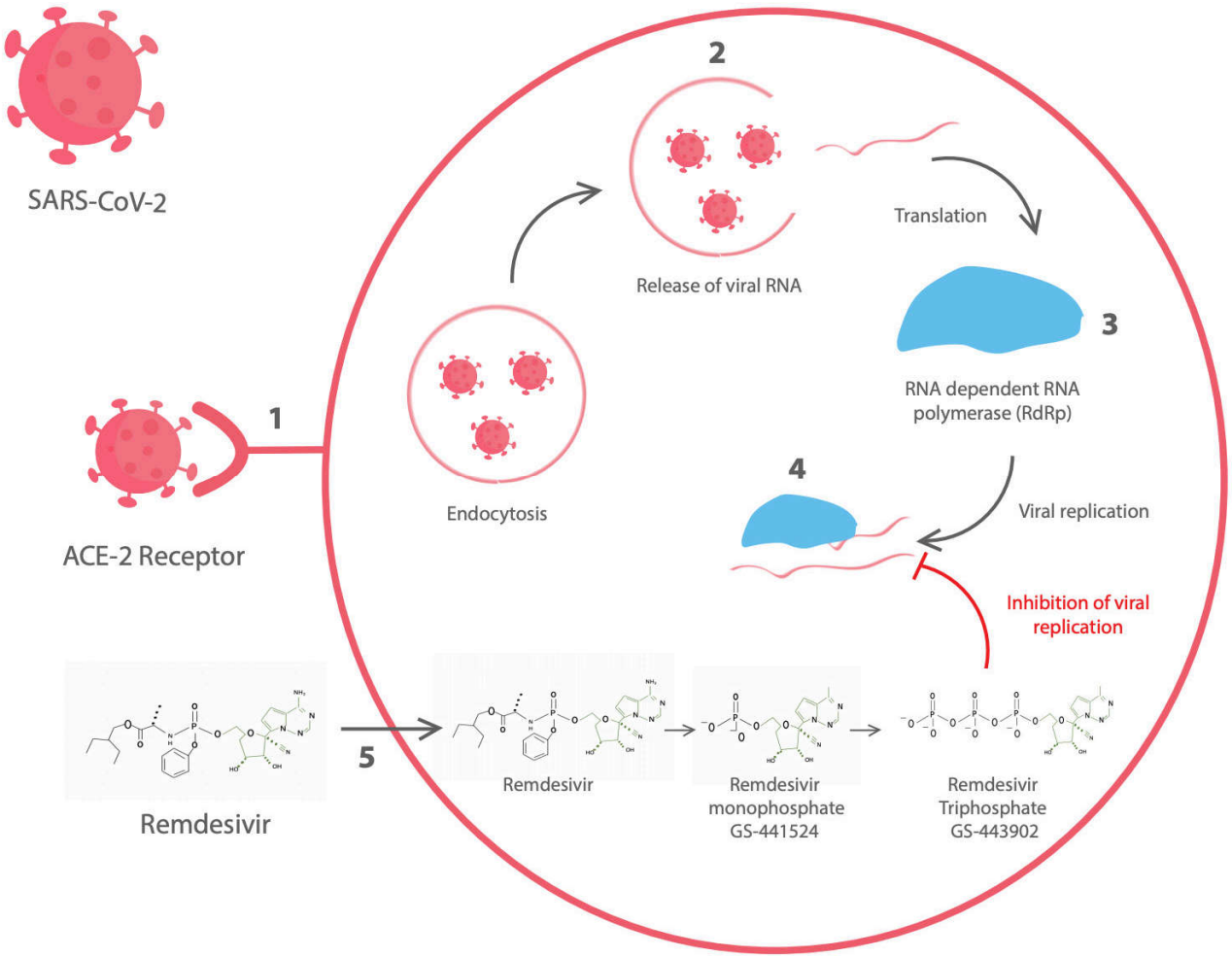
Remdesivir

Foroud shahbazi

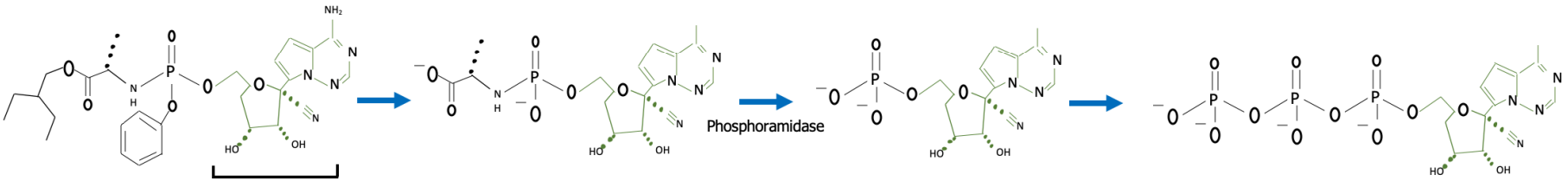

SARS-CoV-2
2
Translation
Release of viral RNA
3
RNA dependent RNA
polymerase (RdRp)
1
ACE-2 Receptor
Endocytosis
4
Viral replication
Inhibition of viral
replication
5
Remdesivir
Remdesivir
Remdesivir
monophosphate
GS-441524
Remdesivir
Triphosphate
GS-443902

Remdesivir (GS-5734)

Alanine Metabolite (GS-704277)

Nucleoside monophosphate (GS-441524)

Nucleoside triphosphate (GS-443902)



Adenosine analogue

Active metabolite

Antiviral spectrum and resistance

- Remdesivir is a potentially broad-spectrum antiviral agent against RNA viruses.
- It has been shown to reduce viral replication in vitro in human macrophages and lung microvascular endothelial cells infected with Pneumoviridae (e.g. Respiratory Syncytial Virus) and Paramixoviridae (e.g. measles, mumps, and Parainfluenza virus.
- It has also been shown to exhibit antiviral activity against Filiviridae (e.g. Ebola and Marburg virus) in a variety of human cell type
- Remdesivir demonstrated potent inhibition of SARS-CoV-1 and MERS-CoV

Pharmacokinetics

- Remdesivir is not suitable for oral administration due to complete first-pass metabolism through the liver
- Following IV administration, remdesivir has a short plasma half-life (T1/2) of ~1 hour,
- It is quickly metabolized by carboxylesterases (CES1) into the intermediate alanine metabolite (GS-704277), followed by the predominant monophosphate metabolite (T1/2 24.5 hours)
- The monophosphate metabolite is then converted into the triphosphate active metabolite of GS-443902, which has a prolonged plasma T1/2 of over 35 hours, supporting the once daily administration of the drug

- Given the prolonged T1/2 of the monophosphate and triphosphate metabolites, steady state is usually achieved after approximately 5 days, hence the need for a loading dose to facilitate a faster achievement of steady state

Administration

- Doses should be administrated intravenously and infused over 30-120 minutes,
