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Original research

C reactive protein utilisation, a biomarker for early COVID-19 treatment, improves lenzilumab efficacy: results from the randomised phase 3 'LIVE-AIR' trial

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ABSTRACT

Objective COVID-19 severity is correlated with granulocyte macrophage colony-stimulating factor (GM-CSF) and C reactive protein (CRP) levels. In the phase three LIVE-AIR trial, lenzilumab an anti-GM-CSF monoclonal antibody, improved the likelihood of survival without ventilation (SWOV) in COVID-19, with the greatest effect in participants having baseline CRP below a median of 79 mg/L. Herein, the utility of baseline CRP to guide lenzilumab treatment was assessed.

Design A subanalysis of the randomised, blinded, controlled, LIVE-AIR trial in which lenzilumab or placebo was administered on day 0 and participants were followed through Day 28.

Participants Hospitalised COVID-19 participants (N=520) with SpO2 ≤94% on room air or requiring supplemental oxygen but not invasive mechanical ventilation.

Interventions Lenzilumab (1800 mg; three divided doses, q8h, within 24 hours) or placebo infusion alongside corticosteroid and remdesivir treatments.

Main outcome measures The primary endpoint was the time-to-event analysis difference in SWOV through day 28 between lenzilumab and placebo treatments, stratified by baseline CRP.

Results SWOV was achieved in 152 (90%; 95% CI 85 to 94) lenzilumab and 144 (79%; 72 to 84) placebo-treated participants with baseline CRP <150 mg/L (HR: 2.54; 95% CI 1.46 to 4.41; p=0.0009) but not with CRP ≥150 mg/L (HR: 1.04; 95% CI 0.51 to 2.14; p=0.9058). A statistically significant interaction between CRP and lenzilumab treatment was observed (p=0.044). Grade ≥3 adverse events with lenzilumab were comparable to placebo in both CRP strata. No treatment-emergent serious adverse events were attributed to lenzilumab.

Conclusion Hospitalised hypoxemic patients with COVID-19 with baseline CRP <150 mg/L derived the greatest clinical benefit from treatment with lenzilumab.

Trial registration number NCT04351152; ClinicalTrials.gov

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Granulocyte macrophage colony-stimulating factor (GM-CSF) is an upstream mediator of the hyperinflammatory immune response following SARS-CoV-2 infection has been shown to correlate with disease progression and increases in C reactive protein (CRP) are driven by elevations of IL-6. In the phase 3, LIVE-AIR study, GM-CSF neutralisation with lenzilumab significantly improved the likelihood of survival without ventilation (SWOV), with no treatment-emergent serious adverse events attributable to lenzilumab.

WHAT THIS STUDY ADDS

⇒ In LIVE-AIR, elevated baseline plasma CRP was the most predictive feature for progression to invasive mechanical ventilation or death (OR, 0.15; 95% CI 0.07 to 0.29; nominal p<0.001). Participants with baseline CRP <150 mg/L represented 78% of the LIVE-AIR study population and demonstrated the greatest improvement in SWOV with lenzilumab, through day 28 (HR: 2.54; 95% CI 1.46 to 4.41; p=0.0009).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest that baseline CRP may be a useful biomarker in determining which participants may be most successfully treated with lenzilumab.

INTRODUCTION

A hyperinflammatory response, characterised by activation and trafficking of myeloid cells, increased secretion of downstream inflammatory chemokines (moncyte chemoattractant protein-1, MCP-1; interleukin-8. IL-8; interferon gamma-induced protein-10, IP-10), cytokines (interleukin-6, IL-6; interleukin-1, IL-1)[1] and markers of systemic inflammation (C reactive protein, CRP, D-dimer, ferritin), has been implicated in the morbidity and mortality due to COVID-19.[1–4] Granulocyte macrophage colony-stimulating factor (GM-CSF) is one of the early upstream mediators and orchestrators of this hyperinflammatory immune response. Increasing levels of circulating GM-CSF have been associated with progression and increasing severity of the disease.[1]

Like GM-CSF, CRP levels directly correlate with COVID-19 disease severity.[1] Increases in CRP are driven by elevations of IL-6 during the hyperinflammatory response following SARS-CoV-2 infection.[5 6] Baseline CRP levels predict subsequent oxygen supplementation requirements in hospitalised patients with patients with COVID-19 from 85 mg/L for those on low-flow O_2 to 110 mg/L for those on high-flow O_2; and 205 mg/L for those on invasive mechanical ventilation (IMV).[1] Baseline CRP levels are also significantly higher in patients who have worsening organ failure (defined as an increase of sequential organ failure assessment score ≥1 point; compared with patients without worsening organ failure (mean CRP of 178 mg/L vs 100 mg/L, respectively, p<0.05).[7] The risk of critical illness among hospitalised patients with CRP >200 mg/L is foldfold greater compared with CRP between 15 mg/L and 100 mg/L (OR, 5.1; 95% CI 2.8 to 9.2 vs 2.4; 95% CI 1.4 to 4.0, respectively).[8] The 30-day risk of intensive care unit (ICU) admission or death progressively increases with CRP levels; 21.5% (95% CI 18.1 to 24.9) in patients with baseline CRP levels of ≤99 mmol/L (99 mg/L) and 39.2% (95% CI 35.6 to 43.0) in patients with baseline CRP levels of 100–400 mmol/L; 100–400 mg/L; p<0.001).[9] Risk of 30-day mortality is similarly increased for patients with elevated CRP levels (p<0.001): normal CRP (7%; 0 to 15), CRP levels above normal but ≤99 mmol/L (18%; 15 to 21) and CRP of 100 mmol/L to 400 mmol/L (29%; 5 to 32).[9] Patients with CRP above 150 mg/L are described as experiencing COVID-19-associated hyperinflammation and are at risk of imminent escalation of respiratory support or death.[10] Such information has led to the emerging use of plasma CRP as a guide to treatment. For example, the efficacy of corticosteroids in COVID-19 treatment has recently been associated with CRP levels[11] and models are being developed in which CRP can be included for treatment guidance.[12]

Prevention of fulminant hyperinflammatory immune response through targeting its orchestration by GM-CSF is a logical approach to prevention of resulting tissue damage. Such 'early' intervention may disrupt the evolving inflammatory processes that lead to myeloid cell trafficking and activation and restore immune homeostasis without disrupting immune surveillance in which GM-CSF also plays a critical role.[13] Lenzilumab, a GM-CSF neutralising monoclonal antibody, administered within a median of 2 days after hospitalisation, improved clinical outcomes in hypoxemic-hospitalised COVID-19, who required supplemental oxygen but not IMV in the randomised, blinded and controlled LIVE-AIR phase 3 clinical trial.[14] Lenzilumab improved the likelihood of survival without ventilation (SWOV, sometimes referred to as ventilator-free survival; HR: 1.54; 95% CI 1.02 to 2.32; p=0.0403) compared with placebo.[14] A univariate sensitivity analyses of the primary endpoint for baseline factors that may influence the primary analysis demonstrated that baseline plasma CRP values below the median level of 79 mg/L were associated with a greater likelihood of achieving SWOV, relative to placebo (HR: 2.71; 95% CI 1.23 to 6.00; nominal p=0·014) than in the overall population.[14]

Given the above, earlier treatment of the hyperinflammatory immune response with lenzilumab could be guided by clinical evaluation of CRP levels at presentation. CRP may be used as a practical and readily available biomarker in routine clinical practice[9 14 15] that could predict which patients were suitable for 'early' intervention with lenzilumab to prevent progression to IMV or death. Therefore, the objective of the following subanalysis of the LIVE-AIR trial was to demonstrate the utility of CRP as a prognostic biomarker to guide the treatment of COVID-19 with lenzilumab.

