Table 5d. Janus Kinase Inhibitors: Selected Clinical Trial Data

Last Updated: August 8, 2022

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

The information in this table may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see ClinicalTrials.gov for more information on clinical trials evaluating kinase inhibitors.

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Baricitinib Versus Usual Care in the United Kingdom[1]		

Key Inclusion Criterion
• Hospitalized with suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criteria
• eGFR <15 mL/min/1.73m^2
• ANC <500 cells/mm^3
• Evidence of active TB
Interventions
• BAR 4 mg PO daily for 10 days or until discharge, whichever comes first (n = 4,148)
• SOC (n = 4,008)
Primary Endpoint
• 28-day mortality
Key Secondary Endpoints
• Time to discharge from hospital
• Composite of MV, ECMO, or death
	Participant Characteristics
	• Mean age 58 years; 66% men; 80% White
	• Median duration of symptoms at enrollment: 9 days
	• 91% with laboratory-confirmed SARS-CoV-2 infection
	• At baseline:
	  • 95% received corticosteroids
	  • 23% received tocilizumab
	  • 20% received remdesivir
	  • 42% received ≥1 COVID-19 vaccine
	  • 6% no supplemental oxygen required
	  • 68% simple oxygen
	  • 24% NIV
	  • 3% MV
	Primary Outcome
	• 28-day mortality: 12% in BAR arm vs. 14% in SOC arm (age-adjusted rate ratio 0.87; 95% CI, 0.77–0.98; *P* = 0.028)
	Secondary Outcomes
	• Discharge within 28 days: 80% in BAR arm vs. 78% in SOC arm (age-adjusted rate ratio 1.10; 95% CI, 1.04–1.15; *P* = 0.002)
	  • Median time to discharge: 8 days in both arms
	• Composite of MV, ECMO, or death: 16% in BAR arm vs. 17% in SOC arm (age-adjusted risk ratio 0.89; 95% CI, 0.81–0.98; *P* = 0.016)
		Key Limitation
		• Open-label study
		Interpretation
		• In patients hospitalized for COVID-19, BAR reduced the risk of death.

Methods	Results	Limitations and Interpretation
COV-BARRIER: Double-Blind, Placebo-Controlled, Randomized Trial of Baricitinib in Hospitalized Adults in 12 Countries in Asia, Europe, North America, and South America[2]		
Key Inclusion Criteria • Laboratory-confirmed SARS-CoV-2 infection • Evidence of pneumonia or active, symptomatic COVID-19 • ≥1 elevated inflammatory marker (CRP, D-dimer, LDH, or ferritin) **Key Exclusion Criteria** • MV or ECMO • Receipt of immunosuppressants (including high-dose steroids) • Prior receipt of CCP or IVIG • ANC <1,000 cells/μL • ALC <200 cells/μL • ALT or AST >5 times ULN • eGFR <30 mL/min **Interventions** • BAR 4 mg PO once daily for up to 14 days (n = 764) • Placebo (n = 761) **Primary Endpoint** • Clinical progression or death by Day 28 **Key Secondary Endpoint** • Mortality by Day 28	**Participant Characteristics** • Mean age 58 years; 63% men • 79% received corticosteroids; 19% received RDV; 13% received oxygen but no steroids **Primary Outcome** • Clinical progression or death by Day 28: 28% in BAR arm vs. 31% in placebo arm (OR 0.85; 95% CI, 0.67–1.08; $P = 0.18$) **Secondary Outcomes** • Mortality by Day 28: 8% in BAR arm vs. 13% in placebo arm (HR 0.57; 95% CI, 0.41–0.78; $P = 0.0018$) • Mortality by Day 28 for those receiving corticosteroids at baseline: 9% in BAR arm vs. 14% in placebo arm (HR 0.63; 95% CI, 0.45–0.89)	**Key Limitation** • Results from the ACTT-2 trial prompted a protocol amendment limiting enrollment to participants who required baseline oxygen. **Interpretation** • Although the primary outcome of clinical progression or death was not significantly different between arms, treatment with BAR plus SOC was associated with reduced mortality in hospitalized adults with COVID-19 who were not receiving MV (see addendum below for results for patients who required MV or ECMO). • For patients receiving oxygen but not steroids at baseline, the primary and secondary outcomes were similar to the outcomes for the overall study population.

