Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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

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Summary

Background Vilobelimab, an anti-C5a monoclonal antibody, was shown to be safe in a phase 2 trial of invasively mechanically ventilated patients with COVID-19. Here, we aimed to determine whether vilobelimab in addition to standard of care improves survival outcomes in this patient population.

Methods This randomised, double-blind, placebo-controlled, multicentre phase 3 trial was performed at 46 hospitals in the Netherlands, Germany, France, Belgium, Russia, Brazil, Peru, Mexico, and South Africa. Participants aged 18 years or older who were receiving invasive mechanical ventilation, but not more than 48 h after intubation at time of first infusion, had a PaO_2/FiO_2 ratio of 60–200 mm Hg, and a confirmed SARS-CoV-2 infection with any variant in the past 14 days were eligible for this study. Eligible patients were randomly assigned (1:1) to receive standard of care and vilobelimab at a dose of 800 mg intravenously for a maximum of six doses (days 1, 2, 4, 8, 15, and 22) or standard of care and a matching placebo using permuted block randomisation. Treatment was not continued after hospital discharge. Participants, caregivers, and assessors were masked to group assignment. The primary outcome was defined as all-cause mortality at 28 days in the full analysis set (defined as all randomly assigned participants regardless of whether a patient started treatment, excluding patients randomly assigned in error) and measured using Kaplan-Meier analysis. Safety analyses included all patients who had received at least one infusion of either vilobelimab or placebo. This study is registered with ClinicalTrials.gov, NCT04333420.

Findings From Oct 1, 2020, to Oct 4, 2021, we included 368 patients in the ITT analysis (full analysis set; 177 in the vilobelimab group and 191 in the placebo group). One patient in the vilobelimab group was excluded from the primary analysis due to random assignment in error without treatment. At least one dose of study treatment was given to 364 (99%) patients (safety analysis set). 54 patients (31%) of 177 in the vilobelimab group and 77 patients (40%) of 191 in the placebo group died in the first 28 days. The all-cause mortality rate at 28 days was 32% (95% CI 25–39) in the vilobelimab group and 42% (35–49) in the placebo group (hazard ratio 0·73, 95% CI 0·50–1·06; p=0·094). In the predefined analysis without site-stratification, vilobelimab significantly reduced all-cause mortality at 28 days (HR 0·67, 95% CI 0·48–0·96; p=0·027). The most common TEAEs were acute kidney injury (35 [20%] of 175 in the vilobelimab group *vs* 40 [21%] of 189 in the placebo), pneumonia (38 [22%] *vs* 26 [14%]), and septic shock (24 [14%] *vs* 31 [16%]). Serious treatment-emergent adverse events were reported in 103 (59%) of 175 patients in the vilobelimab group versus 120 (63%) of 189 in the placebo group.

Interpretation In addition to standard of care, vilobelimab improves survival of invasive mechanically ventilated patients with COVID-19 and leads to a significant decrease in mortality. Vilobelimab could be considered as an additional therapy for patients in this setting and further research is needed on the role of vilobelimab and C5a in other acute respiratory distress syndrome-causing viral infections.

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Introduction

COVID-19 is characterised by severe lung inflammation and activation of coagulation, frequently necessitating mechanical ventilation while in the intensive care unit (ICU; 20% of those admitted to hospital).[1,2] Mortality and morbidity rate are high among mechanically ventilated patients with COVID-19, despite the established broad use of corticosteroids.[3] Poor disease outcomes have been associated with activation of the complement system, specifically the C5a–C5aR axis.[4,5] Experimental studies[5,6]

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See **Online** for appendix

Research in context

Evidence before this study

We searched PubMed, Embase, and Cochrane Reviews from Jan 1, 2020, to July 1, 2022, using the search terms "2019 novel coronavirus", "COVID-19", "SARS-COV-2", "C5 complement", "C5a complement", "complement inhibitor", and "complement system", with no language restrictions. Patients with severe COVID-19 show widespread complement activation in lungs and kidneys and SARS-CoV-2 has been reported to activate the mannose-binding lectin complement pathway. A 2020 study showed that the C5a–C5aR1 signalling axis and high concentrations of C5a and C5b-9 have been associated with unfavourable disease outcomes in patients with COVID-19 and C5a was reported as the key mediator in neutrophil-mediated viral lung damage, as shown in viral disease models. Anti-C5a antibody treatment (vilobelimab) was suggested to be beneficial in a monkey model of avian influenza (H7N9) virus-induced lung injury. A randomised phase 2 study showed that vilobelimab was safe in critically ill patients with COVID-19 and might improve patient outcomes, which supported the investigation of C5a inhibition with vilobelimab in our placebo-controlled, randomised, placebo-controlled, phase 3 trial using 28-day mortality as the primary endpoint.

Added value of this study

This study shows that vilobelimab administration results in a reduction in mortality at 28 days and 60 days in critically ill patients with severe COVID-19 who receive invasive mechanically ventilation. Vilobelimab treatment was added to standard of care, including corticosteroids, anticoagulants, and recommended immunomodulators.

Implications of all the available evidence

Vilobelimab might be considered as an additional therapy for patients in this setting and further research is needed on the role of C5a in patients with acute respiratory distress syndrome causing viral infections.

have shown that C5a is a potent anaphylatoxin, attracting neutrophils and monocytes to the site of infection that causes tissue damage, endothelialitis, and micro-thrombosis. Mice studies also showed that blockade of the C5a–C5aR1 axis limits the infiltration of myeloid cells in damaged organs and prevents excessive lung inflammation and endothelialitis.[5]

The phase 2 part[7] of this PANAMO trial has shown that the anti-C5a monoclonal antibody vilobelimab is safe in critically ill patients with COVID-19. We previously showed that vilobelimab efficaciously suppressed serum C5a concentrations in this patient population.[8] Secondary outcomes of the phase 2 part of PANAMO were in favour of vilobelimab, which supported the investigation of C5a inhibition in a phase 3 trial.[7] Here, we aim to determine whether vilobelimab in addition to standard of care is efficacious in invasively mechanically ventilated patients with COVID-19.

