A Randomized Double-Blinded Placebo Controlled Trial of Clazakizumab for the Treatment of COVID-19 Pneumonia With Hyperinflammation*

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OBJECTIVES: We designed this study to test whether clazakizumab, a direct interleukin-6 inhibitor, benefits patients hospitalized with severe or critical COVID-19 disease accompanied by hyperinflammation.

DESIGN: Multicenter, randomized, double-blinded, placebo-controlled, seamless phase II/III trial.

SETTING: Five U.S. medical centers.

PATIENTS: Adults inpatients with severe COVID-19 disease and hyperinflammation.

INTERVENTIONS: Eighty-one patients enrolled in phase II, randomized 1:1:1 to low-dose (12.5 mg) or high-dose (25 mg) clazakizumab or placebo. Ninety-seven patients enrolled in phase III, randomized 1:1 to high-dose clazakizumab or placebo.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was 28-day ventilator-free survival. Secondary outcomes included overall survival, frequency and duration of intubation, and frequency and duration of ICU admission. Per Data Safety and Monitoring Board recommendations, additional secondary outcomes describing clinical status and status changes, as measured by an ordinal scale, were added. Bayesian cumulative proportional odds, logistic, and Poisson regression models were used. The low-dose arm was dropped when the phase II study suggested superiority of the high-dose arm. We report on 152 patients, 74 randomized to placebo and 78 to high-dose clazakizumab. Patients receiving clazakizumab had greater odds of 28-day ventilator-free survival (odds ratio [OR] = 3.84; p [OR > 1] 99.9%), as well as overall survival at 28 and 60 days (OR = 1.75; p [OR > 1] 86.5% and OR = 2.53; p [OR > 1] 97.7%). Clazakizumab was associated with lower odds of intubation (OR = 0.2; p [OR] < 1; 99.9%) and ICU admission (OR = 0.26; p [OR < 1] 99.6%); shorter durations of ventilation and ICU stay (risk ratio [RR] < 0.75; p [RR < 1] > 99% for both); and greater odds of improved clinical status at 14, 28, and 60 days (OR = 2.32, p [OR > 1] 98.1%; OR = 3.36, p [OR > 1] 99.6%; and OR = 3.52, p [OR > 1] 99.8%, respectively).

CONCLUSIONS: Clazakizumab significantly improved 28-day ventilator-free survival, 28- and 60-day overall survival, as well as clinical outcomes in hospitalized patients with COVID-19 and hyperinflammation.

KEY WORDS: acute respiratory distress syndrome; clazakizumab; COVID-19; cytokine inhibition; hyperinflammation

The worldwide outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in greater than 5.7 million deaths (1). COVID-19 illness manifests across a spectrum ranging from no symptoms to overt acute respiratory distress syndrome (ARDS). Hyperinflammation

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or cytokine storm often accompanies COVID-19 (2–4), and this prompted use of the interleukin-6 receptor (IL-6R) antagonist tocilizumab at the pandemic outset (5–8). Results from studies of tocilizumab in varied clinical populations have been mixed (9–20).

Clazakizumab is a genetically engineered humanized monoclonal antibody with high affinity for human interleukin-6 (IL-6) that has been studied in disease states associated with hyperinflammation, including rheumatologic conditions (21, 22). Because clazakizumab is a direct ligand inhibitor not susceptible to sequestration by circulating soluble receptor, it might have greater potency than IL-6R inhibitors and may benefit patients with severe COVID-19 disease.

We report our multicenter seamless adaptive phase II/III randomized, placebo-controlled trial to assess the safety and efficacy of clazakizumab in severely or critically ill COVID-19 patients with hyperinflammation.

METHODS

Design

This multicenter randomized, placebo-controlled trial enrolled patients between April 1, 2020, and December 3, 2020 (**Fig. 1**). Follow-up was completed on February 3, 2021. Participating were: New York University (NYU) Langone Health (New York, NY), Columbia New York-Presbyterian (New York, NY), the Johns Hopkins Hospital and Howard County General Hospital (Johns Hopkins Medicine, Baltimore, MD), New York United Health Services Hospital (Binghamton, NY), and the Mayo Clinic Arizona (Scottsdale, AZ). The phase II study aimed at dose-finding and employed 1:1:1 randomization to low-dose clazakizumab (12.5 mg), high-dose clazakizumab (25 mg), and placebo. These doses were selected to balance safety and efficacy based on available data from prior trials (21, 22). After reviewing data for 54 phase II patients, the unblinded Data Safety and Monitoring Board (DSMB) recommended dropping the low-dose arm. Subsequent enrollment continued in phase III with 1:1 randomization between high-dose and placebo. One hundred eighty patients were randomized in both phases combined.

Randomization

Block randomization stratified by used variable blocks of size 3 and 6 in phase II and 2, 4, and 6 in phase III. Lists generated by an unblinded statistician were distributed to an unblinded investigator for dissemination to unblinded pharmacists.

