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Regional comparison of efficacy and safety for vilobelimab in critically ill, invasively mechanically ventilated COVID-19 patients

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ABSTRACT

Background Vilobelimab, a first in class C5a-specific monoclonal antibody, improved 28-day and 60-day mortality in intubated COVID-19 patients in PANAMO, a phase 3 randomised, double-blind, placebo-controlled multicentre study. All-cause mortality was pre-specified to be analysed pooling by region (western Europe, South America, South Africa/Russia).

Methods Critically ill, invasively mechanically ventilated COVID-19 patients were randomised in a 1:1 ratio within 48 hours of intubation to receive vilobelimab treatment (six, 800 mg intravenous infusions) or placebo on top of standard of care. We analysed the efficacy and safety of vilobelimab based on prespecified geographic regions.

Results 368 patients were randomised and analysed: 177 in the vilobelimab group and 191 in the placebo group. In western Europe (n=209), 28-day all-cause mortality was significantly lower in the vilobelimab group (21%) compared with placebo (37%) (HR 0.51 (95% CI: 0.30, 0.87), p=0.014). In South America (n=126), mortality was similar between groups (40% vs 37%; HR 0.94 (95% CI: 0.53, 1.67), p=0.83). In South Africa/Russia (n=33), mortality was 69% in the vilobelimab group and 87% in the placebo group (HR 0.62 (95% CI: 0.28, 1.38), p=0.25). Within the Brazilian subpopulation (n=74), a significant age imbalance between the vilobelimab and placebo group was detected (median 53.5 years in the vilobelimab group vs 44.5 years in the placebo group). Occurrence of treatment-emergent adverse events between regions was similar.

Conclusion The most apparent 28-day all-cause mortality benefit for vilobelimab was in western Europe. Age imbalance between treatment groups in Brazil may have resulted in a lower efficacy signal for vilobelimab in South America compared with other regions. Overall, vilobelimab demonstrated a favourable safety profile and reduced mortality in critically ill, intubated COVID-19 patients, with regional variations influencing outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vilobelimab, an anti-C5a monoclonal antibody, showed to decrease mortality in invasively mechanically ventilated COVID-19 patients in an international, double-blind, randomised, placebo-controlled, phase 3 trial (PANAMO).

WHAT THIS STUDY ADDS

⇒ This study found that the effect of vilobelimab on critically ill COVID-19 patients was most apparent in the western Europe region, potentially reflecting a more uniform standard of care.

⇒ An age imbalance between treatment groups in Brazil may have impacted the efficacy signal of vilobelimab in South America.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study demonstrates that, minimally, a continent-specific analysis of clinical study data is necessary due to the different populations and healthcare conditions in different parts of the world.

⇒ These results support the original findings of the PANAMO study that vilobelimab treatment results in a reduction in mortality in critically ill COVID-19 patients.

INTRODUCTION

Even as the WHO has declared that COVID-19 disease may no longer pose as a 'global health emergency', the pandemic is not over and is an established and ongoing global health threat.[1] The impact on patients still ranges from asymptomatic disease to mild symptoms to severe lung inflammation requiring invasive mechanical ventilation and death.[2] Standard of care treatment for intubated and mechanically ventilated COVID-19 patients consists of corticosteroids (dexamethasone),[3] individualised anticoagulant prophylaxis and immunomodulators.[4] Despite the role of some of these immunomodulators in the treatment of COVID-19 patients in need of supplementary oxygen, the mortality rate for hospitalised, intubated COVID-19 patients

Table 1 Baseline characteristics by region.

Parameter	Prespecified region					
	Western Europe (n=209)		South America (n=126)		South Africa/Russia (n=33)	
	Vilobelimab (n=103)	Placebo (n=106)	Vilobelimab (n=58)	Placebo (n=68)	Vilobelimab (n=16)	Placebo (n=17)
Country (n (%))						
Belgium	8 (7.8%)	7 (6.6%)				
Germany	10 (9.7%)	11 (10.4%)				
France	17 (16.5%)	18 (17.0%)				
Netherlands	68 (66.0%)	70 (66.0%)				
Brazil			34 (58.6%)	40 (58.8%)		
Mexico			18 (31.0%)	19 (27.9%)		
Peru			6 (10.3%)	9 (13.2%)		
Russia					11 (68.8%)	12 (70.6%)
South Africa					5 (31.3%)	5 (29.4%)
Race (n (%))						
White	72 (69.9%)	68 (64.2%)	30 (51.7%)	38 (55.9%)	13 (81.3%)	13 (76.5%)
Asian	4 (3.9%)	5 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Black or African American	2 (1.9%)	7 (6.6%)	3 (5.2%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)	22 (37.9%)	24 (35.3%)	0 (0.0%)	0 (0.0%)
Mixed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)
Other	11 (10.7%)	10 (9.4%)	3 (5.2%)	5 (7.4%)	2 (12.5%)	4 (23.5%)
Not reported	14 (13.6%)	16 (15.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity (n (%))						
Hispanic or Latino	1 (1.0%)	2 (1.9%)	58 (100.0%)	66 (97.1%)	1 (6.3%)	0 (0.0%)
Non-Hispanic or Latino	55 (53.4%)	54 (50.9%)	0 (0.0%)	2 (2.9%)	15 (93.8%)	17 (100.0%)
Not reported	28 (27.2%)	35 (33.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown	11 (10.7%)	11 (10.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	8 (7.8%)	4 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sex (n (%))						
Male	77 (74.8%)	76 (71.7%)	40 (69.0%)	43 (63.2%)	8 (50.0%)	8 (47.1%)
Female	26 (25.2%)	30 (28.3%)	18 (31.0%)	25 (36.8%)	8 (50.0%)	9 (52.9%)
Age (years)						
Mean (n (%))	60.4 (12.5)	61.9 (12.1)	49.9 (12.1)	46.1 (13.5)	57.9 (12.6)	58.4 (11.4)
Min–max	23–81	23–81	24–78	22–74	25–80	30–74
Median (Q1–Q3)	63.0 (53.0–71.0)	63.5 (55.0–71.0)	50.0 (41.0–56.0)	45.5 (35.0–55.0)	60.5 (50.5–65.0)	62.0 (53.0–66.0)
Comorbidities (n (%))						
Hypertension	43 (41.7%)	56 (52.8%)	28 (48.3%)	21 (30.9%)	9 (56.3%)	13 (76.5%)
Diabetes	33 (32.0%)	43 (40.6%)	9 (15.5%)	14 (20.6%)	3 (18.8%)	7 (41.2%)
Coronary heart disease	11 (10.7%)	12 (11.3%)	0 (0.0%)	1 (1.5%)	1 (6.3%)	1 (5.9%)
Chronic obstructive lung disease	5 (4.9%)	2 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Carcinoma	1 (1.0%)	3 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chronic kidney disease	7 (6.8%)	12 (11.3%)	0 (0.0%)	1 (1.5%)	1 (6.3%)	2 (11.8%)
Obesity	31 (30.1%)	35 (33.0%)	33 (56.9%)	41 (60.3%)	5 (31.3%)	5 (29.4%)
BMI (kg/m^2)						
Mean (n (%))	30.7 (5.3)	30.4 (6.4)	33.6 (6.6)	34.2 (8.0)	33.9 (7.3)	31.9 (5.2)
Min–max	22–46	18–55	24–54	22–55	23–53	26–42
Median (Q1–Q3)	30.5 (27.1–32.7)	28.9 (26.1–33.2)	32.4 (29.0–37.1)	32.9 (27.8–38.7)	32.7 (29.1–38.0)	29.8 (28.4–34.6)
Estimated glomerular filtration rate (n (%))						
< 60 mL/min per 1.73 m²	28 (27.2%)	35 (33.0%)	15 (25.9%)	19 (27.9%)	4 (25.0%)	7 (41.2%)
≥ 60 mL/min per 1.73 m²	75 (72.8%)	71 (67.0%)	42 (72.4%)	49 (72.1%)	12 (75.0%)	10 (58.8%)