- We prefer administration over 30 minutes whenever possible to achieve higher intracellular concentrations of the active metabolite

Duration

- Adult and pediatric patients with moderate or severe COVID-19 can receive a treatment duration of 5 days, which can be extended for up to 10 days if patients do not demonstrate clinical improvement

- Although rare to date, in some patients with severe immunocompromising conditions, especially those who receive combined T cell and B cell depleting agents for hematological malignancies or autoimmune diseases, we have had to administer additional courses of remdesivir over time for recrudescent clinical disease

Drug interactions

- Substrate for CYP450 enzymes (CYP2C8, CYP2D6, and CYP3A4), Organic Anion Transporting Polypeptides 1B1 (OAPT1B1), and P-glycoprotein (P-gp) proteins.
- In addition, remdesivir can act as an inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, OAPT1B1, OATP1B3, multidrug resistance-associated protein 4 (MRP4), and sodium-taurocholate cotransporting polypeptide (NCTP)
- Don’t administered with HCQ/CQ
- Rifampin

Clinical data

Study	Methods	Study Population	Key results	Strengths/ Limitations	Interpretation
Wang et al. Lancet 2020 (36)	Double-blind, randomized, placebo-controlled trial (200 mg loading dose, 100 mg maintenance dose on days 2-10 or placebo)	• Age ≥18 years • Positive SARS-CoV-2 PCR • Radiographic evidence of pulmonary infiltrates • SpO2 ≤94% on room air • Symptomatic ≤ 12 days • ALT or AST < 5x ULN • eGFR > 30 mL/min	• No difference in time to clinical recovery (21 days vs. 23days), day-28 mortality (15% vs. 13%), or viral load reduction observed between remdesivir and placebo • Incidence of adverse events was similar between the two groups	• Strengths: randomized controlled trial; low loss to follow-up; evaluated SARS-CoV-2 viral-load • Limitations: did not complete enrollment due to the control of the outbreak, resulting in low power for the study	Given that the study was underpowered, results are inconclusive