Methods

Study design

This randomised, double-blind, placebo-controlled, multicentre phase 3 trial was done at 46 hospitals in the Netherlands, Germany, France, Belgium, Russia, Brazil, Peru, Mexico, and South Africa. The trial was approved by the institutional review boards or ethics committees and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

The trial was overseen by an independent data and safety monitoring board, which met approximately after every 60 patients were enrolled during the study until the interim analysis after 180 patients enrolled. The study protocol (appendix pp 38–251) was approved by the institutional review board (Amsterdam UMC, Amsterdam, Netherlands; IRB 2020_067#B2020179).

Participants

Participants aged 18 years or older who were receiving invasive mechanical ventilation within 48 h before the first infusion of study medication, had a PaO_2/FiO_2 ratio of 60–200 mm Hg, and a confirmed SARS-CoV-2 infection in the past 14 days were eligible for this study. Full eligibility criteria are provided in the protocol (version 4.0; appendix pp 184–85). Exclusion criteria were invasive mechanical ventilation for more than 48 h at the first infusion of study medication on expected stop of invasive ventilation or extubation within the next 24 h, history of renal replacement therapy 14 days before random assignment, severe chronic obstructive pulmonary disease, not approved or investigational treatment in the past 7 days, cytokine adsorption therapy in the past 3 days, known hypersensitivity to vilobelimab, pregnancy, organ or bone marrow transplant in past 3 months, cardiopulmonary mechanical resuscitation in the past 14 days, anticancer therapy for haemato-oncological disease in the past 4 weeks, active malignant disease, severe congestive heart failure, chronic liver disease, a moribund state, or expected death within 24 h of random assignment. The rationale of using a PaO_2/FiO_2 ratio of less than 200 mm Hg for the inclusion criteria was based on findings from the initial phase 2 PANAMO study,[7] in which patients with severe COVID-19 showed reduced mortality with vilobelimab in an explorative analysis.

All patients or their legally authorised representatives provided written informed consent. In the Netherlands, Germany, and Russia, deferred consent procedures were allowed. Deferred consent involved randomisation at investigators discretion according to pre-set criteria agreed on during ethical review of the protocol, followed by the request for patient's (deferred patient consent) or

representative's (deferred proxy consent) informed consent during the study.[9]

Randomisation and masking

Patients were randomly assigned (1:1) by the investigator to receive standard of care and vilobelimab or placebo. We performed permuted block randomisation with a block size of 2 or 4 using an Interactive Response Technology system (ClinPhone RTSM; version 4.0), and stratification according to site. Stratification according to site was decided because of expected differences in local guidelines between trial sites and over time, and the potential local and temporary effects of the COVID-19 pandemic. The active treatment and placebo were identical in colour and appearance. Participants, caregivers, and assessors were masked to group assignment.

Procedures

While at the ICU and during hospital stay, patients received standard of care and vilobelimab at a dose of 800 mg intravenously for a maximum of six doses (days 1, 2, 4, 8, 15, and 22) or a matching placebo. Administration of the first infusion was to be completed within 24 h after randomisation. Standard of care in the participating sites consisted of intensive care therapy according to current guidelines of each country; evidence and best practice, including but not limited to lung protective ventilation, thrombosis prophylaxis, and renal replacement therapy when indicated; guidelines conforming COVID-19 medication included use of corticosteroid, anti-coagulants, and other approved or locally recommended medication (such as biologics or other anti-inflammatory drugs); and access to advanced therapies including extracorporeal membrane oxygenation.

Outcomes

The primary outcome was defined as all-cause mortality at 28 days in the full analysis set (defined as all randomly assigned regardless of whether a patient was treated or not, excluding one patient randomly assigned in error who was not treated and did not undergo any study-related procedures). Secondary endpoints, measured in the full analysis set, included all-cause mortality at 60 days, proportion of patients with an improvement in the WHO 8-point ordinal scale (appendix pp 274–78); days 15 and 28), proportion of patients who develop acute kidney failure (estimated glomerular filtration rate [eGFR] of <15 mL/min per 1·73 m², assessed by the chronic kidney disease epidemiology collaboration equation)[10] during ICU stay and at day 28, and the proportion of patients free from any renal replacement therapy 28 days after randomisation. Treatment-emergent adverse events (TEAEs; defined as any event that occurred or worsened at or after the first infusion) were reported by the investigators, recorded from participant's enrolment to the end of the study, and coded by the Medical Dictionary for Regulatory Activities (version 24.1). Immediately reportable serious adverse events (SAE; including SAEs before first treatment and TEAEs) included those that resulted in death and life-threatening events (appendix p 207). Adverse events of special interest were infections other than SARS-CoV-2, infusion reactions, meningitis, and meningococcal sepsis.

In exploratory analysis patients were also stratified by SARS-CoV-2 variant status (either classed as infected by other variants [not specified] or by the delta variant) on the basis of whether the COVID-19 diagnosis was before or after the date when delta became the dominant variant of SARS-CoV-2 in each respective country (ie, made up >80% of sequenced cases; appendix pp 337–38).

Statistical analysis

This study consisted of two stages with an unblinded interim analysis for futility by the independent data monitoring board after the first stage (the first 180 randomly assigned patients). Based on results from the interim analysis, up to 180 additional patients were randomly assigned using the same allocation ratio for the second stage. Additional patients were to be randomised for patients randomly assigned in error who did not receive vilobelimab or matching placebo and those who withdrew consent within 48 h after randomisation. The power calculation was based on 5% two-sided α and an assumed mortality on day 28 of 30% in the placebo group and 15% in the vilobelimab group. The plan to enrol 180 patients (90 per group) in stage one and up to 180 in stage two would result in 90% overall power.