Continued

Table 1 Continued

Parameter	Prespecified region					
	Western Europe (n=209)		South America (n=126)		South Africa/Russia (n=33)	
	Vilobelimab (n=103)	Placebo (n=106)	Vilobelimab (n=58)	Placebo (n=68)	Vilobelimab (n=16)	Placebo (n=17)
Missing	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Acute respiratory distress syndrome (n (%))						
Mild (200 mm Hg < PaO_2/FiO_2≤300 mm Hg)*	1 (1.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate (100 mm Hg < PaO_2/FiO_2≤200 mm Hg)	78 (75.7%)	78 (73.6%)	47 (81.0%)	48 (70.6%)	8 (50.0%)	9 (52.9%)
Severe (PaO_2/FiO_2 ≤100 mm Hg)	24 (23.3%)	27 (25.5%)	11 (19.0%)	20 (29.4%)	8 (50.0%)	8 (47.1%)
Time from first COVID-19 symptoms to randomisation (days†)						
n	91	97	57	68	16	17
Mean (SD)	10.2 (5.4)	9.8 (6.1)	11.6 (4.4)	11.7 (3.5)	13.3 (5.4)	13.4 (7.3)
Min–Max	0–31	0–29	5–34	4–22	6–26	2–28
Median (Q1–Q3)	10.0 (6.0–13.0)	10.0 (5.0–14.0)	12.0 (8.0–13.0)	11.0 (10.0–14.0)	14.0 (8.0–16.5)	13.0 (8.0–19.0
Time from COVID-19 diagnosis to randomisation (days)						
n	103	106	58	68	16	17
Mean	7.8 (4.9)	7.7 (5.2)	6.2 (4.5)	6.6 (4.2)	6.8 (4.7)	5.6 (3.2)
Min–Max	0–24	0–30	0–15	0–16	0–15	0–13
Median (Q1-Q3)	9.0 (3.0–12.0)	7.0 (3.0–11.0)	5.0 (3.0–9.0)	7.0 (3.0–10.0)	6.0 (3.0–11.0)	5.0 (4.0–8.0)
Time from hospital admission to randomisation (days)						
Mean (SD)	3.8 (3.0)	4.6 (4.5)	3.5 (2.3)	3.4 (2.7)	5.8 (3.5)	5.1 (5.3)
Min–Max	0–19	0–27	0–10	0–15	1–12	1–18
Median (Q1–Q3)	3.0 (2.0–5.0)	4.0 (2.0–6.0)	3.0 (2.0–5.0)	3.0 (2.0–4.0)	5.0 (3.0–9.0)	3.0 (1.0–6.0)
Time from intensive care unit admission to randomisation (days‡)						
Mean (SD)	2.1 (1.8)	2.8 (3.8)	1.7 (1.6)	1.7 (1.7)	3.9 (3.6)	4.2 (5.1)
Min to Max	0 to 11	0 to 22	–2 to 7	0 to 10	0 to 11	0 to 17
Median (Q1–Q3)	2.0 (1.0–3.0)	1.0 (1.0–3.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–7.0)	3.0 (1.0–5.0)
8-point WHO COVID-19 ordinal scale score (n (%))						
6 (intubation and mechanical ventilation)	31 (30.1%)	19 (17.9%)	28 (48.3%)	29 (42.6%)	13 (81.3%)	11 (64.7%)
7 (ventilation plus organ support)§	72 (69.9%)	87 (82.1%)	30 (51.7%)	39 (57.4%)	3 (18.8%)	6 (35.3%)