METHODS

The LIVE-AIR trial design has been previously described in detail[14] and is briefly summarised here.

Trial design

LIVE-AIR was a randomised, double-blind, placebo-controlled, phase 3 trial that enrolled hospitalised participants age 18 years or older with virologically confirmed SARS-CoV-2 and pneumonia diagnosed by chest X-ray or CT. The first patient was dosed on 5 May 2020 and the last patient was dosed on 27 January 2021; during which time the original SARS-CoV-2 strain and the B.1.1.7 (alpha) variant were predominant. Eligible participants must have been hospitalised with a clinical ordinal score of 5 (SpO2 ≤94% on room air) or clinical ordinal score of 4 (supplemental oxygen in the form of low-flow oxygen) or clinical ordinal score of 3 (high-flow oxygen or non-invasive positive pressure ventilation) adapted from the NIH-sponsored Adaptive COVID-19 Treatment Trial (ACTT, NCT 04280705).[16] Enrolled participants were randomised 1:1 to receive lenzilumab or matched placebo in addition to current standard treatments per institutional guidelines at each site. Three doses of lenzilumab (1800 mg total, divided into three equal doses) or placebo were administered 8 hours apart (within a total of 24 hours) via a 1 hour intravenous infusion per dose. Participants were stratified by age (<65 or >65) and disease severity (severe vs critical). The primary efficacy endpoint was SWOV by day 28. For purposes of the survival analysis for the primary endpoint, an event was defined as mortality or the requirement for IMV. Secondary endpoints included time to recovery, the proportion of the composite of IMV (ordinal score 2), extracorporeal membrane oxygenation (ECMO, ordinal score 2) or death (ordinal score 1); ventilator-free days; duration of ICU; mortality and safety.

Statistical analysis

The primary endpoint was the difference in SWOV through 28 days following randomisation between lenzilumab and placebo treatments. This analysis was performed in the prespecified modified intent to treat (mITT) population who received at least one dose of investigational treatment under the documented supervision of the principal investigator or sub-investigator. The primary analysis was a Cox proportional hazard model (HR: lenzilumab relative to placebo), which included time to first event (death or IMV) as the dependent variable (1=IMV use or death, 0=alive with no IMV use); treatment (covariate) and strata (age and disease severity). Where data were non-proportional based on a χ^2 test proposed by Grambsch and Therneau with a global p value <0.05, a Cox proportional hazard model with weighted extension was used to correct for non-proportionality. The evaluation of CRP in LIVE-AIR was prespecified;[14] however, the analysis of the CRP less than or greater than 150 mg/L was derived from the findings of the multivariate analysis (see below). Baseline CRP values were determined based on the screening value and if the participant did not have a screening value, then the day 1 value was used.

For each secondary endpoint, the proportion of participants that had the event was calculated by treatment group. An OR was calculated for the composite endpoint of the first incident of IMV, ECMO or death using logistic regression and including the baseline age group and disease category as covariates. For ventilator-free days and duration of ICU, a non-parametric stratified Wilcoxon test was performed using age strata and disease severity strata as stratification variables. HRs were calculated for each of time to death and time to recovery, separately, as

described above. For time to recovery, deaths were censored at day 28. Participants who were alive, yet did not recover, were right censored at the date of the last non-missing assessment of the 8-point clinical status ordinal scale on or prior to day 28. All data are reported through Day 28.

Loss to follow-up was approximately 2% in each arm with only 11 participants (5 and 6 in lenzilumab and placebo, respectively) in the mITT who had no vital status at day 28. Of these 11 participants, 7 had recovered and were discharged and subsequently lost to follow-up. Four participants withdrew from the study prior to day 28 (2 lenzilumab and two placebo). Given the limited amount of missing data, the last observation carried forward method was used. Source data verification was 100%.

A multivariate logistic regression analysis was conducted to assess known key risk factors for progression to IMV or death (see figure 3). Logistic regression models were built to predict day 28 SWOV using known risk factors for progression to IMV or death that were available in the intent-to-treat (ITT) data set. The model selected for analysis used severity as the covariate to maintain consistency with the covariate used in the prespecified primary analysis, in addition to the other risk factors as covariates.

Patient and public involvement

Patients participated in this research. Members of the public participated in the research only if they had a direct role in implementing the research or patient care. No other members of the public participated in this work.

RESULTS

Demographics

Five hundred, twenty-eight participants were screened, of whom 520 were randomised and included in the ITT population (figure 1).[14] Broad inclusion criteria allowed for 98% of the participants to be randomised (520/528). The eight participants who were ineligible to participate either declined participation or withdrew consent. The mITT population represented 92%

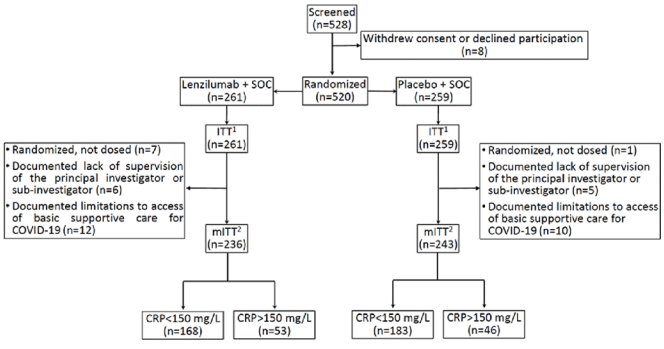

Figure 1 Randomisation and analysis populations. Eight participants were ineligible to participate as they either declined participation or withdrew consent. Broad inclusion criteria allowed for the remainder of the participants to be randomised. The ITT population consisted of all randomised participants.[1] The safety set included all participants who received at least one dose of the study drug and is presented by the actual drug received.[2] Randomised participants who received at least one dose of study drug under the documented supervision of the principal investigator or sub-investigator were included in the mITT population. This population excluded participants from sites that experienced documented limitations to access of basic supportive care for COVID-19. ITT, intent to treat; mITT, modified ITT. SOC represents standard of care

(479/520) of the total population, of which 90% and 94% of each population were randomised to lenzilumab (236/261) and placebo (243/259), respectively. Participants with CRP <150 mg/L comprised 73% of the mITT population (351/479) and 78.0% (351/450) of the mITT population with an evaluable baseline CRP. Baseline characteristics were well balanced between treatment groups in CRP <150 and CRP >150 mg/L populations as well as the overall mITT population (table 1). No major differences were observed between these groups and these groups reflected the demographics of the overall population.

