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LB3. Baricitinib plus Standard of Care for Hospitalized Adults with COVID-19 on Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation: Results of a Randomized, Placebo-Controlled Trial

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Session: 55. Late Breaker Abstracts: COVID-19 Treatment & Prophylaxis
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Background. Interventions to reduce mortality in critically ill patients with COVID-19 are a crucial unmet medical need. Baricitinib (BARI) is an oral, selective Janus kinase (JAK)1/JAK2 inhibitor with efficacy in hospitalized adults with COVID-19. Treatment with BARI 4-mg was evaluated in critically ill adult patients with COVID-19 with baseline need for invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO).

Methods. COV-BARRIER (NCT04421027) was a randomized double-blind, placebo-controlled trial in patients with confirmed SARS-CoV-2 infection and elevation of ≥ 1 serum inflammatory marker. In this newly completed substudy, enrolled participants (not previously reported) from 4 countries on IMV or ECMO at study entry were randomly assigned 1:1 to once-daily BARI 4-mg or placebo (PBO) for up to 14 days plus standard of care (SOC), which included baseline systemic corticosteroid use in 86% of patients. The prespecified exploratory endpoints included all-cause mortality and number of ventilator-free days (VFDs) through Day 28.

Results. Characteristics for 101 participants are shown in Table 1.

Treatment with BARI significantly reduced all-cause mortality by Day 28 compared to PBO [39.2% vs 58.0%, respectively; hazard ratio (HR) = 0.54 (95%CI 0.31, 0.96), p=0.030, relative risk (RR) = 0.68 (95%CI 0.45, 1.02); Figure 1A]. One additional death was prevented for every six BARI-treated patients. Significant reduction in mortality was also observed by Day 60 [45.1% vs 62.0%; HR = 0.56 (95%CI 0.33, 0.97), p=0.027, RR = 0.73 (95%CI 0.50, 1.06); Figure 1B].

Patients treated with BARI showed a numerical reduction in the duration of IMV and duration of hospitalization vs PBO and more BARI treated patients recovered (Table 2). No new safety findings were observed (Table 2).

Table 1: Baseline demographics and disease characteristics

Characteristic Data are presented as n (%) unless otherwise specified	Placebo + SOC (N= 50)	Baricitinib + SOC (N= 51)	Total (N=101)
Age (years)			
Mean (SD)	58.8 (15.2)	58.4 (12.4)	58.6 (13.8)
Gender			
Male	30 (60.0)	25 (49.0)	55 (54.5)
Female	20 (40.0)	26 (51.0)	46 (45.5)
Key Concomitant Medications at baseline			
Remdesivir use	2 (4.0)	0 (0.0)	2 (2.0)
Corticosteroid use	44 (88.0)	43 (84.3)	87 (86.1)
Preexisting Comorbid Conditions of Interest[a]			
Obesity	29 (58.0)	28 (54.9)	57 (56.4)
Diabetes (Type I and Type II)	16 (32.0)	20 (39.2)	36 (35.6)
Chronic respiratory disease	2 (4.0)	1 (2.0)	3 (3.0)
Hypertension	24 (48.0)	31 (60.8)	55 (54.5)
Region			
Rest of World (Argentina, Brazil, Mexico)	40 (80.0)	41 (80.4)	81 (80.2)
United States (incl Puerto Rico)	10 (20.0)	10 (19.6)	20 (19.8)
Race			
American Indian or Alaska Native (includes Hispanic descent)	17 (34.7)	15 (30.0)	32 (32.3)
Asian	1 (2.0)	0 (0.0)	1 (1.0)
Black or African American	1 (2.0)	1 (2.0)	2 (2.0)
Multiple	0	2 (4.0)	2 (2.0)
White	30 (61.2)	32 (64.0)	62 (62.6)
Missing	1	1	2
Inflammatory Markers, median (range)			
CRP (mg/L)	109.5 (11.6–1320)	124.9 (23.5–765)	115.4 (11.6–1320)
D-dimer (mg/L)	1.6 (0.0–30.1)	1.6 (0.0–94.7)	1.6 (0.0–94.7)
Lactate dehydrogenase (U/L)	543.6 (232–1376)	499.5 (239–6698)	531.5 (232–6698)
Ferritin (pmol/L)	2836.9 (101.1–7535.9)	2622.0 (397.7–23395.8)	2711.0 (101.1–23395.8)

[a]Patients with estimated glomerular filtration rate <30 mL/min/1.73 m² were excluded from study enrollment
CRP, C-reactive protein; N, number of patients in the analysis population; n, number of subjects in the specified category; SD, standard deviation; SOC, standard of care.