The primary endpoint was initially planned to be analysed as a censored time-to-event variable using Cox regression, without site stratification. During the second half (protocol version 4.0; May 12, 2021) of the study, the primary endpoint was changed to Cox regression analysis stratified by site after a recommendation from the US Food and Drug Administration, which was included in the statistical analysis plan (appendix pp 334–35). The primary analysis was performed in the full analysis set (defined as all randomly assigned patients, except one assigned in error). Explanatory variables were age and treatment group for the primary endpoint, prespecified unstratified Cox regression, and the key secondary endpoint of all-cause mortality at 60 days.

Prespecified sensitivity analyses for the primary endpoint were based on all randomly assigned patients, including those assigned in error and those who did not receive vilobelimab or matching placebo, and were done using logistic regression with the binary outcome of all-cause mortality at day 28 and missing values imputed using multiple imputation (based on age, treatment group, and the last documented WHO COVID-19 ordinal scale status before withdrawal).

Additional prespecified sensitivity analyses using logistic regression considered all patients who withdrew before day 28 as either all alive or all dead.

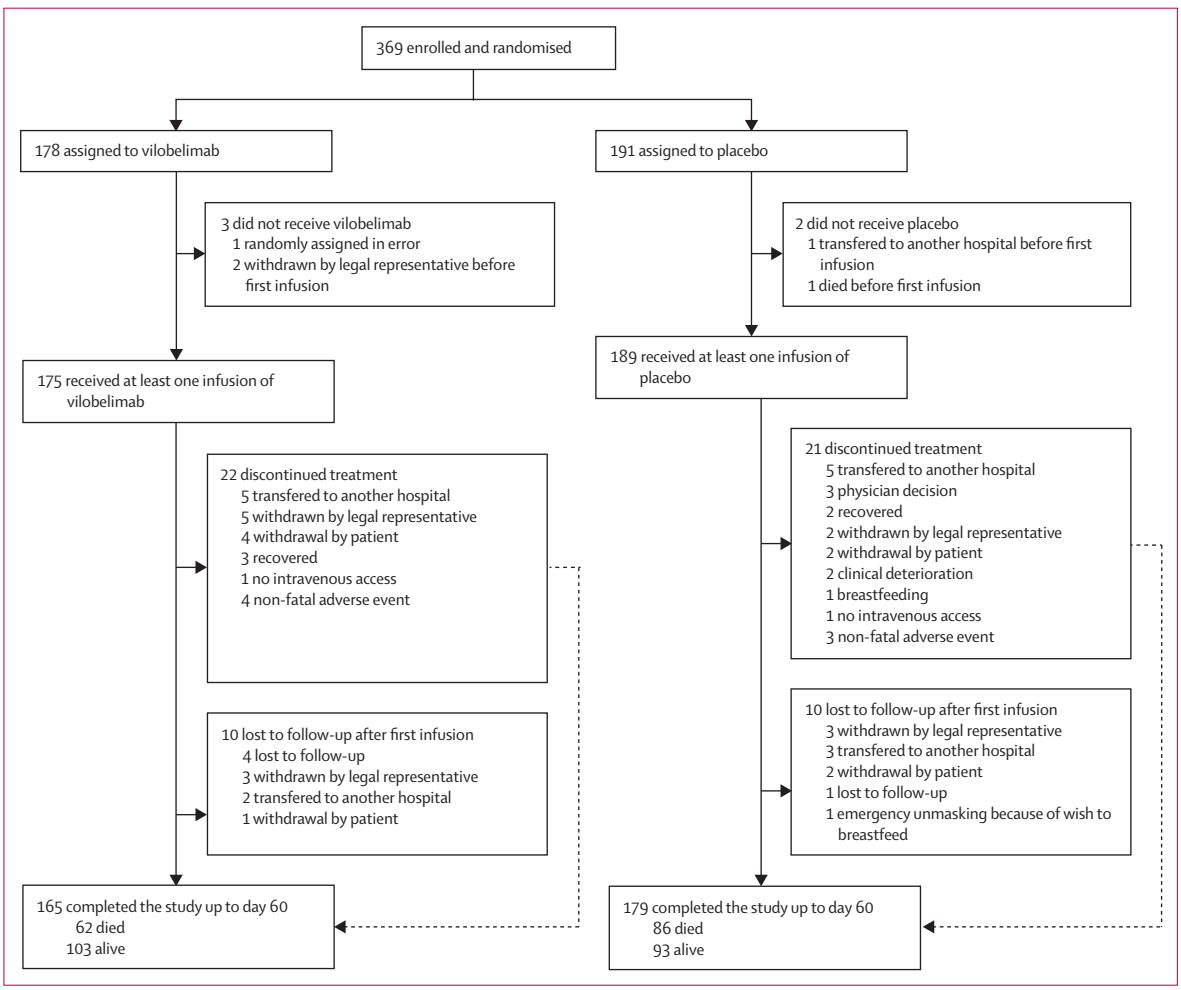

Figure 1: **Trial profile**
12 additional patients who discontinued due to transfer to another hospital but completed survival follow-up until day 60 are not shown separately and are included in the number of patients with complete survival follow-up. Patients who discontinued before or after day 28 are not shown separately.

Secondary efficacy endpoints were analysed using statistical hypothesis tests only if the primary endpoint was statistically significant. The secondary endpoint of ordinal scale improvement was analysed using logistic regression and adjusted for age (but not for site). The secondary endpoints concerning acute kidney failure and renal replacement therapy were analysed using Cox regression and accounted for death as a competing risk and these analyses were also adjusted for age (but not for site). The secondary endpoint of all-cause mortality at day 60 was assessed by follow-up visits. Safety analyses were performed in all patients who received at least one infusion of either vilobelimab or placebo. An external data safety monitoring committee oversaw the trial and assessed safety within prespecified interim analyses.