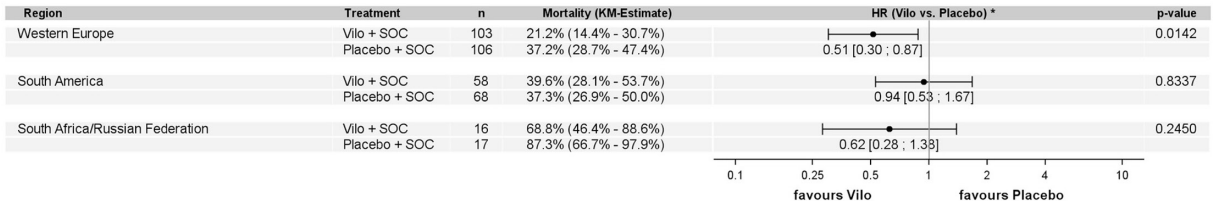
Data are n (%), mean (SD), median (IQR), unless stated otherwise.
*Two patients with values greater than 300 mm Hg are included in the mild ARDS severity category. The inclusion criterion was PaO_2/FiO_2 60–200 mm Hg, but some patients were included despite violating this criterion.
†Data available for 164 patients in the vilobelimab group and 182 in the placebo group.
‡Data available for 163 patients in the vilobelimab group and 171 in the placebo group.
§Organ support included vasopressors, renal replacement therapy and extracorporeal membrane oxygenation.
ARDS, acute respiratory distress syndrome; BMI, body mass index; COVID-19, coronavirus disease 2019; n, number of patients in the analysis in the respective treatment group; PaO_2/FiO_2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; Q, quartile.

remains high[5] which confirms a still unmet medical need in this critically ill population. Some patients, even when vaccinated, progress to receiving higher levels of oxygenation by high flow nasal canula, non-invasive ventilation prior to or after being admitted to the intensive care unit (ICU) or require mechanical ventilation.[6]

The complement anaphylatoxin, C5a, is highly elevated in severe COVID-19 patients and correlated with disease severity.[7 8] C5a activation directly induces endothelial tissue factor upregulation, neutrophil-mediated coagulation activation to switch inflammatory cells from a profibrinolytic (tissue-type plasminogen activator release) to a prothrombotic phenotype (plasminogen activator inhibitor type 1 release).[9] This results in the production of enzymes such as trypsin and thrombin that can cleave C5 to C5a outside the well-known complement pathways.[10 11]

Vilobelimab (IFX-1) is a monoclonal antibody that specifically binds to the C5 complement split product C5a.[12 13] Preclinical studies targeting the C5a/C5aR axis conducted in avian influenza virus H7N9-induced acute respiratory distress syndrome (ARDS) in non-human primates[14] and Middle East Respiratory Syndrome (MERS) Coronavirus in a mouse model[15 16] demonstrated that vilobelimab and an antibody specific to C5aR significantly reduced H7/N9-induced and MERS-induced lung

A



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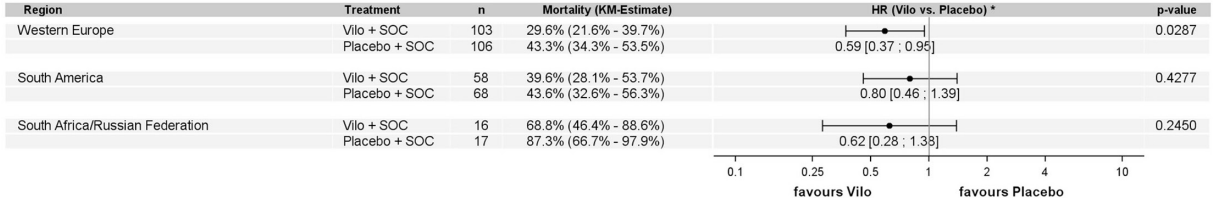


Figure 1 Forest plot of 28-day and 60-day all-cause mortality in each region. KM, Kaplan-Meier; n, number of patients in the analysis in the respective treatment group; SOC, standard-of-care; Vilo, vilobelimab. *HR from the Cox proportional hazards regression model with outcome 28-day all-cause mortality as a censored time-to-event variable and explanatory variables treatment arm and age. HRs are only displayed for subgroups with at least 10 patients and for which at least one event per treatment group has been observed.

inflammation and injury, respectively. More specifically, the preclinical models demonstrated that C5a inhibition strongly reduced neutrophil and macrophage influx into infected lungs, maintained tissue integrity as evidenced by histological analysis, and significantly reduced systemic cytokine generation.

In PANAMO, which was a double-blind, randomised, placebo-controlled, multicentre, global phase three study, the aim was to determine whether vilobelimab in addition to standard of care improves survival outcomes in invasively mechanically ventilated patients with COVID-19.[17] We demonstrated that vilobelimab improved survival in this patient population. The results of this study have led to Emergency Use Authorization in the USA for use in hospitalised patients with COVID-19 within 48 hours of starting invasive mechanical ventilation or extracorporeal membrane oxygenation.[18] Pre-specified subgroup analyses for the primary endpoint of 28-day all-cause mortality were conducted for each country and region, as part of exploratory analysis. In this study, the results of the analysis of pre-specified pooled countries on the efficacy and safety of vilobelimab in the different geographic regions are reported.