Eligibility

Eligible adult subjects had confirmed SARS-CoV-2 infection by reverse transcriptase-quantitative polymerase chain reaction testing and hypoxemia indicated by any of the following: Pao_2/Fio_2 ratio less than 200, saturation of less than 90% on at least 4 L supplemental oxygen, or increasing oxygen requirements over 24 hours preceding enrollment. The latter criterion was included to ensure that patients suspected to be rapidly deteriorating could enroll prior to frank decompensation. Two or more indicators of hyperinflammation were required: C-reactive protein (CRP) greater than 35 mg/L, ferritin greater than 500 mg/mL, D-dimer greater than 1,000 ng/mL, neutrophil:lymphocyte ratio greater than 4, lactate dehydrogenase greater than 200 U/L, or elevated troponin absent cardiac disease. IL-6 levels were drawn prior to study drug administration but were a formal enrollment criterion due to test turnaround time. Subjects with capacity provided written consent; consent was otherwise obtained from legally authorized representatives.

Patients were excluded for irreversible conditions deemed nonsurvivable, active inflammatory bowel disease, active untreated diverticulitis, untreated bacteremia, pregnancy, or known hypersensitivity to clazakizumab. Subjects were permitted to receive all available therapies, excluding other IL-6/IL6-R inhibitors.

Oversight

This investigator-initiated trial was designed by the NYU Langone team. The protocol was approved by the NYU Grossman Institutional Review Board (s20_00392). Each site's submitted an investigational new drug (IND) application to the U.S. Food and Drug Administration (FDA), and each IND was approved prior to site activation. A single DSMB reviewed all data.

Procedures

Baseline laboratory tests to assess eligibility were performed at screening. Consented patients were

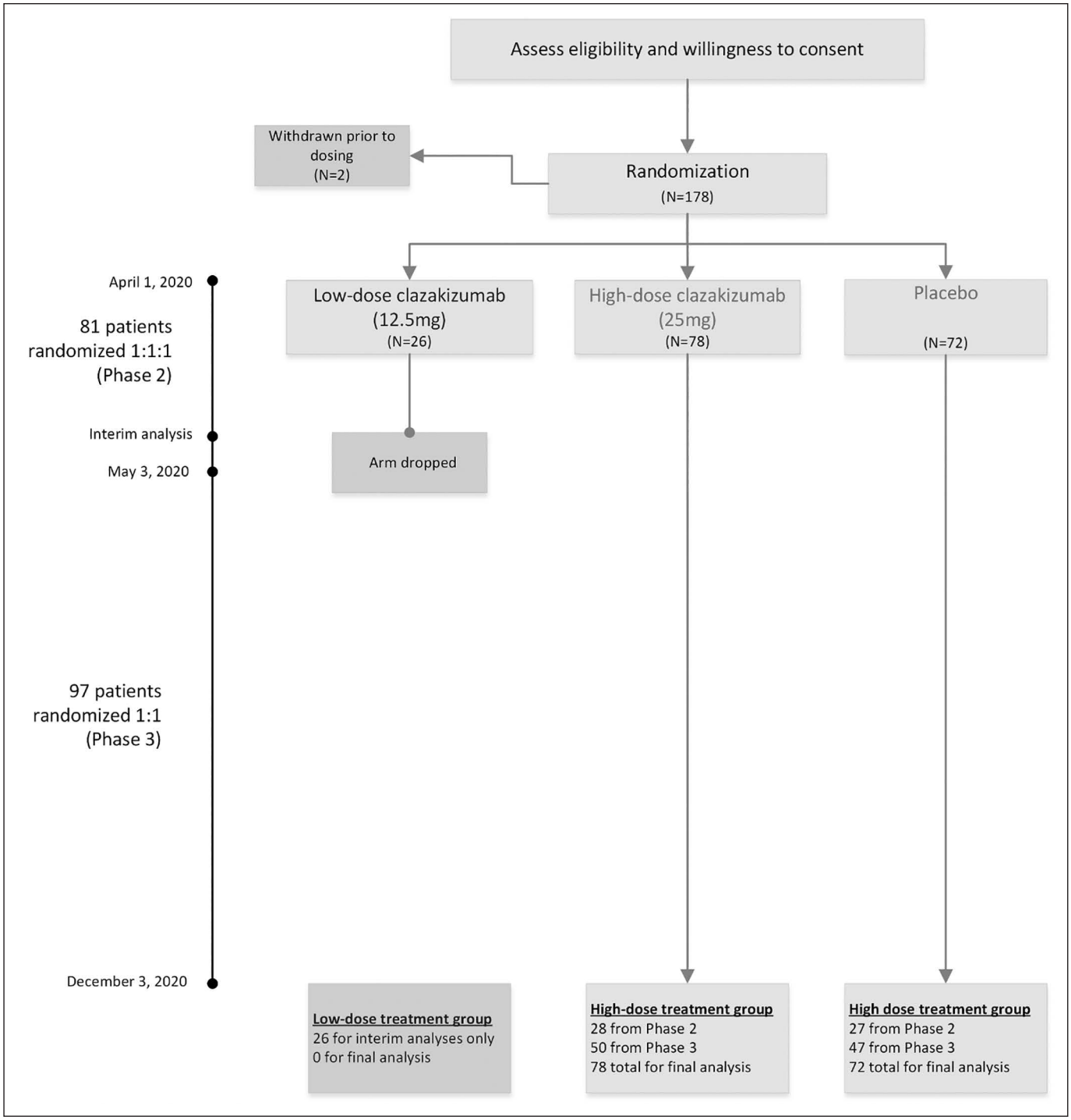

Figure 1. Enrollment and randomization. Eighty-one patients were enrolled in the phase 2 dose-finding portion of the trial beginning on April 1, 2020. On May 3, 2020, the low-dose clazakizumab arm was dropped for lack of efficacy and the 26 patients who received low-dose were excluded from efficacy analyses. Ninety-seven additional patients were enrolled in the phase 3 portion and were randomized 1:1 (high-dose clazakizumab: placebo). The efficacy analyses were based on data collected from 78 patients who received high-dose clazakizumab and 72 patients who received placebo.

