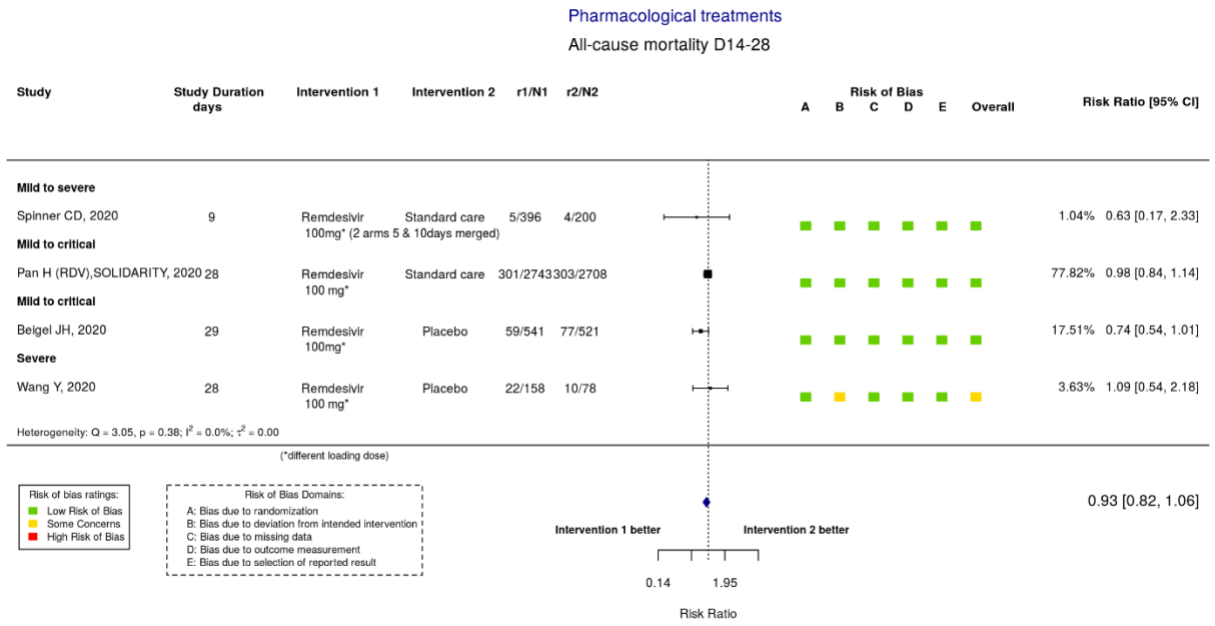

Figure 1. Pooled effect of remdesivir on all-cause mortality. Source: covid-nma.com