Table 2: Overview of efficacy outcomes (intent-to-treat population) and adverse events (safety population) by Day 28

Efficacy Outcomes Data are presented as mean (SD) unless otherwise specified	Placebo + SOC (N= 50)	Baricitinib + SOC (N= 51)	p-value vs PBO
All-cause mortality			
n (%)	29 (58.0)	20 (39.2)	
KM Estimates (95% CI)	59.0 (41.1, 77.7)	40.6 (25.8, 59.7)	
Hazard ratio (95% CI)	0.54 (0.31, 0.96)		
Time to mortality, days; median (95% CI)	17.0 (11.0, NA)	NA (24.0, NA)	0.0296
VFDs (days)	5.5 (8.4)	8.1 (10.2)	0.2132
Duration of hospitalization (days)	26.1 (3.9)	23.7 (7.1)	0.0498
Recovery[a]			
n (%)	13 (26.0)	19 (37.3)	
KM estimates (95% CI)	27.0 (15.0, 45.5)	38.7 (18.8, 52.6)	
Rate ratio (95% CI)	1.57 (0.8, 3.2)		
Time to recovery, days; median (95% CI)	NA (NA, NA)	NA (28.0, NA)	0.1567
Adverse Events[b] Data are presented as n (%) unless otherwise specified	**Placebo + SOC (N= 49)**	**Baricitinib + SOC (N= 50)**	**Total (N=99)**
Treatment-emergent adverse event[c] (TEAE)	47 (95.9)	44 (88.0)	91 (91.9)
Mild	3 (6.1)	3 (6.0)	6 (6.1)
Moderate	11 (22.4)	17 (34.0)	28 (28.3)
Severe	33 (67.3)	24 (48.0)	57 (57.6)
Death due to AE[d]	3 (6.1)	5 (10.0)	8 (8.1)
Serious adverse event	35 (71.4)	25 (50.0)	60 (60.6)
Discontinuation from study treatment due to AE (including death)	17 (34.7)	14 (28.0)	31 (31.3)
VTE[e]	3 (6.1)	3 (6.0)	6 (6.1)
DVT	2 (4.1)	1 (2.0)	3 (3.0)
PE	0	2 (4.0)	2 (2.0)
Other peripheral venous thrombosis	1 (2.0)	1 (2.0)	2 (2.0)

[a]Recovery defined as clinical status of 1, 2, or 3 in the 8-point ordinal scale i.e., not hospitalized or no longer requiring medical care
[b]Safety population is comprised of all participants randomly assigned to study intervention who received at least 1 dose of study intervention and who did not discontinue from the study for the reason 'Lost to Follow-up' at the first postbaseline visit
[c]Patients with multiple occurrences of the same event are counted under the highest severity
[d]Included in the overall mortality together with deaths due to disease progression
[e]Includes patients with at least one positively adjudicated treatment emergent VTE
AE, adverse event; CI, confidence interval; DVT, deep vein thrombosis; KM, Kaplan-Meier; N, number of patients in the analysis population; n, number of subjects in the specified category; NA, not applicable; PE, pulmonary artery embolus; SoC, standard of care; VFDs, ventilator-free days; VTE, venous thromboembolic event.

Conclusion. Treatment with BARI+SOC (corticosteroids) resulted in an absolute risk reduction in mortality of 19% at Day 28 and 17% at Day 60 in patients with COVID-19 who were on IMV or ECMO at enrollment. These results are consistent with the reduction in mortality observed in the less severely ill hospitalized patients in the primary COV-BARRIER study population.