Beigel etl al. NEJM 2020 (ACTT-1) (38)	Double-blind, randomized, placebo-controlled trial (200 mg loading dose, 100 mg maintenance dose for up to 9 days or placebo)	• Age ≥18 years • Positive SARS-CoV-2 PCR • Radiographic evidence of pulmonary infiltrates • SpO2 ≤94% or requiring supplemental oxygen, mechanical ventilation or ECMO • ALT or AST < 5x ULN • eGFR > 30 mL/min	• Patients who received remdesivir had a significantly shorter recovery time by day-29 (10 vs. 15 days). The odds of clinical improvement at day 15 were higher in the remdesivir group (OR 1.50). This change was more evident in patients requiring supplemental oxygen (OR 1.47) • Day-14 and -29 mortality were lower for the remdesivir group (7% vs. 12%) and (11% vs. 15%) though not statistically significant • No difference in incidence of serious adverse events	• Strengths: Adequate power; high protocol adherence • Limitations: did not evaluate SARS-CoV-2 viral-load	Remdesivir is effective at improving clinical recovery in COVID-19 patients. Remdesivir may be beneficial in preventing progression to more severe respiratory disease and its benefit is most apparent in those requiring supplemental oxygen.

Disease definition

1. Not hospitalized and no limitations of activities;
2. Not hospitalized, with limitation of activities, home oxygen requirement, or both;
3. Hospitalized , not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons);
4. Hospitalized , not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions);
5. Hospitalized , requiring any supplemental oxygen;
6. Hospitalized , requiring noninvasive ventilation or use of high-flow oxygen devices;
7. Hospitalized , receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
8. Death

Goldman et al. NEJM 2020 (SIMPLE Severe) (39)	Randomized, open-label, phase 3 trial (Group 1: 200 mg loading dose, 100 mg maintenance dose for up to 4 days Group 2: 200 mg loading dose, 100 mg maintenance dose for up to 9 days) Group 3 Standard care	• Age ≥12 years • Positive SARS-CoV-2 PCR • Radiographic evidence of pulmonary infiltrates • SpO2 ≤94% or requiring supplemental oxygen • ALT or AST < 5x ULN • eGFR > 50 mL/min	• There was no difference in clinical improvement of at least 2-points in the ordinal scale between 5-day and a 10-day course (65% vs. 54%) • Among patients receiving noninvasive ventilation or high-flow oxygen on day 5, day-14 mortality was 10% in the 5-day group vs. 15% in the 10-day group • Among patients receiving mechanical ventilation or ECMO on day 5, day-14 mortality was 40% in the 5-day group vs. 17% in the 10-day group	• Strengths: first study to evaluate optimal duration of remdesivir in COVID-19; adequate power; high protocol adherence • Limitations: did not evaluate SARS-CoV-2 viral-loads; excluded patients on mechanical ventilation or ECMO	5 days of remdesivir is sufficient to treat COVID-19 patients who are not receiving mechanical ventilation/ECMO. Patients who progress to mechanical ventilation or ECMO may benefit from a 10 days course

- The benefit of remdesivir was larger when given earlier in the illness, though the benefit persisted in most analyses of duration of symptoms

Spinner et al. JAMA, 2020 (SIMPLE Moderate) (40)	Randomized, open-label, phase 3 trial (Group 1: 200 mg loading dose, 100 mg maintenance dose for up to 4 days Group 2: 200 mg loading dose, 100 mg maintenance dose for up to 9 days Group 3: standard care	• Age ≥12 years • Positive SARS-CoV-2 PCR • Radiographic evidence of pulmonary infiltrates • SpO2 >94% and breathing on room air at screening • ALT or AST < 5x ULN • eGFR > 50 mL/min	• Those randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard of care at day 11, but not those randomized to a 10-day group. This difference was of uncertain clinical importance	• Strengths: first study to evaluate remdesivir in patients with moderate COVID-19 pneumonia; had adequate power • Limitations: did not evaluate SARS-CoV-2 viral-loads; did not stratify by sites, which could have influenced the results, given the differences in patient care and discharge practices	A 5-day course of remdesivir may be sufficient to treat patients with moderate COVID-19 pneumonia