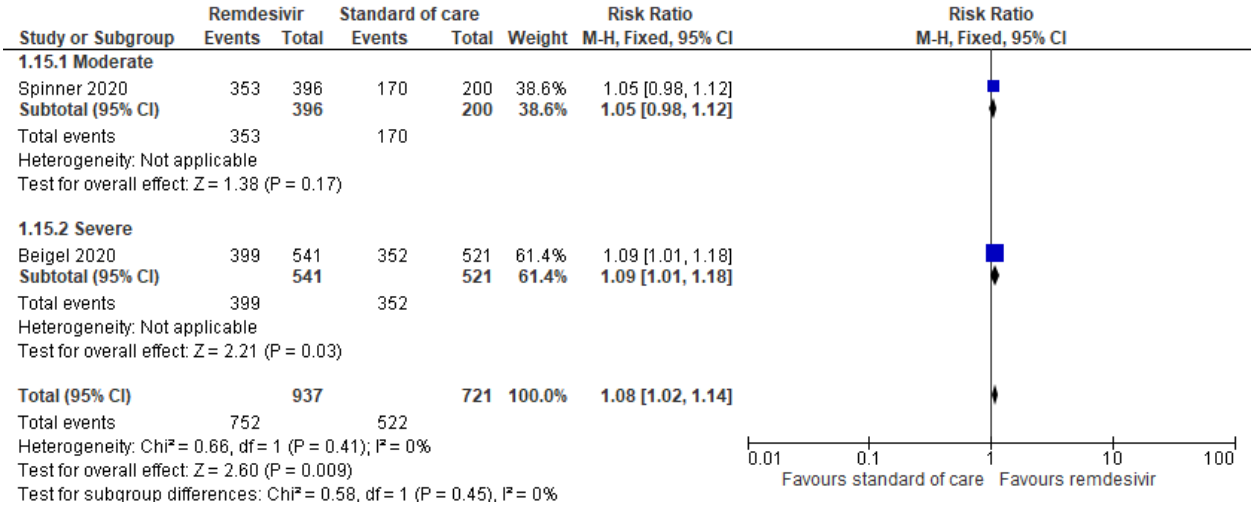

Figure 2. Pooled effect of remdesivir on incidence of recovery

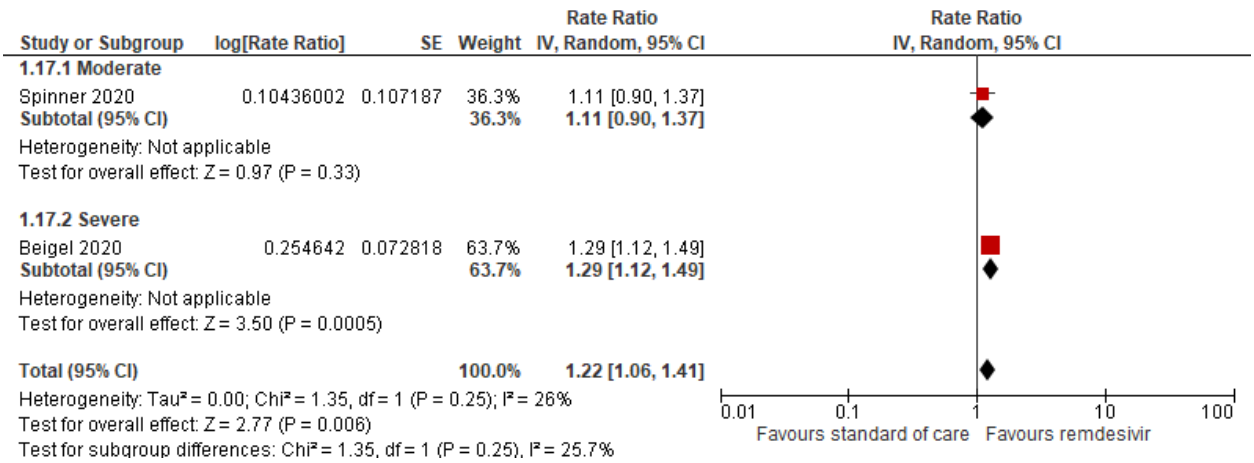

Figure 3. Pooled effect of remdesivir on recovery rate

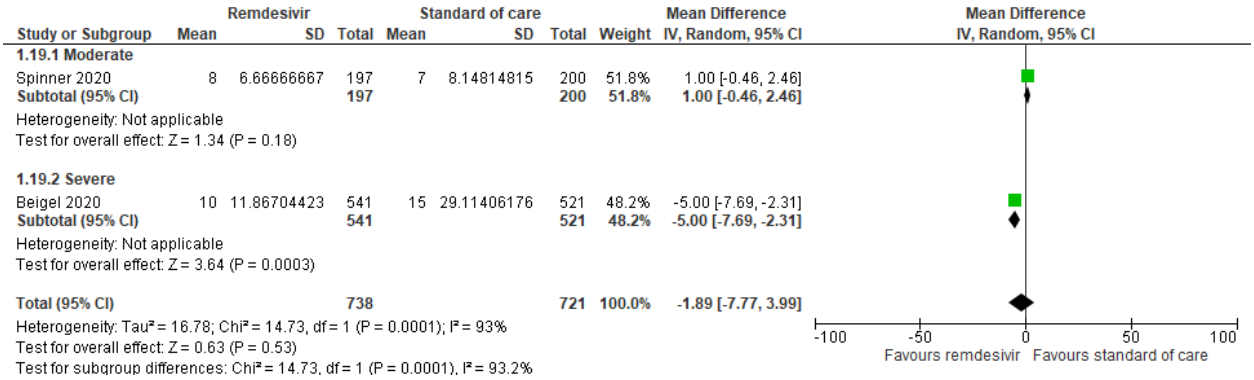

Figure 4. Pooled effect of remdesivir on time to recovery (days)