randomized, and the first dose of study drug was administered on the day of consent or the following day. Study day 1 was the day of first study drug administration. Clazakizumab or placebo was administered intravenously over 30 minutes. Clazakizumab was diluted in 50 mL 0.9% sodium chloride. Placebo consisted of 50 mL 0.9% sodium chloride. Clazakizumab is colorless and odorless in solution and indistinguishable

from placebo. CRP levels were drawn on days 1–7 and 14. On day 3, CRP was compared with day 1 and if the CRP failed to decrease by greater than or equal to 50%, a second dose identical to the day 1 dose (clazakizumab or placebo) was administered. Vital signs, respiratory status, concomitant medications, and adverse events (AEs) were collected during inpatient hospitalization up to 28 days. Patients were followed remotely postdischarge for clinical status and AEs to 60 days. AEs were considered serious (SAEs) if the outcome was death or if they were otherwise unexpected. The World Health Organization (WHO) ordinal 11-point scale (23) was used to capture clinical status at baseline and days 14, 28, and 60. For patients discharged from the hospital prior to day 14, WHO score on the day of discharge was captured. Outpatient day 28 and day 60 visits were conducted by phone.

Outcomes

The primary efficacy outcome was 28-day ventilator-free survival. This was selected as a clinically relevant measure (24) that could be captured by research staff who stationed off-site. Secondary outcomes included overall survival at 28 and 60 days, frequency and duration of intubation, frequency and duration of ICU admission, trends in CRP, frequency and severity of acute kidney injury (AKI), and need for renal replacement therapy. Upon DSMB request, the following secondary outcomes were added as protocol amendments: "poor outcome" defined as WHO score greater than or equal to 6 at 14, 28, and 60 days and those with "improvement" defined as decrease in WHO score of at least 2 points at those timepoints compared with baseline. Subgroup analyses based on the presence or absence of severe hypoxemia at enrollment (defined as $Pao_2/Fio_2 < 300$) were performed post hoc.

Statistical Methods

The trial was initially designed as a randomized phase II dose-finding study, with 20 patients in each of three arms (placebo, low-dose and high-dose clazakizumab) to assess safety and gage efficacy of the two doses. We amended the protocol to an adaptive seamless phase II/III design to formally assess efficacy of the dose identified in phase II. This amendment was approved by the institutional review board, DSMB, and the FDA. The phase II study had at greater than or equal to 80% power to detect a 70–90% reduction in the 28-day mortality rate, assuming placebo group mortality of 5–15%; power calculations were based on overall survival rather than ventilator-free survival because of lack of information on prevalence of the primary endpoint when the study was initially designed. The revised protocol stipulated a phase III portion in which patients were randomized 1:1 to placebo or clazakizumab at the dose deemed superior based on phase II data. The phase II sample size was increased from 20 per treatment group in an effort to best ascertain the optimal dose for phase III. The target sample size for phase III was 75 patients per group (total 150, including patients from phase II), which provided 80% power to detect a 40–90% reduction in the 28-day mortality rate, assuming control group mortality rate of 5–30%. This mortality range was updated based on the observed mortality in the early stage of the pandemic in NYC in April 2020.

The phase II/III study was designed following the approach of Stallard (25) to determine which arm(s) should proceed phase III. Assuming standardized effect sizes of 0.3 and 0.6 for the low- and high-dose clazakizumab arms, respectively, the design ensured greater than 95% probability of selecting the higher-performing arm to continue from phase II to phase III. In addition, the design afforded greater than 85% power to detect a meaningful improvement in the active arm in phase III.

Analysis

Baseline characteristics were compared between arms to assess balance. AEs were summarized and those deemed potentially related to clazakizumab were assessed separately. Analysis of all outcomes employed Bayesian models (26). Binary outcomes were analyzed using logistic regression. Ordinal outcomes were analyzed with cumulative proportional odds models. Models were adjusted for age, sex, baseline WHO score, and site. Odds ratios (ORs), the p (OR < 1) or p (OR > 1) and 95% credible intervals are reported. In these analyses, OR = 1 indicates no benefit to clazakizumab. OR greater than 1.25 indicates meaningful benefit to clazakizumab for the following outcomes: ventilator-free survival, overall survival, and improved clinical outcome by WHO score. OR less than 0.8 indicates meaningful benefit to clazakizumab for the following outcomes: overall WHO score (lower score indicates more favorable clinical status), poor outcome

(as indicated by WHO score 6–10), new intubation, and new ICU admission. Additional details regarding analysis of secondary outcomes are outlined in the supplement. Post hoc analyses evaluating efficacy of clazakizumab in patients with and without Pao_2/Fio_2 less than 300 at enrollment were performed. This criterion was selected since, due to lack of universal performance of echocardiography to rule out cardiac causes of pulmonary edema, formal diagnoses of ARDS by Berlin criteria (27) could often not be made.