Primary outcome of LIVE-AIR

As reported previously, treatment with lenzilumab was associated with a greater likelihood of achieving SWOV compared with the placebo group (HR, 1·54; 95% CI 1·02 to 2·32; p=0·0403; table 2A, figure 2A).[14] The estimate of SWOV, through day 28 was 198 (84%; 95% CI 79 to 89) and 190 (78%; 72 to 83) in patients treated with lenzilumab or placebo, respectively. Separation of the survival curves occurred as early as 3 days following treatment (figure 2A), continued to increase through approximately day 10 and was maintained for the duration of the 28-day observation period. SWOV was also improved in those concomitantly administered remdesivir and corticosteroids.

Risk factors affecting SWOV in LIVE-AIR

Twelve risk factors were evaluated for their influence on SWOV. Incorporating these known risk factors as covariates into an iterative multivariate logistic regression analysis demonstrated a statistically significant positive outcome for SWOV with lenzilumab treatment (OR, 1.51; 95% CI 1.18 to 1.94; nominal p=0.0006; figure 3). This model also demonstrated that elevated baseline plasma CRP was the most predictive factor for progression to IMV or death (OR, 0.15; 95% CI 0.07 to 0.29; nominal p<0.001; figure 3).

LIVE-AIR was not stratified by baseline CRP level nor was CRP a covariate in any of the prespecified outcome measures. The *post hoc* inclusion of CRP as a covariate in the overall mITT analysis population, along with age and disease severity, resulted in a statistically significant lenzilumab treatment effect on SWOV (HR: 1.74; 95% CI 1.14 to 2.66; p=0.0101) as well as several key secondary endpoints, including the incidence of IMV, ECMO or death (OR: 0.55; 95% CI 0.32 to 0.94; p=0.029) and ventilator-free days (mean 24.5 vs 22.6, p=0.021). Further analysis demonstrated a significant statistical interaction between lenzilumab treatment and CRP (p=0.044).

Exploratory analysis for the effect of lenzilumab on SWOV was conducted by the CRP baseline quartile. Response to lenzilumab was observed in the first through third quartiles of baseline CRP with the greatest lenzilumab treatment effect observed in the first quartile (CRP <41 mg/L; HR: 8.20; 95% CI 1.74 to 38.69; p=0.0079) and a numeric difference that did not reach statistical significance in the second quartile and a significant treatment effect observed in the third quartile (CRP 79<137 mg/L; HR: 2.25; 95% CI 1.04 to 4.88; p=0.0407 (table 3)).

Given the greatest treatment effect for lenzilumab was observed in the first through third quartiles, an analysis of baseline plasma CRP levels and the likelihood to achieve SWOV with lenzilumab was further explored at baseline CRP greater than 100 mg/L (figure 4). This CRP level and the 25 mg/L increments explored were arbitrarily selected with the knowledge that the highest quartile value for baseline CRP levels was ≥137 mg/L. In this analysis, the HR for SWOV was calculated for all cumulative participants with CRP levels below the indicated cut-off value.

Table 1 Baseline characteristics

	CRP <150 mg/L			CRP ≥150 mg/L			
	Lenzilumab (n=168)	Placebo (n=183)	CRP total (n=351)	Lenzilumab (n=53)	Placebo (n=46)	CRP total (n=99)	Total overall (n=479)
Gender							
Male (%)	106 (63)	115 (63)	221 (63)	38 (72)	35 (76)	73 (74)	311 (65)
Age							
Mean (SD)	60.9 (13.7)	60.4 (14.3)	60.6 (13.4)	60.8 (13.7)	61.1 (14.1)	60.9 (13.7)	61 (14)
BMI							
Mean (SD)	33.4 (8.8)	32.5 (8.2)	32.9 (8.5)	32.5 (7.7)	30.3 (6.2)	31.5 (7.1)	32.5 (8.2)
≥30 Kg/m^2 (%)	58.3	57.4	57.8	56.6	41.3	49.5	55.1
Race (%)							
American Indian	3 (2)	0 (0)	3 (1)	1 (2)	0 (0)	1 (1)	5 (1)
Asian	6 (4)	5 (3)	11 (3)	2 (4)	0 (0)	2 (2)	14 (3)
Black	25 (15)	26 (14)	51 (15)	9 (17)	6 (13)	15 (15)	72 (15)
White	121 (72)	134 (73)	255 (73)	38 (71.7)	31 (67)	69 (70)	347 (72)
Multiple	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	12 (7)	18 (10)	30 (9)	3 (6)	9 (20)	12 (12)	46 (9)
Ethnicity (%)							
Hispanic or Latino	48 (29)	74 (40)	122 (36)	25 (47)	21 (46)	46 (47)	185 (39)
Not Hispanic or Latino	119 (71)	108 (59)	227 (65)	27 (51)	23 (50)	50 (51)	290 (60)
Supplemental oxygen (%)							
Room air (Clinical ordinal score=5)	13 (8)	10 (6)	23 (7)	2 (4)	2 (4)	4 (4)	41 (9)
Low-flow oxygen (Clinical ordinal score=4)	90 (54)	93 (51)	183 (52)	26 (49)	23 (50)	49 (50)	242 (50)
High flow oxygen or NPPV (Clinical ordinal score=3)	65 (39)	80 (44)	145 (41)	25 (47)	21 (46)	46 (47)	197 (41)
CRP (mg/L)							
Mean (SD)	62.8 (39.8)	67.1 (38.4)	65.1 (39.1)	219 (56.6)	210 (53.4)	215 (55.0)	98.0 (76.0)
Median	58.8	64.0	61.1	204	200	201	79.0
IQR	(27.7–92.0)	(34.9–98.7)	(32.2–96.8)	(185-238)	(168-226)	(175-232)	(41.0–137.1)
Concomitant medications (%)							
Corticosteroids only	31 (18)	44 (24)	75 (21)	17 (32)	8 (18)	25 (26)	118 (25)
Remdesivir only	5 (3)	6 (3)	11 (3)	1 (2)	2 (4)	3 (1)	16 (3)
Corticosteroids and remdesivir	127 (75)	132 (71)	259 (73)	33 (62)	33 (73)	66 (67)	331 (69)
Co-morbidity (%)							
Hypertension	106 (63)	131 (72)	237 (68)	26 (49)	25 (54)	51 (52)	314 (66)