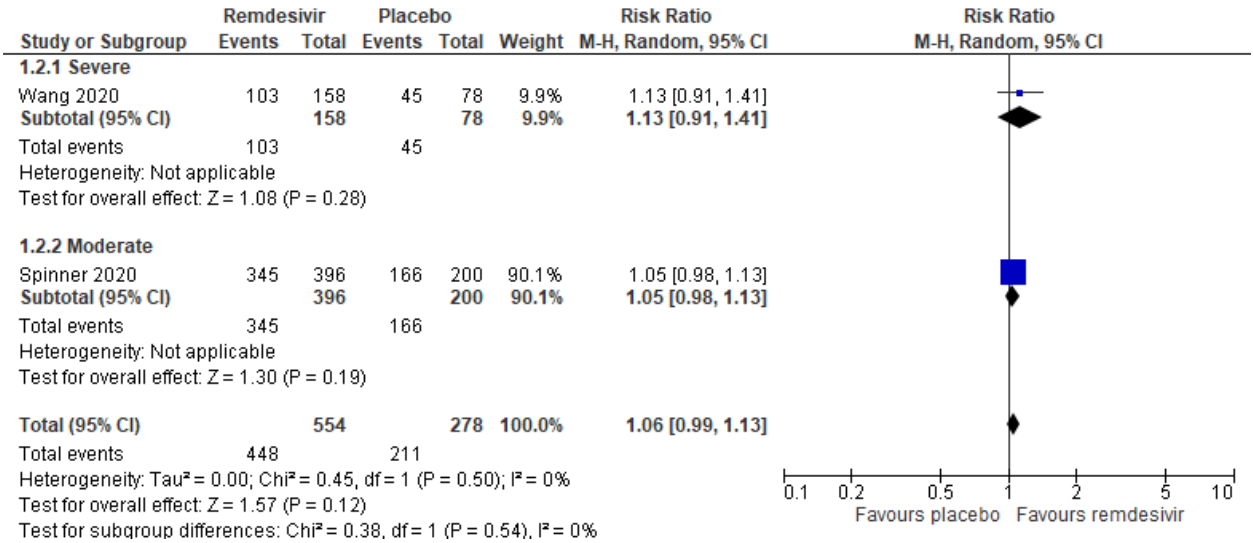

Figure 5. Pooled effect of remdesivir on the incidence of clinical improvement

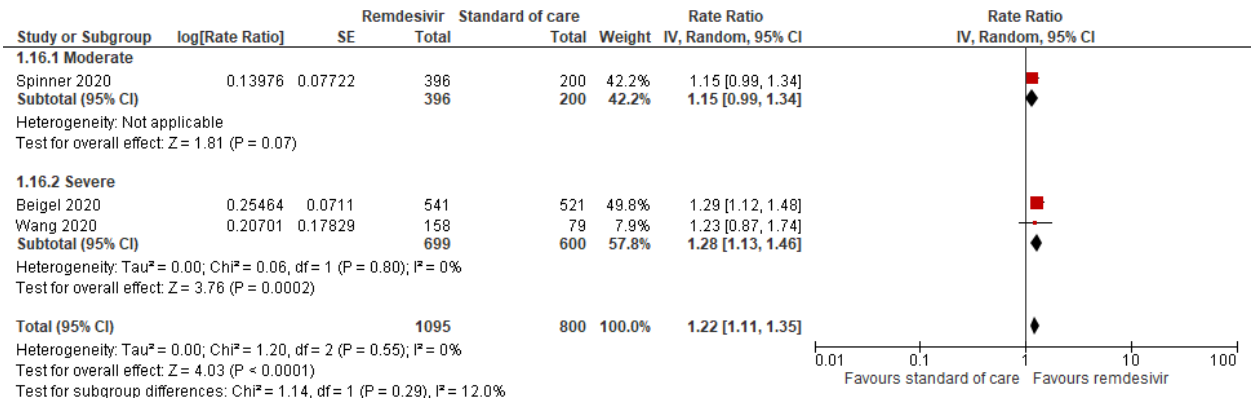

Figure 6. Pooled effect of remdesivir on clinical improvement rate

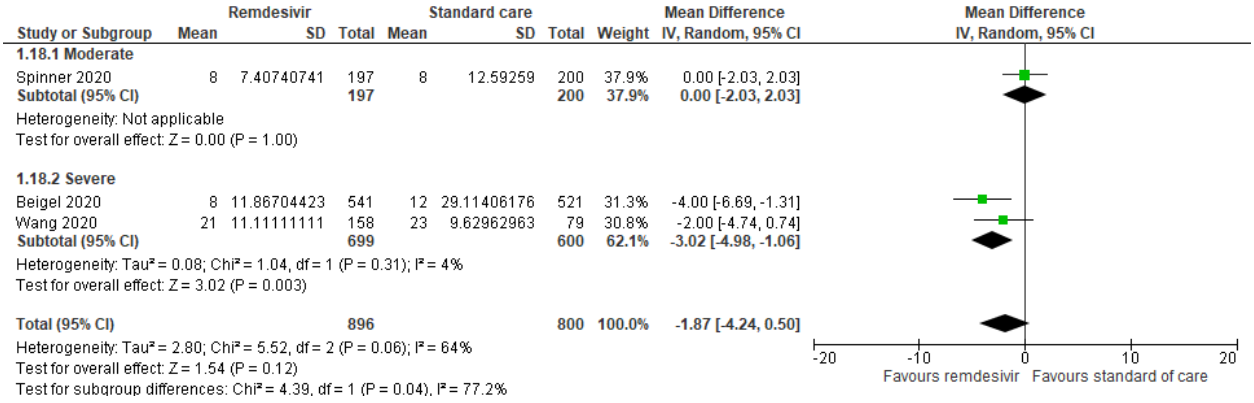

Figure 7. Pooled effect of remdesivir on time to clinical improvement

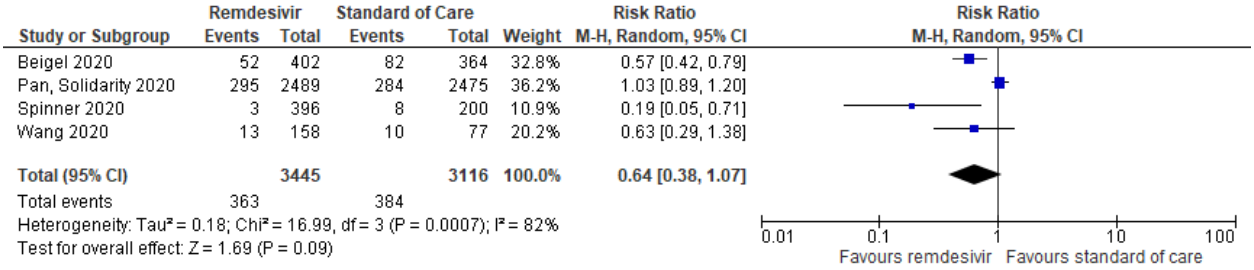

