

Supplemental materials to:

Reversal of propofol-induced depression of the hypoxic ventilatory response by BK-channel blocker ENA-001: a randomized controlled trial

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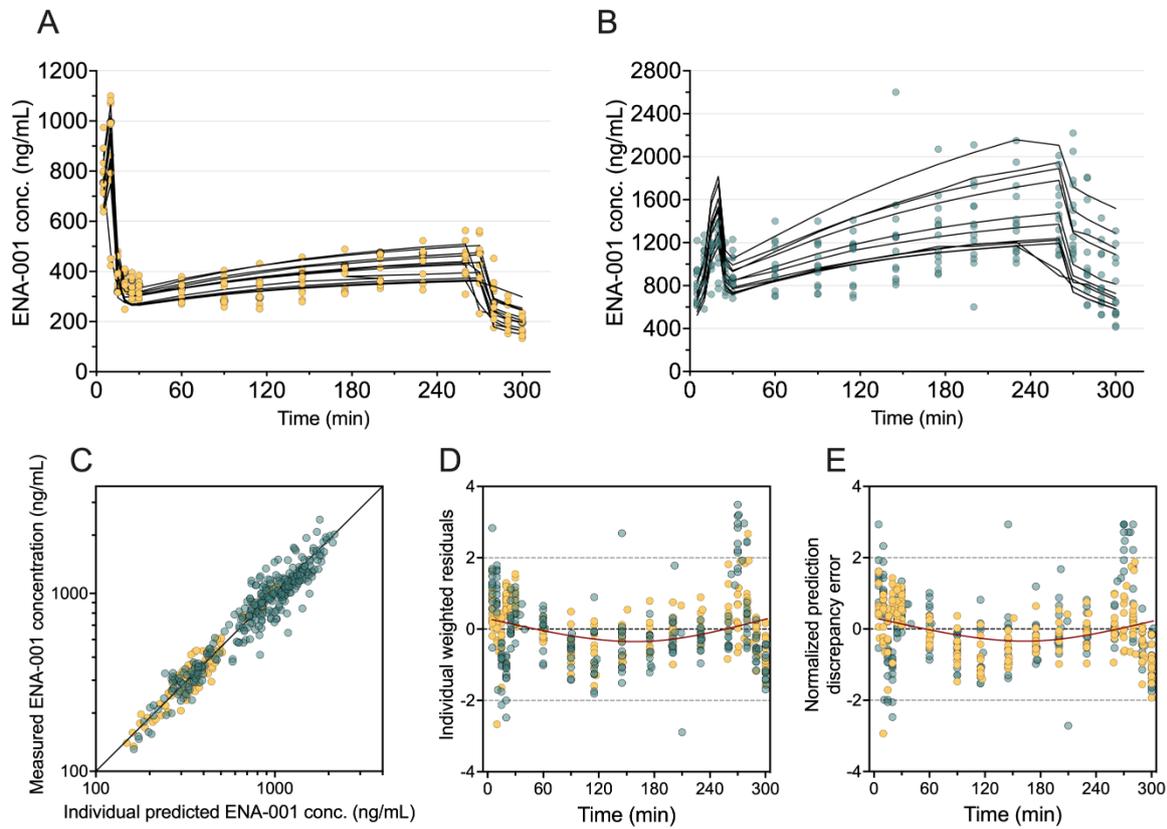
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Supplemental Table 1: Pharmacokinetic parameter estimates.

Parameter	Estimate ± SEE	Between-subject variability (ω^2) ± SEE	Inter-occasion variability (v^2) ± SEE
ENA-001			
V ₁ (L)	8.3 ± 1.0	0.047 ± 0.021	
V ₂ (L)	82.4 ± 11.2		
CL ₁ (L/h)	0.88 ± 0.10		0.080 ± 0.021
CL ₂ (L/h)	1.82 ± 0.10		0.067 ± 0.017
σ^2	0.029 ± 0.002		
Propofol			
V ₁ (L)	9.9 ± 2.2		0.388 ± 0.215
V ₂ (L)	51.4 ± 5.7		
CL ₁ (L/h)	2.09 ± 0.10	0.017 ± 0.008	0.024 ± 0.007
CL ₂ (L/h)	1.61 ± 0.16		0.035 ± 0.019
σ^2	0.025 ± 0.003		