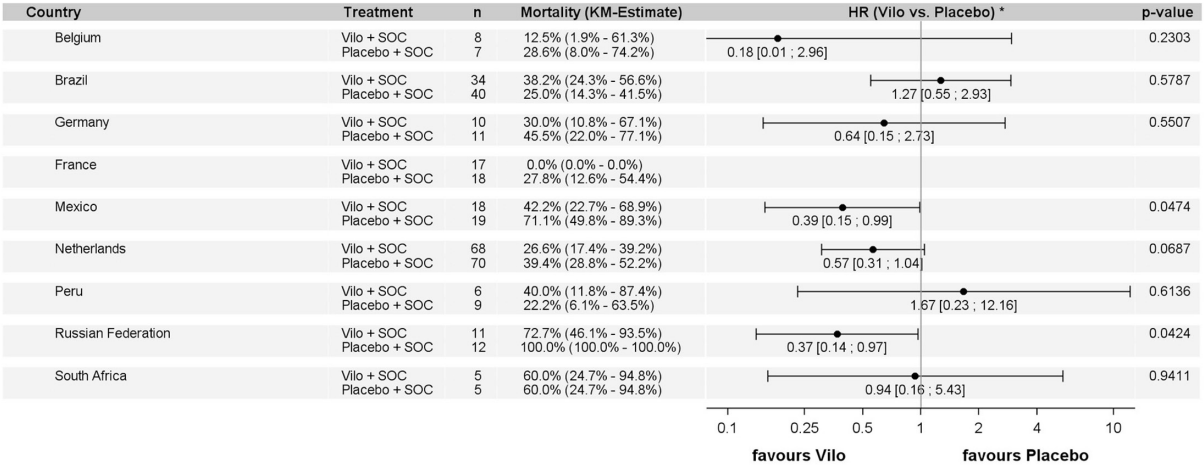
METHODS

Study design

The study design, recruited participants, randomisation and blinding, procedures, and outcomes as well as statistical analysis of the PANAMO study in critically ill COVID-19 patients are described in the original article.[17] The study was performed at 46 sites worldwide on four continents. Patients were recruited from Belgium, Brazil, Germany, France, Mexico, the Netherlands, Peru, Russia and South Africa. Although a site in the USA was opened, no patients were enrolled due to competing studies during the pandemic. Inclusion criteria were an age of 18 or older, invasive mechanical ventilation but not more than 48 hours after intubation at time of first infusion of study drug, a PaO_2/FiO_2 ratio of 60–200 mm Hg, and a confirmed SARS-CoV-2 infection in the past 14 days. The median number of patients randomised per site was 4 and 11 sites randomised one single patient. For the overall study, 369 patients were enrolled between 1 October 2020 and 4 October 2021 with 178 patients randomly assigned to receive vilobelimab and 191 patients randomly assigned to placebo. One patient in the vilobelimab group was excluded from the primary analysis due to a randomisation error. Therefore, 368 patients were included in the full analysis set (177 in the vilobelimab group and 191 in the placebo group). This study was registered with ClinicalTrials.gov, NCT04333420.

Prespecified subgroup analyses for the primary endpoint of 28-day all-cause mortality were conducted for each country and region, comorbidities, standard of care, ordinal scale at baseline, ARDS severity and estimated glomerular filtration rate (eGFR) categories as part of exploratory analysis.[17] ARDS severity at baseline was defined according to the ARDS Definition Task Force[19] for moderate: 100 mm Hg < PaO_2/FiO_2 ≤200 mm Hg and severe: PaO_2/FiO_2 ≤100 mm Hg. The prespecified regions (and countries) for all-cause mortality analyses were as follows: (1) western Europe: Belgium, France, Germany, the Netherlands; (2) South America: Brazil, Mexico, Peru; and (3) South Africa and Russia combined as a region. Russia and South Africa were

A



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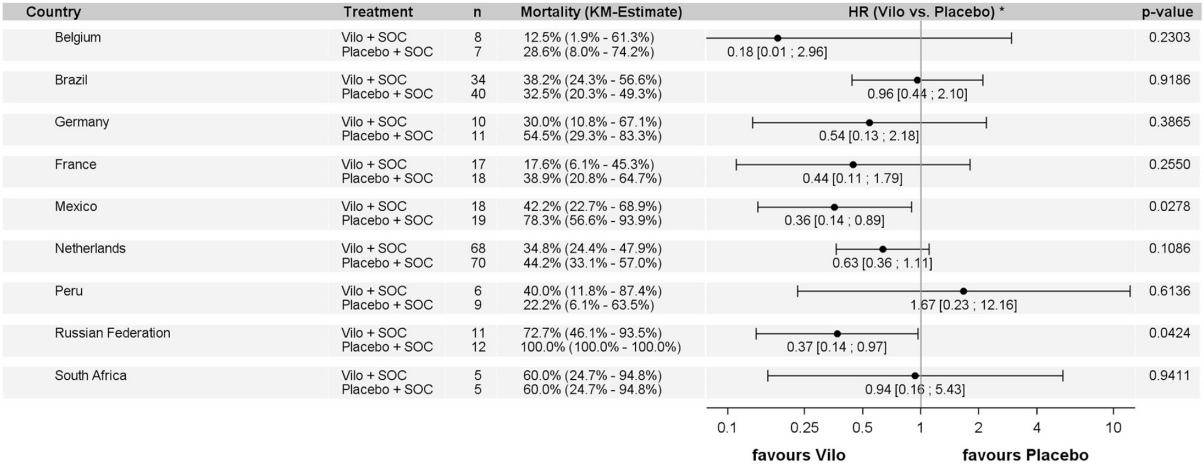

Figure 2 Forest plot for 28-day (A) and 60-day (B) all-cause mortality by country. KM, Kaplan-Meier; n, number of patients in the analysis in the respective treatment group; SOC, standard-of-care; Vilo, vilobelimab *HR from the Cox proportional hazards regression model with outcome 28-day all-cause mortality as a censored time-to-event variable and explanatory variables treatment arm and age. HRs are only displayed for subgroups with at least 10 patients and for which at least one event per treatment group has been observed.

analysed collectively due to a limited number of patients enrolled in the two countries.

Outcomes

Comparisons for the primary endpoint of 28-day all-cause mortality and secondary endpoint of 60-day all-cause mortality were performed on the full analysis set for each region and individual countries. Finally, treatment-emergent adverse events (TEAEs) and serious adverse events were reported by region using the safety analysis set.

Statistical Analysis

The primary (28-day all-cause mortality) and key secondary endpoint (60-day all-cause mortality) were evaluated as a censored time-to-event variable by the Kaplan-Meier-type method and Cox regression. Kaplan-Meier and Cox regression analyses were performed comparing the two treatment arms within pre-specified regions (western Europe, South America and South Africa/Russia as well as western Europe) versus the rest of world (South America, South Africa/Russia). The Cox regression analysis had been prespecified to be adjusted for age as a linear factor. We also present analyses where an age adjustment by age in categories (≤30, 31–40, 41–50, 51–60, >60) was used. The following baseline characteristics were evaluated by region and treatment group: sex (male vs female); comorbidities (yes, no, unknown); ordinal scale score at baseline (6 vs 7); and body mass index (BMI) categories (< 18.5 (underweight), ≥ 18.5 and < 25 (normal weight), ≥ 25 and < 30 (overweight), ≥ 30 and < 35 (obesity class 1), and ≥35 (obesity classes 2/3) kg/m^2). The full analysis set was used in all cases. All statistical analyses were

