Vilobelimab in Combination With Tocilizumab May Synergistically Improve Mortality in Critically Ill Covid-19 Patients: A Post-hoc Analysis of the Phase III PANAMO Study

Christian Sandrock MD[1], Alexander P.J. Vlaar MD[2], Endry H.T. Lim MD[2], Bruce P. Burnett PhD[3], Camilla Chong MD[4], Carina Zink, MSc[5], Robert Zerbib, MSc[4], Raymond M. Panas PhD[3], Renfeng Guo MD[3], Niels Riedemann MD[6], Diederik van de Beek MD[2]

Affiliations: 1. University of California Davis Health, Sacramento, CA, USA; 2. Amsterdam UMC, Amsterdam, the Netherlands; 3. InflaRx Pharmaceuticals, Inc, Ann Arbor, MI, USA; 4. InflaRx GmbH, Munich, Germany; 5. Metronomia Clinical Research GmbH, Munich, Germany; 6. InflaRx GmbH, Jena, Germany.

Purpose: Vilobelimab, an anti-C5a complement blocker, significantly reduced 28-day all-cause mortality in a global study of critically ill, septic and moderate to severe ARDS COVID-19 patients on top of standard-of-care (SOC) (PANAMO, N=368: NCT04333420).[1] Vilobelimab treated patients 28-day mortality was 32% *vs* placebo at 42% (HR 0.67, 95%CI:0.48-0.96, p=0.027). SoC included concomitant corticosteroids (97%) and anti-thrombotic agents (98%). In addition, ~20% of patients received immunomodulators, predominantly tocilizumab over baricitinib. C5a is involved in IL-6 generation in neutrophils *in vitro* and experimental sepsis.[2,3] C5a receptor (C5aR1) expression is strongly transcriptionally upregulated by IL-6 in experimental settings of inflammation and particularly sepsis.[4,5] Inhibition of IL-6 greatly reduces the C5aR1 expression on neutrophils. A post-hoc analysis was performed to evaluate whether any prior or concomitant treatment with tocilizumab provided additional survival benefit on top of vilobelimab and SOC. A mechanism of action is proposed to describe this potential synergistic interaction between vilobelimab and tocilizumab.

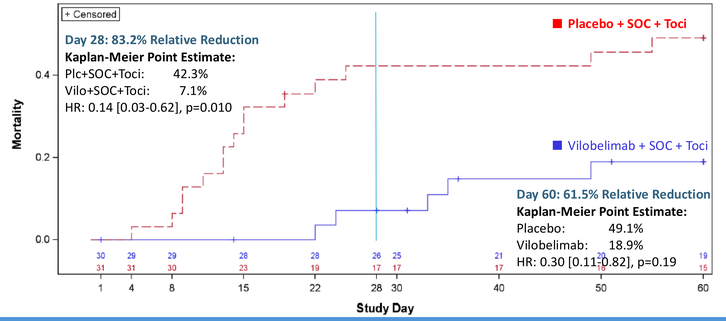
Methods: A post-hoc Cox regression subgroup analysis was performed for 28- and 60-Day all-cause mortality in patients with or without prior or concomitant use of tocilizumab when receiving vilobelimab+SoC (Vilo+ or Vilo-) or placebo+SoC (Plc+ or Plc-). Safety was also assessed.

