

Evaluation of the Safety and Tolerability of ENA-001 in Addressing the Pharmacologically-induced Respiratory Depression

Errol Gould, PhD; Thomas Miller, PhD; Joseph Pergolizzi, MD, MBA; Robert Raffa, PhD

Enalare Therapeutics Inc.

Poster #4645

BACKGROUND

Depression of the respiratory drive (respiratory depression; RD) is a potential contributor to the long-term complications following anesthesia, a substantial risk to the use of medications for pain management and leading cause of death amongst drug abusers. ENA-001 is being developed as a short-duration intravenous agent acting through inhibition of BK(Ca2+) (Maxi K channels) in the carotid body to stimulate respiration and increase minute ventilation by primarily increasing tidal volume and secondarily through minor increases to respiratory rate. As the mechanism is independent of opioid and other agents used for pain and anesthesia, ENA-001 should provide reversal of respiratory depressant effects of these compounds without interfering with their primary pharmacology. In this study, the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics of ENA-001 administered through continuous intravenous (IV) infusion were assessed in healthy adults, covering a higher dosage range than previously evaluated.

METHODS

This was a single center, randomized, double-blind, placebo-controlled, four-period, single rising dose study in alternating cohorts of healthy subjects. ENA-001 was administered via IV at rates of 0.96, 1.44, and 1.92 mg/kg/h over a 2-hour duration. Two cohorts of 9 subjects each were randomized to treatment in a ratio of 2:1 (6 treated, 3 placebo) in a rotating panel design. Subjects in the first cohort participated in dosing periods 1 and 3, with the second cohort participating in dosing periods 2 and 4. The subjects received placebo at most once during the study. During the 4th and final treatment period, subjects were reassigned to the 2 lower dose levels based on their previous treatment to increase the total number of subjects receiving these dose levels. Safety, tolerability, pharmacokinetic and pharmacodynamic endpoints were assessed.

CONCLUSION

• ENA-001 was generally safe and well tolerated over the dose range studied

• ENA-001 was able to drive hyperventilation in a dose-dependent manner in healthy subjects

• ENA-001 increases in ventilation were not associated with like-magnitude blood pressure responses

• ENA-001 stimulated decreases in ET/CO₂ were associated with small statistically significant increases in SpO₂ levels

• ENA-001 demonstrated well behaved PK following two-hour IV infusion
• Both the mean peak plasma concentrations and the mean total systemic exposure values are approximately dose proportional in the dose range studied

FINANCIAL SUPPORT: The study was sponsored by Enalare Therapeutics Inc. and conducted by SGS Life Sciences Services (Antwerpen, Belgium).

DISCLAIMER: ENA- 001 is for research use only and it's not been approved by the FDA for human use.

RESULTS

Table 1: Demography

N	18
Male gender, n	16 (89)
Age, years	35.6 ± 6.95
Weight, Kg	76.5 ± 7.87
BMI, Kg/m ²	25.0 ± 2.14
Mean FEV ₁ , % (Range)	99.8 (85-130)
FVC, Liters (Range)	4.95 (3.14-6.59)

Data are mean ± standard deviation (SD) or n (%). BMI: body mass index. FEV₁: forced expiratory volume in 1 second. FVC: forced vital capacity.

Table 2: Summary of Adverse Events

Period	1/4	2/4	3	All	Total subjects reporting AE
Rate (mg/kg/h)	0.96	1.44	1.92	Placebo	
# Subjects	9	8	6	12	
Abdominal pain		2			2
Dizziness	1	2			2
Headache	1	1		2	4
Hyperventilation			2		2
Loose stools		2			2
Nausea		4	5		9
Venous pain infusion site	1	4	3		8
Vomiting		2	1		3
# Subjects with any AE	3	7	5	3	14
*Total number of individual subjects with specific adverse event; **Adverse Events with >1 occurrence					

Blood Pressure: Diastolic and systolic blood pressure had no significant changes during the infusion compared to placebo.