RESULTS

Patients

One-hundred eighty patients underwent randomization. In phase II, 81 patients were randomized 1:1:1 (26: low-dose clazakizumab, 28: high-dose clazakizumab, 27: placebo; Fig. 1). Interim analyses suggested superiority of high-dose clazakizumab, and the low-dose arm was dropped. Phase II results are summarized in the **Supplement** (http://links.lww.com/CCM/H142). All references hereafter to the "clazakizumab group" indicate patients who received high-dose clazakizumab. In phase III, 99 patients were randomized 1:1 to receive high-dose clazakizumab or placebo. Two patients were enrolled but withdrawn after randomization due to changes in clinical status; neither withdrawn patient received study drug nor was included in data analysis. Ninety-seven patients proceeded to dosing (50: high-dose clazakizumab, 47: placebo). The groups for final analysis, combining patients in both phases, totaled 78 randomized to high-dose clazakizumab and 74 randomized to placebo. Demographic, medical history, and baseline clinical characteristics were similar between groups (**Supplementary Table S1**, http://links.lww.com/CCM/H142). Mean age was 61.8 years and 70.4% were male. Among the overall enrolled cohort, 34.2% were White, 18.4% were Black, 10.5% were Asian; 27% were of Hispanic ethnicity. Hypertension (63.2%), diabetes (42.1%), and cardiac disease (34.2%) were the most common preexisting conditions. The median number of days from symptom onset to first dose of study drug was 10 (interquartile range [IQR], 7–13) and from positive test to first dose was 4 (IQR, 2–7). Corticosteroids and remdesivir were administered in 75% and 49.3%, respectively, and this was similar between treatment groups (**Supplementary Table S2**, http://links.lww.com/CCM/H142). Corticosteroid drug choice and treatment course were highly variable among participants. All patients had baseline WHO scores between 5 and 9. Noninvasive ventilation or high flow oxygen was required in 59.2%, and 24.3% were intubated at enrollment. Statistically significant differences in baseline inflammatory parameters were not observed between the clazakizumab and placebo groups (Supplementary Table S1, http://links.lww.com/CCM/H142).

Primary Outcome

Ninety-six patients (63.2%) were alive and ventilator-free at 28 days. In the clazakizumab group, 55 (70.5%) achieved this outcome compared with 41 (55.4%) in the placebo group. Adjusted Bayesian logistic regression models revealed patients in the clazakizumab group had significantly greater odds of 28-day ventilator-free survival than those receiving placebo (**Fig. 2*A***). The estimated median of the posterior distribution of the OR comparing the clazakizumab and placebo groups was OR = 3.84 (95% CI, 1.54–10.62). The probability that the OR exceeded 1, indicating significant benefit of clazakizumab, was 99.9% (p [OR > 1] 99.9%).

Secondary Outcomes

Overall Survival. At 28 days, 113 patients (74.3%) were alive. This included 59 (75.6%) in the clazakizumab group and 54 (73%) in the placebo group. At 60 days, 102 patients (67.1%) were alive, including 56 (71.8%) in the clazakizumab group and 46 (62.2%) in the placebo group. Adjusted models for overall 28-day and 60-day survival (**Fig. 2**, ***B*** and ***C***) indicated greater odds of survival for clazakizumab compared with placebo (28 d: OR = 1.75; 95% CI = 0.65–4.79; [p (OR > 1) 86.5%] and 60 d: OR = 2.53; 95% CI = 1.02–6.73; [p (OR > 1) 97.7%]).

Clinical Status Outcomes. Treatment effect with respect to clinical status indicated by WHO scores at the specified timepoints post-treatment were tabulated (**Table 1**). A poor outcome was defined as a WHO score of greater than or equal to 6. For the overall cohort, the numbers of patients with a poor outcome at 14, 28, and 60 days, respectively, were 68 (44.7%), 61 (40.1%), and 65 (36.8%). For the clazakizumab group at the same timepoints, 30 (38.5%), 25 (21.1%), and 24 (30.8%) patients had poor outcomes, and for the placebo group, 38 (51.4%), 36 (48.6%), 32 (43.2%) had poor outcomes. Bayesian analyses estimated the