Continued

Table 1 Continued

	CRP <150 mg/L			CRP ≥150 mg/L			Total overall (n=479)
	Lenzilumab (n=168)	Placebo (n=183)	CRP total (n=351)	Lenzilumab (n=53)	Placebo (n=46)	CRP total (n=99)	
Congestive heart failure	24 (14)	15 (8)	39 (11)	7 (13)	7 (15)	14 (14)	55 (12)
Coronary artery disease	24 (14)	23 (13)	47 (13)	10 (19)	6 (13)	16 (16)	64 (14)
Diabetes	86 (51)	103 (56)	189 (54)	26 (49)	24 (52)	50 (51)	158 (53)
Chronic liver disease	8 (5)	11 (6)	19 (5)	2 (4)	3 (7)	5 (5)	17 (5)
Chronic kidney disease	26 (16)	25 (14)	51 (15)	8 (15)	6 (13)	14 (14)	67 (14)
Asthma	23 (14)	10 (6)	33 (9)	9 (17)	6 (13)	15 (15)	52 (11)
Interstitial lung disease	3 (2)	0 (0)	3 (1)	–	1 (2)	1 (1.0)	2 (0)
COPD	14 (8)	15 (8)	29 (8)	4 (7.5)	1 (2)	5 (5)	36 (7)

BMI, body mass index; CRP, C reactive protein.

The lenzilumab treatment effect and baseline CRP level demonstrated a sigmoidal relationship. The HR resulting from lenzilumab treatment was above 2.25 for baseline CRP levels between 100 and 150 mg/L and progressively declined above 150 mg/L until 275 mg/L, where the HR plateaued at approximately 1.5.

Effect of CRP<150 mg/L on SWOV and secondary endpoints in LIVE-AIR

In participants with baseline CRP <150 mg/L, lenzilumab improved the likelihood of SWOV compared with placebo (HR: 2.54; 95% CI 1.46 to 4.41; nominal p=0.0009; table 2a, figure 2B). Separation of the survival curves appeared earlier than in the overall population and followed a similar pattern as the overall population thereafter (figure 2B). The number needed to treat (NNT) was nine for this group compared with 17 for the overall population (table 2A). SWOV, in response to lenzilumab treatment, was similar to placebo in participants with CRP ≥150 mg/L at baseline (table 2A and figure 2C). The NNT for this group was 37 (table 2A).

Secondary outcomes

Secondary outcomes were improved with lenzilumab treatment in participants with CRP <150 mg/L. Incidence of IMV, ECMO or death with lenzilumab treatment was not statistically improved in the overall mITT population but was less in participants with baseline CRP <150 mg/L (OR 0.38; 0.19 to 0.75; nominal p=0.0053; table 2B). Additional secondary endpoints were improved with lenzilumab treatment in participants with baseline CRP <150 mg/L (table 2B). Ventilator-free days were 25.7 (SD: 7.6) and 22.7 (10.5) with lenzilumab or placebo treatment, respectively (nominal p=0.0045). This difference was not observed with baseline CRP ≥150 mg/L. ICU days were also less with lenzilumab compared with placebo treatment in participants with baseline CRP <150 mg/L (nominal p=0.0458). Time to recovery with lenzilumab treatment was improved with lenzilumab treatment relative to placebo in participants with a baseline CRP <150 mg/L (p=0.0219).

The LIVE-AIR trial was not powered to demonstrate a mortality benefit. The likelihood of mortality was numerically lowest in baseline CRP <150 mg/L but did not reach statistical significance (HR:0.57; 95% CI, 0.29 to 1.12; p=0.104).

Time course of changes in CRP

In the overall mITT population regardless of treatment assignment, baseline CRP levels were related to COVID-19 severity at baseline. CRP levels at baseline increased with ordinal scale where participants on room air exhibited average CRP levels of 83.6 (SE: 11.8) mg/L; low flow O_2, 95.2 (4.5); and high flow O_2, 104.0 (5.9).

In participants who required IMV or died, mean CRP levels were elevated and remained so through day 28 compared with participants who achieved SWOV (figure 5A). The mean CRP time course in participants who achieved SWOV rapidly decreased from baseline through day four and remained low through day 28. The CRP level at baseline for participants who required IMV or died was 128.5 (SE: 86.2) mg/L compared with 91.2 (71.1) mg/L in those who achieved SWOV. For those participants who required IMV or died, CRP level within ±1 day of the event was 178 (52.4) mg/L (median: 167 mg/L). Mean CRP >100 mg/L during the hospital course was associated with all events of IMV and/or death in the trial, whereas mean CRP was <50 mg/L during the hospital course in participants who achieved SWOV. Participants in the placebo arm with baseline

Table 2 (A) Primary endpoint according to baseline CRP**†† (B) Key secondary endpoints according to baseline CRP**††

(A)

	CRP<150 mg/L (n=351)				Overall population (N=479)				CRP≥150 mg/L (n=99)			
	Median CRP, 61 mg/L; IQR (32 to 97 mg/L)				Median CRP, 79 mg/L; IQR (41 to 137 mg/L)				Median CRP, 201 mg/L; IQR (175 to 232 mg/L)			
Outcome	Lenzilumab (n=168)	Placebo (n=183)	HR or OR (95% CI)	P value	Lenzilumab (n=236)	Placebo (n=243)	HR or OR (95% CI)	P value	Lenzilumab (n=53)	Placebo (n=46)	HR or OR (95% CI)	p value
SWOV (%)	152 (90)*	144 (79)*	2.54†	0.0009	198 (84)*	190 (78)*	1.54†	0.0403	37 (69)*	33 (72)*	1.04†	0.9058
(95% CI)	(85 to 94)	(72.1 to 84.1)	(1.46 to 4.41)		(79 to 89)	(72 to 83)	(1.02 to 2.32)		(55 to 80)	(56 to 83)	(0.51 to 2.14)	
Number needed to treat		9				17				37		

(B)