Methods	Results	Limitations and Interpretation
COV-BARRIER Addendum: Double-Blind, Placebo-Controlled, Randomized Trial of Baricitinib in Hospitalized Adults on Mechanical Ventilation or Extracorporeal Membrane Oxygenation in Argentina, Brazil, Mexico, and the United States[3]		
Key Inclusion Criteria • Laboratory-confirmed SARS-CoV-2 infection • Evidence of pneumonia or active, symptomatic COVID-19 • ≥1 elevated inflammatory marker (CRP, D-dimer, LDH, or ferritin) • MV or ECMO at baseline **Key Exclusion Criteria** • Receipt of immunosuppressants (including high-dose steroids) • Prior receipt of CCP or IVIG • ANC <1,000 cells/μL • ALC <200 cells/μL • ALT or AST >5 times ULN • eGFR <30 mL/min **Interventions** • BAR 4 mg PO once daily for up to 14 days (n = 51) • Placebo (n = 50) **Key Endpoints** • Mortality at Day 28 • Number of ventilator-free days • Duration of hospitalization	**Participant Characteristics** • Mean age 59 years; 55% men • 86% received corticosteroids; 2% received RDV **Outcomes** • Mortality at Day 28: 39% in BAR arm vs. 58% in placebo arm (HR 0.54; 95% CI, 0.31–0.96; $P = 0.030$) • Number of ventilator-free days and duration of hospitalization: no significant difference between arms	**Key Limitations** • Very small sample size, exploratory analysis • High mortality in placebo arm **Interpretation** • In critically ill patients with COVID-19 receiving MV or ECMO, treatment with BAR and SOC (including corticosteroids) may decrease mortality.

Methods	Results	Limitations and Interpretation
ACTT-2: Double-Blind, Placebo-Controlled, Randomized Trial of Baricitinib Plus Remdesivir in Hospitalized Adults With COVID-19 in 8 Countries in Europe, North America, and Asia[4]		

Key Inclusion Criteria
• Positive SARS-CoV-2 PCR result
• Radiographic infiltrates, SpO_2 ≤94% on room air, or requiring supplemental oxygen, MV, or ECMO
Key Exclusion Criteria
• Use of glucocorticoids for COVID-19 indications
• ALT or AST >5 times ULN
• Impaired renal function
Interventions
• BAR 4 mg PO once daily for 14 days or until discharge, plus RDV for 10 days or until discharge (n = 515)
• Placebo plus RDV (n = 518)
Primary Endpoint
• Time to recovery by Day 28
Key Secondary Endpoints
• Clinical status at Day 15 as measured by OS
• Mortality at Day 28
	Participant Characteristics
	• Mean age 55 years; 63% men; 48% White, 15% Black, 10% Asian
	• At baseline:
	  • 13% no supplemental oxygen required
	  • 55% conventional oxygen
	  • 21% HFNC oxygen or NIV
	  • 11% MV or ECMO
	Primary Outcomes
	• Median time to recovery: 7 days in BAR arm vs. 8 days in placebo arm (rate ratio 1.16; 95% CI, 1.01–1.32; $P = 0.03$)
	• Median time to recovery for those receiving HFNC oxygen or NIV: 10 days in BAR arm vs. 18 days in placebo arm (rate ratio for recovery 1.51; 95% CI, 1.10–2.08)
	Secondary Outcomes
	• Improvement in clinical status at Day 15: greater in BAR arm vs. placebo arm (OR 1.3; 95% CI, 1.0–1.6)
	• Mortality at Day 28: 5% in BAR arm vs. 8% in placebo arm (HR 0.65; 95% CI, 0.39–1.09)
		Key Limitations
		• Not powered to detect difference in mortality between arms
		• Steroids not part of SOC
		Interpretation
		• Compared with RDV alone, BAR plus RDV reduced recovery time and improved clinical status, particularly for patients who received HFNC oxygen or NIV at baseline.

Methods	Results	Limitations and Interpretation
ACTT-4: Double-Blind, Placebo-Controlled, Randomized Trial of Remdesivir With Baricitinib Versus Dexamethasone for Hospitalized Patients Requiring Supplemental Oxygen in Japan, Mexico, Singapore, South Korea, and the United States[5]		

