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Supplementary appendix

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Supplement to: Mehta P, Titanji B K. Baricitinib in COVID-19: a coming-of-age from artificial intelligence to reducing mortality. *Lancet* 2022; **400:** 338–339.

		ACTT-2 Kalil et al, NEJM, 2021	COV-BARRIER Marconi et al, Lancet Resp Med, 2021	ACTT-4 Wolfe et al, Lancet Resp Med, 2022	RECOVERY Horby et al, Lancet, 2022
Study Design		• Double-blind, placebo-controlled RCT • International: 67 sites, 8 countries, n=1033 • Stratified by disease severity, trial site • Analysis: Intention-to-treat • Enrollment: 8th May 2020 – 19th July 2020 • Primary Outcome: time to recovery • Key secondary outcome: clinical status D15	• Double-blind, placebo-controlled RCT, Phase III • International: 101 sites, 11 countries, n=1525 • Stratified by disease severity, age, region, steroid use • Analysis: Intention-to-treat • Enrollment: 11th June 2020-15th Jan 2021 • Primary Outcome: composite of progression in NIAID-OS or death • Key secondary outcome: mortality	• Double-blind, double-placebo-controlled RCT • International, 67 sites, 5 countries, n=1010 • Stratified by disease severity, trial site • Analysis: Intention-to-treat • Enrolment: 1st Dec 2020 – 13th April 2021 • Primary Outcome: difference in mechanical ventilation-free survival by day 29 • Key secondary outcome: Clinical status at D15 based on the NIAID-OS	• Open-label, adaptive RCT • UK, 159 sites, n = 8156 • Analysis: Intention-to-treat • Enrolment: 2nd Feb 2021-29th Dec 2021 • Primary outcome: 28-day mortality • Key secondary outcome: composite progression to IMV or death (for those not on IMV at baseline)

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Population
		Key inclusion criteria:
		• Hospitalized, confirmed COVID-19, Age ≥18 years
		• Evidence of COVID-pneumonia, one of:
		  ○ Radiographic infiltrates
		  ○ SpO2 ≤94% on room air
		  ○ Requiring supplemental oxygen, IMV, ECMO (i.e. NIAID 5-7)
		
		Key Exclusion criteria:
		• Pregnancy / Breast-feeding
			Key inclusion criteria:
			• Hospitalized, confirmed COVID-19, Age ≥18 years
			• NIAID-OS 4 (hospitalized, but no supplemental oxygen), 5 or 6. After Oct 2020 (results of ACTT-2), limited to requiring at supplemental oxygen or NIV, i.e. NIAID-OS 5 or 6
			• At least one elevated inflammatory marker above ULN: CRP, D-dimer, LDH or ferritin
			
			Key Exclusion criteria:
			• Mechanical ventilation or ECMO (NIAID-OS 7)
			• Pregnancy / Breast-feeding
				Key inclusion criteria:
				• Hospitalized, confirmed COVID-19, Age ≥18 years
				• Supplemental oxygen i.e. NIAID-OS 5 or 6
				
				Key Exclusion criteria:
				• Mechanical ventilation or ECMO (NIAID-OS 7)
				• Pregnancy / Breast-feeding
					Key inclusion criteria:
					• Hospitalized, suspected or confirmed COVID-19, Age ≥2 years
					