	CRP<150 mg/L (n=351)				Overall population (n=479)				CRP≥150 mg/L (n=99)			
	Median CRP, 61 mg/L; IQR (32 to 97 mg/L)				Median CRP, 79 mg/L; IQR (41 to 137 mg/L)				Median CRP, 201 mg/L; IQR (175 to 232 mg/L)			
Outcome	Lenzilumab (n=168)	Placebo (n=183)	HR or OR (95% CI)	p value	Lenzilumab (n=236)	Placebo (n=243)	HR or OR (95% CI)	p value	Lenzilumab (n=53)	Placebo (n=46)	HR or OR (95% CI)	p value
IMV, ECMO or mortality (%)	14 (8)‡	34 (19)‡	0.38§	0.0053	35 (15)‡	51 (21)‡	0.67§	0.111	19 (30)‡	12 (27)‡	1.14§	0.7731
(95% CI)	(5 to 14)	(13 to 26)	(0.19 to 0.75)		(11 to 21)	(16 to 27)	(0.41 to 1.10)		(19 to 44)	(16 to 43)	(0.46 to 2.86)	
IMV (%)	10 (6)*	36 (20)*	0.28†	0.0002	26 (11)*	49 (20)*	0.52†	0·0059	13 (24)*	13 (28)*	0.77†	0.5098
(95% CI)	(3 to 11)	(14 to 26)	(0.15 to 0.54)		(8 to 16)	(16 to 26)	(0.32 to 0.82)		(14 to 38)	(17 to 44)	(0.34 to 1.68)	
Mortality (%)	13 (8)*	26 (14)*	0.57†	0.104	24 (10)*	34 (14)*	0.72†	0.241	7 (13)*	6 (13)*	0.88†	0.8165
(95% CI)	(5 to 13)	(10 to 20)	(0.29 to 1.12)		(6 to 14)	(10 to 19)	(0.42 to 1.23)		(7 to 26)	(6 to 27)	(0.29 to 2.63)	
Ventilator-Free Days, Mean	25.7	22.7		0.0045¶	24.5	22.6		0.0766¶	20.8	21.7		0.83¶
(SD)	(7.6)	(10.5)			(8.8)	(10.5)			(11.2)	(10.6)		
ICU days, Mean	3.9	6.2		0.0458¶	5.4	6.6		0.1604¶	9.6	8.5		0.9400¶
(SD)	(8.3)	(10.6)			(9.6)	(10.7)			(11.5)	(11.2)		
Time to recovery (days)												
Quartile												
25%	4 (4-5)	5 (5-5)			5 (4-5)	5 (5-5)			8 (6–9)	6 (5–8)		
50%	7 (6–8)	8 (7–9)		0.0219†	8 (7–9)	8 (7–9)		0.432†	12 (9–19)	11 (7–18)		0.153 †
75%	11 (10–14)	17 (12-NA)			15 (11–20)	19 (13-NA)			NA (19-NA)	NA (17-NA)		

*Kaplan-Meier estimates for proportion of participants.
†Cox proportional hazard model for time to event with age (≤65,>65) and severity (severe, critical) strata as covariates.
‡Estimated marginal mean.
§OR with age (≤65,>65) and severity (severe, critical) strata as covariates.
¶Stratified Wilcoxon Rank Sum Test with age (≤65,>65) and severity (severe, critical) strata as covariates.
**All data censored at 28 days following enrollment.
††mITT, modified intention to treat population.
CRP, C reactive protein; ECMO, extracorporeal membrane oxygenation ; ICU, Intensive care unit; IMV, invasive mechanical ventilation; SWOV, survival without invasive mechanical ventilation.