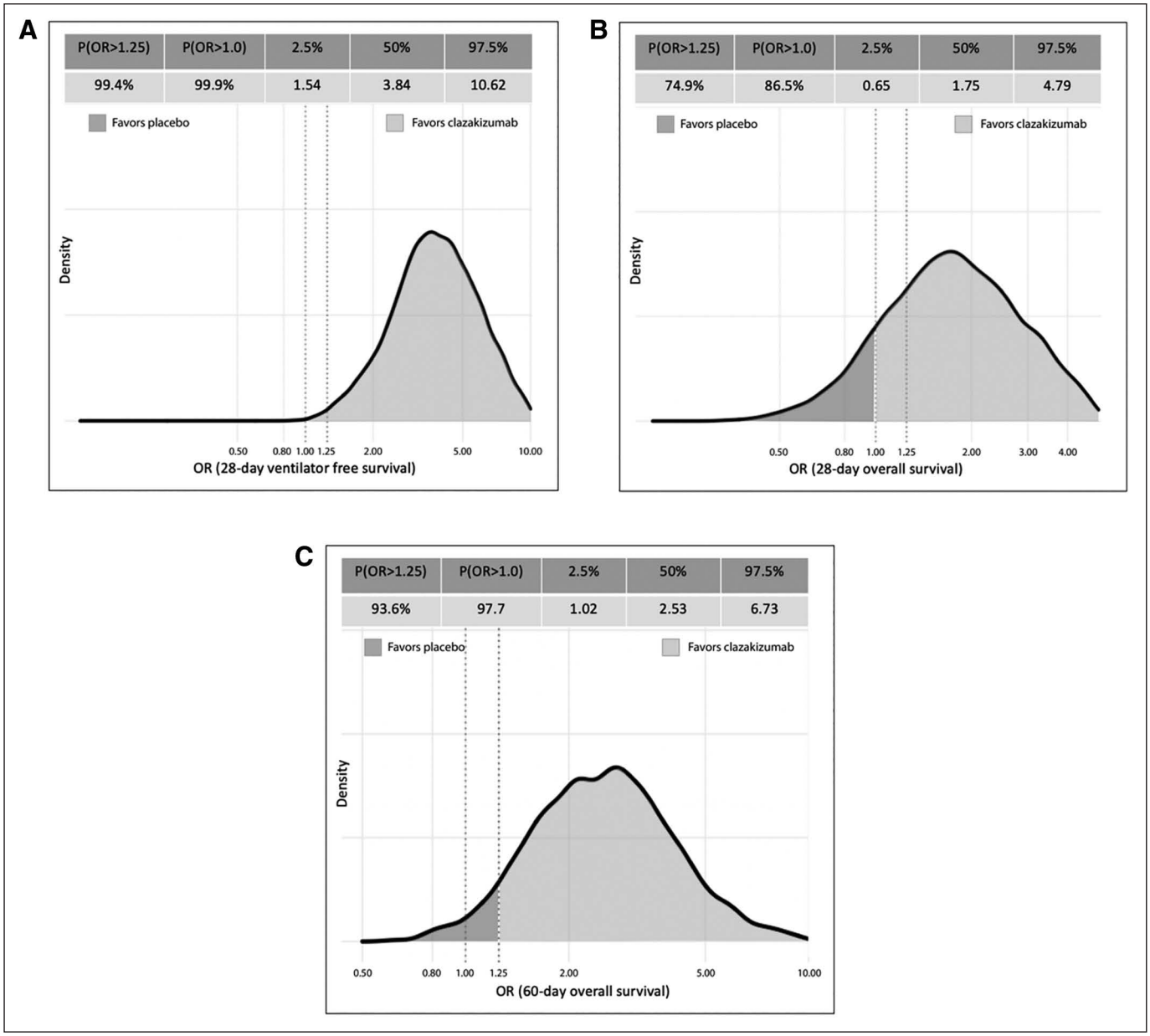

Figure 2. Bayesian models of primary and secondary outcomes. For the primary outcome of 28-d ventilator-free survival (**A**) as well as for overall 28-d (**B**), and 60-d (**C**) survival, *curves* illustrate the estimated posterior distribution of the odds ratio (OR) comparing clazakizumab to placebo. ORs greater than 1 (*shaded light gray*) indicate a benefit of clazakizumab compared with placebo. *Vertical lines* indicate the reference values for the ORs of 1.0 (no benefit of clazakizumab) and 1.25 (meaningful clinical benefit of clazakizumab). Ninety-five percent credible intervals are depicted in the *inset tables*, along with the posterior probabilities of the ORs exceeding the reference values.

median OR of a higher WHO score (worse clinical status) for clazakizumab compared with placebo was 0.62 at 14 days (95% CI = 0.34–1.14; p [OR < 1] 94.2%; **Supplementary Fig. S1*A***, http://links.lww.com/CCM/H142), 0.58 at 28 days (95% CI = 0.31–1.06; p [OR < 1] 96.3%; **Supplementary Fig. S1*B***, http://links.lww.com/CCM/H142), and 0.49 at 60 days (95% CI = 0.25–0.96; p [OR < 1] 98.2%; **Supplementary Fig. S1*C***, http://links.lww.com/CCM/H142). Clazakizumab was associated with lower odds of having a poor outcome at all timepoints (**Table 2**). The estimated median of the posterior distribution of the OR was 0.36 at 14 days (95% CI = 0.16–0.81; p [OR < 1] 99.5%; **Supplementary Fig. S2*A***, http://links.lww.com/CCM/H142), 0.26 at 28 days (95% CI = 0.1–0.61; p [OR < 1] 99.9%; **Supplementary Fig. S2*B***, http://links.lww.com/CCM/H142),

TABLE 1.
Composite World Health Organization Scores and Changes in World Health Organization Scores at 14, 28, and 60 Days