Table 3: Pharmacokinetic Parameters for ENA-001 in Human Plasma^a

N	Infusion Rate		Duration (h)	Dose (mg/kg)	T _{max} (h)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng•h/mL)	AUC _{0-∞} (ng•h/mL)	AUC _{0-∞} /D (mg•h/mL)	t _{1/2} (h)	CL _p (mL/min/kg)	V _d (L/kg)	V _{ss} (L/kg)
	(mg/kg/min)	(mg/kg/h)											
9	0.016	0.96	2	1.92	1.97 (1.50-2.00)	860 (23)	2595 (24)	2680 (25)	1397 (25)	6.81 (20)	11.9 (28)	7.04 (22)	2.48 (31)
8	0.024	1.44	2	2.88	1.97 (1.50-2.00)	1319 (22)	3828 (23)	3875 (23)	1345 (23)	5.15 (19)	12.4 (24)	5.53 (19)	1.79 (16)
6 ^b	0.032	1.92	2	3.84	1.97 (1.50-2.00)	1919 (14)	5834 (14)	6058 (14)	1578 (14)	8.10 (6.5)	10.5 (15)	7.41 (10)	2.47 (14)
17	0.016-0.032	0.96-1.92	2	All						6.33 (24)	11.8 (25)	6.48 (22)	2.19 (29)

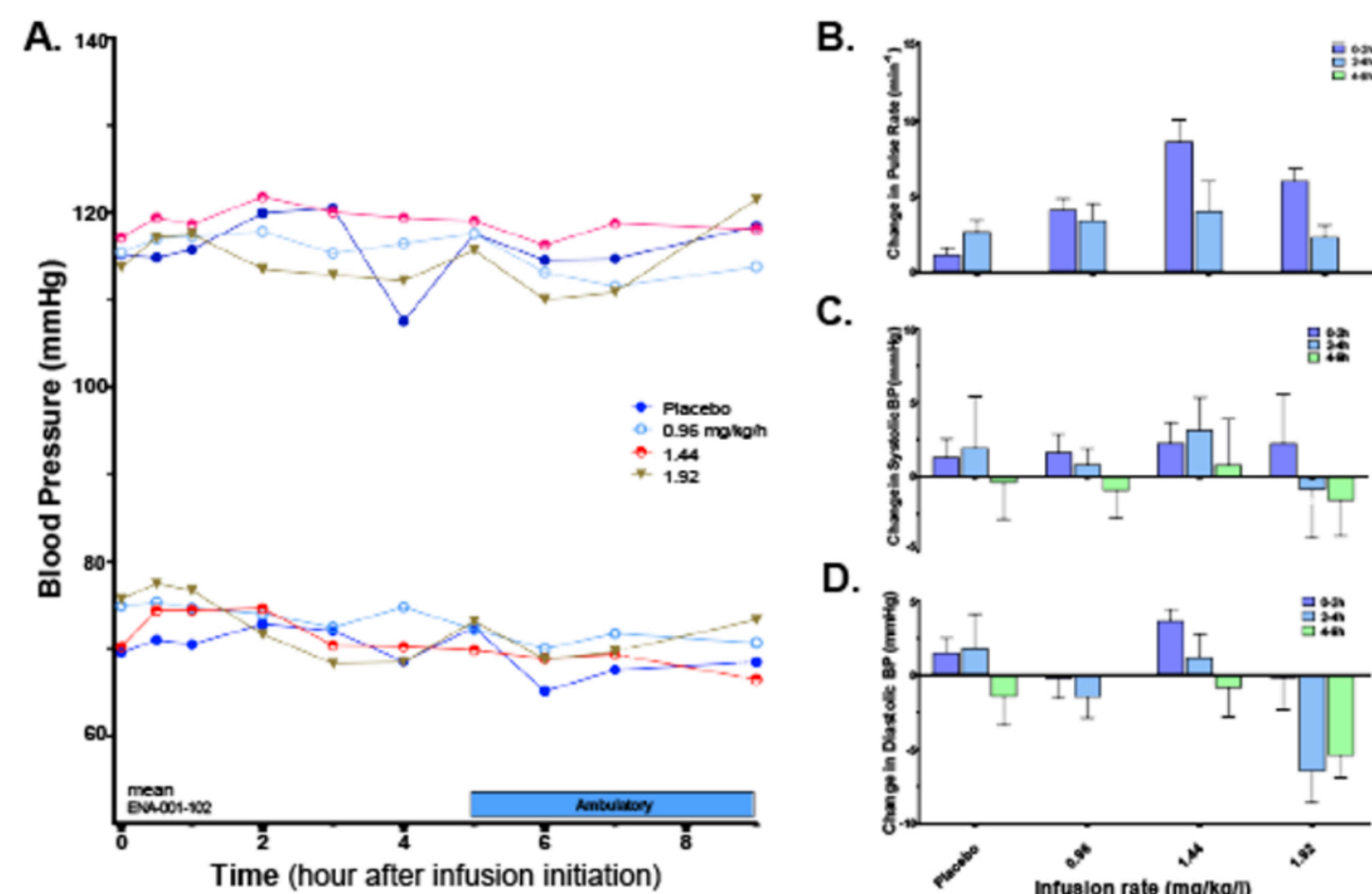
^aData are geometric mean values (% coefficient of variation) for each parameter except for T_{max} expressed as median values (range)

^bMean values are from 4 subjects due to premature termination of infusions in 2 subjects.