					Key exclusion criteria:
					• Pregnancy / Breast-feeding

I **Intervention**		**Baricitinib + Remdesivir + SOC (n=515)** Baricitinib dose: 4mg once daily (≤14 days) Any corticosteroids 11%; Dexamethasone 6%	**Baricitinib + SOC (n=764)** Baricitinib dose: 4mg once daily (≤14 days) Dexamethasone 92% (566/612)	**Baricitinib + Remdesivir + Placebo (n=516)** Baricitinib dose: 4mg once daily (≤14 days)	**Baricitinib + SOC n=4148** Baricitinib dose: 4mg once daily for 10 days Corticosteroids 96% (3962/4148) Tocilizumab 23% (951/4148)
C **Comparator**		**Placebo + Remdesivir + SOC (n=518)** Any corticosteroids 13%; Dexamethasone 7%	**Placebo + SOC (n=761)** Dexamethasone 90% (533/592)	**Dexamethasone + Remdesivir + Placebo (n=494)**	**SOC alone n=4008** Corticosteroids 95% (3809/4008) Tocilizumab 23% (921/4008)
O **Outcome**	**Primary**	**MET** the primary end-point. Time to recovery significantly shorter in Baricitinib vs control group (median, 7 days vs. 8 days; rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03).	Did **NOT** meet the primary end-point. No significant difference in composite of progression in NIAID-OS (score 6, 7 or 8) or death by D28 in baricitinib group vs control.	**Terminated early for futility**, as low probability of superiority. Did not show a difference between arms. Mechanical ventilation-free survival by day 29 was similar between the study groups (Kaplan-Meier estimates of 87·0% [95% CI 83·7 to 89·6] in the Baricitinib + Remdesivir + placebo group and 87·6% [84·2 to 90·3] in the Dexamethasone + Remdesivir + placebo group; risk difference 0·6 [95% CI –3·6 to 4·8]; p=0·91).	**MET** the primary end-point. 28-day mortality lower in Baricitinib group 12% vs usual care 14%, age-adjusted rate ratio 0.87; 95% CI 0.77-0.98; p=0.026) 13% proportional reduction in mortality
	Secondary	Combination group had 30% higher odds of improvement in clinical status at D15 than the control group (OR 1.3; 95% CI, 1.0 to 1.6)	A significant reduction in all-cause mortality between baricitinib vs control at • D28, 8% vs 13% [HR 0.57, 95% CI 0.41-0.78, p=0.0018], NNT 20 • D60, 10% vs 15% [HR 0.62, 95% CI 0.47-0.83, p=0.005]	Similar outcomes for clinical status at D15	Among patients not on IMV at baseline, allocation to Baricitinib was associated with a lower risk of progressing to the composite secondary outcome of invasive mechanical ventilation or death (16% vs. 17%, age-adjusted risk ratio 0·89, 95% CI 0·81 to 0·98)
Comments		Very few patients on corticosteroids. Not powered to detect a difference in mortality between the groups. Greatest benefit of combination treatment in more severe disease i.e. patients with baseline NIAID-OS 6 (HFO or NIV) – time to recovery 10 days (combination) vs 18 days (control) (rate ratio for recovery 1.51: 95% CI 1.10-2.08)	Subgroup analysis suggests greatest benefit in more severe disease, i.e. NIAID-OS 6, reduction in 28-day mortality significantly lower with Baricitinib vs. control (17% vs 29%, p=0.0065) Safety: Similar TEAE Baricitinib (45%) vs. control (44%), serious infections, thromboembolic events and MACE similar between groups	Dexamethasone associated with significantly more • Adverse events (risk difference 7·5% [1·6 to 13·3]; p=0·014) • TEAE (risk difference 6·0% [2·8 to 9·3) • Severe or life-threatening AE (risk difference 7·7% [1·8 to 13·4]; p=0·012)	Very large sample size. No significant differences in the rates of non-coronavirus infection, thrombotic events, or clinically significant bleeding, but allocation to Baricitinib was associated with a significant reduction in new onset cardiac arrythmia (2.3% vs 3.1%, p=0.017). 959 received both Baricitinib and Tocilizumab, 95% of whom were on Dexamethasone at baseline. The was no significant heterogeneity in primary outcome estimates when stratified by co-administration of Tocilizumab.

RCT Randomised Controlled Trial, NIAID-OS (National Institute of Allergy and Infectious Disease Ordinal Scale); ULN; upper limit of normal; HR Hazard Ratio, NNT Number needed to treat; TEAE treatment emergent adverse event; MACE major adverse cardiovascular event; IMV invasive mechanical ventilation, ECMO extracorporeal membrane oxygenation; HFO high flow oxygen; NIV non-invasive ventilation

References:

1.Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. New England Journal of Medicine 2020; 384(9): 795-807.

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): 1407-18.

3.Wolfe CR, Tomashek KM, Patterson TF, et al. Baricitinib versus dexamethasone for adults hospitalised with COVID19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial. The Lancet Respiratory Medicine 2022.

4.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.