Prespecified subgroup analyses for the primary endpoint were conducted for region, comorbidities, standard of care, ordinal scale at baseline, date of randomisation (post-hoc analysis), ARDS severity, and eGFR categories. Moderate and severe ARDS was defined using BERLIN criteria.[11] All analyses were performed with SAS (version 9.4) and figures were generated using R (version 4.0.0). This study is registered with ClinicalTrials.gov, NCT04333420.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

From Oct 1, 2020, to Oct 4, 2021, 369 patients were enrolled and 178 randomly assigned to receive vilobelimab with 191 randomly assigned to placebo. One patient in the vilobelimab group was excluded from the primary analysis due to random assignment in error. 368 patients were included in the full analysis set

	Vilobelimab (n=177)	Placebo (n=191)
Country		
Belgium	8 (5%)	7 (4%)
Brazil	34 (19%)	40 (21%)
Germany	10 (6%)	11 (6%)
France	17 (10%)	18 (9%)
Mexico	18 (10%)	19 (10%)
Netherlands	68 (38%)	70 (37%)
Peru	6 (3%)	9 (5%)
Russia	11 (6%)	12 (6%)
South Africa	5 (3%)	5 (3%)
Race		
White	115 (65%)	119 (62%)
Asian	4 (2%)	5 (3%)
Black or African American	5 (3%)	8 (4%)
American Indian or Alaskan Native	22 (12%)	24 (13%)
Native Hawaiian or other Pacific Islander	0	0
Multiple	1 (1%)	0
Other	16 (9%)	19 (10%)
Not reported	14 (8%)	16 (8%)
Ethnicity		
Hispanic or Latino	60 (34%)	68 (36%)
Not Hispanic or Latino	70 (40%)	73 (38%)
Not reported	28 (16%)	35 (18%)
Unknown	11 (6%)	11 (6%)
Missing	8 (5%)	4 (2%)
Sex		
Male	125 (71%)	127 (66%)
Female	52 (29%)	64 (34%)
Age, years		
Mean	56·7 (13·2)	55·9 (14·5)
Min–max	23–81	22–81
Median	58·0 (47·0–67·0)	57·0 (46·0–68·0)
Comorbidities		
Hypertension	80 (45%)	90 (47%)
Diabetes	45 (25%)	64 (34%)
Coronary heart disease	12 (7%)	14 (7%)
Chronic obstructive lung disease	5 (3%)	2 (1%)
Carcinoma	1 (1%)	3 (2%)
Chronic kidney disease	8 (5%)	15 (8%)
Obesity	69 (39%)	81 (42%)
BMI, kg/m²		
Mean	31·9 (6·1)	31·9 (7·1)
Min–max	22–54	18–55
Median	31·1 (27·8–34·5)	30·8 (26·9–36·5)
Estimated glomerular filtration rate		
<60 mL/min per 1·73m²	47 (27%)	61 (32%)
≥60 mL/min per 1·73m²	129 (73%)	130 (68%)
Missing	1 (1%)	0

(Table 1 continues in next column)

(Continued from previous column)

	Vilobelimab (n=177)	Placebo (n=191)
Acute respiratory distress syndrome		
Mild (PaO_2/FiO_2 200–300 mm Hg)*	1 (1%)	1 (1%)
Moderate (PaO_2/FiO_2 100–200 mm Hg)	133 (75%)	135 (71%)
Severe (PaO_2/FiO_2 ≤100 mm Hg)	43 (24%)	55 (29%)
Time from first COVID-19 symptoms to randomisation, days†		
Mean	11·0 (5·1)	10·8 (5·5)
Min–max	0–34	0–29
Median	11·0 (8·0–14·0)	11·0 (8·0–14·0)
Time from COVID-19 diagnosis to randomisation, days		
Mean	7·2 (4·8)	7·1 (4·8)
Min–max	0–24	0–30
Median	7·0 (3·0–11·0)	7·0 (3·0–10·0)
Time from hospital admission to randomisation, days		
Mean	3·9 (2·9)	4·2 (4·1)
Min–max	0–19	0–27
Median	3·0 (2·0–5·0)	3·0 (2·0–5·0)
Time from intensive care unit admission to randomisation, days‡		
Mean	2·1 (2·1)	2·6 (3·5)
Min–max	–2 to 11	0 to 22
Median	2·0 (1·0–2·0)	1·0 (1·0–3·0)
8-point WHO COVID-19 ordinal scale		
6 (intubation and mechanical ventilation)	72 (41%)	59 (31%)
7 (ventilation plus organ support)§	105 (60%)	132 (69%)

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 participants in the vilobelimab group and 182 in the placebo group. ‡Data available for 163 participants in the vilobelimab group and 171 in the placebo group. §Organ support included pressors, renal replacement therapy, and extracorporeal membrane oxygenation).

Table 1: **Baseline characteristics (full analysis set)**

(177 in the vilobelimab group and 191 in the placebo group).