Pan et al. (SOLIDARITY) (41)	Randomized, open-label, phase 3 trial (Remdesivir 200 mg loading dose, 100 mg maintenance dose for up to 9 days or standard of	• Age ≥18 years • Diagnosis of Definitive COVID-19	• Remdesivir was not associated with a reduction in in-hospital mortality compared to standard of care (11% vs. 11.2%) • Remdesivir was not associated with educed initiation of ventilation or hospital length of stay	• Strengths: large sample size • Limitations: open-label study; no definition of COVID-19 or definitive COVID-19, did not stratify by oxygen requirements or site; has not reported duration of symptoms prior to start of treatment;	Remdesivir was not associated with improved in-hospital mortality among patients hospitalized with COVID-19

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 5, 2020 VOL. 383 NO. 19

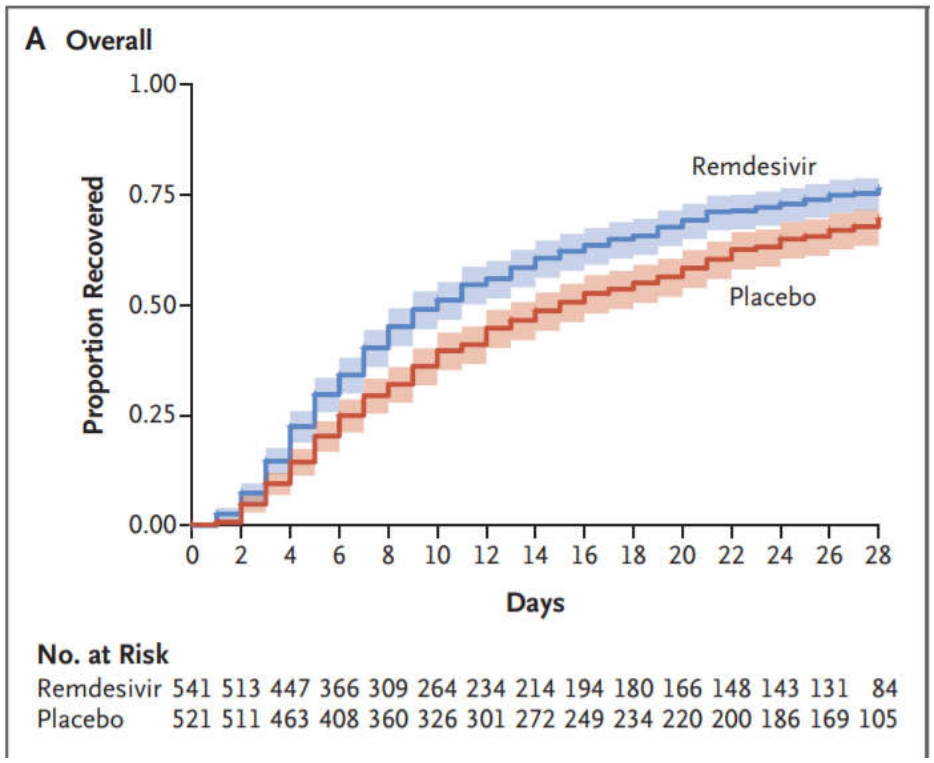
Remdesivir for the Treatment of Covid-19 — Final Report

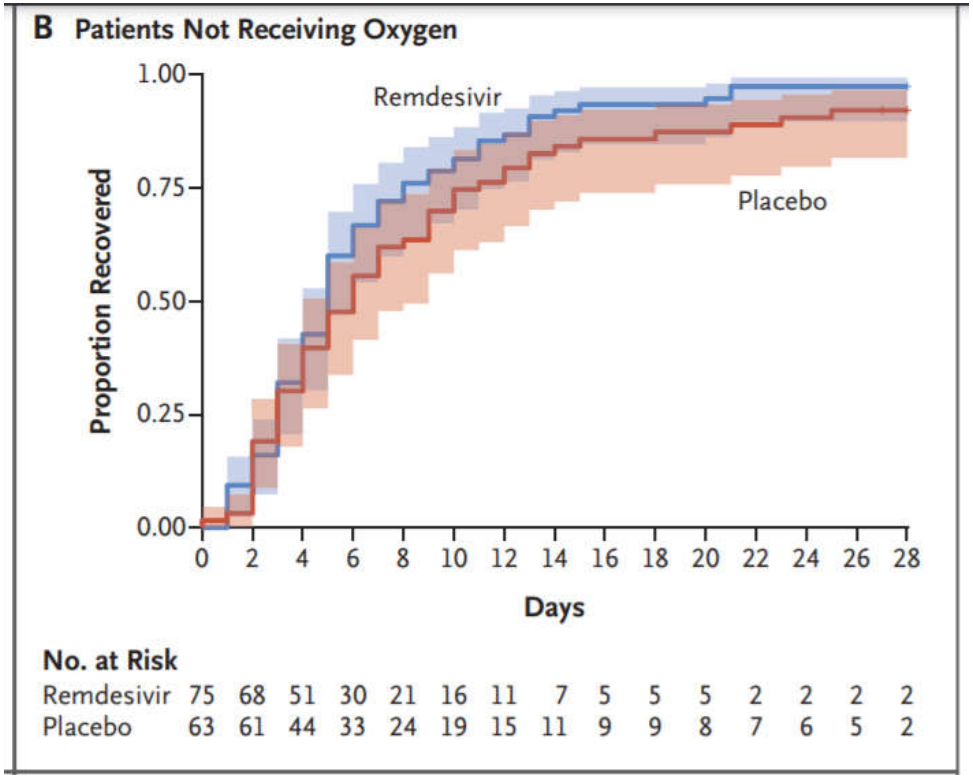
J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

