Table 4a. Remdesivir: Selected Clinical Trial Data

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The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for RDV. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Methods	Results	Limitations and Interpretation
ACTT-1: Double-Blind, Placebo-Controlled Trial of Remdesivir in Hospitalized Patients With COVID-19 in 10 Countries[1]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• ≥1 of the following:
  • Pulmonary infiltrates
  • SpO_2 ≤94% on room air
  • Need for supplemental oxygen, HFNC oxygen, NIV, MV, or ECMO
Key Exclusion Criteria
• ALT or AST >5 times ULN
• eGFR <30 mL/min
Interventions
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for up to 9 days (n = 541)
• Placebo for up to 10 days (n = 521)
Primary Endpoint
• Time to clinical recovery
Key Secondary Endpoints
• Clinical status at Day 15, as measured by an OS
• Mortality by Day 29
• Occurrence of SAEs
	Participant Characteristics
	• Mean age 59 years; 64% men; 53% White, 21% Black, 13% Asian, 24% Hispanic/Latinx
	• Coexisting conditions: 26% with 1; 55% with ≥2
	• 13% not on oxygen; 41% on supplemental oxygen; 18% on HFNC oxygen or NIV; 27% on MV or ECMO
	• Median of 9 days (IQR 6–12 days) from symptom onset to randomization
	• 23% received corticosteroids during study.
	Primary Outcomes
	• Time to clinical recovery: 10 days in RDV arm vs. 15 days in placebo arm (rate ratio for recovery 1.29; 95% CI, 1.12–1.49; $P < 0.001$)
	• Benefit of RDV was greatest in patients randomized during first 10 days after symptom onset and in those who required supplemental oxygen at enrollment.
	• No difference between arms in time to recovery for patients on HFNC oxygen, NIV, MV, or ECMO at enrollment
	Secondary Outcomes
	• Improvement in clinical status at Day 15 was more likely in RDV arm (OR 1.5; 95% CI, 1.2–1.9; $P < 0.001$).
	• No difference between arms in mortality by Day 29
	• Occurrence of SAEs: 25% in RDV arm vs. 32% in placebo arm
		Key Limitations
		• Wide range of disease severity among patients; study not powered to detect differences within subgroups
		• Study not powered to detect differences in mortality between arms
		• No data on longer-term morbidity
		Interpretation
		• In patients with severe COVID-19, RDV reduced the time to clinical recovery.
		• The benefit was most apparent in hospitalized patients who were randomized within 10 days of symptom onset and were receiving supplemental oxygen.
		• There was no observed benefit in those on HFNC oxygen, NIV, MV, or ECMO, but the study was not powered to detect differences within subgroups.

Methods	Results	Limitations and Interpretation
CATCO: Multicenter, Open-Label, Pragmatic RCT of Remdesivir in Hospitalized Patients With COVID-19 in Canada[2]		

Key Inclusion Criterion
• Laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criterion
• Already receiving RDV
Interventions
• RDV 200 mg IV on Day 0, then RDV 100 mg IV once daily on Days 1–9 (n = 634)
• Local SOC (n = 647)
Primary Endpoint
• In-hospital mortality
Key Secondary Endpoints
• New need for MV
• Hospital LOS
• Incidence of new hepatic dysfunction, incidence of need for dialysis, and change in SCr at Day 5
	Participant Characteristics
	• Median age 66 years; 60% men; 41% White
	• Median of 8 days from symptom onset to randomization
	• At entry:
	  • 54% on low-flow oxygen
	  • 24% on HFNC oxygen
	  • 9% on MV
	• Rates of comorbidities were similar between arms.
	• 87% in both arms were receiving corticosteroids at baseline.
	Primary Outcome
	• In-hospital mortality: 19% in RDV arm vs. 23% in SOC arm (relative risk 0.83; 95% CI, 0.67–1.03)
	Secondary Outcomes
	• New need for MV: 8% in RDV arm vs. 15% in SOC arm (relative risk 0.53; 95% CI, 0.38–0.75)
	• No significant difference between arms in hospital LOS
	• No difference between arms in incidence of new hepatic dysfunction, incidence of need for dialysis, or change in SCr at Day 5
		Key Limitations
		• Open-label study
		• Information on comorbidities was not available for 26% of patients.
		Interpretation
		• Compared to SOC, RDV did not decrease in-hospital mortality among hospitalized patients with COVID-19.
		• Patients who received RDV were less likely to require MV than patients who received SOC.