Adverse Events

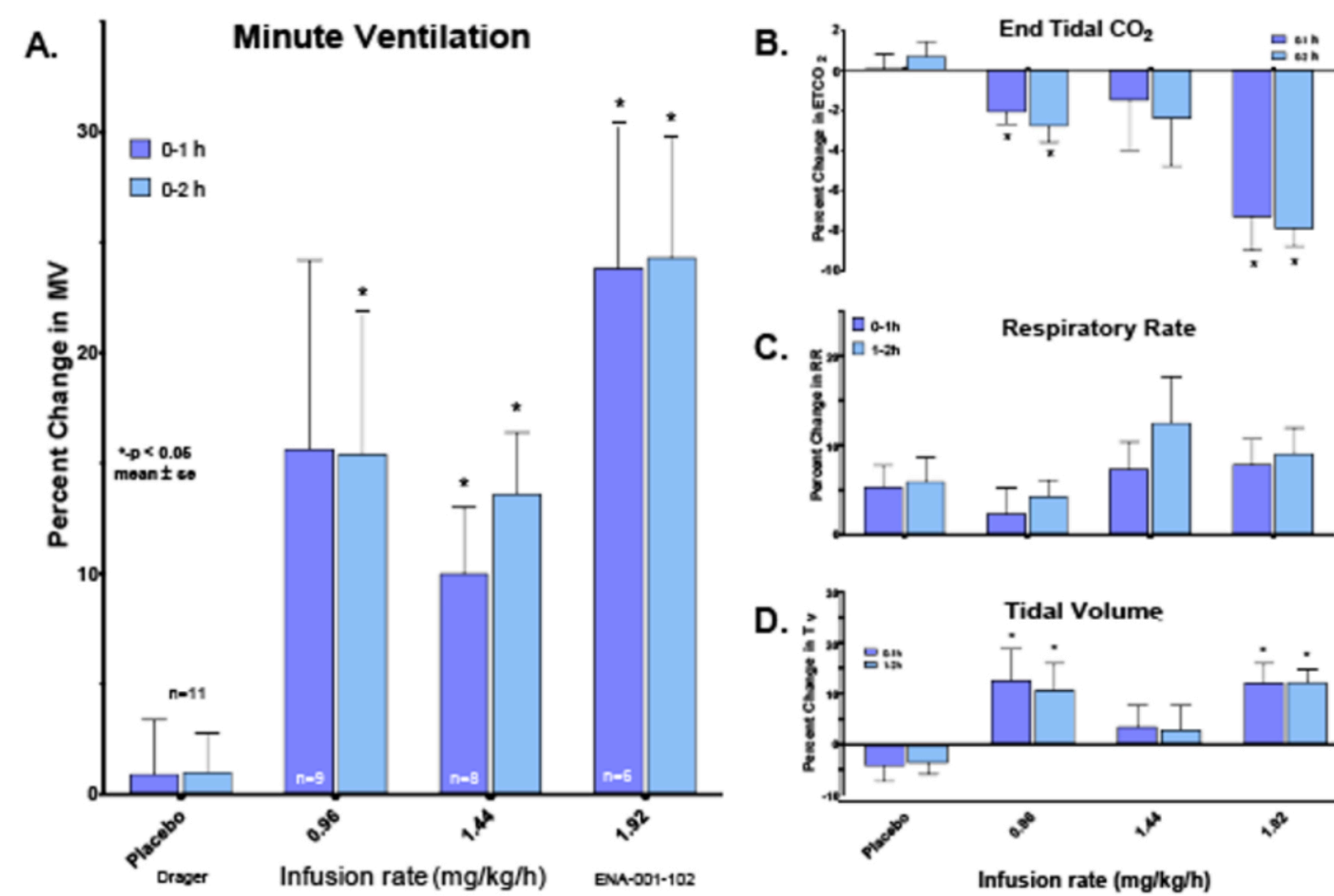
Fourteen subjects (78%) reported at least one adverse event (AE) during the study. All of the AE were reported as mild to moderate in severity. There were no deaths or serious AE.