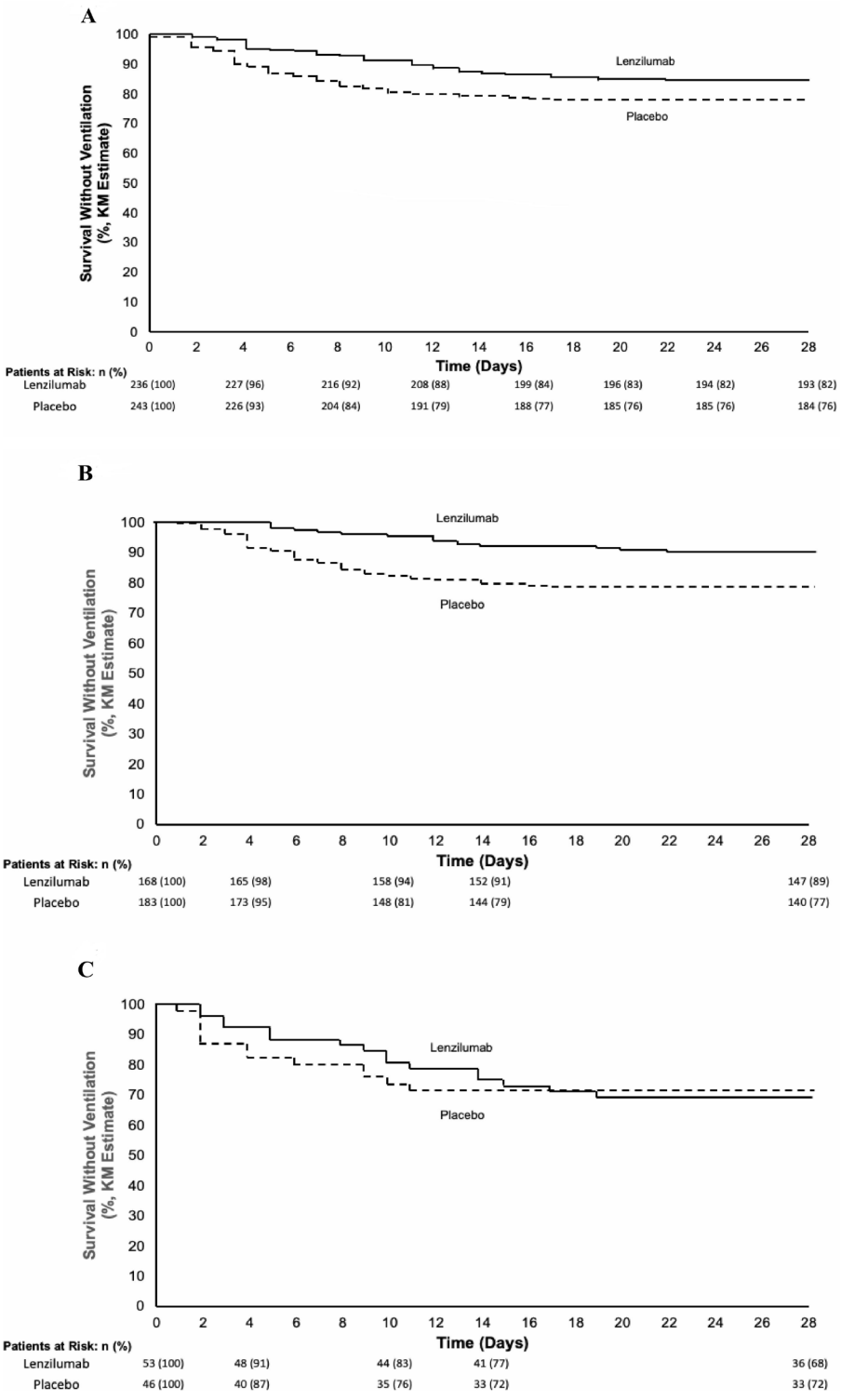

Figure 2 Kaplan-Meier estimate for survival without ventilation. (A) KM estimate for survival without ventilation (primary endpoint). The primary efficacy analysis was based on the overall mITT population. Separation of the survival curves occurred as early as 3 days following treatment. Following day 10, separation maintained for the duration of the observation period. Lenzilumab treatment improved the relative likelihood of achieving SWOV compared with placebo (HR: 1.54; 95% CI: 1.02 to 2.32, p=0.0403). The log-rank p-value=0.0457. Reprinted from Lancet Respiratory Medicine. Temesgen Z, Burger CD, Baker J, Polk C, Libertin CR, Kelley CF, Marconi VC, Orenstein R, Catterson VM, Aronstein WS, Durrant CD, Chappell, D, Ahmed O, Chappell G, Badley AD, for the LIVE-AIR Study Group, Lenzilumab in hospitalised patients with COVID-19 pneumonia (LIVE-AIR): a phase 3, randomised, placebo-controlled trial, DOI:https://doi.org/10.1016/S2213-2600(21)00 494-X, Copyright (2021), with permission from Elsevier. (B). KM estimate for survival without ventilation in participants with baseline CRP <150 mg/L. Separation of the survival curves occurred after 2 days post treatment. The separation of the curves was more pronounced than in the overall mITT analysis. Lenzilumab treatment improved the relative likelihood of achieving SWOV compared with placebo (HR: 2.54; 95% CI: 1.46 to 4.41, p=0.0009). The log-rank p-value=0.0002. (C) KM estimate for survival without ventilation in participants with baseline CRP ≥150 mg/L. The survival curves fail to separate through the 28-day follow-up period (HR: 1.04; 95% CI: 0.51 to 2.14, p=0.9058). The log-rank p-value=0.4938. ITT, intent to treat; mITT, modified ITT; SWOV, survival without ventilation.

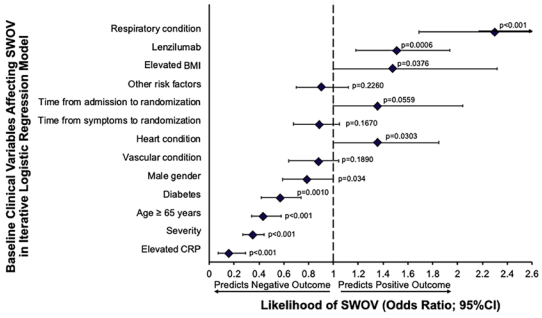

Figure 3 Impact of baseline demographics and risk factors on survival without ventilation using an iterative multivariate logistic regression model. A multi-variate logistic regression analysis was conducted to assess known key risk factors for progression to IMV or death. Logistic regression models were built to predict Day 28 SWOV using known risk factors for progression to IMV or death that were available in the intent-to-treat (ITT) dataset. Three versions of the model were built: one with baseline ordinal score and not severity (stratification variable: severe or critical), one with severity and not baseline ordinal scale, and one with neither baseline ordinal scale nor severity. The set of covariates included in the models were: lenzilumab or placebo treatment; age ≥ 65 or <65 years; gender; linear transformed BMI (BMI 17=0.0, BMI 45=1.0); number of days before randomization of symptom onset (SYMDAY); number of days before randomization of hospital admission (DIADAY); baseline CRP; diabetes; heart condition: prior diagnosis of hypertension, coronary artery disease, or congestive heart failure; respiratory condition: prior diagnosis of asthma, COPD, or interstitial lung disease; vascular condition: prior diagnosis of cerebrovascular disorders or thrombosis and embolism; other risk factors: prior diagnosis of cancers (haematological or non-haematological), chronic kidney disease (including renal failure), chronic liver disease (including hepatic failure), or being a smoker. Model type training was performed by bootstrapping, where 10,000 logistic regression models were built on random subsets of the ITT analysis set (n=520). For each bootstrapped model iteration, metrics were evaluated on the 20% test set and the feature coefficients of the model were recorded. This gave a distribution of 10,000 samples for the metrics and coefficients. All models produced similar outcomes. Therefore, the model chosen used severity as the covariate to be consistent with the covariate used in the pre-specified primary analysis, in addition to the other risk factors as covariates. Statistical significance was reached for all features with a displayed p-value. CRP, C reactive protein.

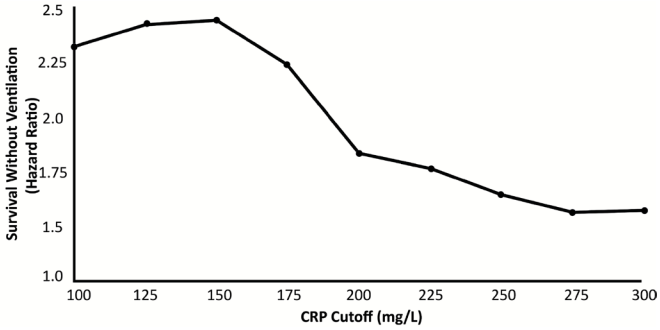

Figure 4 Likelihood of survival without ventilation by level of CRP Cut-off. The HR for SWOV was calculated for all participants, with CRP level below the indicated cut-off value. Participants with CRP <150 mg/L had the greatest likelihood of achieving SWOV. CRP, C reactive protein; SWOV, survival without ventilation.

CRP >150 mg/L progressed to IMV and death with time to event in the 25th and 50th percentiles of 2 and 4 days, respectively. Those with CRP >150 mg/L at any time are at significant risk of an event, accounting for 72% of all failures to achieve SWOV in LIVE-AIR.

CRP levels were reduced by lenzilumab treatment (figure 5B). By day 2 following lenzilumab treatment, mean CRP levels were lower than in the placebo group. CRP levels remained lower throughout the study until the day of discharge or day 28 when mean CRP recovered regardless of treatment.

Safety

In the safety population, adverse events ≥grade 3 were reported in 18% of the participants treated with lenzilumab and 28% of participants treated with placebo in those with baseline CRP <150 mg/L (table 4). Respiratory, thoracic and mediastinal disorders were less common in the lenzilumab group with CRP <150 mg/L relative to placebo. The differences in this group were driven mostly by a lower incidence of respiratory failure and acute respiratory failure associated with lenzilumab treatment. Additionally, infections and infestations, vascular disorders and renal and urinary disorders and general and administration site disorders were all lower in the lenzilumab group with CRP <150 mg/L relative to placebo. No infusion-related reactions or serious adverse events; including, haematologic laboratory abnormalities, liver enzyme abnormalities, increased incidence of infection or cases of pulmonary alveolar proteinosis were reported with lenzilumab treatment.

Table 3 Analysis of treatment on SWOV according to baseline CRP quartile†‡

Quartile	CRP (mg/L)	Kaplan-Meier estimate (n=450)		HR (95% CI)*	p value
		Lenzilumab	Placebo		
1	<41 (n=113)	54/56 (96) (86 to 99)	47/57 (82) (69 to 90)	8.20 (1.74 to 38.69)	0.0079
2	41<79 (n=112)	50/56 (89) (77 to 95)	46/56 (82) (69 to 90)	1.55 (0.58 to 4.15)	0.3860
3	79<137 (n=112)	40/47 (85) (71 to 92)	48/65 (73) (60 to 82)	2.25 (1.04 to 4.88)	0.0407
4	≥137 (n=113)	45/62 (72) (59 to 82)	37/51 (72) (58 to 83)	1.17 (0.58 to 2.35)	0.6582

*Cox proportional hazard model for time to event with age (≤65,>65) and severity (severe, critical) strata as covariates.
†All data censored at 28 days following enrolment.
‡mITT, modified intention to treat population; all participants with baseline CRP values collected.
CRP, C reactive protein; SWOV, survival without invasive mechanical ventilation.