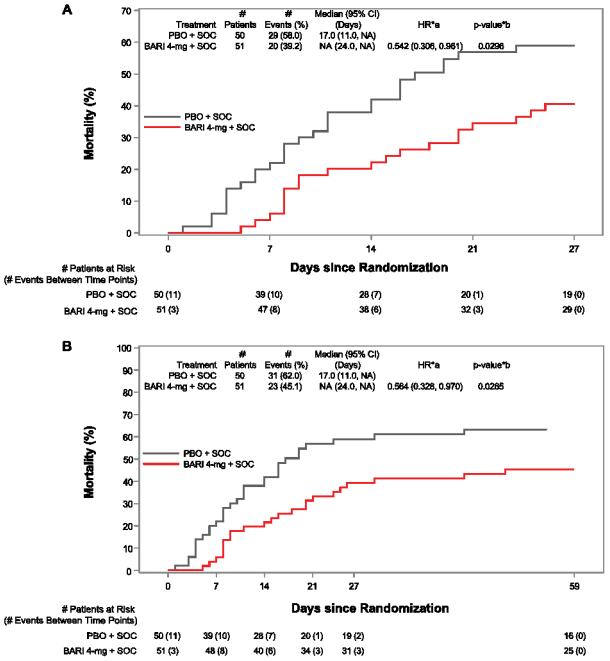

Figure 1: Kaplan-Meier estimates of all-cause mortality (including potentially related with COVID-19 and attributed to adverse events) at Day 28 (A) and Day 60 (B). The numbers at risk at Days 27 and 59 represent the numbers of participants with available data at Days 28 and 60, respectively.
***a HR and 95% CIs were calculated using cox proportional hazard regression model adjusted for age (<65 years, >=65 years), region (United States, rest of world); unstratified.**
***b p-value was calculated from unstratified log-rank test.**
BARI, baricitinib; CI, confidence interval; HR, hazard ratio; NA, not applicable; PBO, placebo; SOC, standard of care.

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LB4. Casirivimab and Imdevimab for Treatment of Hospitalized Patients With COVID-19 Receiving Low Flow or No Supplemental Oxygen

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COVID-19 Phase 2/3 Hospitalized Trial Team

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Background. Casirivimab and imdevimab (CAS/IMDEV) is authorized for emergency use in the US for outpatients with COVID-19. We present results from patient cohorts receiving low flow or no supplemental oxygen at baseline from a phase 1/2/3, randomized, double-blinded, placebo (PBO)-controlled trial of CAS/IMDEV in hospitalized patients (pts) with COVID-19.

Methods. Hospitalized COVID-19 pts were randomized 1:1:1 to 2.4 g or 8.0 g of IV CAS/IMDEV (co-administered) or PBO. Primary endpoints were time-weighted average (TWA) change in viral load from baseline (Day 1) to Day 7; proportion of pts who died or went on mechanical ventilation (MV) through Day 29. Safety was evaluated through Day 57. The study was terminated early due to low enrollment (no safety concerns).

Results. Analysis was performed in pooled cohorts (low flow or no supplemental oxygen) as well as combined treatment doses (2.4 g and 8.0 g). The prespecified primary virologic analysis was in seronegative (seroneg) pts (combined dose group n=360; PBO n=160), where treatment with CAS/IMDEV led to a significant reduction in viral load from Day 1–7 (TWA change: LS mean (SE): -0.28 (0.12); 95% CI: -0.51, -0.05; P=0.0172; **Fig. 1**). The primary clinical analysis had a strong positive trend, though it did not reach statistical significance (P=0.2048), and 4/6 clinical endpoints prespecified for hypothesis testing were nominally significant (**Table 1**). In seroneg pts, there was a 47.0% relative risk reduction (RRR) in the proportion of pts who died or went on MV from Day 1–29 (10.3% treated vs 19.4% PBO; nominal P=0.0061; **Fig. 2**). There was a 55.6% (6.7% treated vs 15.0% PBO; nominal P=0.0032) and 35.9% (7.3% treated vs 11.5% PBO; nominal P=0.0178) RRR in the prespecified secondary endpoint of mortality by Day 29 in seroneg pts and the overall population, respectively (**Fig. 2**). No harm was seen in seropositive patients, and no safety events of concern were identified.