Key Inclusion Criteria
• Hospitalized and requiring conventional oxygen, HFNC oxygen, or NIV
• Laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criterion
• Receipt of CCP or >1 dose DEX 6 mg (or equivalent) or BAR before enrollment
Interventions
• RDV IV for ≤10 days plus BAR 4 mg PO daily for ≤14 days plus DEX placebo IV (n = 516)
• RDV IV for ≤10 days plus BAR placebo PO plus DEX 6 mg IV daily ≤10 days (n = 494)
Primary Endpoint
• MV-free survival by Day 29
Key Secondary Endpoints
• Clinical status at Day 15 as measured by OS
• Time to recovery
Key Safety Endpoints
• Occurrence of treatment-related AEs
• Occurrence of SAEs
	Participant Characteristics
	• Median age 58 years; 58% men; 58% White, 34% Hispanic/Latinx
	• At baseline:
	  • 85% low-flow oxygen
	  • 15% HFNC oxygen or NIV
	• Mean duration of symptoms at enrollment: 8 days
	Primary Outcome
	• MV-free survival by Day 29: 87% in BAR arm vs. 88% in DEX arm (risk difference 0.6%; 95% CI, -3.6% to 4.8%; $P = 0.91$)
	Secondary Outcomes
	• Improved clinical status at Day 15: similar between arms (OR 1.01; 95% CI, 0.80–1.27)
	  • For low-flow oxygen at baseline: OR 0.91; 95% CI, 0.70–1.17
	  • For HFNC oxygen or NIV at baseline: OR 1.64; 95% CI, 0.92–2.90
	• Median time to recovery: 6 days in BAR arm vs. 5 days in DEX arm (rate ratio 1.04; 95% CI, 0.91–1.19)
	Safety Outcomes
	• Occurrence of treatment-related AEs: 4% in BAR arm vs. 10% in DEX arm (risk difference 6.0%; 95% CI, 2.8%–9.3%; $P = 0.0004$)
	• Occurrence of SAEs: 28% in BAR arm vs. 36% in DEX arm (risk difference 7.7%; 95% CI, 1.8%–13.4%; $P = 0.012$)
	• Most SAEs and treatment-related AEs were laboratory abnormalities.
		Key Limitations
		• Study closed before completing enrollment of 1,500 as it was unlikely to show a difference between arms.
		• Not powered to analyze differences between ordinal score subgroups HFNC oxygen or NIV at baseline.
		• Few patients died or required MV, which may have decreased the power to detect a difference between arms for MV-free survival.
		• Treatment-related differences in AEs for BAR vs. DEX were mainly related to laboratory abnormalities, not clinical events. The clinical relevance of these differences in laboratory abnormalities is unclear.
		Interpretation
		• In hospitalized patients requiring conventional oxygen, HFNC oxygen, or NIV, the use of BAR or DEX resulted in similar MV-free survival by Day 29.

Methods	Results	Limitations and Interpretation
STOP-COVID: Double-Blind, Placebo-Controlled, Randomized Trial of Tofacitinib in Hospitalized Patients With COVID-19 Pneumonia in Brazil[6]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• COVID-19 pneumonia on CXR or CT
• Hospitalized for <72 hours
Key Exclusion Criteria
• Receiving NIV, MV, or ECMO at baseline
• History of or current thrombosis
• Immunosuppression or active cancer treatment
Interventions
• Tofacitinib 10 mg PO twice daily for up to 14 days or until discharge (n = 144)
• Placebo (n = 145)
Primary Endpoint
• Mortality or respiratory failure through Day 28
Key Secondary Endpoint
• Mortality through Day 28
	Participant Characteristics
	• Mean age 56 years; 35% women
	• Median 10 days symptom onset to randomization
	• At baseline:
	  • 75% supplemental oxygen
	  • 13% HFNC oxygen
	• Use of glucocorticoids: 79% at baseline, 89% during hospitalization
	Primary Outcome
	• Mortality or respiratory failure through Day 28: 18% in tofacitinib arm vs. 29% in placebo arm (risk ratio 0.63; 95% CI, 0.41–0.97; *P* = 0.04)
	Secondary Outcome
	• Mortality through Day 28: 2.8% in tofacitinib arm vs. 5.5% in placebo arm (HR 0.49; 95% CI, 0.15–1.63)
		Key Limitations
		• Small sample size
		• RDV not available during trial
		Interpretation
		• Tofacitinib, when compared with placebo, led to a lower risk of mortality or respiratory failure among hospitalized adults with COVID-19 pneumonia, most of whom received glucocorticoids.

Key: AE = adverse event; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; BAR = baricitinib; CCP = COVID-19 convalescent plasma; CRP = C-reactive protein; CT = computed tomography; CXR = chest X-ray; DEX = dexamethasone; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HFNC = high-flow nasal cannula; IVIG = intravenous immunoglobulin; LDH = lactate dehydrogenase; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = orally; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SOC = standard of care; SpO_2 = oxygen saturation; TB = tuberculosis; ULN = upper limit of normal

References

1. RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *Lancet*. 2022;400(10349):359-368. Available at: https://pubmed.ncbi.nlm.nih.gov/35908569.
2. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled Phase 3 trial. *Lancet Respir Med*. 2021;9(12):1407-1418. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/34480861.

3. Ely EW, Ramanan AV, Kartman CE, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. *Lancet Respir Med*. 2022;10(4):327-336. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35123660.
4. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med*. 2021;384(9):795-807. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33306283.
5. Wolfe CR, Tomashek KM, Patterson TF, et al. Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial. *Lancet Respir Med*. 2022;10(9):888-899. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35617986.
6. Guimaraes PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;385(5):406-415. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34133856.