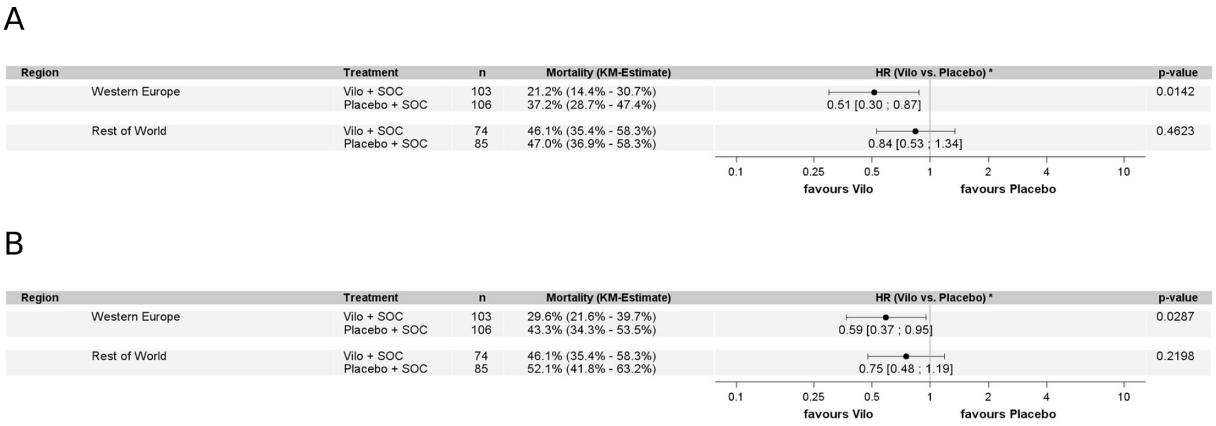

Figure 3 Forest plot for 28-day (A) and 60-day (B) all-cause mortality for western Europe compared with the rest of the world. KM, Kaplan-Meier; n, number of patients in the analysis in the respective treatment group; SOC, standard-of-care; Vilo, vilobelimab. *HR from the Cox proportional hazards regression model with outcome 28-day all-cause mortality as a censored time-to-event variable and explanatory variables treatment arm and age. HRs are only displayed for subgroups with at least 10 patients and for which at least one event per treatment group has been observed.

performed with SAS (V.9.4), and figures were generated using R (V.4.0.0).

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Between 1 October 2020 and 4 October 2021, 368 patients were enrolled and randomised: 177 in the vilobelimab group and 191 in the placebo group (table 1). Patient were recruited from three pre-specified geographical reThis study was gions: western Europe (209 of 368 (56.7%)), South America (126 of 368 (34.2%)) and South Africa/Russia (33 of 368 (9.0%)). Baseline demographics and clinical characteristics were generally balanced across treatment groups and regions except for the age of patients. The mean (SD) of patients was 56.3 (13.9) years overall, with regional differences: 61.1 (12.3) years in western Europe, 47.8 (12.9) years in South America, and 58.1 (12.0) years in South Africa/Russia. Most patients were male (252 of 368 (68.5%)), with regional variation: 73.2% in western Europe, 65.9% in South America, and 48.5% in South Africa/Russia (table 1).

In the PANAMO study, all patients who were on invasive mechanical ventilation at baseline were randomised and treated within 48 hours of intubation and had a baseline WHO COVID-19 8-point ordinal scale score of 6 or 7.[17] In the overall study, a slightly higher proportion of patients in the placebo group (132 patients (9%) than in the vilobelimab group (105 patients (59.3%)) had a score of 7 at baseline, which included patients intubated with invasive mechanical ventilation as well as one or more additional organ support therapies (eg, vasopressors, extracorporeal membrane oxygenation or renal replacement therapy). Time from symptoms to randomisation was slightly longer in the South Africa/Russia region compared with the other regions. There were no significant differences in time from hospital admission to randomisation and in time from ICU admission to randomisation among regions (table 1). By region, western Europe recruited fewer ordinal scale score 7 patients in the vilobelimab group (n=72 (69.9%)) compared with placebo (n=87 (82.1%)) (table 1). Similarly, South America also had fewer ordinal scale score 7 patients in the vilobelimab group (n=30 (51.7%)) versus placebo (n=30 (57.1%)). South Africa/Russia had a greater proportion of patients treated with vilobelimab with ordinal scale score 6, but the numbers were small. Almost all patients had signs and symptoms consistent with COVID-19, with no considerable differences for any COVID-19 symptoms between the two treatment groups in the overall study population or in any region. The use of immunomodulators such as tocilizumab was highest in western Europe (26.7%) compared with South America (11.1%) and South Africa/Russia (12.1%) (online supplemental table 1).

Although there was no mean age difference between the treatment groups in the overall phase 3 PANAMO study,[17] the age distribution between the treatment groups differed between the western Europe (mean age (years): vilobelimab 60.4 (12.5), placebo 61.9 (12.1)) and South America (mean age (years): vilobelimab 49.4 (12.1), placebo 46.1 (13.5)) regions (table 1). For South Africa/Russia region, the mean age was comparable to that of western Europe. The median age (years, quartile (Q)1–Q3) also differed between regions: western Europe (vilobelimab 63.0 (53.0–71.0), placebo 63.5 (55.0–71.0)); South America (vilobelimab 50.0 (41.0–56.0), placebo 45.5 (35.0–55.0)); South Africa/Russia (vilobelimab 60.5 (50.5–65.0), placebo 62.0 (53.0–66.0)). Overall, the patients recruited in South American countries compared with western European and South Africa/Russian countries were younger in both the vilobelimab and placebo groups (online supplemental table 2).