Timepoint	All (*n* = 152)	Clazakizumab (*n* = 78)	Placebo (*n* = 74)
A) Composite WHO scores, mean (SD)			
Baseline	6.3 (1.1)	6.3 (1.1)	6.3 (1.1)
Day 14	5.5 (2.9)	5.3 (2.9)	5.7 (2.9)
Day 28	5.0 (3.6)	4.6 (3.5)	5.4 (3.8)
Day 60	4.6 (4.0)	4.2 (3.9)	5.1 (4.2)
B) Poor outcome (WHO score ≥ 6 at listed time point), *n* (%)			
Day 14	68 (44.7)	30 (38.5)	38 (51.4)
Day 28	61 (40.1)	25 (32.1)	36 (48.6)
Day 60	56 (36.8)	24 (30.8)	32 (43.2)
C) Improved outcome (WHO score at listed time point decreased by ≥ 2 from baseline), *n* (%)			
Day 14	69 (45.3)	39 (50)	30 (40.5)
Day 28	87 (57.2)	50 (64.1)	37 (50)
Day 60	94 (61.8)	54 (69.2)	40 (54.1)

WHO = World Health Organization.

and 0.49 at 60 days (95% CI = 0.25–0.96; *p* [OR < 1] 98.2%; **Supplementary Fig. S2C**, http://links.lww.com/CCM/H142).

Improvement (decrease in WHO score by ≥ 2 points from baseline) was assessed at 14, 28, and 60 days. For the overall cohort at these timepoints, the numbers of patients whose WHO scores improved by greater than or equal to 2 points were 69 (45.3%), 87 (57.2%) and 94 (61.8%). For the clazakizumab group at the same timepoints, 39 (50%), 50 (64.1%), and 54 (69.2%) patients had scores improved by greater than or equal to 2 points. For the placebo group, only 30 (40.5%), 37 (50%), and 40 (54.1%) met criteria for improvement (Table 2). At each timepoint, clazakizumab was associated with greater odds of clinical improvement. The estimated median of the posterior distribution

TABLE 2.
Bayesian Analysis for Clinical Outcomes at 14, 28, and 60 Days

A) Poor Outcome[a]	Median OR (95% CI)	*p* (OR < 0.8)	*p* (OR < 1.0)
Day 14	0.36 (0.16–0.81)	97.4%	99.5%
Day 28	0.26 (0.1–0.61)	99.5%	99.9%
Day 60	0.49 (0.25–0.96)	92.3%	98.2%
B) Improved Outcome[b]	Median OR (95% CI)	*p* (OR > 1.25)	*p* (OR > 1.0)
Day 14	2.32 (1.06–5.21)	93.7%	98.1%
Day 28	3.36 (1.39–8.77)	98.6%	99.6%
Day 60	3.52 (1.34–8.88)	99.0%	99.8%

OR = odds ratio.

[a]Poor outcome defined as having World Health Organization (WHO) clinical score of 6–10 at the specified time point.

[b]Improved outcome defined as WHO clinical score having decreased by two or more points between baseline and the specified time point.

Reported are the ORs of the clazakizumab group relative to the placebo group for the two outcomes at each time point. For the poor outcome, OR < 1 supports clinical benefit to clazakizumab. For the improved outcome, OR > 1 supports a clinical benefit to clazakizumab.

of the OR was 2.32 at 14 days (95% CI = 1.06–5.21; *p* [OR > 1] 98.1%; **Supplementary Fig. S3*A***, http://links.lww.com/CCM/H142), 3.36 at 28 days (95% CI = 1.39–8.77; *p* [OR > 1] 99.6%; **Supplementary Fig. S3*B***, http://links.lww.com/CCM/H142), and 3.52 at 60 days (95% CI = 1.45–8.88; *p* [OR > 1] 99.8%; **Supplementary Fig. S3*C***, http://links.lww.com/CCM/H142). The frequency and duration of both intubation and ICU admission were less in patients who received clazakizumab (**Supplementary Fig. S4** and