DISCUSSION

Lenzilumab significantly improved SWOV in adults hospitalised with COVID-19 pneumonia compared with placebo, with an NNT of 17. This improvement was most marked in participants with baseline CRP <150 mg/L, resulting in an NNT of 9. Incidence of IMV, ECMO or death; ventilator-free days; ICU days and time to recovery were also significantly improved in participants with a baseline CRP <150 mg/L who received lenzilumab compared with placebo. When baseline risk factors were analysed in a multivariate model for their impact on SWOV, lenzilumab was a significant predictor of SWOV, and baseline CRP was the greatest predictor of IMV and death. Response to lenzilumab was observed in the first through third quartiles of baseline CRP. Patients that progressed to IMV or death had elevated mean CRP levels through the hospital course. While baseline CRP levels were associated with COVID-19 severity at baseline and the likelihood of achieving SWOV regardless of treatment allocation, lenzilumab decreased CRP more rapidly than placebo and to levels more predictive of SWOV. Lenzilumab was well tolerated with no attributable serious adverse events.

The utilisation of CRP as a biomarker of the extent of hyperinflammatory immune response to guide treatment in COVID-19 is supported by numerous reports and aligns with the immunopathophysiology as described herein. Elevation of CRP is driven by IL-6,[5 6] a downstream proinflammatory effector cytokine of hyperinflammatory immune response,[17] resulting from GM-CSF production. GM-CSF itself is elevated early in the hyperinflammatory immune response of COVID-19 and is associated with increased severity and poor outcomes.[1 18] In LIVE-AIR, participants that progress to IMV or death had mean CRP values consistently above 100 mg/L during their hospital course. Seventy-two per cent of participants who progressed to IMV and/or death in LIVE-AIR had CRP >150 mg/L at some point during their hospitalisation and those with CRP >150 mg/L at baseline required rapid escalation of respiratory care within 2–4 days. The LIVE-AIR results confirm previous reports that elevated CRP (>150 mg/L) is predictive of the imminent risk of IMV or death.[1 10] Taken together, the evidence suggests that lenzilumab interferes with GM-CSF signalling resulting in the prevention of the multiplicity of downstream cytokine release, including IL-6, which leads to elevated CRP levels.[5 6 19] This also explains why improvements in both primary and secondary endpoints were not seen in participants whot had baseline CRP >150 mg/L. This level of CRP may reflect stages of hyperinflammatory immune response in which sufficient myeloid activation was already ongoing for GM-CSF neutralisation to adequately prevent disease progression.

Recently published evaluations have begun to suggest patients with COVID-19 phenotypes that may benefit most from various treatments. The IL-6 receptor blocker tocilizumab improved outcomes in patients with more advanced COVID-19 disease with a median baseline CRP of 143 mg/L.[20 21] Separately, tocilizumab decreased the risk of death and ICU admission or death among patients with baseline CRP >150 mg/L but not among those with baseline CRP ≤150 mg/L.[22 23] Tocilizumab is now recommended for use in ICU patients who require IMV or have rapidly increased oxygen demands and have CRP >75 mg/L.[24] While the temporal relationship between proinflammatory cytokines and CRP is likely complex, the use of CRP levels to guide treatment selection is emerging. In patients with CRP ≥200 mg/L, systemic glucocorticoids, administered within 48 hours of admission, were most effective in reducing progression to IMV and/or death compared with control (adjusted OR: 0.20; 95% CI 0.05 to 0.67); however, in patients with CRP <99 mg/L systemic corticosteroid use caused harm (adjusted OR: 3.14; 95% CI 1.52 to 6.50).[11] Other clinical makers have also been associated with positive treatment effects. A four-phase model of progressive COVID-19 severity has been postulated from clinical experience based on objective endpoints (including CRP), combined with preclinical rationale, to propose the use of anti-spike monoclonal and anti-GM-CSF antibodies in less severe COVID-19 and direct dexamethasone, anti-IL-6 antibodies, and JAK inhibitors for use in more advanced disease.[12]

CRP is emerging as a potential biomarker for prognostic use in COVID-19 clinical trials. This analysis of the LIVE-AIR trial is the first to comprehensively evaluate clinical outcomes in the context of baseline CRP levels and drug treatment. Other clinical biomarkers are available and evaluated for prognostic purposes in COVID-19. In a comparative study, D-dimer is predictive of 30-day risk of mortality or ICU admission is not linearly associated as is CRP.[25] Additionally, D-dimer measurements are less readily available than CRP measurements as 34.3% and 95.9% of patients had respective measurements.[25] D-dimer is not included in the ISARIC 4C mortality score nor the deterioration score, whereas CRP is included in both.[26 27] Lymphopenia and ferritin both poorly predict 30-day risk of mortality or ICU admission[25] and lymphopenia is only included in the ISARIC

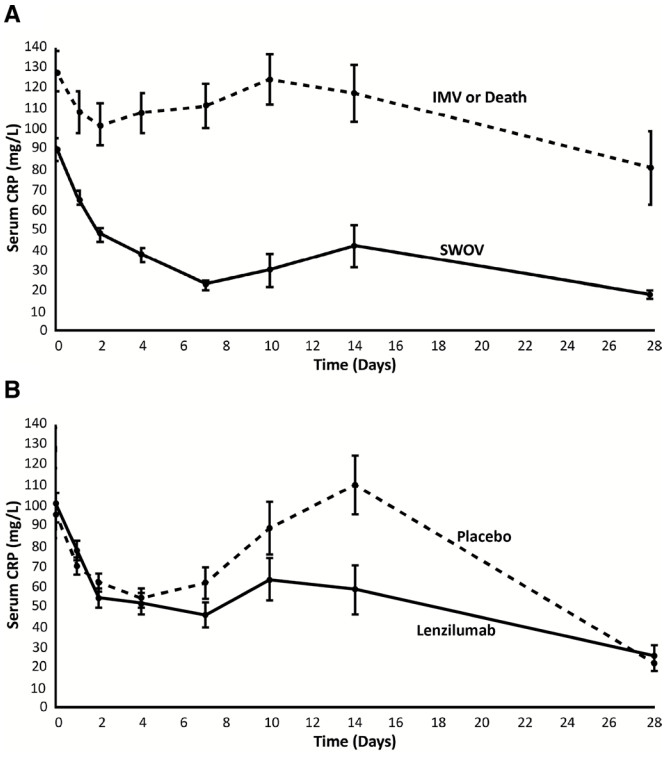

Figure 5 Analysis of CRP levels over time through day 28. (A) CRP levels over time in participants who met primary endpoint (SWOV) versus participants who progressed to IMV and/or death. This analysis was conducted on the entire mITT population without regard to treatment. CRP levels in participants requiring IMV or who died remained elevated through the hospital course. CRP levels were lower in participants who achieved SWOV. (B) CRP levels over time in participants treated with lenzilumab versus placebo. Lenzilumab decreased plasma CRP levels relative to placebo by day 7 and through day 14 following treatment. (Values are mean±SE; mITT population). CRP, C reactive protein; ITT, intent to treat; IMV, invasive mechanical ventilation; mITT, modified ITT; SWOV, survival without ventilation.