Figure 8. Pooled effect of remdesivir on initiation of mechanical ventilation

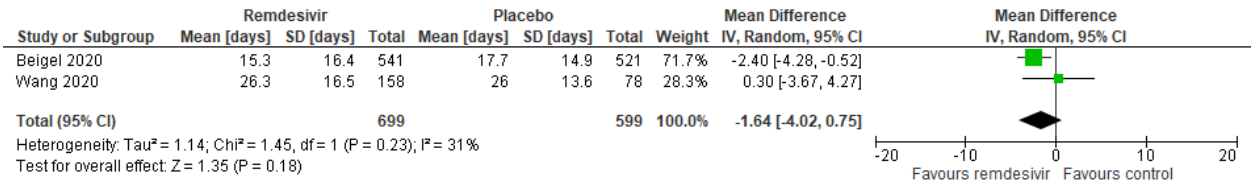

Figure 9. Pooled effect of remdesivir on duration of hospital stay (days)

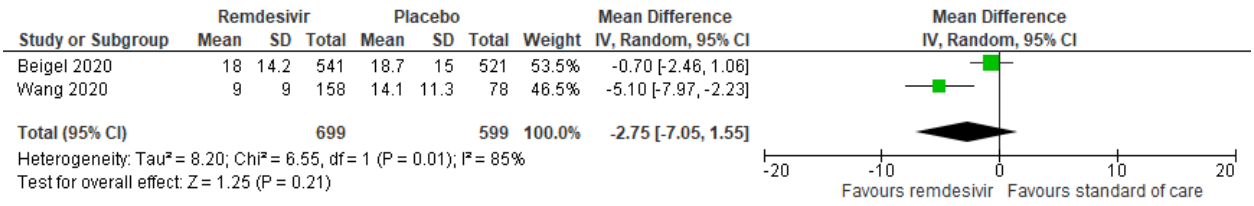

Figure 10.Pooled effect of remdesivir on duration on mechanical ventilation (days)

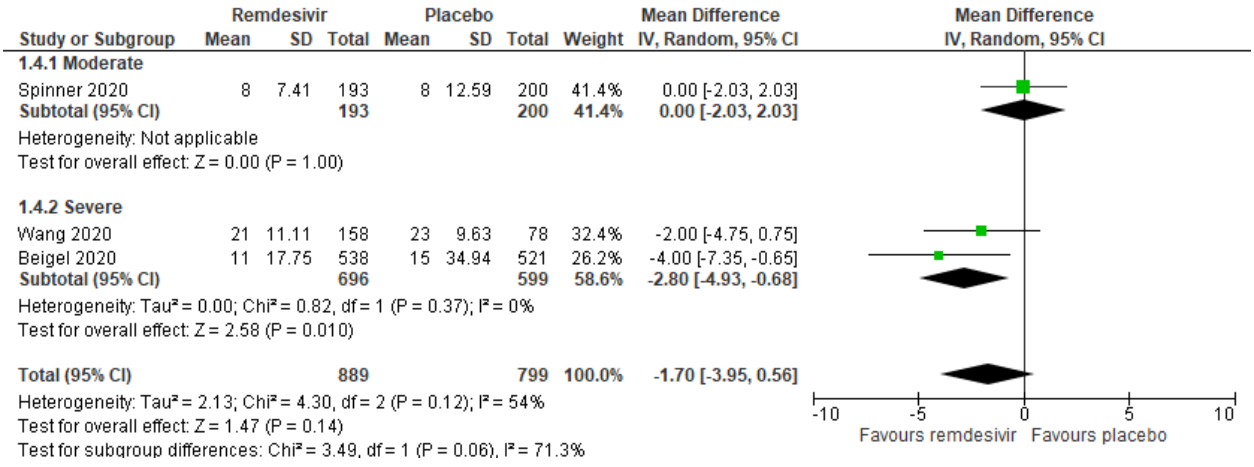

Figure 11. Pooled effect of remdesivir on time to clinical improvement/recovery(days)