Figure 1. Enrollment and Randomization.

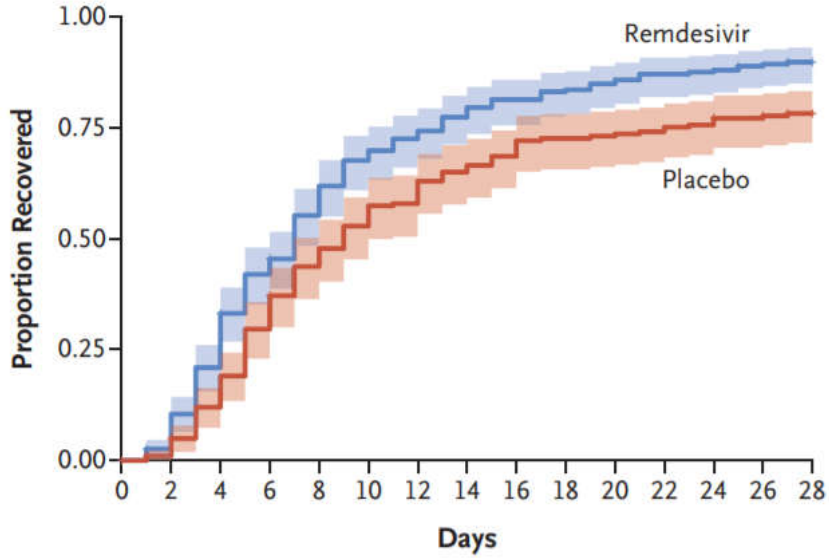
Disease definition

1. Not hospitalized and no limitations of activities;
2. Not hospitalized, with limitation of activities, home oxygen requirement, or both;
3. Hospitalized , not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons);
4. Hospitalized , not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions);
5. Hospitalized , requiring any supplemental oxygen;
6. Hospitalized , requiring noninvasive ventilation or use of high-flow oxygen devices;
7. Hospitalized , receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
8. Death


A Overall
Proportion Recovered
1.00
0.75
0.50
0.25
0.00
Remdesivir
Placebo
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days
No. at Risk
Remdesivir 541 513 447 366 309 264 234 214 194 180 166 148 143 131 84
Placebo 521 511 463 408 360 326 301 272 249 234 220 200 186 169 105


B Patients Not Receiving Oxygen
Proportion Recovered
1.00
0.75
0.50
0.25
0.00
Remdesivir
Placebo
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days
No. at Risk
Remdesivir 75 68 51 30 21 16 11 7 5 5 5 2 2 2 2
Placebo 63 61 44 33 24 19 15 11 9 9 8 7 6 5 2