Baseline Patient Demographics

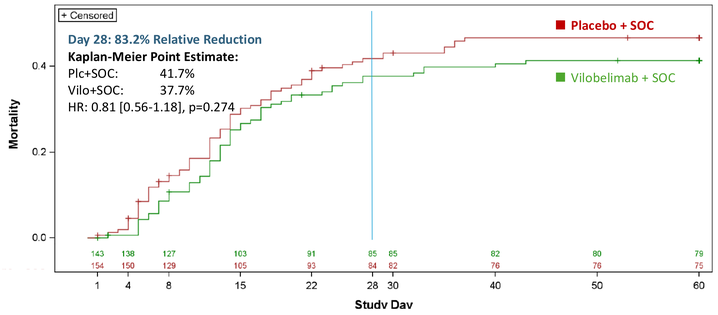
Baseline Characteristics	Total (N=61)	Vilo + Toci (n=30)	Plc + Toci (n=31)
Sex [n (%)]			
Male	41 (67.2%)	21 (70.0%)	20 (64.5%)
Female	20 (32.8%)	9 (30.0%)	11 (35.5%)
Childbearing potential	4 (20.0%)	2 (22.2%)	2 (18.2%)
Age [years]			
n	61	30	31
Mean (SD)	59.3 (12.7)	56.6 (14.1)	62.0 (10.7)
Min – Max	24 – 79	24 – 78	30 – 79
Median (Q1 – Q3)	61.0 (53.0 – 68.0)	59.5 (48.0 – 68.0)	61.0 (55.0 – 71.0)
BMI [kg/m²]			
n	61	30	31
Mean (SD)	30.9 (5.6)	30.4 (4.8)	31.3 (6.4)
Min – Max	22 – 55	22 – 45	23 – 55
Median (Q1 – Q3)	30.2 (27.7 – 32.7)	30.3 (27.1 – 32.7)	30.2 (27.7 – 33.2)
eGFR categories [n (%)]			
< 60 mL/min/1.73m²	19 (31.1%)	7 (23.3%)	12 (38.7%)
≥ 60 mL/min/1.73m²	42 (68.9%)	23 (76.7%)	19 (61.3%)
8-point ordinal scale evaluation [n (%)]			
6 - Intubation and mechanical ventilation	17 (27.9%)	11 (36.7%)	6 (19.4%)
7 - Ventilation + additional organ support – pressors, RRT, ECMO	44 (72.1%)	19 (63.3%)	25 (80.6%)
Acute Respiratory Distress Syndrome (ARDS) severity [n (%)]			
Mild (200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg)*	1 (1.6%)	1 (3.3%)	0 (0.0%)
Moderate (100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg)	38 (62.3%)	20 (66.7%)	18 (58.1%)
Severe (PaO_2/FiO_2 ≤ 100 mmHg)	22 (36.1%)	9 (30.0%)	13 (41.9%)
Hypertension [n (%)]	33 (54.1%)	12 (40.0%)	21 (67.7%)
Diabetes [n (%)]	19 (31.1%)	8 (26.7%)	11 (35.5%)
Coronary heart disease [n (%)]	9 (14.8%)	4 (13.3%)	5 (16.1%)
Chronic obstructive pulmonary disease [n (%)]	2 (3.3%)	1 (3.3%)	1 (3.2%)
Carcinoma [n (%)]	2 (3.3%)	1 (3.3%)	1 (3.2%)

Results: Efficacy (Full Analysis Set)

Kaplan Meier Graph of 60-Day All-Cause Mortality with Tocilizumab



Kaplan Meier Graph of 60-Day All-Cause Mortality without Tocilizumab



Conclusion and Clinical Implication

In addition to corticosteroid and anti-thrombotic agent administration, this post-hoc analysis with a small number of patients demonstrates that the co-administration of vilobelimab with tocilizumab may have further potential to improve survival in critically ill COVID-19 patients. The co-administration of vilobelimab and tocilizumab suggests an interplay between C5a- and IL-6-induced inflammatory pathways involved in septic and ARDS COVID-19 patients. Co-administration of vilobelimab and tocilizumab may result in a synergistic survival benefit for certain critically ill ARDS patients. Prospective randomized studies are warranted to further study this observed promising effect.