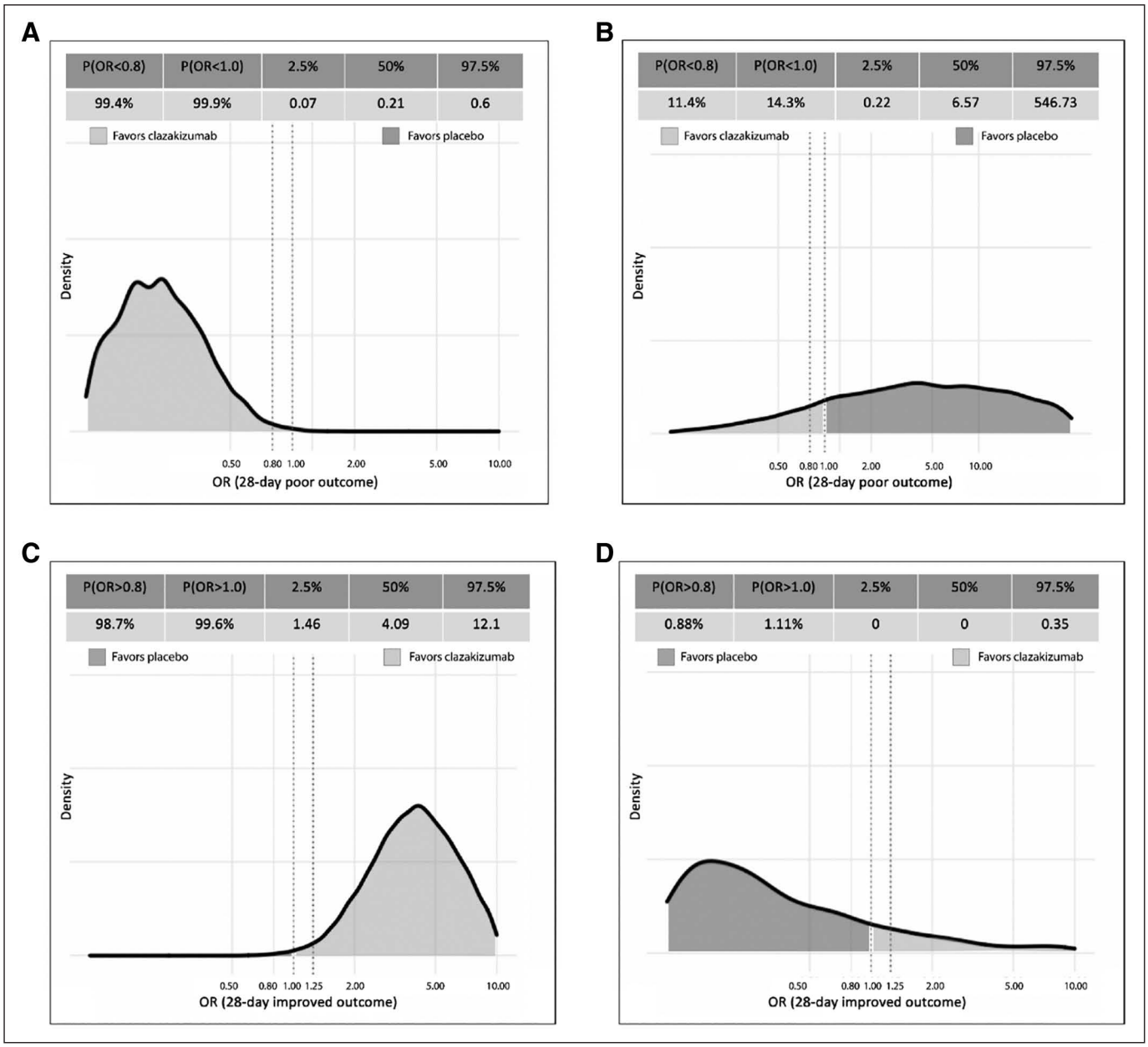

Figure 3. Bayesian models of subgroup analysis outcomes. Subgroups were defined based on the presence or absence of severe hypoxemia (defined as $Pao_2/Fio_2 < 300$) at the time of enrollment. **A** and **B**, Results for poor outcome at 28 d (**A**: patients without severe hypoxemia) and (**B**: patients with severe hypoxemia) at enrollment. *Curves* illustrate the estimated posterior distribution of the odds ratio (OR) comparing clazakizumab to placebo. ORs less than 1 (*shaded light gray*) indicate a benefit of clazakizumab compared with placebo. *Vertical lines* indicate the reference values for the ORs of 1.0 (no benefit of clazakizumab) and 0.8 (meaningful clinical benefit of clazakizumab). **C** and **D**, Results for improved outcome at 28 (**C**: patients without severe hypoxemia) and (**D**: patients with severe hypoxemia). *Curves* illustrate the estimated posterior distribution of the OR comparing clazakizumab to placebo. ORs greater than 1 (*shaded light gray*) indicate a benefit of clazakizumab compared with placebo. *Vertical lines* indicate the reference values for the ORs of 1.0 (no benefit of clazakizumab) and 1.25 (meaningful clinical benefit of clazakizumab). Ninety-five percent credible intervals are depicted in the *inset tables*, along with the posterior probabilities of the ORs exceeding the reference values.

Supplementary Table S3, http://links.lww.com/CCM/H142).

Post Hoc Analysis.. Twenty-nine patients met criteria for severe hypoxemia (Pao_2/Fio_2 < 300) at enrollment, while 123 patients had Pao_2/Fio_2 greater than or equal to 300 at enrollment. Patients without severe hypoxemia were significantly less likely to have a poor outcome at 28 days if they received clazakizumab compared with placebo (OR = 0.21; 95% CI = 0.07–0.6; *p* [OR < 1] 99.6%; **Fig. 3*A***). For patients with severe hypoxemia, poor outcomes were no less likely in patients who received clazakizumab compared with placebo (OR = 6.57; 95% CI = 0.22–546.73; *p* [OR < 1] 14.3%; **Fig. 3*B***).

Patients without severe hypoxemia were significantly more likely to have had clinical improvement at 28 days if they received clazakizumab compared with placebo (OR = 4.09; 95% CI = 1.46–12.1; *p* [OR > 1] 99.6%; **Fig. 3*C***). For patients with severe hypoxemia, improved outcomes at 28 days were no more likely inpatient who received clazakizumab compared with placebo (OR = 0; 95% CI = 0–0.35; *p* [OR > 1] 1.1%; **Fig. 3*D***).

Change in C-Reactive Protein and Repeated Dosing. Clazakizumab was associated with a decrease in CRP compared with placebo. In the clazakizumab group, median CRP decreased from 161 mg/L (IQR, 92.2–239.1 mg/L) to 60.8 mg/L (IQR, 32.0–120.0 mg/L) on day 3, whereas in the placebo group, median CRP decreased from 153 mg/L (IQR, 86.9–242 mg/L) to 113 mg/L (IQR, 56.9–228 mg/L) on day 3 ($p < 0.001$; **Table 3**).