Three discontinuations (one randomly assigned by error and two withdrawals by legal representative) occurred in the vilobelimab group and one discontinuation and one death in the placebo group before the first infusion (figure 1; appendix p 8). Ten discontinuations (without follow-up data) occurred after the first infusion per group. Of those ten, one patient per group discontinued after day 28. There were 12 additional patients who discontinued due to transfer to another hospital (but still completed survival follow-up until day 60). At least one dose of study treatment was given to 364 (99%) patients. Loss to follow-up before day 28 occurred in nine (5%) patients in the vilobelimab group and nine (5%) in the placebo group (one additional patient

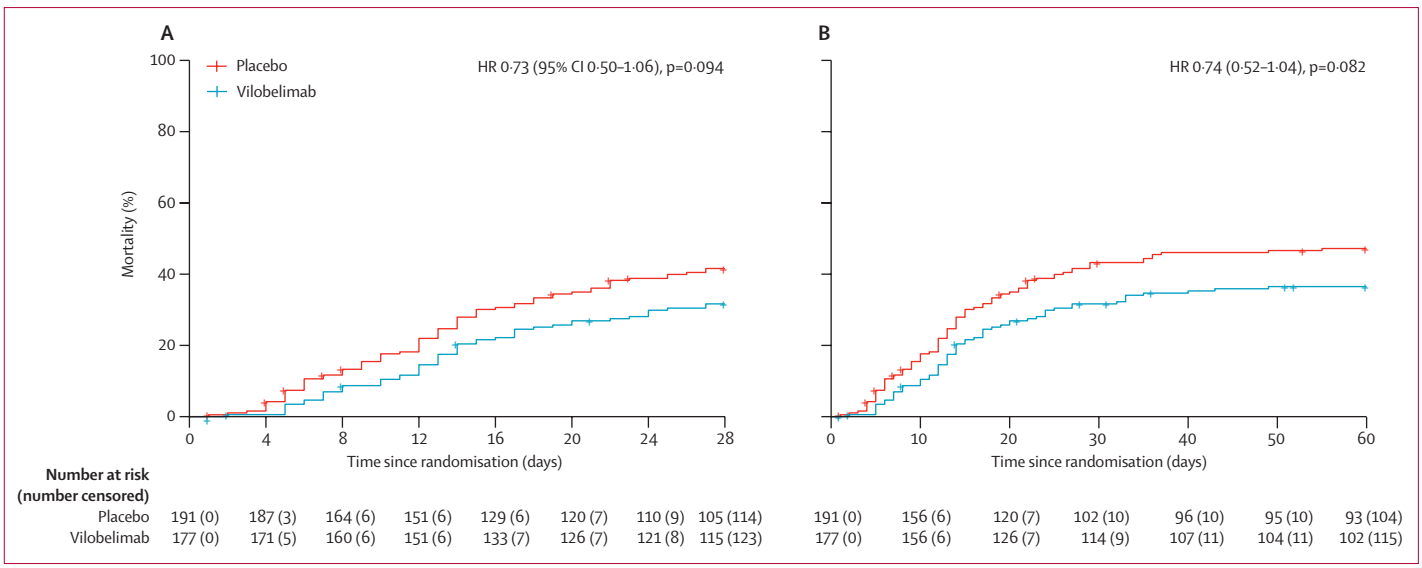

Figure 2: **Kaplan-Meier curves for mortality (full analysis set)**
(A) All-cause mortality at day 28 (primary endpoint). (B) All-cause mortality at day 60 (secondary endpoint).

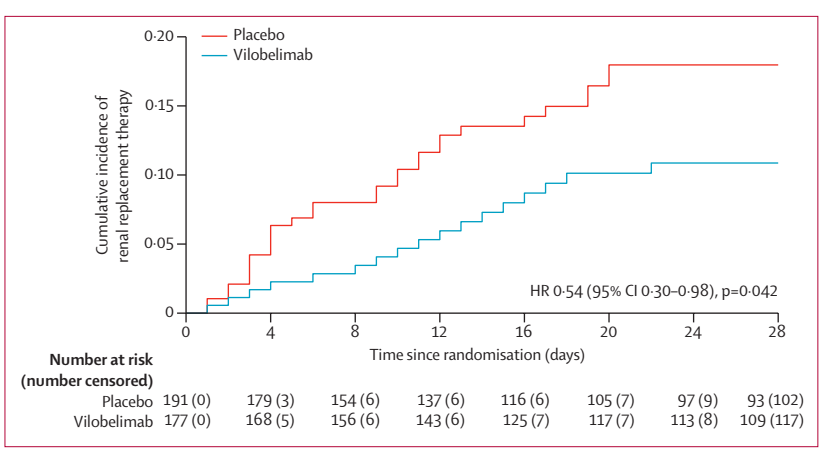

Figure 3: **Cumulative incidence for first renal replacement therapy (full analysis set)**

discontinued the study but had documented day 28 survival data; appendix p 9). These patients were lost to follow-up after a median of 4·5 days (range 1–23; IQR 2·0–12·5) because of consent withdrawal (ten patients), transfer to another hospital (four patients), lost to follow-up after hospital discharge (two patients), unmasking (one patient), and random assignment by mistake (one patient; appendix pp 8–10). Five additional patients discontinued the trial between days 28 and 60. None of these patients discontinued participation because of safety reasons (withdrawal due to a non-fatal adverse event occurred in four [2%] of 175 patients in the vilobelimab group and three [2%] of 189 in the placebo group; figure 1). The SARS-CoV-2 variants of concern and estimated number of patients infected by the delta variant are shown in the appendix (p 13).

Baseline characteristics were similar in both groups, although a slightly higher number of patients in the placebo group had a score of 7 on the 8-point WHO COVID-19 ordinal scale (table 1). The median age of patients was 58·0 years (IQR 47·0–68·0) and 252 (68%) of 368 were men. The mean oxygenation index PaO_2/FiO_2 was 131·9 (SD 39·2) in the vilobelimab group and 130·6 (44·8) in the placebo group. Before and after randomisation, 62 (17%) patients received anti-interleukin-6 treatment and 56 (82%) of those were randomly assigned in western Europe (Belgium, Germany, France, and the Netherlands). Concomitant use of glucocorticosteroids occurred in 356 (97%) of 368 patients, antithrombotic agents in 362 (98%) of 368, and anti-interleukin-6 in ten (3%) of 368 (data not shown). Previous or concomitant use of remdesivir or immunomodulators according to region and ordinal scale is shown in the appendix (p 17).

