treatment of patients hospitalized with moderate to severe COVID-19. This Phase 3 (GS-US-540–9012) double-blind, placebo-controlled study compared the efficacy and safety of 3 days of RDV to standard of care in non-hospitalized, high-risk participants with confirmed COVID-19.

Table 1. COVID-19 related hospitalization or death, COVID-19 related medically attended visits or death, and Treatment Emergent Adverse Events

	Remdesivir	Placebo	Risk reduction	Hazard ratio (95%CI), p-value
COVID-19 related hospitalization or death by day 28	2/279 (0.7%)	15/283 (5.3%)	87%	0.13 (0.03-0.59), p =0.008
COVID-19 related medically attended visits or death by day 28	4/246 (1.6%)	21/252 (8.3%)	81%	0.19 (0.07-0.56) p= 0.002
	Remdesivir	Placebo		
Treatment-emergent adverse events (TEAE)	42.3%	46.3%		
Grade ≥ 3 TEAE	3.6%	7.1%		
Serious TEAE	1.8%	6.7%		

Methods. Participants were randomly assigned 1:1 to receive intravenous (IV) RDV (200 mg on day 1, 100 mg on days 2 to 3) or placebo. The primary efficacy endpoint was composite COVID-19 hospitalization or all-cause death by day 28 and compared using Cox proportional hazards model with baseline stratification factors as covariates. The primary safety endpoint was proportion of participants with treatment-emergent adverse events. Study enrollment was terminated early for administrative reasons in light of the evolving pandemic.

Results. 562 patients underwent randomization and started their assigned treatment (279, RDV; 283, placebo). Baseline demographics and characteristics were balanced across arms. Overall, 52% were male, 44% were Hispanic/Latino ethnicity and 30% were ≥ 60 years old. The most common comorbidities were diabetes mellitus (62%), obesity (56%; median BMI, 30.7), and hypertension (48%). Median baseline SARS-CoV-2 RNA nasopharyngeal viral load was 6.2 $\log_{10}$ copies/mL. Treatment with RDV significantly reduced COVID-19 hospitalization or all-cause death by day 28 (HR, 0.13; 95% CI, 0.03 – 0.59; p = 0.008; Table 1) compared to placebo. Participants receiving RDV also had significantly lower risk for COVID-19-related medically attended visits or all-cause death by day 28 compared to placebo (HR, 0.19; 95% CI, 0.07 – 0.56; p = 0.002; Table 1). No deaths occurred in either arm by day 28. There was no difference between arms in time-weighted average change in nasopharyngeal viral loads from baseline up to day 7. The proportion of patients with AEs was similar between arms (Table 1); the most common AEs in the RDV arm were nausea (11%), headache (6%), and diarrhea (4%).

Conclusion. A 3-day course of IV RDV was safe, well tolerated and highly effective at preventing COVID-19 related hospitalization or death in high-risk non-hospitalized COVID-19 patients.

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LB2. Safety and Efficacy of Combination SARS-CoV-2 Monoclonal Neutralizing Antibodies (mAb) BRII-196 and BRII-198 in Non-Hospitalized COVID-19 Patients

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ACTIV-2 and AIDS Clinical Trials Group

Session: 55. Late Breaker Abstracts: COVID-19 Treatment & Prophylaxis
Thursday, September 30, 2021: 5:30 PM

Background. SARS-CoV-2 continues to spread and the development of safe and effective therapeutics for the prevention of severe disease remains a priority. BRII-196 and BRII-198 are non-competing anti-SARS-CoV-2 mAbs with YTE triple amino acid substitution in Fc to extend half-life and reduce receptor binding, that are being studied for treatment of COVID-19 in the ACTIV-2 Trial, sponsored by NIAID and led by ACTG.

Methods. ACTIV-2 evaluates safety/efficacy of investigational agents for treatment of non-hospitalized adults with mild-moderate COVID-19 under a randomized, blinded, controlled adaptive platform. BRII-196/BRII-198 (1000 mg each) as a single dose given as sequential infusions, or placebo to those at high risk of clinical progression (i.e., age ≥ 60 years or presence of other medical conditions) within 10 days of symptom onset and positive test for SARS-CoV-2. The primary endpoint was hospitalization and/or death through day 28. We report Phase 3 BRII-196/BRII-198 trial results per DSMB recommendation following an interim analysis.

Results. Between January and July 2021, 837 participants (418 active, 419 placebo) from sites in the US (66%), Brazil, South Africa, Mexico, Argentina and the Philippines were randomized and received study product at time of emerging variants. Median age 49 years (Q1, Q3: 39, 58), 51% female, 17% Black/African-American and 49% Hispanic/Latino, with median 6 days from symptom onset. At interim analysis 71% and 97% had a day 28 and 7 visit, respectively. For all available data at interim review, BRII-196/BRII-198 compared to placebo had fewer hospitalizations (12 vs. 45) and deaths (1 vs. 9). At day 28 of follow-up, there was an estimated 78% reduction in hospitalization and/or death (2.4 vs. 11.1%), relative risk 0.22 (95% CI: 0.05, 0.86), P=0.00001 (nominal one-sided). Grade 3 or higher adverse events (AEs) were observed less frequently among BRII-196/BRII-198 participants than placebo (3.8% vs. 13.4%) with no severe infusion reactions or drug related serious AEs.

Conclusion. BRII-196/BRII-198 was safe, well-tolerated, and demonstrated significant reduction compared to placebo in the risk of hospitalization and/or death among adults with mild-moderate COVID-19 at high risk for progression to severe disease.

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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.

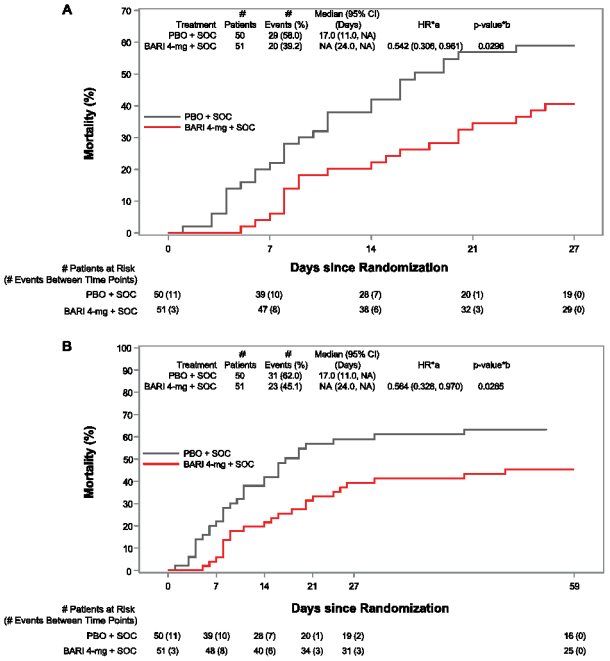

Figure 1: Kaplan-Meier estimates of all-cause mortality (including potentially related with COVID-19 and attributed to adverse events) at Day 28 (A) and Day 60 (B). The numbers at risk at Days 27 and 59 represent the numbers of participants with available data at Days 28 and 60, respectively.
***a HR 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.