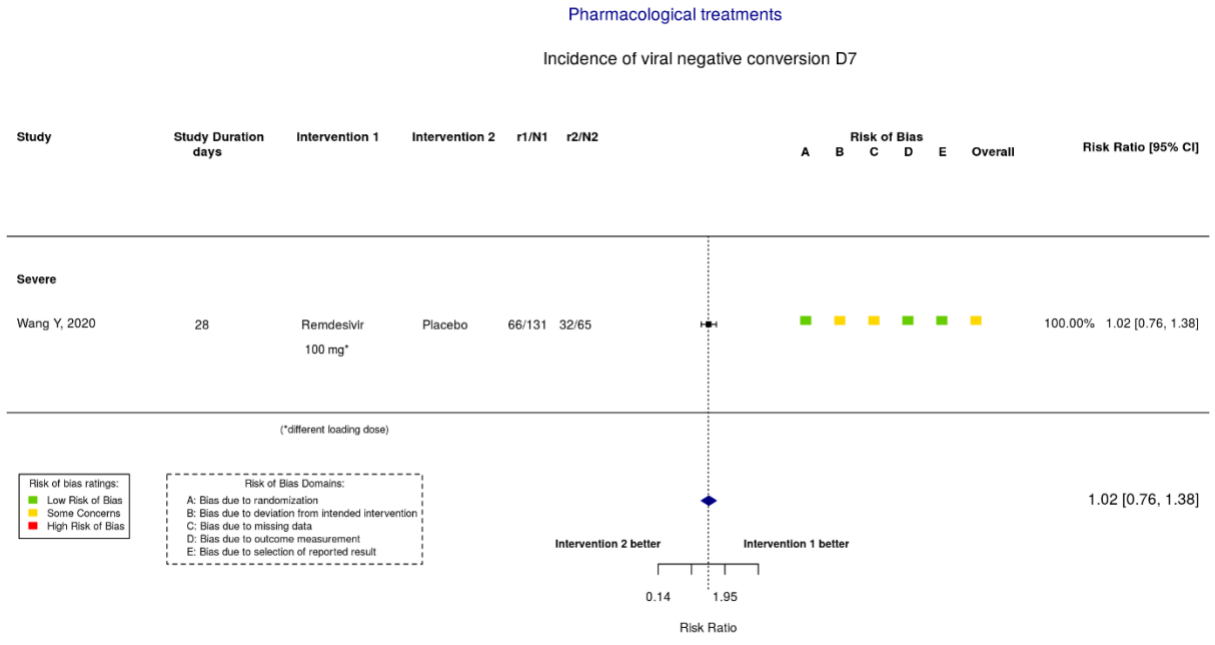

Figure 12. Effect of remdesivir on negative viral conversion. Source: COVID-nma.com

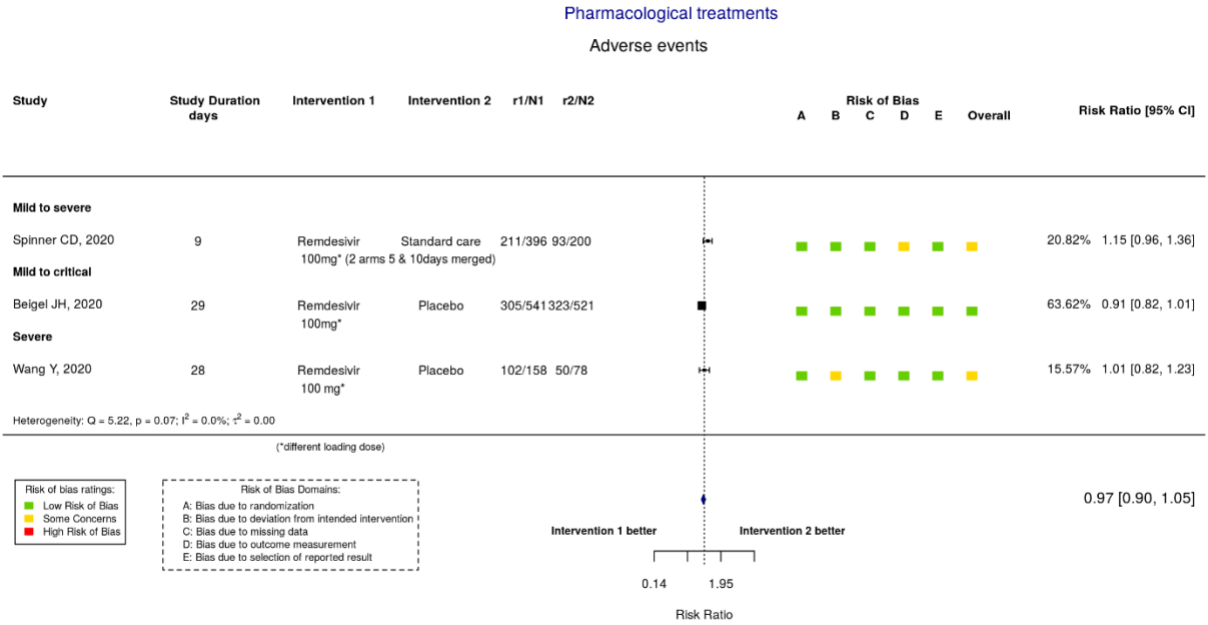

Figure 13. Pooled effect of remdesivir on the incidence adverse event. Source: covid-nma.com