All-cause mortality at 28 days was observed in 54 (31%) of 177 patients in the vilobelimab group and 77 (40%) of 191 in the placebo group. Kaplan-Meier estimates showed a mortality rate of 32% (95% CI 25–39) in the vilobelimab group and 42% (35–49) in the placebo group (Cox model stratified by site and adjusted for age, hazard ratio [HR] 0·73, 95% CI 0·50–1·06; p=0·094; figure 2A). In the predefined analysis without site-stratification, vilobelimab significantly reduced mortality at 28 days (HR 0·67, 95% CI 0·48–0·96; p=0·027; appendix p 14). Prespecified logistic regression analyses (including all 369 randomly assigned patients) handling missing 28-day outcomes for the 18 patients lost to follow-up (nine per group) using multiple imputation (age-adjusted odds ratio [OR] 0·62, 95% CI 0·40–0·95; p=0·029), the last observation carried forward (all alive OR 0·62, 0·40–0·97; p=0·034), or all-death imputation (OR 0·65, 0·42–0·99; p=0·044), also showed that vilobelimab significantly reduced all-cause mortality at 28 days (appendix p 11).

Post-hoc analyses of the primary outcome using Cox regression with stratification by country (age-adjusted HR 0·61, 95% CI 0·43 to 0·87; p=0·0067) and analyses using a frailty model (assigning random effects per site; age-adjusted HR 0·65, 0·45 to 0·93; p=0·018) also showed that vilobelimab significantly reduced all-cause mortality at 28 days (appendix p 14). Similarly, post-hoc analysis of the age-adjusted Cox regression with stratification by score on the WHO COVID-19 ordinal scale at baseline resulted in a similar benefit with vilobelimab (HR 0·67, 0·47 to 0·95; p=0·024; appendix p14). The prespecified sensitivity analysis with logistic regression for all-cause mortality at 28 days resulted in an age-adjusted risk difference of –11% (95% CI –21 to –1; p=0·029; appendix p 14), which corresponds to a number needed to treat of nine patients (95% CI 5 to 82) to prevent one additional death.

All-cause mortality at 60 days was observed in 62 (35%) of 177 patients in the vilobelimab group and in 87 (46%) of 191 in the placebo group, leading to mortality rate estimates of 37% (95% CI 30–44) in the vilobelimab group and 47% (40–55) in the placebo group; Cox model stratified by site and adjusted for age HR 0·74, 0·52–1·04; p=0·082; figure 2B). As per the original version of the protocol, predefined Cox regression analysis without site stratification showed a significant reduction in all-cause mortality at 60 days (HR 0·67, 95% CI 0·48–0·93; p=0·016; appendix p 15). Prespecified and post-hoc analyses of this secondary outcome in either 368 or 369 patients resulted in p values lower than 0·05 (appendix p 15). 90 (51%) of 177 patients in the vilobelimab group and 85 (45%) of 191 in the placebo group had an improvement of at least 1 point on the WHO COVID-19 ordinal scale on day 28 (age-adjusted OR 1·40, 95% CI 0·92–2·14; p=0·12). At day 28, the proportion of patients with kidney failure between treatment groups were not statistically significant (eight [5%] of 177 in the vilobelimab group *vs* 12 [6%] of 191 in the placebo), but vilobelimab protected against renal replacement therapy (age-adjusted HR 0·54, 95% CI 0·30–0·98; p=0·042; figure 3).

In the safety population, treatment-emergent adverse events (TEAEs) up to day 60 were reported in 159 (91%) of 175 patients in the vilobelimab group versus 172 (91%) of 189 in the placebo group, whereas serious TEAEs were reported in 103 (59%) versus 120 (63%; table 2). The most common TEAEs were acute kidney injury (35 [20%] of 175 in the vilobelimab group *vs* 40 [21%] of 189 in the placebo), pneumonia (38 [22%] *vs* 26 [14%]), and septic shock (24 [14%] *vs* 31 [16%]). TEAEs and serious TEAEs were similar between treatment groups in terms of frequency, severity, and type of events. Infusion reactions occurred in three patients (presented as a rash) in the vilobelimab group and one patient (with cardio-respiratory arrest) in the placebo group. Infections were reported in 110 (63%) of 175 patients in the vilobelimab group versus 112 (59%) of 189 in the placebo group, with similar proportions of bacterial infections between treatment groups (68 [39%] *vs* 75 [40%]). No cases of bacterial meningitis were reported. TEAEs that led to drug withdrawal were reported in five (3%) patients in the vilobelimab group versus three (2%) in the placebo group.

In the prespecified subgroup analyses, vilobelimab reduced all-cause mortality at 28 days in a subgroup of patients with a WHO COVID-19 ordinal scale score of 7 (HR 0·62, 95% CI 0·40–0·95; p=0·028), PaO_2/FiO_2 of

	Vilobelimab (n=175)	Placebo (n=189)
TEAE	159 (91%)	172 (91%)
Related TEAE	20 (11%)	16 (8%)
Serious TEAE	103 (59%)	120 (63%)
Serious related TEAE	8 (5%)	9 (5%)
Fatal TEAE*	62 (35%)	85 (45%)

Adverse events were recorded up to 60 days after randomisation. TEAE=treatment-emergent adverse event. *149 deaths were observed in all randomly assigned patients but two patients in the placebo group occurred before treatment start and were not considered as fatal TEAEs. One patient died before receiving the first vilobelimab infusion and one died on day 4 in the placebo group, but the fatal adverse event started before the first infusion.