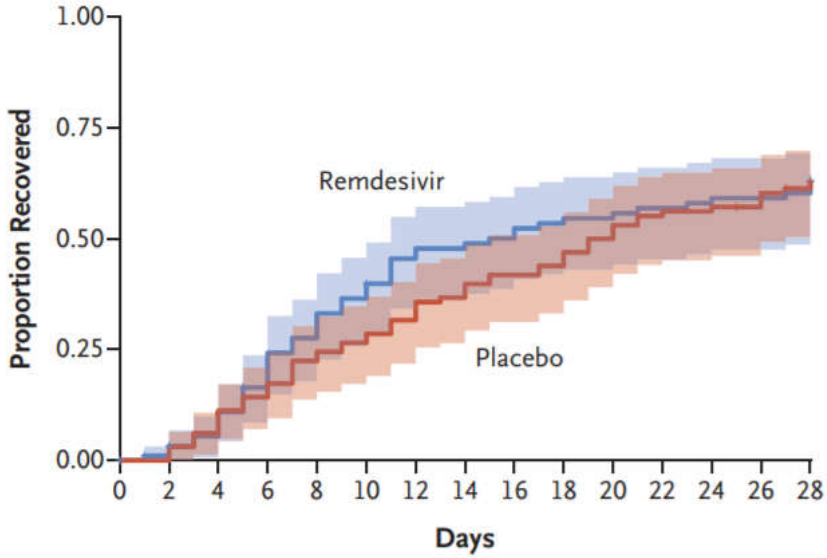
C Patients Receiving Oxygen



No. at Risk

Remdesivir	232	223	181	132	101	73	62	51	42	38	34	29	28	24	13
Placebo	203	199	175	140	111	93	83	69	62	54	53	51	48	44	28

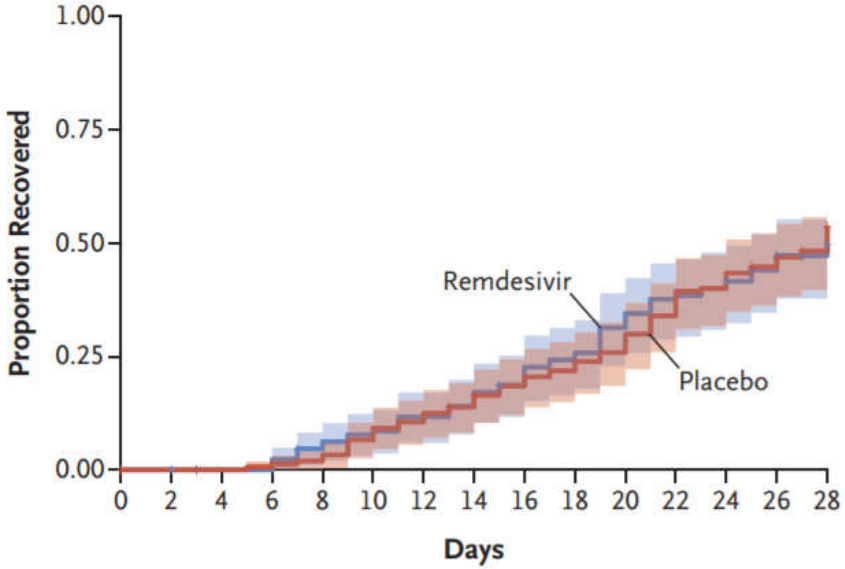
D Patients Receiving High-Flow Oxygen or Noninvasive Mechanical Ventilation



No. at Risk

Remdesivir	95	91	86	75	65	57	48	46	44	41	40	38	37	36	27
Placebo	98	98	92	84	76	72	67	62	57	55	49	44	43	41	27

E **Patients Receiving Mechanical Ventilation or ECMO**



No. at Risk

Remdesivir	131	131	129	129	122	118	113	110	103	96	87	79	76	69	42
Placebo	154	153	152	151	149	142	136	130	121	116	110	98	89	79	48

Special population

- Pregnancy and Lactation:
- Remdesivir has not shown genotoxicity in vitro or adverse embryo-fetal developmental effects in animal models
- Another report of 67 pregnant patient who received remdesivir through the compassionate use program demonstrated that 93% recovered within 28 days.
- Pregnant women not requiring invasive ventilation at baseline had the highest rates of recovery (98%) and shortest median time to recovery (5 days), of whom 98% recovered, 95% were discharged
- It does not appear that remdesivir should be avoided in the setting of lactation

Formulation	A remdesivir 100 mg lyophilized powder vial is reconstituted with 19 mL of sterile water for injection and diluted into 0.9% saline. Remdesivir is also supplied as aqueous-based concentrated 5 mg/mL solution. Remdesivir is solubilized with sulfobutylether-β-cyclodextrin (SBECD). Each vial of remdesivir lyophilized powder contains 3 grams of SBECD, while each aqueous solution vial contains 6 grams of SBECD each.	Only available for IV administration, as of October 2020 The lyophilized formulation allows for longer-term storage compared to aqueous-based concentrated solution.