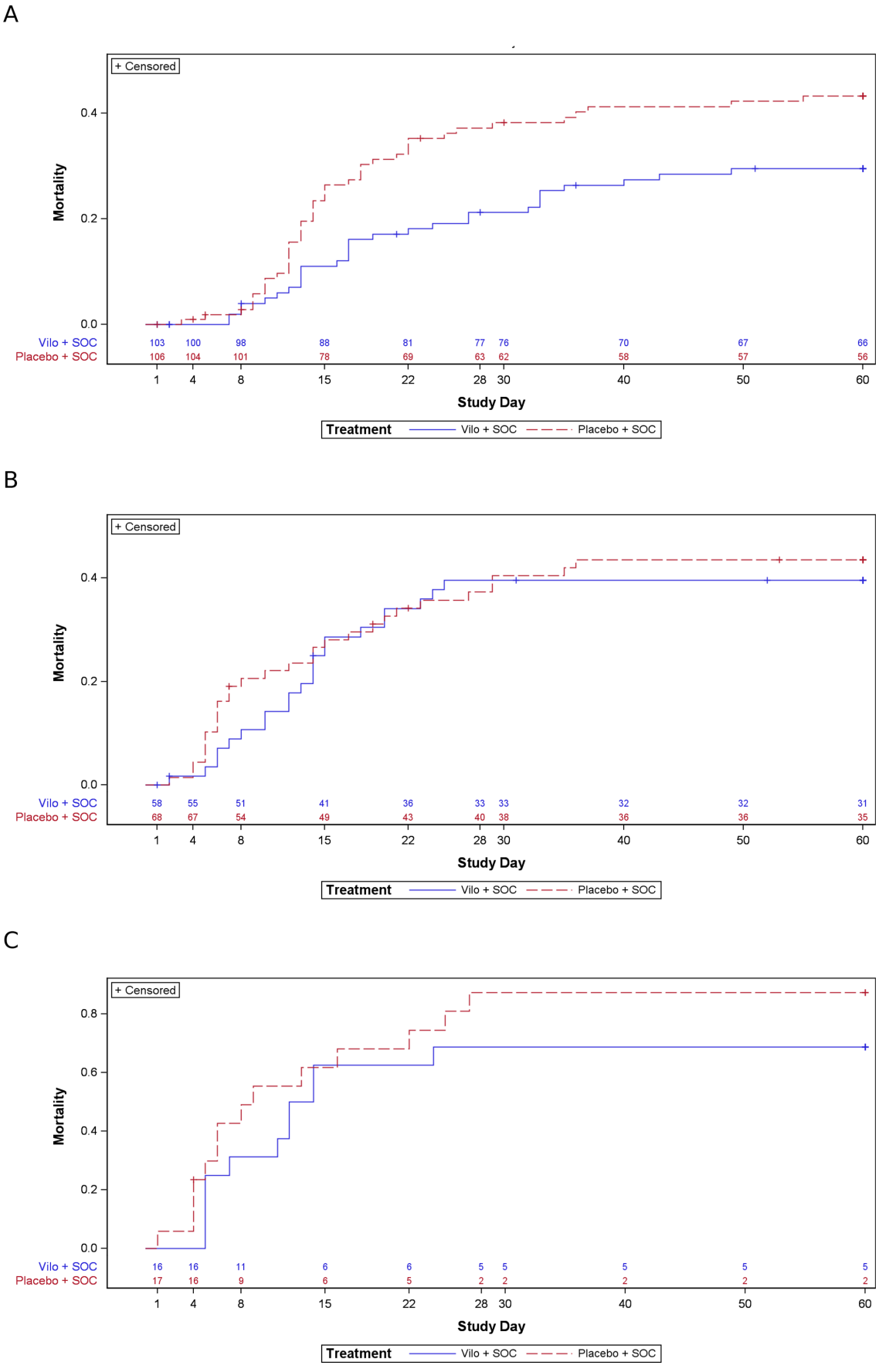

Figure 4 Kaplan-Meier estimates for 60-day all-cause mortality by region (western Europe (A); South America (B); South Africa/Russia (C)). SOC, standard-of-care; Vilo, vilobelimab.

In Brazil, the placebo group was significantly younger compared with the vilobelimab-treated group (p=0.033); the placebo group showed a mean of approximately 7 years and a median of 9 years younger population (mean age 45.8 years, median age 44.5 years) compared with the vilobelimab group (mean age 52.5 and median age 53.5 years) (online supplemental table 2). The proportion of patients in Brazil who were <50 years of age was 65.0% (26 of 40 patients) in the placebo group compared with 38.2% (13 of 34 patients) in the vilobelimab group.

A significant treatment benefit of vilobelimab over placebo was observed in western Europe, with a Kaplan-Meier estimated 28-day all-cause mortality rate of 21.2% in the vilobelimab group compared with 37.2% in the placebo group (HR 0.51 (95% CI: 0.30, 0.87), p=0.014) (figure 1A). The 28-day all-cause mortality rate in South America was 39.6% in the vilobelimab group and 37.3% in the placebo group (HR 0.94 (95% CI: 0.53, 1.67), p=0.83). In South Africa/Russia, the 28-day all-cause mortality rate was 68.8% in the vilobelimab group compared with 87.3% in the placebo group (HR 0.62 (95% CI: 0.28, 1.38), p=0.25). Mortality rate comparisons at day 60 per region were similar to day 28 and are shown in figure 1B. These results were in line with the results of the analysis by country, where a benefit of vilobelimab over placebo at 28 and 60 days was observed in Belgium, Germany, the Netherlands, France, Mexico and Russia, while results favouring placebo over vilobelimab were observed in Brazil and Peru (figure 2). When 28-day all-cause mortality in western Europe (HR 0.51 (95% CI: 0.30, 0.87), p=0.014) was compared with the rest of the world (HR 0.84 (95% CI: 0.53, 1.34), p=0.46), western Europe demonstrated a large vilobelimab treatment benefit (figure 3A). This benefit persisted until 60 days (figure 3B). Similarly, Kaplan-Meier estimates showed a significant treatment benefit for vilobelimab compared with placebo in the western European patient population with a 43% relative reduction in 28-day all-cause mortality (HR 0.51 (95% CI: 0.30, 0.87), p=0.014) and a 31.6% relative reduction in 60-day all-cause mortality (HR 0.59 (95% CI: 0.37, 0.95), p=0.029) (figure 4A). The treatment benefit was less pronounced in South Africa/Russia at either day 28 or day 60 (figure 4C) and there was no evident treatment benefit observed for South America (figure 4B).