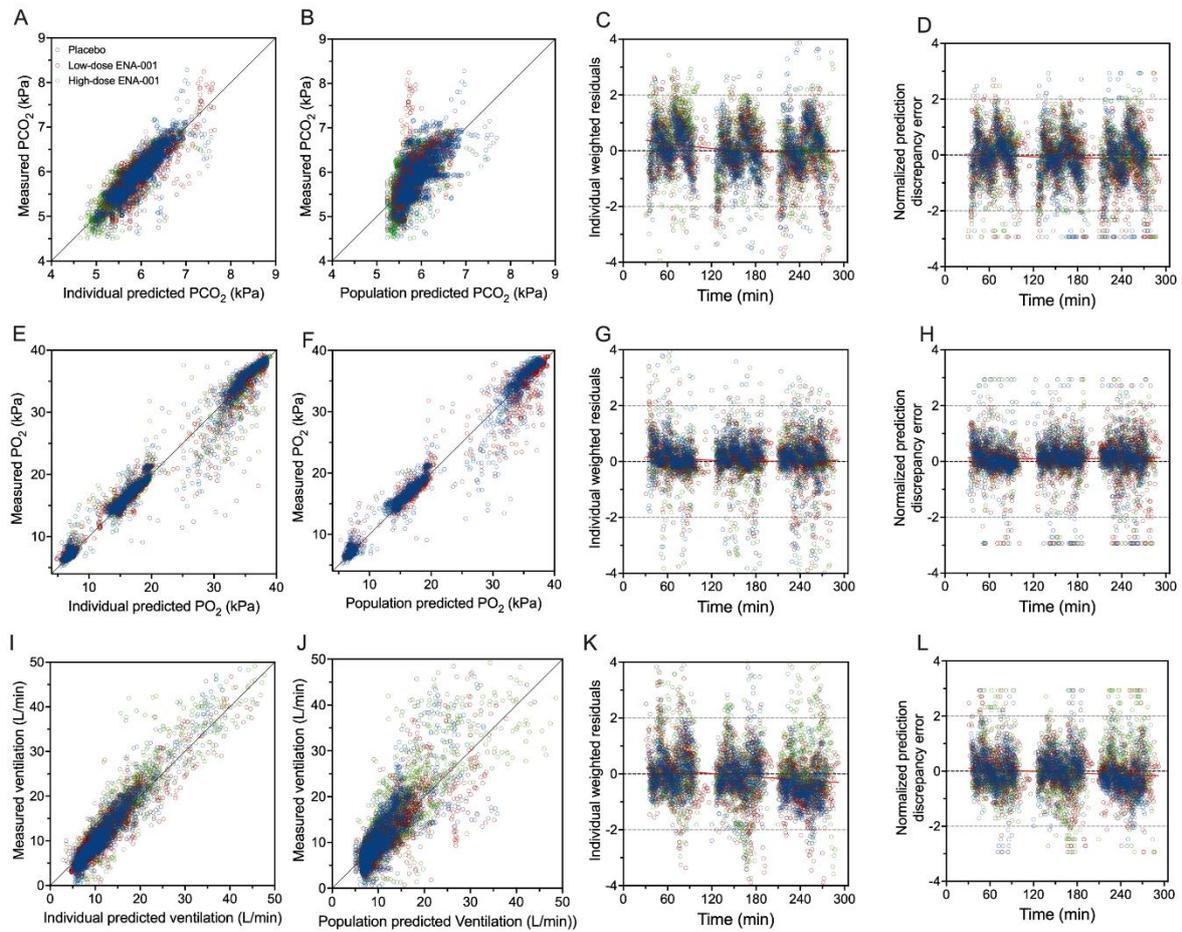
V₁ and V₂ are volumes of compartment 1 and 2, CL₁ is clearance from compartment 1, CL₂ is the intercompartmental clearance. σ^2 is residual error. SEE is the standard error of the estimate.

Supplemental Figure 1.