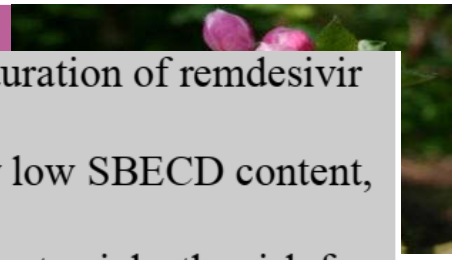
Storage

- Injection solution concentrate (5 mg/mL): Store intact vials refrigerated at 2°C to 8°C (36°F to 46°F). Prior to dilution, allow vial to warm to room temperature; intact vials can be stored up to 12 hours at room temperature prior to dilution. Once diluted for infusion, may store at 20°C to 25°C (68°F to 77°F) for 24 hours or refrigerated at 2°C to 8°C (36°F to 46°F) for 48 hours. Discard unused portion of the injection solution vial.
- Lyophilized powder: Store intact vials at <30°C (<86°F). After reconstitution, use vials immediately to prepare diluted solution. Once diluted for infusion, may store at 20°C to 25°C (68°F to 77°F) for 24 hours or refrigerated at 2°C to 8°C (36°F to 46°F) for 48 hours. Discard unused portion of the reconstituted vial.

- Single-dose vials containing 100 mg of lyophilized remdesivir should be reconstituted by adding 19 mL of sterile water for injection and immediately shaking the vial for 30 seconds.
- The contents of the vial should be allowed to settle for 2–3 minutes, resulting in a clear solution.
- If the contents of the vial are not completely dissolved, this process should be repeated as necessary until the drug is completely dissolved
- The reconstituted remdesivir solution contains 100 mg/20 mL (5 mg/mL).
- For use in adults and pediatric patients weighing 40 kg or more, the reconstituted remdesivir solution should then be further diluted in a 100- or 250-mL IV infusion bag containing 0.9% sodium chloride injection prior to IV infusion

Dosage	Adults and pediatrics weighing ≥ 40: loading dose of 200 mg on day 1, followed by a maintenance dose of 100 mg. Pediatric patients weighing 3.5-40 kg: loading dose of 5 mg/kg, followed by a maintenance dose of 2.5 mg/kg. Treatment duration is up to 5 days, and can be extended to 10 days if patients do not experience clinical improvement. For mechanically ventilated patients or those receiving ECMO 10 days of treatment is recommended.	We favor a 30 minutes infusion time to maximize intracellular concentration of the pharmacologically active metabolite. From clinical trials data and our experience, patients in general wards can recover quickly (no longer need oxygen, no constitutional symptoms) and are ready for discharge before 5 days of treatment. These patients do not need to complete 5 days of treatment.

Pharmacokinetics	Absorption: remdesivir is not suitable for oral administration due to extensive first pass metabolism resulting in poor bioavailability and low systemic absorption. Metabolism: Remdesivir is a substrate of metabolizing CYP450 enzymes (CYP2C8, CYP2D6, and CYP3A); transporters OATP1B1 and P-gp. Distribution: remdesivir widely distributed into tissues, but has poor blood-brain barrier penetration. Elimination: 74% excreted renally and 18% in the feces.	Remdesivir should only be administered via the IV route.



Renal dysfunction	No recommendations regarding dose adjustment for renal dysfunction. Current trials have exclusion criteria for eGFR <30 mL/min or those requiring renal replacement therapy, due to the presence of the excipient SBECD.	Given the short duration of remdesivir and the relatively low SBECD content, we think benefit outweighs the risk for patients hospitalized with COVID-19 and renal dysfunction.
Hepatic dysfunction	No recommendations regarding dose adjustment for hepatic dysfunction. Current trials have exclusion criteria for elevated liver function enzymes.	Given the risk of liver function enzyme elevation with remdesivir, it should be used with caution in patients with underlying hepatic dysfunction when the benefits outweigh the risks.

- **Warnings/Precautions**
- ***Concerns related to adverse effects:***
- Hepatic effects: Transaminase elevations have been observed in healthy volunteers and patients with coronavirus disease 2019 (COVID-19). Perform hepatic laboratory testing before remdesivir initiation and while receiving remdesivir as clinically appropriate.
- Consider discontinuation in patients who develop ALT >10 times the ULN and discontinue if ALT elevation is accompanied by signs or symptoms of liver inflammation.