Table 2: **Treatment-emergent Adverse events in patients who received at least one infusion**

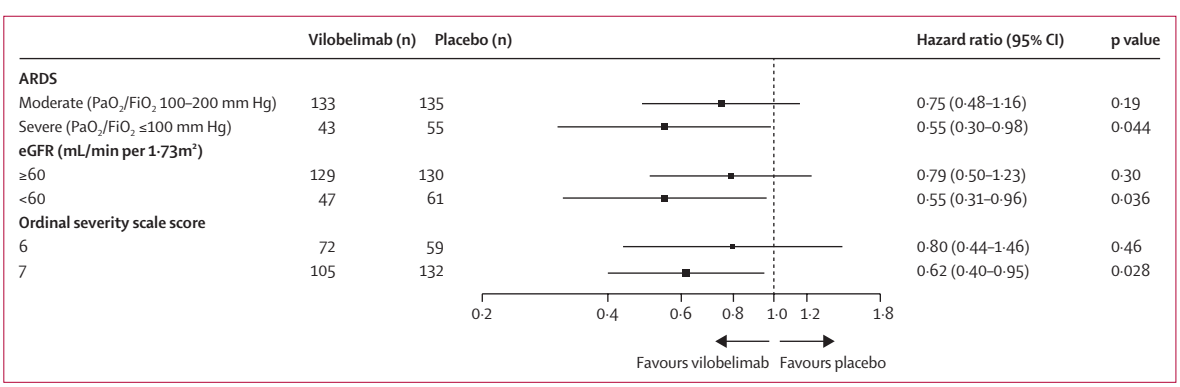

Figure 4: **Prespecified subgroup analysis for all-cause mortality at 28 days in patients with higher disease severity**
Moderate and severe ARDS was defined using BERLIN criteria. ARDS=acute respiratory distress syndrome. eGFR=estimated glomerular filtration rate.

100 mm Hg or less (HR 0·55, 0·30–0·98; p=0·044), and eGFR of less than 60 mL/min per 1·73m² (HR 0·55, 0·31–0·96; p=0·036; figure 4). In regional analysis, all-cause mortality at 28 days differed substantially between treatment and regions ($p_{interaction}$<0·0001) and the effect of vilobelimab was most apparent in western Europe (Belgium, Germany, France, and the Netherlands; HR 0·51 [0·30–0·87]; p=0·014; appendix p 2). However, a model predicting all-cause mortality at 28 days showed no interaction between treatment and region (appendix p 12). Subgroup analysis according to the standard of care, comorbidity, and time of randomisation are shown in the appendix (pp 3–7).

Discussion

This study shows that vilobelimab improves survival of invasive mechanically ventilated patients with COVID-19 and leads to a significant decrease in mortality with an absolute risk reduction of 11% using age-adjusted logistic regression, resulting in a number needed to treat of nine patients to prevent one death. Time-to-event Cox regression analysis stratified for site (the primary endpoint as specified in the protocol) was not statistically significant between the vilobelimab and placebo groups; however, analysis without site stratification and pre-specified analyses based on logistic regression with imputation of missing outcomes showed a consistent and significant decrease in all-cause mortality at 28 days, which persisted until 60 days (end of follow-up). The safety and tolerability analysis did not result in any signals of concern.

The effect of vilobelimab was most apparent in western Europe. However, a beneficial effect in other countries (South America and South Africa and Russia) cannot be ruled out, because the number of patients in these subgroups were smaller. Overall, data from this study warrant recommending vilobelimab treatment for patients with COVID-19 who require invasive mechanical ventilation.

Previous and concomitant COVID-19 medication was allowed in this study, including treatment with the immunomodulators tocilizumab and baricitinib. Glucocorticosteroids and antithrombotic agents were given to almost all patients during the study period. A considerable proportion (56 [27%] of 209) of patients in western Europe received anti-interleukin-6 treatment before and after being randomly allocated to treatment. After publication of randomised controlled trials on anti-interleukin-6 treatment in patients with COVID-19,[12,13] the European Medicines Agency started a review on tocilizumab in August, 2021, and approved this anti-interleukin-6 for patients with COVID-19 in December, 2021.[14] The randomisation part of our study was closed in November, 2021. The use of concomitant medication reflects current treatment guidelines for patients with severe COVID-19. One strength of our study is that patients could be treated according to current guidelines (including local guidelines), and evidence and best practice in their institution and country.

Initial studies[15] that evaluated the use of tocilizumab for patients with COVID-19 produced conflicting results. Subsequently, in the setting of background corticosteroid therapy, the two largest REMAP-CAP and RECOVERY trials[12,16] reported a mortality benefit with tocilizumab compared with standard of care in some patients, including those exhibiting rapid respiratory decompensation associated with an inflammatory response. In an exploratory substudy[17] of the COV-BARRIER trial in critically ill adults admitted to hospital with COVID-19 and on invasive mechanical ventilation or extracorporeal membrane oxygenation, baricitinib significantly reduced all-cause mortality at 28 days compared with placebo (20 died [39%] of 51 patients *vs* 29 died [58%] of 50; HR 0·54, 95% CI 0·31–0·96; p=0·030). 87 (86%) of 101 patients received corticosteroids as part of standard of care in the COV-BARRIER trial substudy;[17] however, the exploratory analysis of mortality was done in a small sample size. To our knowledge, the PANAMO study is the largest multicentre, randomised, placebo-controlled, phase 3 trial in critically ill, invasively mechanically ventilated patients with COVID-19, measuring mortality as the primary outcome.

The dosing of vilobelimab in our study was based on pharmacokinetic and pharmacodynamic data from the phase 2 part of PANAMO,[7,8] which showed that vilobelimab can reduce C5a concentrations in critically ill patients with COVID-19, with no observed safety issues. Complement inhibition upstream of C5a, such as inhibition of C5 or C3, is associated with increased infection risk because of blocking the C5b-dependent membrane attack complex (also known as C5b-9).[18] Vilobelimab selectively blocks C5a leaving the membrane attack complex function intact.[19] This selective mode of action explains the favourable safety profile of vilobelimab, particularly in terms of infection risk, compared with other upstream complement inhibitors.[20] Additionally, upstream complement inhibitors might not be able to substantially block and control C5a because enzymes in the tissue and during coagulation can activate C5 directly (cleave off C5a), outside of the common complement pathways and thus, bypass the mechanism of action of upstream complement inhibitors.[21] The effect of vilobelimab in critically ill patients with COVID-19 suggests that disease symptoms are fostered by an overactive complement system and more specifically by C5a. Indeed, observational studies have shown that the hyperinflammation, endothelial permeability, and coagulopathy observed in patients with severe COVID-19 are associated with complement activation.[1,5,22] Our findings further show that C5a plays a key role in patients with severe COVID-19 and the PANAMO study is a result of more than 20 years of research on the role of C5a in neutrophil-mediated viral and bacterial septic organ dysfunction.