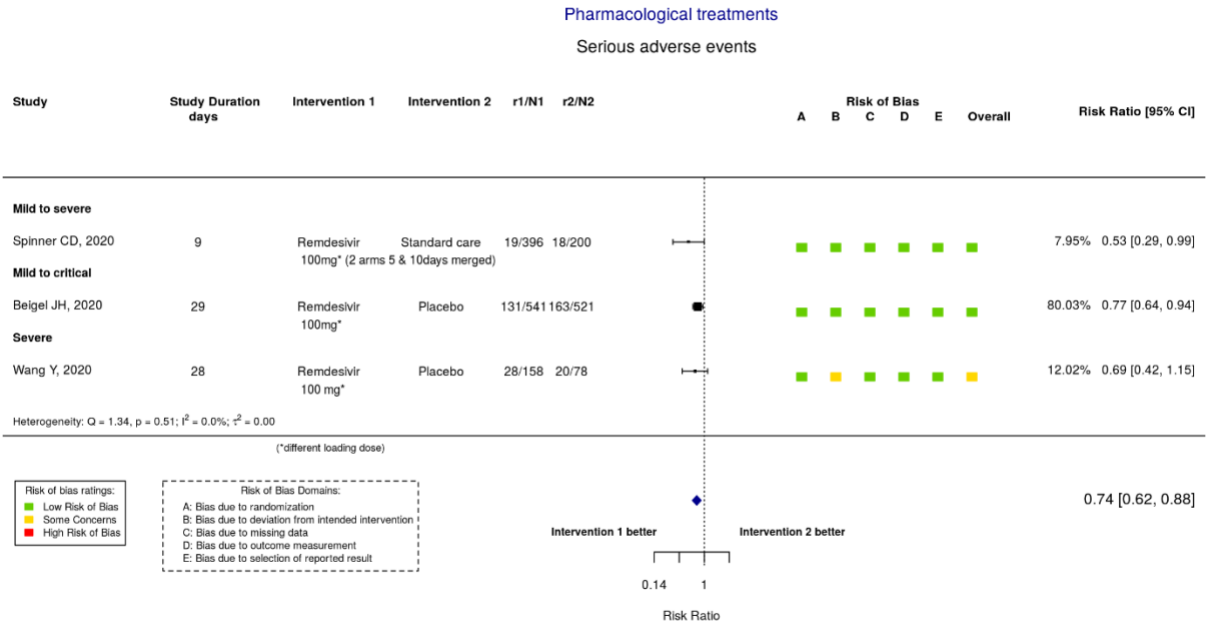

Figure 14. Pooled effect of remdesivir on the incidence of serious adverse events. Source: covid-nma.com

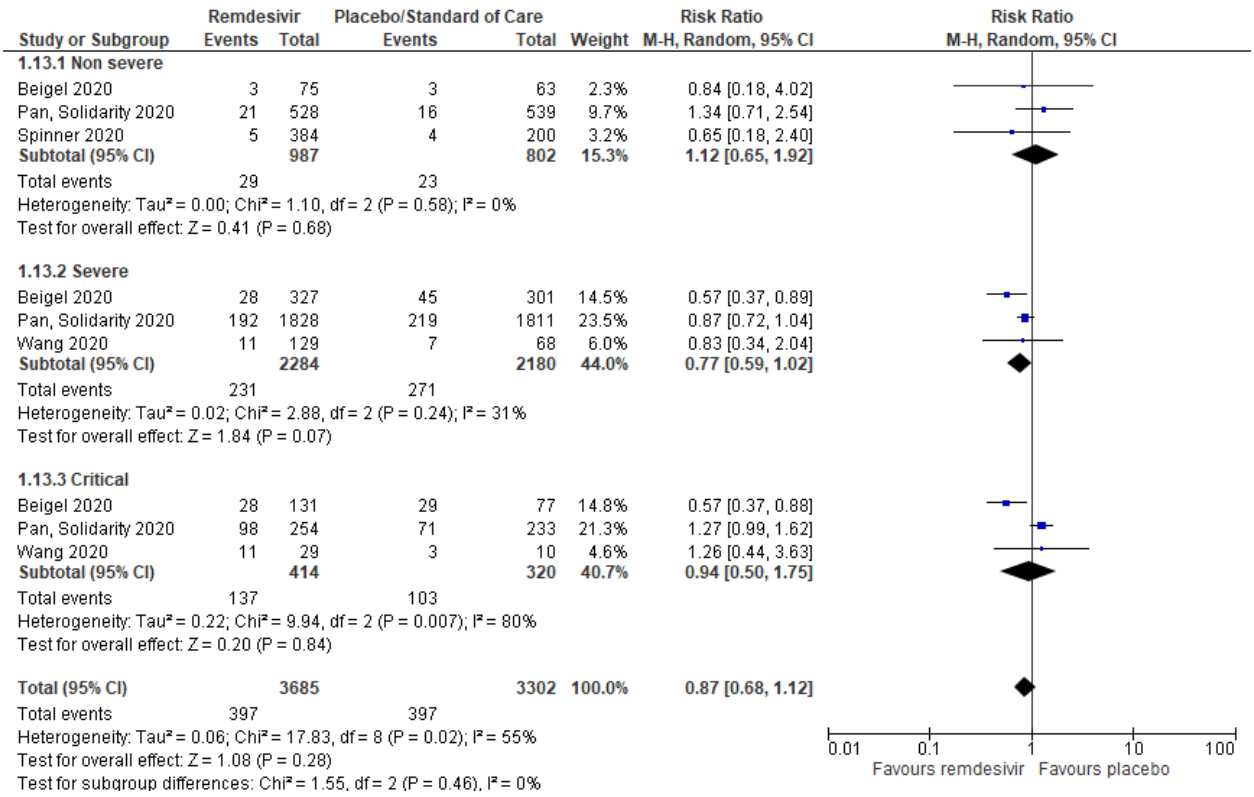

Figure 15. Sub-analysis of the results on mortality according to severity of disease