Methods	Results	Limitations and Interpretation
DisCoVeRy: Open-Label, Adaptive RCT of Remdesivir in Hospitalized Patients With Moderate or Severe COVID-19 in Europe[3]		
Key Inclusion Criteria • Laboratory-confirmed SARS-CoV-2 infection • Illness of any duration • SpO_2 ≤94% on room air or use of supplemental oxygen, HFNC oxygen, NIV, or MV **Key Exclusion Criteria** • ALT or AST >5 times ULN • Severe chronic kidney disease **Interventions** • RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for up to 9 days (n = 429) • SOC (n = 428) **Primary Endpoint** • Clinical status at Day 15, as measured by an OS **Key Secondary Endpoints** • Mortality by Day 29 • Occurrence of SAEs	**Participant Characteristics** • Median age 64 years; 70% men; 69% White • 74% with ≥1 coexisting conditions • 40% received corticosteroids. • Median of 9 days from symptom onset to randomization in both arms • 61% with moderate disease; 39% with severe disease **Primary Outcome** • No difference between arms in clinical status at Day 15 (OR 0.98; 95% CI, 0.77–1.25; $P = 0.85$) • A prespecified subgroup analysis based on duration of symptoms found no significant difference in clinical status between arms. **Secondary Outcomes** • Mortality by Day 29: 8% in RDV arm vs. 9% in SOC arm • Occurrence of SAEs: 33% in RDV arm vs. 31% in SOC arm ($P = 0.48$)	**Key Limitations** • Open-label study • 440 participants in this study also enrolled in the WHO Solidarity trial. **Interpretation** • There was no clinical benefit of RDV in hospitalized patients with COVID-19 who were symptomatic for >7 days and who required supplemental oxygen.

Methods	Results	Limitations and Interpretation
WHO Solidarity Trial, Final Report: Open-Label, Adaptive RCT in Hospitalized Patients With COVID-19 in 35 Countries[4]		

Key Inclusion Criterion
• Not known to have received any study drug
Interventions
• RDV 200 mg IV on Day 0, then RDV 100 mg IV once daily on Days 1–9 (n = 4,146)
• Local SOC (n = 4,129)
Primary Endpoint
• In-hospital mortality
Key Secondary Endpoint
• Initiation of MV
	Participant Characteristics
	• 46% aged 50–69 years; 22% aged ≥70 years; 63% men
	• Rates of comorbidities were similar between arms.
	• At entry:
	  • 71% on supplemental oxygen
	  • 9% on MV
	• 68% received corticosteroids during study; 4.6% received IL-6 inhibitors.
	Primary Outcome
	• In-hospital mortality: 14.5% in RDV arm vs. 15.6% in SOC arm (rate ratio 0.91; 95% CI, 0.82–1.02; $P = 0.12$)
	  • On MV: 42.1% vs. 38.6% (rate ratio 1.13; 95% CI, 0.89–1.42; $P = 0.32$)
	  • Not on MV but receiving oxygen: 14.6% vs. 16.3% (rate ratio 0.87; 95% CI, 0.76–0.99; $P = 0.03$)
	  • Not on oxygen initially: 2.9% vs. 3.8% (rate ratio 0.76; 95% CI, 0.46–1.28; $P = 0.30$)
	Secondary Outcome
	• Initiation of MV: 14.1% in RDV arm vs. 15.7% in SOC arm (rate ratio 0.88; 95% CI, 0.77–1.00; $P = 0.04$)
		Key Limitations
		• Open-label study
		• No data on time from symptom onset to enrollment
		• Data analysis did not separate receipt of low-flow and high-flow oxygen.
		Interpretation
		• There was no benefit of RDV in hospitalized patients with COVID-19 who were on MV at baseline.
		• Compared to SOC, RDV had a modest but statistically significant effect on reducing the risk of death or progression to MV in hospitalized patients who required oxygen.

Methods	Results	Limitations and Interpretation
GS-US-540-5774 Study: Open-Label RCT of 10 Days or 5 Days of Remdesivir in Hospitalized Patients With Moderate COVID-19 in Asia, Europe, and the United States[5]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• Pulmonary infiltrates
• SpO_2 >94% on room air
Key Exclusion Criteria
• ALT or AST >5 times ULN
• CrCl <50 mL/min
Interventions
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 9 days (n = 193)
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 4 days (n = 191)
• Local SOC (n = 200)
Primary Endpoint
• Clinical status at Day 11, as measured by an OS
	Participant Characteristics
	• Demographic and baseline disease characteristics were similar across arms.
	• Median age 57 years; 61% men; 58% White
	• 84% required no supplemental oxygen; 15% required low-flow oxygen; 1% required HFNC oxygen or NIV.
	• Concomitant medication use in the 10-day RDV, 5-day RDV, and SOC arms:
	  • Steroids: 15% vs. 17% vs. 19%
	  • Tocilizumab: 1% vs. 1% vs. 5%
	  • HCQ or CQ: 11% vs. 8% vs. 45%
	  • LPV/RTV: 6% vs. 5% vs. 22%
	  • AZM: 21% vs. 18% vs. 31%
	• Median duration of therapy: 6 days in 10-day RDV arm vs. 5 days in 5-day RDV arm
	Primary Outcome
	• Clinical status at Day 11:
	  • Significantly better in 5-day RDV arm than in SOC arm (OR 1.65; 95% CI, 1.09–2.48; $P = 0.02$)
	  • No difference between 10-day RDV arm and SOC arm ($P = 0.18$)
		Key Limitations
		• Open-label design may have affected decisions about concomitant medications (e.g., more patients in SOC arm received AZM, HCQ or CQ, and LPV/RTV) and time of hospital discharge.
		• No data on time to return to activity for discharged patients
		Interpretation
		• Hospitalized patients with moderate COVID-19 who received 5 days of RDV had better clinical status at Day 11 than those who received SOC.
		• There was no difference in clinical status at Day 11 between patients who received 10 days of RDV and those who received SOC.