Although this study is one of the largest randomised controlled trials in invasively mechanically ventilated patients admitted to the ICU with viral pneumonia, there are also some limitations. First, because we enrolled patients from Oct 1, 2020, to Oct 4, 2021, a considerable proportion of patients were probably infected with the Delta variant of SARS-CoV-2, whereas over time, other variants such as Omicron became more dominant. However, in this context, the mechanism of action of vilobelimab is directed against the immune response causing viral sepsis with organ failure, which has been described for all SARS-CoV-2 variants identified so far. Second, most of the patients included in our study were not yet vaccinated against SARS-CoV-2.[23] Although the Omicron variant is milder than the previous SARS-CoV-2 variants, patients are still at risk of developing immune-response driven organ failure caused by SARS-CoV-2. Furthermore, COVID-19 vaccines effectively protect against severe disease,[24] however this protection is not at 100% and case fatality rates in vaccinated patients with COVID-19 who require invasive mechanical ventilation remain high.[25] Many people around the world have no access to vaccines or are not willing to get vaccinated and remain at higher risk of requiring invasive mechanical ventilation as a result of COVID-19 disease. Third, the time-to-event Cox regression analysis stratified for site did not reach statistical significance, whereas all other analyses showed a significant reduction in all-cause mortality at 28 and 60 days with vilobelimab compared with placebo.

Stratification according to site was decided because of expected differences in local guidelines between trial sites and over time, and the potential local and temporary effects of the COVID-19 pandemic. This study was performed at 46 hospitals and the median number of patients enrolled per site was four and 11 sites enrolled only one patient. Based on the mathematical algorithm, adjusting for site stratification in the Cox regression analysis leads to no factual contribution to the analysis outcome of patients from all sites in whom no events (ie, deaths) occurred or sites where only one patient was enrolled regardless of the event. In the PANAMO study, this limitation was the case for 61 (17%) of 368 patients in 23 sites on day 28 (also measuring all-cause mortality), who made no factual contribution to the analysis outcome. For a clinical trial analysis, adjusting for many small sites (including a low number of patients) is an analytical problem for which there is no best solution.[26] Both ignoring site level as well as directly including site into statistical models can result in unreliable treatment effects and p values. Although analysis of the primary endpoint stratified by site was not significant, based on various reasonable ways to analyse the primary endpoint and the fact that all prespecified and post-hoc analyses of the primary endpoint which considered the full analysis set showed p values lower than 0·05, we think the treatment benefit is robust and provides evidence that C5a inhibition with vilobelimab can reduce all-cause mortality at 28 and 60 days (appendix pp 14–15). The primary outcome and population were appropriate, and there were no major limitations in trial conduct.[27]

Our study confirms previous exploratory findings from the phase 2 PANAMO trial, which showed an adjusted HR for all-cause mortality at 28 days of 0·65 (95% CI 0·10–4·14). In this phase 3 PANAMO trial, we only enrolled invasive mechanically ventilated patients with COVID-19 who had more severe disease than those included in the phase 2 study.[7] We showed a consistent reduction of all-cause mortality at 28 days in patients with COVID-19 who receive invasive mechanical ventilation in addition to standard of care. Vilobelimab could be considered as an additional therapy for patients in this setting and further research is needed on the role of C5a in other acute respiratory distress syndrome-causing viral infections.

Contributors

APJV, MCB, DvdB, KP, MW, PvP, RZ, SR, RG, and NCR designed the study; collected, managed, and interpreted the data; and wrote the manuscript. APJV and DvdB wrote the first draft of the manuscript with input from authors employed by InflaRx. Data analysis was performed by Metronomia Clinical Research. All authors reviewed and edited the manuscript. APJV, EHTL, and SdB collected the data and critically reviewed the manuscript. SR was a statistical consultant and critically reviewed the statistical analysis of study data. APJV, MCB, DvdB, RG, NCR, and KP conceptualised and designed the study, interpreted the study data, and critically reviewed the manuscript. APJV, SR, MCB, DvdB, RG, KP, and NCR have accessed and verified all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. SR (the trial statistician) and all authors (InflaRx representatives) had full access to the data. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (appendix pp 38–251). All authors had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

NCR and RG are founders, active officers, and executive directors of the board, and hold shares and stock options in InflaRx. KP is the chief clinical development officer and holds stock options in InflaRx. RZ is the program director and holds stock options in InflaRx. SR is an employee of Metronomia Clinical Research and a contracted statistical service provider for InflaRx. MW receives grants from the German Research Foundation (SFB-TR84 C6, SFB-TR84 C9, and SFB 1449 B02) and German Ministry of Education and Research (e:Med CAPSyS [01ZX1304B], SYMPATH [01ZX1906A], NUM-NAPKON [01KX2021], and PROVID [01KI20160A]). APJV received consulting fees from InflaRx for advisory work, paid to the institution. GM received honoraria for lecturing and consulting from B Braun, 4TEEN4, Adrenomed, and Philips. All other authors declare no competing interests.

Data sharing

As part of the site agreement signed before trial participation, investigators agreed to keep all aspects of the trial (including the resulting data) confidential. Data for the completed PANAMO trial will be shared according to applicable regulatory requirements.

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