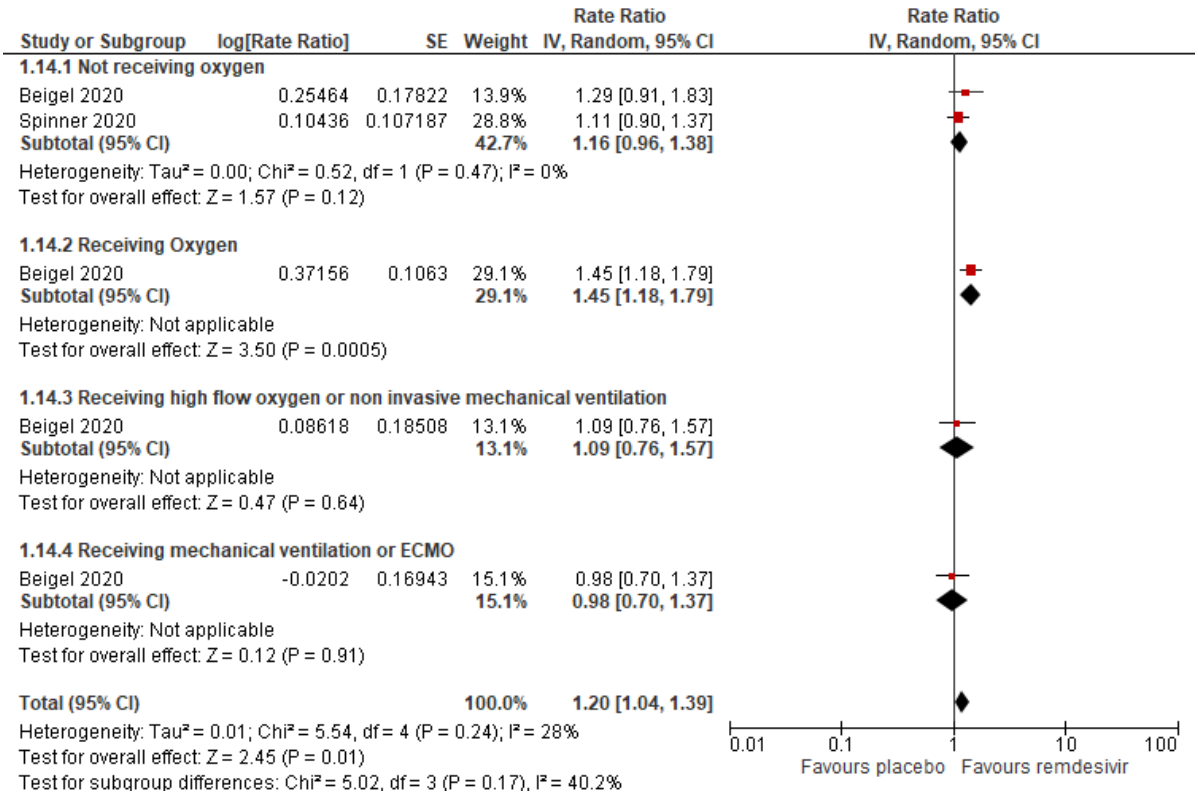

Figure 16. Sub-analysis of the results on recovery rate according to severity of disease

Appendix 4: Characteristics of Ongoing Studies

Title	Interventions	Sample Size
Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734â„¢) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19)	Drug: Remdesivir	52
Study in Participants With Early Stage Coronavirus Disease 2019 (COVID-19) to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation	Drug: Remdesivir (RDV)|Drug: Placebo	282
IFN-beta 1b and Remdesivir for COVID19	Drug: Interferon beta-1b|Drug: Remdesivir	100
Efficacy and Safety of Remdesivir and Tociluzumab for the Management of Severe COVID-19: A Randomized Controlled Trial	Drug: Remdesivir|Drug: Tocilizumab	150
Study to Evaluate the Efficacy and Safety of Remdesivir (GS-5734â„¢) Treatment of Coronavirus Disease 2019 (COVID-19) in an Outpatient Setting	Drug: RDV|Drug: Placebo to Match RDV	1264
A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared With Remdesivir Plus Placebo in Hospitalized Participants With Severe COVID-19 Pneumonia	Drug: Remdesivir|Drug: Tocilizumab|Drug: Placebo	500
Antiviral Activity and Safety of Remdesivir in Bangladeshi Patients With Severe Coronavirus Disease (COVID-19)	Drug: Remdesivir|Other: Standard of Care	60
Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial	Drug: Interferon beta-1a|Drug: Remdesivir	2900
REMdesivir-HU Clinical Study and Severe Covid-19 Patients	Drug: Remdesivir-HU	2000
Adaptive COVID-19 Treatment Trial 3 (ACTT-3)	Drug: Interferon beta-1a|Other: Placebo|Drug: Remdesivir	969