When the difference in age distributions of the Brazilian population was examined, the 28-day mortality rate of 25% was observed in the placebo group in Brazil, lower compared with the placebo mortality rates seen in the other countries (figure 2A). At 60 days, the vilobelimab mortality rate in Brazil was approximately the same as that at day 28, and there was a rise in the placebo group to 32.5% (figure 2B). Adjusting for age group categories (≤ 30, 31–40, 41–50, 51–60, >60 years of age) within the Cox regression, rather than linear age adjustment as default for all other conducted Cox regression analyses, changed the HR for the 60-day all-cause mortality in Brazil from 0.96 (95% CI: 0.44, 2.10; p=0.92) to 0.77 (95% CI: 0.35, 1.69; p=0.51), similar to the overall study results (HR 0.73)[17] (online supplemental figure 1A,B).

TEAEs were similar between the placebo and treatment groups across different regions (online supplemental table 3). There were fewer serious acute kidney injuries for vilobelimab (n=10 (9.8%)) versus placebo (n=17 (16.2%)) and septic shock (vilobelimab n=8 (7.8%), placebo n=16 (15.2%)) in the western Europe region. In South America, there were more serious pulmonary sepsis incidents for vilobelimab (n=12 (21.1%)) compared with placebo (n=9 (13.2%)) as well as pneumonia (n=13 (22.8%)) versus placebo (n=7 (10.3%)). In South America, similar to western Europe, serious acute kidney injury was less in the vilobelimab group (n=5 (8.8%)) compared with the placebo group (n=10 (14.7%)). Related TEAEs were comparable in western Europe and South America while serious TEAEs were less in western Europe for vilobelimab (46.1%) compared with placebo (59.0%) but showed an inverse pattern in South America with vilobelimab having more serious TEAEs (78.9%) compared with placebo (66.2%). In each geographic region, TEAEs classified as fatal were lower for vilobelimab compared with placebo. Overall safety evaluation of PANAMO suggested vilobelimab was well tolerated (online supplemental table 3).

DISCUSSION

In the phase 3 PANAMO study, a prespecified exploratory analysis using censored time-to-event variable by Kaplan-Meier-type methods and Cox regression stratified by region (western Europe (Belgium, France, Germany, the Netherlands), South America (Brazil, Mexico, Peru) and South Africa/Russian Federation) was used to assess primary outcomes. The 28-day and 60-day mortality rates in vilobelimab-treated patients were significantly reduced compared with placebo patients in western Europe. A reduction in mortality by vilobelimab treatment compared with placebo was also detected in South Africa/Russia but not in South America. In the Brazilian patient population, a significant age imbalance between the vilobelimab group and the median 9-year younger placebo group was found, resulting in an unusually low 28-day mortality in the placebo group in the range of only 25%, lower than the placebo death rate found in western Europe with 37.2%. This finding suggests that an age difference may explain the lack of observed efficacy for vilobelimab compared with placebo in the South America region. Indeed by adjusting for age group categories within the Cox regression analysis, rather than linear age adjustment only, which was the preplanned adjustment in the PANAMO trial, we found that the HR improved for the 60-day all-cause mortality in the vilobelimab group in Brazil, more in line with the global data set. The 60-day rather than the 28-day all-cause mortality was used as Kaplan-Meier estimates as day 60 may be more suitable for analysis of smaller subgroups due to longer follow-up time and higher number of events. This

provided further evidence for the decrease in the survival signal for vilobelimab compared with placebo in South America being most likely driven by chance recruitment imbalance in age in Brazil and not a weaker efficacy of vilobelimab. In a model with treatment effect and age as covariates, the estimation algorithm of the Cox regression can be influenced by data artefacts affecting only a subset of the data. This may have occurred in the study, namely a generally younger age, which led to a higher mortality in the vilobelimab group and an age imbalance between the vilobelimab and placebo groups in Brazil.

Occurrence of TEAEs between regions was similar but there were fewer serious TEAEs in western Europe compared with South America. One consistent reduction in TEAEs for vilobelimab compared with placebo treatment was a decrease in acute kidney injury across regions. South America contributed a higher number of serious TEAEs (vilobelimab 45 (78.9%), placebo 45 (66.2%)) as compared with western Europe (vilobelimab 47 (46.1%), placebo 62 (59.0%)) although enrolment for South America was only 34% of the entire study compared with 56% for western Europe.

It has been noted that standard of care both medical and pharmaceutical varied worldwide across different randomised clinical trials and these studies could be affected by the quality of the control groups compared with the treatment arms.[20] In the overall study population of the phase 3 PANAMO study, standard of care was defined as concomitant use of corticosteroids and antithrombotic prophylaxis which was high with 356 (97%) of 368 patients and 362 (98%) of 368 patients, respectively.[17] There were no differences found between countries or regions in the use of corticosteroids and antithrombotic agents. However, the use of immunomodulators was highest in western Europe, where a considerable proportion of patients (27%) received anti-interleukin-6 treatment, as this was approved by the European Medicines Agency after the last patient was included. This could also have influenced the mortality differences across regions. Though it is possible that patients' medical care and pharmaceutical intervention in ICUs could vary between regions and differ according to national treatment guidelines,[21] reduced efficacy for the treatment arm in South America was more likely driven by younger patients recruited particularly in the placebo arm in Brazil, the second largest recruiting country in the study.

A significant proportion of patients included in our study were likely infected with the Delta variant of SARS-CoV-2, although other variants, such as Omicron, became predominant over time.[17] Despite this, the mechanism of action of vilobelimab exclusively targets the immune response responsible for viral sepsis and organ failure, a phenomenon observed across all identified SARS-CoV-2 variants. While the Omicron variant is generally less severe than earlier variants, patients remain at risk of developing immune-mediated organ failure caused by SARS-CoV-2. Thereby, vilobelimab only targets the immune response to a virus rather than the virus itself.