Safety Outcomes. COVID-19 expected AEs including infections, thromboembolic events, and AKI were observed at similar frequency in the clazakizumab and placebo groups (**Supplementary Table S4**, http://links.lww.com/CCM/H142). AEs of specific concern with clazakizumab include hypersensitivity-type reactions, transaminitis, elevation in serum lipids, and bowel perforations. No bowel perforations or hypersensitivity reactions occurred. Transaminitis and hyperlipidemia occurred at similar rates in the clazakizumab and placebo groups. No AE or SAE was deemed likely or definitely related to study drug infusion.

DISCUSSION

We report the results of our multicenter seamless phase II/III randomized controlled trial of clazakizumab for the treatment of patients with severe COVID-19 disease and hyperinflammation. Significant reduction in CRP seen in the clazakizumab group supports that the dose tested was adequately inhibitory. High-dose (25 mg) clazakizumab improved 28-day ventilator-free survival, as well as overall survival at 28 and 60 days compared with placebo. The estimated posterior median of the OR for this outcome was OR = 3.84 (95% CI = 1.54–10.62), which constitutes very strong evidence of meaningful improvement. Compared with placebo, patients given clazakizumab were more likely to have a greater than or equal to 2 point improvement (decrease) in WHO score at all timepoints. Similarly, scores were more likely to be poor (≥ 6) among those who received placebo. These

TABLE 3.
Median C-Reactive Protein Daily Levels by Treatment Group

C-Reactive Protein Time Point	All	Clazakizumab		Placebo		Difference (Clazakizumab–Placebo)	*p*
	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)		
Baseline	155 (91,241)	78	161 (92.2,239)	74	153 (86.9,242)	−8	0.821
Day 1	145 (86,211)	20	139 (80.3,221)	17	156 (93.8,186)	−17	0.707
Day 2	147 (73,230)	69	153 (71.1,230)	71	130 (74.5,229)	23	0.858
Day 3	75.8 (41.0,167)	77	60.8 (32.0,120)	74	113 (56.9,228)	−52.2	< 0.001
Day 4	52.3 (25.5,129)	69	33.6 (18.0,52,6)	67	110 (54.2,235)	−76.4	< 0.001
Day 5	41.0 (16.3,133)	67	19.6 (12.4,35.7)	58	133 (43.5,221)	−113.4	< 0.001
Day 6	26.8 (10.3,133)	61	11.9 (7.30,18.0)	60	134 (34.5,210)	−122.1	< 0.001
Day 7	19.8 (7.03,94.7)	56	8.12 (44.5,13.8)	56	98.7 (40.3,210)	−90.58	< 0.001
Day 14	15.0 (1.6,121)	35	1.55 (0.67,3.95)	39	114 (26.9,170)	−112.5	< 0.001

IQR = interquartile range.

analyses showed a striking degree of consistency in strength and direction of effect in favor of clazakizumab. AEs occurred at similar rates in both groups.

Consistent with two studies of IL-6R inhibitors (12,15), we found that adding clazakizumab to standard therapies benefitted patients with severe manifestations of COVID-19 and hyperinflammation. Post hoc analysis revealed that the benefit of clazakizumab was limited to patients who had not yet progressed to severe hypoxemia at enrollment, suggesting that to achieve benefit, initiating treatment prior to the development of severe hypoxemia is necessary.

Despite vaccines (28–30) SARS-CoV-2 persists (31) and effective treatments remain needed to abrogate morbidity and mortality. Remdesivir and corticosteroids appear to provide modest benefit (32–34). Critically ill patients have been theorized to benefit from cytokine inhibitory therapies but conflicting results were obtained from early studies of tocilizumab in heterogeneous patient populations. In comparison to receptor antagonists, the mechanism of action of clazakizumab as a direct IL-6 ligand inhibitor is potentially advantageous. IL-6R is upregulated in response to influenza infection (35), and if similar up-regulation occurs in SARS-CoV-2 infection, this could potentially lead to sequestration of IL-6R inhibitor drugs and might impact their efficacy (14, 36, 37). Our study enrolled only patients with evidence of hyperinflammation and thus excluded those unlikely to benefit from a cytokine inhibitor. This study provides evidence that clazakizumab appears to be of benefit and should be administered to COVID-19 patients at the outset of disease progression marked by hyperinflammation.

Limitations of our study include that it was conducted across a 9-month period and at multiple sites. Over this time, new treatment agents were introduced, and clinical practice patterns evolved. Standard treatments, in particular steroids, also varied widely among patients and over time. Our sample size does not support subgroup analyses based on temporal trends in treatment options; however, our randomization was site-stratified to account for center-level differences in clinical management. The hypoxemia criteria for enrollment may appear broad, however, these criteria do not necessarily capture the dynamic nature of hypoxemia, nor the often-rapid decompensation seen in these patients. We outlined these criteria enable enrollment across a range of disease severity in an effort to identify optimal timing of drug administration. Finally, given that our study was completed prior to the emergence (or identification of) viral variants including Delta and Omicron, we cannot draw conclusions as to strain-specific efficacy.

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