



Vilobelimab

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Vilobelimab is an anti-C5a monoclonal antibody. High concentrations of C5a have been reported in patients with severe COVID-19.¹ C5a activates innate immune system responses, including inflammation and the release of histamines, and can increase damage to local tissues.² A study in mice demonstrated that an anti-C5a monoclonal antibody reduced immune system activation and inhibited lung injury.³ Vilobelimab targets C5a, which is a product of complement activation, and preserves membrane attack complex function.⁴ Vilobelimab is not approved by the Food and Drug Administration (FDA) for any indication.

On April 4, 2023, the FDA issued an Emergency Use Authorization (EUA) for the use of vilobelimab for the treatment of COVID-19 in hospitalized adults when it is administered within 48 hours of mechanical ventilation or extracorporeal membrane oxygenation.⁵

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vilobelimab for the treatment of COVID-19.

Rationale

Results from the PANAMO study were used to support the FDA EUA.⁵ However, the prespecified analysis that stratified by study site showed that 28-day mortality among participants who received vilobelimab was not significantly different from 28-day mortality among those who received placebo. The study included a separate analysis that did not stratify by study site. That analysis demonstrated that all-cause mortality through Day 28 was significantly lower in the vilobelimab arm than in the placebo arm. However, the Panel determined that the overall results from the PANAMO study were insufficient to recommend either for or against the use of vilobelimab for the treatment of COVID-19.

The study population did not include any patients infected with an Omicron variant. Concomitant use of corticosteroids (97%) and antithrombotic agents (98%) was high in this study population. However, prior or concomitant use of tocilizumab (17% in the vilobelimab arm, 16% in the placebo arm) and baricitinib (3% in each arm) was low.

Clinical Data

Results from the small (n = 30) Phase 2 portion of the Phase 2/3 PANAMO trial support the safety of vilobelimab for the treatment of COVID-19. However, the Phase 2 portion of the trial was too underpowered to draw any additional conclusions about secondary outcomes, including physiologic improvement at 5 days.⁶

The Phase 3 portion of the trial was a double-blind, placebo-controlled, randomized trial performed at 46 hospitals in Western Europe (i.e., Netherlands, France, Germany, Belgium), Brazil, Mexico, Russia, Peru, and South Africa from October 1, 2020, to October 4, 2021.⁷ The trial evaluated vilobelimab and standard of care compared with placebo and standard of care in participants aged ≥ 18 years who had confirmed SARS-CoV-2 infection, were receiving mechanical ventilation (within 48 hours of intubation), and had a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of 60 to 200 mm Hg at study entry. Vilobelimab 800 mg was administered intravenously on Days 1, 2, 4, 8, 15, and 22, if the patient remained hospitalized, for a maximum of 6 doses.

The primary outcome was all-cause mortality at 28 days.⁷ Secondary outcomes included all-cause mortality at 60 days, the proportion of participants who improved on a World Health Organization (WHO) 8-point ordinal scale, the proportion of patients who developed acute kidney failure by Day 28, and the proportion of patients free from renal replacement therapy at Day 28.

Results

- The trial enrolled 369 participants; 368 participants were included in the full analysis (177 in the vilobelimab arm, 191 in the placebo arm).
- For the prespecified analysis that stratified by study site, 28-day mortality was not significantly different in the vilobelimab and placebo arms (HR 0.73; 95% CI, 0.50–1.06; $P = 0.094$).
- In the analysis that did not stratify by study site, 28-day mortality was lower in the vilobelimab arm, and the difference between arms was statistically significant (HR 0.67; 95% CI, 0.48–0.96; $P = 0.027$).
- Prespecified subgroup analyses identified a significant reduction in 28-day mortality in the vilobelimab arm for subgroups of patients with severe acute respiratory distress syndrome (HR 0.55; 95% CI, 0.30–0.98; $P = 0.044$), patients with an estimated glomerular filtration rate of <60 mL/min (HR 0.55; 95% CI, 0.31–0.96; $P = 0.036$), and patients receiving mechanical ventilation and additional organ support (category 7 on the WHO 8-point ordinal scale; HR 0.62; 95% CI, 0.40–0.95; $P = 0.028$).
- In a prespecified analysis for the Western Europe subgroup (i.e., Netherlands, Belgium, Germany, France), the vilobelimab arm had significantly lower 28-day mortality than the placebo arm (HR 0.51; 95% CI, 0.30–0.87; $P = 0.014$).
- For the secondary outcomes:
 - The analysis that stratified by study site showed no significant difference between arms for all-cause mortality at 60 days (HR 0.74; 95% CI, 0.52–1.04; $P = 0.082$).
 - The vilobelimab arm had significantly fewer patients who required renal replacement therapy at Day 28 than the placebo arm (age-adjusted HR 0.54; 95% CI, 0.30–0.98; $P = 0.042$).

Limitations

- The results for the study's site-stratified, prespecified analysis were not significant.
- The analysis for 28-day mortality that stratified by study site excluded the 61 participants (16.6%) from sites that had no deaths or had only 1 treatment group.
- Very few participants received a second immunomodulator (tocilizumab or baricitinib).
- All patients in the trial were infected with Alpha or Delta variants; no patients were infected with an Omicron variant.

Monitoring, Adverse Effects, and Drug-Drug Interactions

Reports of adverse effects of vilobelimab are limited to a Phase 3 trial that included critically ill adult patients with COVID-19 who received 800 mg of intravenous vilobelimab for up to 6 doses. Common adverse reactions (i.e., with an incidence $\geq 3\%$ and observed at least 1% more frequently in the vilobelimab arm than in the placebo arm through Day 60) were pneumonia, sepsis, delirium, pulmonary embolism, hypertension, pneumothorax, deep vein thrombosis, herpes simplex, enterococcal infection, bronchopulmonary aspergillosis, increased hepatic enzymes, urinary tract infection, hypoxemia, thrombocytopenia, pneumomediastinum, respiratory tract infection, supraventricular tachycardia, constipation, and rash. Vilobelimab is not expected to be associated with any pharmacokinetic

drug-drug interactions.

Considerations in Pregnancy

There are no available data on the use of vilobelimab in pregnancy, as pregnant individuals were excluded from the PANAMO trial.

Considerations in Children

There are no available data on the use of vilobelimab in children. Vilobelimab is not authorized for emergency use in pediatric patients for the treatment of COVID-19.

References

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