Methods	Results	Limitations and Interpretation
GS-US-540-5773 Study: Open-Label RCT of 10 Days or 5 Days of Remdesivir in Hospitalized Patients With Severe COVID-19 in Asia, Europe, and the United States[6]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• Aged ≥12 years
• Pulmonary infiltrates and SpO_2 ≤94% on room air or receipt of supplemental oxygen
Key Exclusion Criteria
• Need for MV or ECMO
• Multiorgan failure
• ALT or AST >5 times ULN
• Estimated CrCl <50 mL/min
Interventions
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 4 days (n = 200)
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 9 days (n = 197)
Primary Endpoint
• Clinical status at Day 14, as measured by an OS
	Participant Characteristics
	• Median age: 61 years in 5-day RDV arm vs. 62 years in 10-day RDV arm
	• 60% men in 5-day RDV arm vs. 68% men in 10-day RDV arm
	• Oxygen requirements at baseline for 5-day RDV arm vs. 10-day RDV arm:
	  • None: 17% vs. 11%
	  • Low-flow oxygen: 56% vs. 54%
	  • HFNC oxygen or NIV: 24% vs. 30%
	  • MV or ECMO: 2% vs. 5%
	• Baseline clinical status was worse in 10-day RDV arm than in 5-day RDV arm ($P = 0.02$).
	Primary Outcome
	• After adjusting for baseline clinical status:
	  • Proportion with improved clinical status at Day 14: 65% in 5-day RDV arm vs. 54% in 10-day RDV arm ($P = 0.14$)
		Key Limitations
		• Open-label study
		• Lack of placebo arm
		• Baseline imbalances in clinical status of patients in 5-day RDV and 10-day RDV arms
		Interpretation
		• In hospitalized patients with severe COVID-19 who were not receiving MV or ECMO, using RDV for 5 or 10 days had similar clinical benefits.

Methods	Results	Limitations and Interpretation
PINETREE: Double-Blind, Placebo-Controlled Trial of Remdesivir for 3 Days in Nonhospitalized Patients With COVID-19 Who Were at High Risk of Disease Progression in Denmark, Spain, the United Kingdom, and the United States[7]		
Key Inclusion Criteria • Laboratory-confirmed SARS-CoV-2 infection ≤4 days from screening • Aged ≥12 years • ≥1 risk factor for disease progression or aged ≥60 years • Symptom onset ≤7 days from randomization • ≥1 ongoing COVID-19 symptom **Key Exclusion Criteria** • COVID-19 vaccination • Receipt of supplemental oxygen • Previous hospitalization or treatment for COVID-19 **Interventions** • RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily on Days 2 and 3 (n = 279) • Placebo (n = 283) **Primary Endpoints** • COVID-19–related hospitalization or death from any cause by Day 28 • Occurrence of AEs **Key Secondary Endpoint** • COVID-19–related, medically attended visit or death from any cause by Day 28	**Participant Characteristics** • Mean age 50 years; 30% aged ≥60 years; 52% men; 80% White, 8% Black • 62% with DM; 55% with obesity; 48% with HTN • Median of 5 days (IQR 3–6 days) of symptoms before first infusion • Median of 2 days (IQR 1–4 days) from RT-PCR confirmation to screening for study participation. **Primary Outcomes** • COVID-19–related hospitalization or death from any cause by Day 28: 2 (0.7%) in RDV arm vs. 15 (5.3%) in placebo arm (HR 0.13; 95% CI, 0.03–0.59; *P* = 0.008) • Occurrence of AEs: 42% in RDV arm vs. 46% in placebo arm **Secondary Outcome** • COVID-19–related, medically attended visit or death from any cause by Day 28: 4 (1.6%) in RDV arm vs. 21 (8.3%) in placebo arm (HR 0.19; 95% CI, 0.07–0.56)	**Key Limitations** • Study halted early due to administrative issues. • Vaccinated individuals were excluded. **Interpretation** • Among nonhospitalized patients with COVID-19, 3 consecutive days of RDV resulted in an 87% relative reduction in the risk of hospitalization or death when compared to placebo.

Key: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; AZM = azithromycin; CQ = chloroquine; CrCl = creatinine clearance; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; HTN = hypertension; IV = intravenous; IL = interleukin; LOS = length of stay; LPV/RTV = lopinavir/ritonavir; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SCr = serum creatinine; SOC = standard of care; SpO_2 = oxygen saturation; ULN = upper limit of normal; WHO = World Health Organization

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