ACTIV-5 / Big Effect Trial (BET-B) for the Treatment of COVID-19	Biological: Lenzilumab|Other: Placebo|Drug: Remdesivir	200
ACTIV-5 / Big Effect Trial (BET-A) for the Treatment of COVID-19	Other: Placebo|Drug: Remdesivir|Biological: Risankizumab	200
Adaptive COVID-19 Treatment Trial 4 (ACTT-4)	Drug: Baricitinib|Drug: Dexamethasone|Other: Placebo|Drug: Remdesivir	1500
Efficacy of Ramdicivir and Baricitinib for the Treatment of Severe COVID 19 Patients	Drug: Remdesivir|Drug: Baricitinib|Drug: Tocilizumab	150
Efficacy of Favipiravir in Treatment of Mild & Moderate COVID-19 Infection in Nepal	Drug: Favipiravir|Drug: Placebo|Drug: Remdesivir	676
An International Randomized Trial of Additional Treatments for COVID-19 in Hospitalized Patients Who Are All Receiving the Local Standard of Care - WHO-SOLIDARITY-GERMANY	Other: Standard of Care (SoC)|Drug: Remdesivir	400
Remdesivir in COVID-19 Lahore General Hospital	Drug: Remdesivir	30
Remdesivir vs Chloroquine in Coronavirus Disease	Drug: Chloroquine or hydroxychloroquine|Drug: Remdesivir	120
Immune Modulators for Treating COVID-19	Drug: Infliximab|Drug: Abatacept|Drug: Remdesivir|Drug: cenicriviroc	2160
I-SPY COVID-19 TRIAL: An Adaptive Platform Trial for Critically Ill Patients	Drug: Remdesivir|Drug: Cenicriviroc|Drug: Icatibant|Drug: Razuprotafib|Drug: Apremilast	1500
The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients	Drug: Hydroxychloroquine|Drug: Remdesivir|Other: (Standard of Care) SoC	700
World Health Organization (WHO) COVID-19 Solidarity Trial for COVID-19 Treatments	Drug: Remdesivir|Drug: Acalabrutinib|Drug: Interferon beta-1a|Other: Standard of Care	100
Trial of Treatments for COVID-19 in Hospitalized Adults	Drug: Remdesivir|Drug: Lopinavir/ritonavir|Drug: Interferon Beta-1A|Drug: Hydroxychloroquine|Other: Standard of care	3100
Inpatient Treatment With Anti-Coronavirus Immunoglobulin (ITAC)	Drug: Hyperimmune immunoglobulin to SARS-CoV-2 (hIVIG)|Other: Placebo|Drug: Remdesivir	500
ACTIV-3: Therapeutics for Inpatients With COVID-19	Biological: LY3819253|Drug: Placebo|Biological: Remdesivir|Biological: VIR-7831|Biological: BRII-196/BRII-198	10000
Safety, Tolerability and Pharmacokinetics of Inhaled Nanoparticle Formulation of Remdesivir (GS-5734) and NA-831	Drug: Drug: NA-831 - 0.10 mg/kg|Drug: Placebo- 0.10 mg/kg|Drug: Drug: NA-831 - 0.20 mg/kg|Drug: Placebo- 0.20 mg/kg|Drug: Drug: GS-5734 - 1.00 mg/kg|Drug: Placebo- 1.00 mg/kg|Drug: Drug: GS-5734 - 2.00 mg/kg|Drug: Placebo- 2.00	45

	mg/kg|Combination Product: Drugs: NA-831 (0.10 mg/kg) plus GS-5734 (1.00 mg/kg)|Combination Product: Placebo 0.10 mg + 1.00 mg/kg|Combination Product: Drugs: NA-831 (0.20 mg/kg) plus GS-5734 (2.00 mg/kg)|Combination Product: Placebo 0.20 mg + 2.00 mg/kg	

Appendix 5: Subgroup analysis of outcomes on mortality, clinical improvement/ recovery rate, time to clinical improvement/recovery stratified according to severity

Outcomes	Pooled Relative Risk	95% CI
Mortality		
Non-severe (3 RCTs, n = 1,789)	1.12	0.65 to 1.92
Severe (3 RCTs, n = 4,464)	0.77	0.59 to 1.02
Critical (3 RCTs, n = 734)	0.94	0.50 to 1.75
Incidence of recovery		
Moderate (1 RCT, n = 596)	1.05	0.98 to 1.12
Severe (1 RCTs, n = 1062)	1.09	1.01 to 1.18
Recovery rate		
Non-severe (Not receiving O2) (2 RCTs, n= 734)	1.16	0.96 to 1.38
Severe		
Receiving O2 (1 RCT, n=435)	1.45	1.18 to 1.79
Receiving high flow O2 or non-invasive mechanical ventilation (1 RCT, n= 193)	1.09	0.76 to 1.57
Critical (Receiving mechanical ventilation) (1 RCT, n =285)	0.98	0.70 to 1.37
Time to recovery (days)		
Moderate (1 RCT, n = 596)	Mean Difference: 1	-0.46 to 2.46
Severe to Critical (2 RCTs, n =1295)	Mean Difference: -5	-7.69 to -2.31
Incidence of clinical improvement		
Moderate (1 RCT, n = 596)	1.05	0.98 to 1.13
Severe (1 RCT, n = 236)	1.13	0.91 to 1.41
Clinical Improvement Rate		
Moderate (1 RCT, n = 596)	1.15	0.99 to 1.34
Severe (2 RCTs, n = 1299)	1.28	1.13 to 1.46
Time to clinical improvement		
Moderate (1 RCT, n = 397)	Mean difference: 0	-2.03 to 2.03
Severe (2 RCTs, n = 1,299)	Mean difference: 3.02	-4.98 to -1.06