Thought this analysis of the prespecified regions from PANAMO provides further details for the efficacy and safety of vilobelimab and may explain the observed low efficacy signal seen in South America, our study does have limitations. Even though the prespecified Cox regression analysis using stratification by region showed that vilobelimab demonstrated a significant reduction for the primary study endpoint, 28-day all-cause mortality, there were differences in the size of populations recruited in each region with nearly twice as many patients recruited in western Europe vs South America and over sixfold more than in South Africa/Russia. This could contribute to the greater treatment benefit of vilobelimab observed in western Europe compared with the two other regions. Mortality rates differed across regions, although almost all patients received concomitant corticosteroids and antithrombotic agents as standard of care. Intensive care therapy was defined according to, at the time, current guidelines of each country. Therefore, patients were also treated with approved, or guideline-recommended treatments, reflecting the regionally or locally applied standards. More global trials are needed, especially in critical care medicine, in order to investigate a homogenous population, as few interventions have shown to be effective in large clinical trials likely because of between-patient heterogeneity.[22]

CONCLUSION

The effect of vilobelimab was most apparent in the western Europe region potentially reflecting a more uniform standard of care, while age imbalance between treatment groups in Brazil may have impacted the efficacy signal of vilobelimab in South America. There were no major differences in the total occurrence of TEAEs across different regions. Overall, this post hoc analysis supports the original findings of the PANAMO study but does point to the difficulty in recruiting balanced populations worldwide which can influence outcomes.

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Competing interests SR is an employee of Metronomia Clinical Research, a contracted statistical service provider for InflaRx. CT, BPB, RZ and CC are employees of InflaRx and may hold shares and/or stock options in InflaRx. NCR and RG are founders, active officers, and executive directors of the board, and hold shares and stock options in InflaRx. APJV received consulting fees from InflaRx for advisory work, paid to the institution. All other authors declare no competing interests.

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REFERENCES

1 World Health Organization. Statement on the fifteenth meeting of the IHR, 2005. Available: https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic
2 Long B, Carius BM, Chavez S, *et al*. Clinical update on COVID-19 for the emergency clinician: Presentation and evaluation. *Am J Emerg Med* 2022;54:46–57.
3 Nigro M, Chalmers JD, Aliberti S. A patient-tailored approach for corticosteroid treatment in COVID-19: still not there yet. *Eur Respir J* 2023;61:2300270.
4 Li G, Hilgenfeld R, Whitley R, *et al*. Therapeutic strategies for COVID-19: progress and lessons learned. *Nat Rev Drug Discov* 2023;22:449–75.
5 Chomistek AK, Liang C, Doherty MC, *et al*. Predictors of critical care, mechanical ventilation, and mortality among hospitalized patients with COVID-19 in an electronic health record database. *BMC Infect Dis* 2022;22:413.
6 Grapsa E, Adamos G, Andrianopoulos I, *et al*. Association Between Vaccination Status and Mortality Among Intubated Patients With COVID-19-Related Acute Respiratory Distress Syndrome. *JAMA Netw Open* 2022;5:e2235219.
7 Demaria O, Carvelli J, Benmansour NC, *et al*. 483 Association of covid-19 inflammation with activation of the c5a-c5ar1 axis. 35th Anniversary Annual Meeting (SITC 2020); November 2020:146–50.
8 de Bruin S, Bos LD, van Roon MA, *et al*. Clinical features and prognostic factors in Covid-19: A prospective cohort study. *EBioMedicine* 2021;67:103378.
9 Vlaar APJ, de Bruin S, Busch M, *et al*. Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial. *Lancet Rheumatol* 2020;2:e764–73.
10 Huber-Lang M, Sarma JV, Zetoune FS, *et al*. Generation of C5a in the absence of C3: a new complement activation pathway. *Nat Med* 2006;12:682–7.
11 Riedemann NC, Habel M, Ziereisen J, *et al*. Controlling the anaphylatoxin C5a in diseases requires a specifically targeted inhibition. *Clin Immunol* 2017;180:25–32.
12 Vlaar APJ, Lim EHT, de Bruin S, *et al*. The anti-C5a antibody vilobelimab efficiently inhibits C5a in patients with severe COVID-19. *Clin Transl Sci* 2022;15:854–8.
13 Lim EHT, Vlaar APJ, de Bruin S, *et al*. Pharmacokinetic analysis of vilobelimab, anaphylatoxin C5a and antidrug antibodies in PANAMO: a phase 3 study in critically ill, invasively mechanically ventilated COVID-19 patients. *Intensive Care Med Exp* 2023;11:37.
14 Sun S, Zhao G, Liu C, *et al*. Treatment with anti-C5a antibody improves the outcome of H7N9 virus infection in African green monkeys. *Clin Infect Dis* 2015;60:586–95.
15 Jiang Y, Li J, Teng Y, *et al*. Complement Receptor C5aR1 Inhibition Reduces Pyroptosis in hDPP4-Transgenic Mice Infected with MERS-CoV. *Viruses* 2019;11:39.
16 Jiang Y, Zhao G, Song N, *et al*. Blockade of the C5a-C5aR axis alleviates lung damage in hDPP4-transgenic mice infected with MERS-CoV. *Emerg Microbes Infect* 2018;7:77.
17 Vlaar APJ, Witzenrath M, van Paassen P, *et al*. Anti-C5a antibody (vilobelimab) therapy for critically ill, invasively mechanically ventilated patients with COVID-19 (PANAMO): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2022;10:1137–46.
18 Harris E. FDA Approves Vilobelimab for Emergency Use in Hospitalized Adults. *JAMA* 2023;329:1544.
19 ForceADT, RanieriVM, RubenfeldGD, *et al*. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–33.
20 Addis A, Amato L, Cruciani F, *et al*. The Standard of Care Definitions on COVID-19 Pharmacological Clinical Trials: A Systematic Review. *Front Pharmacol* 2021;12:749514.
21 Ranzani OT, Bastos LSL, Gelli JGM, *et al*. Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. *Lancet Respir Med* 2021;9:407–18.
22 van Amstel RBE, van Vught LA, Bos LDJ. Integrating biology into clinical trial design. *Curr Opin Crit Care* 2023;29:26–33.