Results: Safety (Safety Analysis Set)

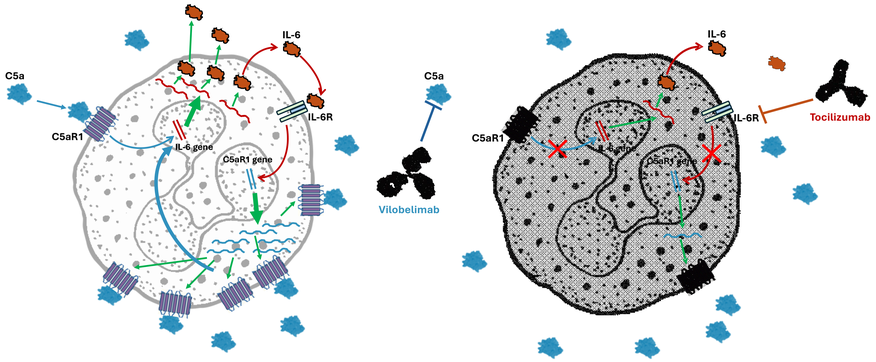
Adverse event category	Vilo + SOC + Toci (n=29)*	Plc + SOC + Toci (n=31)	Vilo + SOC (n=146)	Plc + SOC (n=158)
Any fatal TEAE	5 (17.2%)	15 (48.4%)	57 (39.0%)	70 (44.3%)
Any TEAE	27 (93.1%)	30 (96.8%)	132 (90.4%)	142 (89.9%)
Any related TEAE	9 (31.0%)	8 (25.8%)	11 (7.5%)	8 (5.1%)
Any serious TEAE	13 (44.8%)	21 (67.7%)	90 (61.6%)	99 (62.7%)
Any serious related TEAE	2 (6.9%)	4 (12.9%)	6 (4.1%)	5 (3.2%)

MedDRA High Level Group Term	Vilo + SOC + Toci (n=29)*	Plc + SOC + Toci (n=31)	Vilo + SOC (n=146)	Plc + SOC (n=158)
Any TEAE infections & infestations	16 (55.2%)	20 (64.5%)	94 (64.4%)	92 (58.2%)
Infections – pathogen unspecified	11 (37.9%)	18 (58.1%)	80 (54.8%)	70 (44.3%)
Bacterial infectious disorders	10 (34.5%)	14 (45.2%)	58 (39.7%)	61 (38.6%)
Fungal infectious disorders	6 (20.7%)	6 (19.4%)	16 (11.0%)	10 (6.3%)
Viral infectious disorders	6 (20.7%)	4 (12.9%)	15 (10.3%)	9 (5.7%)

Plc = placebo; SOC = standard of care; TEAE = treatment emergent adverse events; Toci = tocilizumab; Vilo = vilobelimab
*One patient in the vilobelimab + tocilizumab arm was randomized but consent was withdrawn by the patient´s relative before first infusion of study drug. Hence the patient was not considered for the Safety Analysis Set.

Potential Mechanism for Dual Immunomodulator Effect in Severe COVID-19

Hyperinflammatory Cellular Response | **Dual Inhibition with Vilobelimab and Tocilizumab**



References: 1. Vlaar et al. *Lancet Resp Med*. 2022; 2. Riedemann et al. *J Immunol*. 2003; 3. Riedemann et al. *FASEB J*. 2004; 4. Mäck et al. *J Immunol*. 2001; 5. Riedemann et al. *J Clin Invest*. 2002.

Disclosures: C.S. and E.H.T.L. have no conflicts. A.P.J.V. and D.vB. are advisors to InflaRx GmbH. C.Z. is a paid consultant for statistical analysis. B.P.B., R.M.P. and R.G. are employees of InflaRx Pharmaceuticals, Inc. C.C., R.Z. & N.R. are employees of InflaRx GmbH.

The phase 3 PANAMO trial was funded by InflaRx and partly funded by the German Federal Government (grant number 16LW0113; VILO-COVID). This study has been labeled as a National Research Priority by the French National Orientation Committee for Therapeutic Trials and other research on Covid-19 (CAPNET).