Figure 1: TWA daily viral load decreased from baseline (Day 1) in seronegative patients receiving low flow or no supplemental oxygen

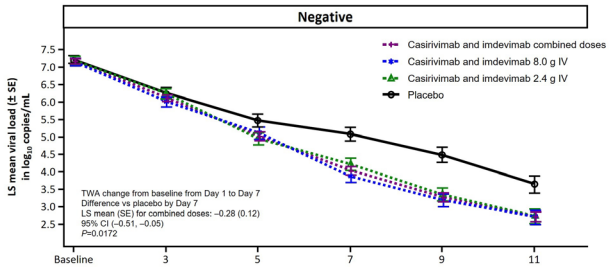
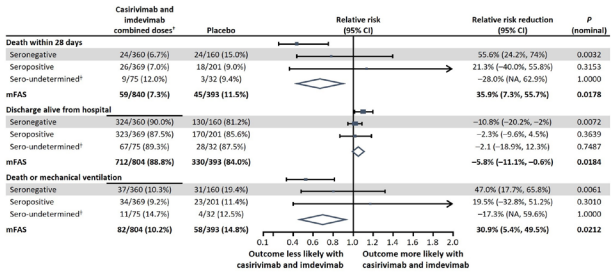


Table 1. Primary virologic and clinical endpoints

Hierarchy	Endpoint	Placebo	Casirivimab and Imdevimab Combined Doses
Primary virologic endpoint			
1.	**Time-weighted average change in viral load from baseline (day 1) to day 7 in seronegative mFAS**		
	No. of patients	131	310
	Least-squares mean change (SE) — log_{10} copies/mL	-1.03 (0.10)	-1.31 (0.06)
	95% CI	-1.22, -0.84	-1.43, -1.18
	Difference vs. placebo at day 7 — log_{10} copies/mL		
	Least-squares mean (SE)	-	-0.28 (0.12)
	95% CI	-	-0.51, -0.05
	P value	-	0.0172
Primary clinical endpoints			
2.	**Proportion of patients who died or went on mechanical ventilation from day 6 to day 29 in high viral load mFAS**		
	No./total no. (%)	28/211 (13.3)	44/445 (9.9)
	Relative risk reduction — %	-	25.5
	95% CI — %	-	-16.2, 52.2
	P value	-	0.2048*
3.	**Proportion of patients who died or went on mechanical ventilation from day 6 to day 29 in seronegative mFAS**		
	No./total no. (%)	22/147 (15.0)	27/341 (7.9)
	Relative risk reduction — %	-	47.1
	95% CI — %	-	10.2, 68.8
	P value		0.0195*
4.	**Proportion of patients who died or went on mechanical ventilation from day 6 to day 29 in overall mFAS**		
	No./total no. (%)	39/367 (10.6)	62/770 (8.1)
	Relative risk reduction — %	-	24.2
	95% CI — %	-	-10.9, 48.2
	P value		0.1486*
5.	**Proportion of patients who died or went on mechanical ventilation from day 1 to day 29 in high viral load mFAS**		
	No./total no. (%)	43/229 (18.8)	57/467 (12.2)
	Relative risk reduction — %	-	35.0
	95% CI — %	-	6.6, 54.8
	P value		0.0249*
6.	**Proportion of patients who died or went on mechanical ventilation from day 1 to day 29 in seronegative mFAS**		
	No./total no. (%)	31/160 (19.4)	37/360 (10.3)
	Relative risk reduction — %	-	47.0
	95% CI — %	-	17.7, 65.8
	P value		0.0061*
7.	**Proportion of patients who died or went on mechanical ventilation from day 1 to day 29 in overall mFAS**		
	No./total no. (%)	58/393 (14.8)	82/804 (10.2)
	Relative risk reduction — %	-	30.9
	95% CI — %	-	5.4, 49.5
	P value		0.0212*

*nominal P-value
CI, confidence interval; mFAS, modified full analysis set; SE, standard error.

Figure 2: Clinical outcomes in hospitalized patients receiving low flow or no supplemental oxygen*



* Pooled cohorts (low flow or no supplmental oxygen), Day 1 through Day 29
† 2.4 g IV and 8.0 g IV
‡ Sero-undetermined indicates missing or inconclusive serology results.

Conclusion. Co-administration of CAS/IMDEV led to a significant reduction in viral load in hospitalized, seroneg pts requiring low flow or no supplemental oxygen. In seroneg pts and the overall population, treatment also demonstrated clinically meaningful, nominally significant reductions in 28-day mortality and proportion of pts dying or requiring MV.

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