Table 4 Most common grade≥3 adverse events (overall incidence ≥1.0%)

System organ class preferred term n (%)	CRP <150 mg/L			CRP ≥150 mg/L			Overall
	Lenzilumab (n=181)	Placebo (n=193)	Total (n=374)	Lenzilumab (n=59)	Placebo (n=50)	Total (n=109)	Total (n=512)
Any AE ≥grade 3	32 (17)	54 (28)	86 (23)	24 (41)	16 (32)	40 (37)	152 (30)
Respiratory, thoracic and mediastinal disorders	30 (17)	48 (25)	78 (21)	23 (39)	15 (30)	38 (35)	135 (26)
Respiratory failure	9 (5)	22 (11)	31 (8)	–	–	–	55 (11)
Acute respiratory failure	8 (4)	15 (8)	23 (6)	6 (10)	6 (12)	12 (11)	40 (8)
Hypoxia	9 (5)	10 (5)	19 (5)	3 (5)	1 (2)	4 (3)	30 (6)
Pulmonary embolism	2 (1)	3 (2)	5 (1)	–	–	–	8 (2)
Cardiac disorders	7 (4)	10 (5)	17 (5)	4 (7)	3 (6)	7 (6)	29 (6)
Cardiac arrest	5 (3)	3 (2)	8 (2)	3 (5)	1 (2)	4 (4)	12 (2)
Acute myocardial infarction	0 (0)	3 (2)	3 (1)	–	–	–	3 (1)
Vascular disorders	4 (2)	8 (4)	12 (3)	–	–	–	25 (5)
Shock	1 (1)	3 (2)	4 (1)	–	1 (2)	1 (1)	9 (2)
Infections and infestations	4 (2)	7 (4)	11 (3)	3 (5)	1 (2)	4 (4)	26 (5)
Septic shock	4 (2)	5 (3)	9 (2)	–	1 (2)	1 (1)	14 (3)
Sepsis	0 (0)	3 (2)	3 (1)	–	–	–	7 (1)
General disorders and administration site conditions	2 (1)	8 (4)	10 (3)	–	–	–	15 (3)
Multiple organ dysfunction syndrome	2 (1)	6 (3)	8 (2)	–	–	–	9 (2)
Renal and urinary disorders	1 (1)	7 (4)	8 (2)	–	–	–	16 (3)
Acute kidney injury	1 (1)	4 (2)	5 (1)	–	–	–	13 (3)
Nervous system disorders	0 (0)	3 (2)	3 (1)	–	–	–	4 (1)
General disorders	0 (0)	3 (2)	3 (1)	–	–	–	3 (1)

CRP, C reactive protein.

4C deterioration score while ferritin is included in neither.[26 27] Therefore, the relevance of CRP over other biomarkers for use in guiding lenzilumab treatment is plausible.

Inhibition of GM-CSF signalling, guided by CRP as a biomarker for emerging hyperinflammatory immune response, and prior to excessive elevations in CRP (ie, >150 mg/L), may be an opportune, variant-agnostic, therapeutic approach to prevent progression to advanced disease. GM-CSF activity could fit into the recently proposed four-phase model.[12] Elevation in GM-CSF may occur during the 'early treatment phase', referred to as phase 2, when viral replication and symptoms of the emerging hyperinflammatory immune response are evident. The proinflammatory cytokine cascade during this phase is consistent with GM-CSF orchestrated myeloid activation and may be when GM-CSF neutralisation is most effective. Accordingly, janus kinase (JAK) inhibitors, corticosteroids and anti-IL-6 monoclonal antibodies are proposed in the 'dyspnoea to adult respiratory distress syndrome (ARDS) phase (phase 3) and the 'ARDS' phase (phase 4) where their activity on targets downstream from GM-CSF may have greater utility.[12]

Limitations are associated with the analytic approach herein. The exploratory analysis of CRP as it relates to the primary endpoint of the likelihood of achieving SWOV was prespecified, all other analyses were *post hoc*, and none was prospectively powered. Therefore, the results should be interpreted with this caveat in mind. Finally, the trial was not powered to prospectively evaluate an impact on mortality; instead, given the relationship between IMV and mortality, the composite endpoint of SWOV was selected as the primary endpoint. The analysis herein suggested a mortality improvement in participants with baseline CRP <150 mg/L (HR, 0.57; 95% CI 0.29 to 1.12) above that observed in the overall LIVE-AIR population (HR, 0.72; 95% CI 0.42 to 1.23); yet again failed to achieve statistical significance (p=0.1040 vs p=0.2410 in the overall population) due to the small number of events. The findings herein will be further evaluated in the NIH-sponsored ACTIV-5/BET-B trial, which includes lenzilumab and where the primary efficacy analysis prospectively evaluates the incidence of IMV, ECMO or death in participants with baseline CRP <150 mg/L.

In summary, this comprehensive analysis of LIVE-AIR CRP data provide evidence for the utility of CRP to predict progression to IMV and death. GM-CSF neutralisation with lenzilumab significantly improved SWOV in adults hospitalised with COVID-19 pneumonia compared with placebo. Those participants who had baseline CRP levels <150 mg/L responded more favourably to lenzilumab treatment than those with CRP >150 mg/L. These findings suggest that CRP may be a useful biomarker in determining which participants may be most successfully treated with lenzilumab.

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Contributors ZT, DC and CD were responsible for overall content of the study. ZT, DC, and CD were responsible for the planning and conduct of the study. ZT, CFK, FC, AK, DC, CD, OA, GC, VMC, CP, AB and VCM interpreted the findings, wrote, and reviewed the manuscript. DC and VMC were responsible for the study's statistical analysis. ZT, CFK, CP, AB and VCM participated in the study. ZT accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests ZT has received research support from Humanigen, Inc, unrestricted education support from Gilead, ViiV, and Merck (all to the institution); CP is a paid consultant to Gilead; CFK has received research support grants (to the institution) from NIH, CDC, Gilead Sciences and ViiV; VCM has received investigator-initiated research grants (to the institution) and consultation fees (both unrelated to the current work) from Eli Lilly, Bayer, Gilead Sciences and ViiV; CD, DC, OA, AK and GC are employees of, or consultants to, Humanigen, Inc.; VMC and FC are third-party agency consultants to Humanigen.

Patient consent for publication Not applicable.

Ethics approval The protocol was approved by Advarra which participated as a central IRB. The ID number is Pro00043147. As well as local institutional review boards or ethics committees at each site (Mayo Clinics, University of Southern California). All participants provided written informed consent. This study was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonization E6 and the principles of the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Not Applicable.

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