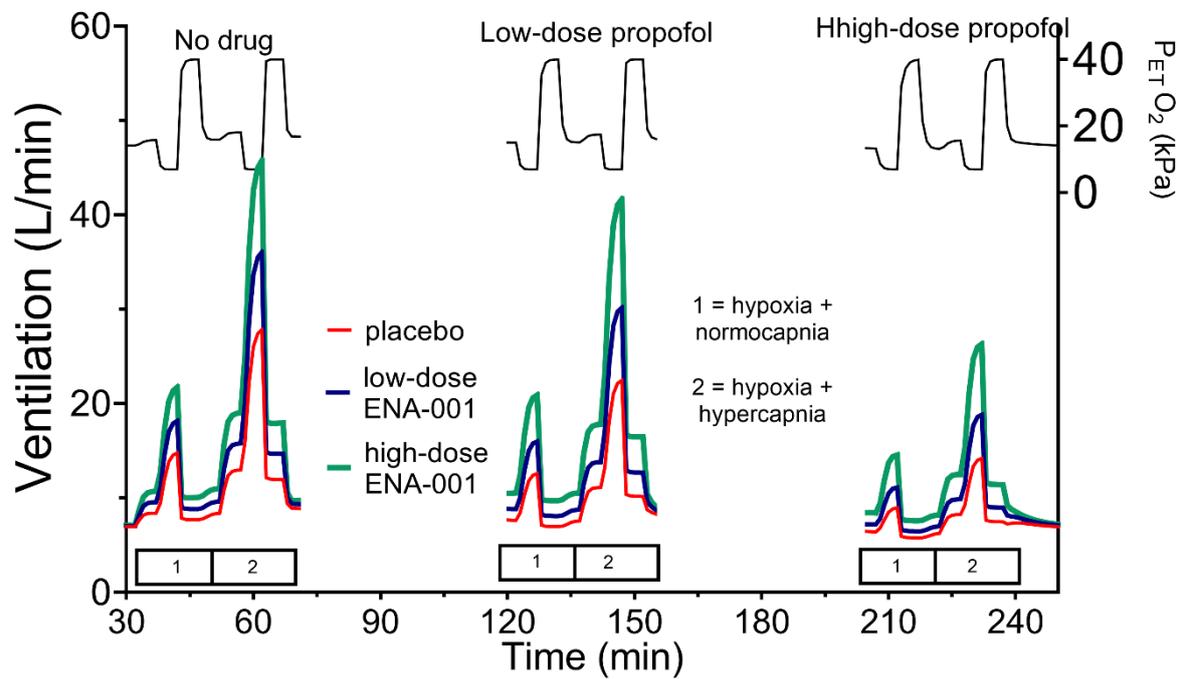
Individuals measured plasma ENA-001 concentrations (yellow and green symbols) following infusion of low-dose (**A**) and high-dose (**B**) ENA-001, with corresponding data fits (continuous lines). **C-D**. Goodness of fit plots of the ENA-001 data fits. **C**. Measured ENA-001 concentration *versus* individual predicted concentrations. **D**. Individual weighted residuals *versus* time. **E**. Normalized prediction discrepancy error *versus* time. The red lines through the data are smoothed curves. Yellow symbols are low-dose ENA-001, green symbols high-dose ENA-001.

Supplemental Figure 2.



Goodness of fit plots of the population data fits. **A-D.** Alveolar PCO₂. **E-H.** Alveolar PO₂. **I-L.** Ventilation. **A, E** and **I.** Measured *versus* individual predicted data. **B, F** and **J.** measured *versus* population predicted data. **C, G** and **K.** Individual weighted residuals *versus* time. **D, H** and **L.** Normalized prediction discrepancy error *versus* time. The red lines through the data are smoothed curves. Blue symbols: placebo, red symbols: low-dose ENA-001, and green symbols: high-dose ENA-001.

Supplemental Figure 3.



Population predicted ventilatory response to hypoxia + normocapnia (time window 1) and hypoxia + hypercapnia (time window 2) for placebo (red lines), low-dose ENA-001 (blue lines) and high-dose ENA-001 (green lines) during administration of placebo (left), low-dose propofol (middle) and high-dose propofol (right). The top panel depicts the end-tidal oxygen concentration ($P_{ET}O_2$).