- Hypersensitivity including infusion-related and anaphylactic reactions:
- Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been reported during and following remdesivir administration. Signs/symptoms may include angioedema, bradycardia, diaphoresis, dyspnea, hypotension, hypertension, hypoxia, fever, nausea, rash, shivering, tachycardia, and wheezing; slowing infusion rate (maximum infusion time: 120 minutes) may be considered to potentially prevent these reactions.
- Discontinue administration and institute appropriate treatment if a clinically significant hypersensitivity reaction occurs.

Disease-related concerns:

- Renal impairment: Although the manufacturer's labeling recommends against use in patients with eGFR <30 mL/minute, significant toxicity with a short duration of therapy (eg, 5 to 10 days) is unlikely (Adamsick 2020).
- In 1 observational report, 46 patients with acute kidney injury and/or chronic kidney disease (36 of whom were receiving either hemodialysis or slow low efficiency dialysis) received remdesivir (injection solution formulation) at the usual recommended dosage for an average of 5 days and did not experience severe rises in AST/ALT or changes in kidney function attributable to the drug (Thakare 2020).

- ***Dosage form specific issues:***
- Injection: Contains the excipient cyclodextrin (sulfobutylether-beta-cyclodextrin; 6 g per 100 mg remdesivir [injection solution] or 3 g per 100 mg remdesivir [lyophilized powder]), which may accumulate in patients with renal impairment.

Dose adjustment in liver failure

FEATURE	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT	<1.25	1.25-2.5	>2.5-5.0	>5.0-10	>10
AST	<1.25	1.25-2.5	>2.5-5.0	>5.0-10	>10
Alkaline Phosphatase	<1.25	1.25-2.5	>2.5-5.0	>5.0-10	>10
GGT	<1.25	1.25-2.5	>2.5-5.0	>5.0-10	>10
Bilirubin	Normal	>1.0-1.5	>1.5-2.5	>2.5-5	>5

- Grade 3 or 4 adverse events occurred on or before day 29 in 273 patients (51.3%) in the remdesivir group and in 295 (57.2%) in the placebo group; 41 events were judged by the investigators to be related to remdesivir and 47

MedDRA System Organ Class	Preferred Term	Remdesivir (N = 532) No.(%)	Placebo (N = 516) No.(%)
Investigations	Glomerular filtration rate decreased[c]	55 (10.3)	74 (14.3)
	Haemoglobin decreased[a]	48 (9.0)	62 (12.0)
	Lymphocyte count decreased[b]	44 (8.3)	54 (10.5)
	Blood creatinine increased[c]	31 (5.8)	36 (7.0)
	Blood glucose increased[c]	39 (7.3)	27 (5.2)
	Aspartate aminotransferase increased[d]	18 (3.4)	33 (6.4)
	Alanine aminotransferase increased[d]	12 (2.3)	24 (4.7)
	Prothrombin time prolonged	26 (4.9)	8 (1.6)
	Blood bilirubin increased	9 (1.7)	16 (3.1)
	Transaminases increased[d]	7 (1.3)	11 (2.1)
	Blood albumin decreased	7 (1.3)	4 (0.8)
	Creatinine renal clearance decreased[c]	4 (0.8)	6 (1.2)
	Oxygen saturation decreased	4 (0.8)	5 (1.0)
	Platelet count decreased	6 (1.1)	2 (0.4)
	Electrocardiogram QT prolonged	2 (0.4)	5 (1.0)
	Liver function test increased	3 (0.6)	3 (0.6)
	Troponin increased	1 (0.2)	5 (1.0)

Table 3. Summary of Adverse Events According to Remdesivir Treatment Group.*

Event or Abnormality	5-Day Group (N=200)	10-Day Group (N=197)
Any grade ≥3 laboratory abnormality — no. of patients/total no. (%)	53/195 (27)	64/191 (34)
Selected grade ≥3 laboratory abnormalities — no. of patients/total no. (%)		
Creatinine clearance decreased		
Grade 3	13/193 (7)	13/188 (7)
Grade 4	5/193 (3)	23/198 (12)
ALT elevation		
Grade 3	8/194 (4)	11/191 (6)
Grade 4	4/194 (2)	5/191 (3)
AST elevation		
Grade 3	11/194 (6)	7/190 (4)
Grade 4	3/194 (2)	4/190 (2)
Bilirubin increased		
Grade 3	1/193 (1)	3/190 (2)
Grade 4	0	1/190 (1)

Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed

Conclusion