Figure 1: Mean systolic and diastolic blood pressure after the start of the infusion



Minute Ventilation, End Tidal CO₂, Respiratory Rate, and Tidal Volume

Figure 2: Integrated percent change from baseline during the first hour (0-1h) and during first 2 hours (0-2h) after starting the infusion for minute ventilation, end tidal CO₂, respiratory rate, and tidal volume.



During the 3rd treatment period, 2 subjects had increasing ventilatory efforts and declining ET/CO₂ (nadirs: 22 and 29 mmHg), and the infusions were stopped with rapid diminution of the respiratory efforts.

Figure 3: Transcutaneous hemoglobin oxygen saturation (Dräger)

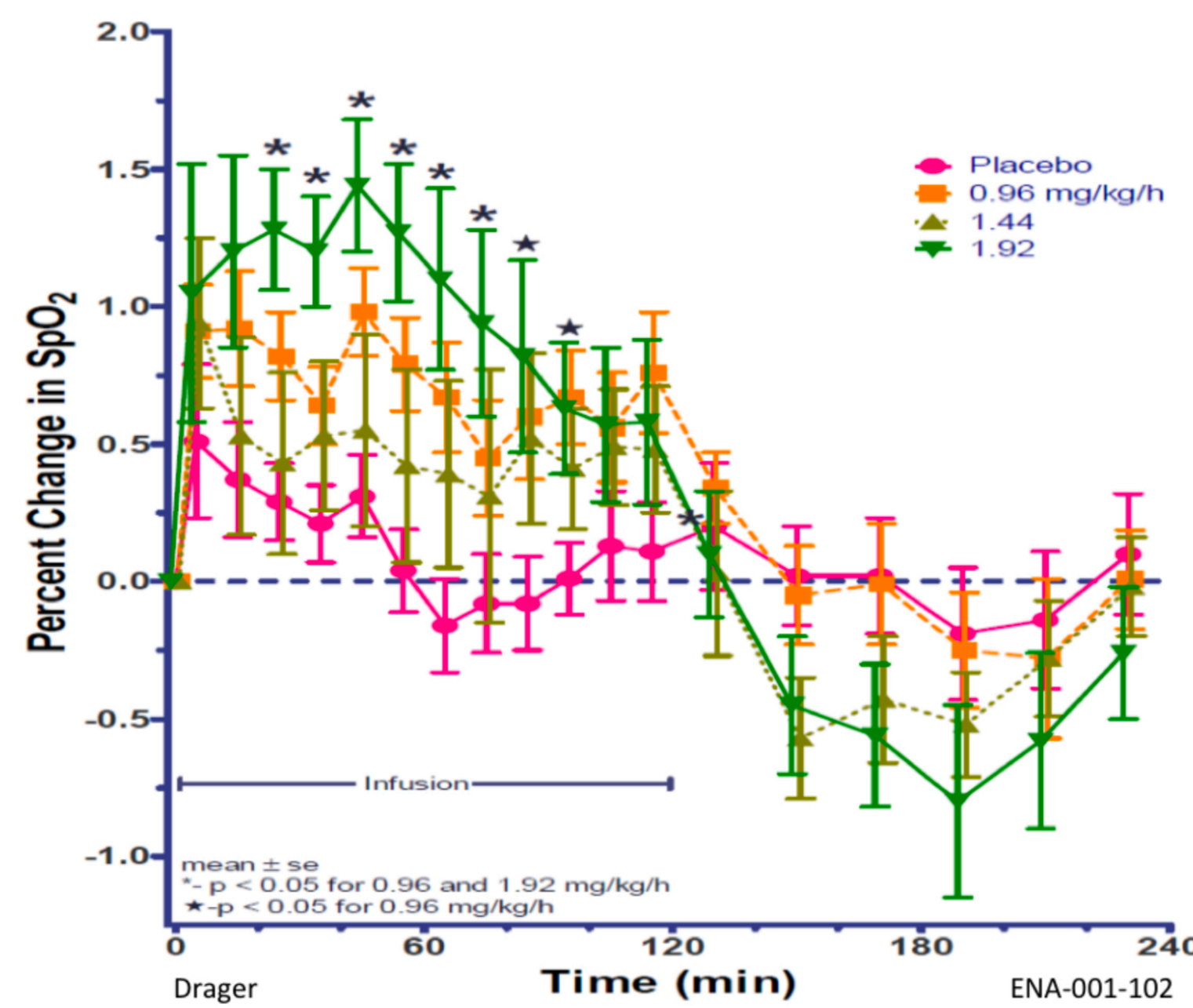
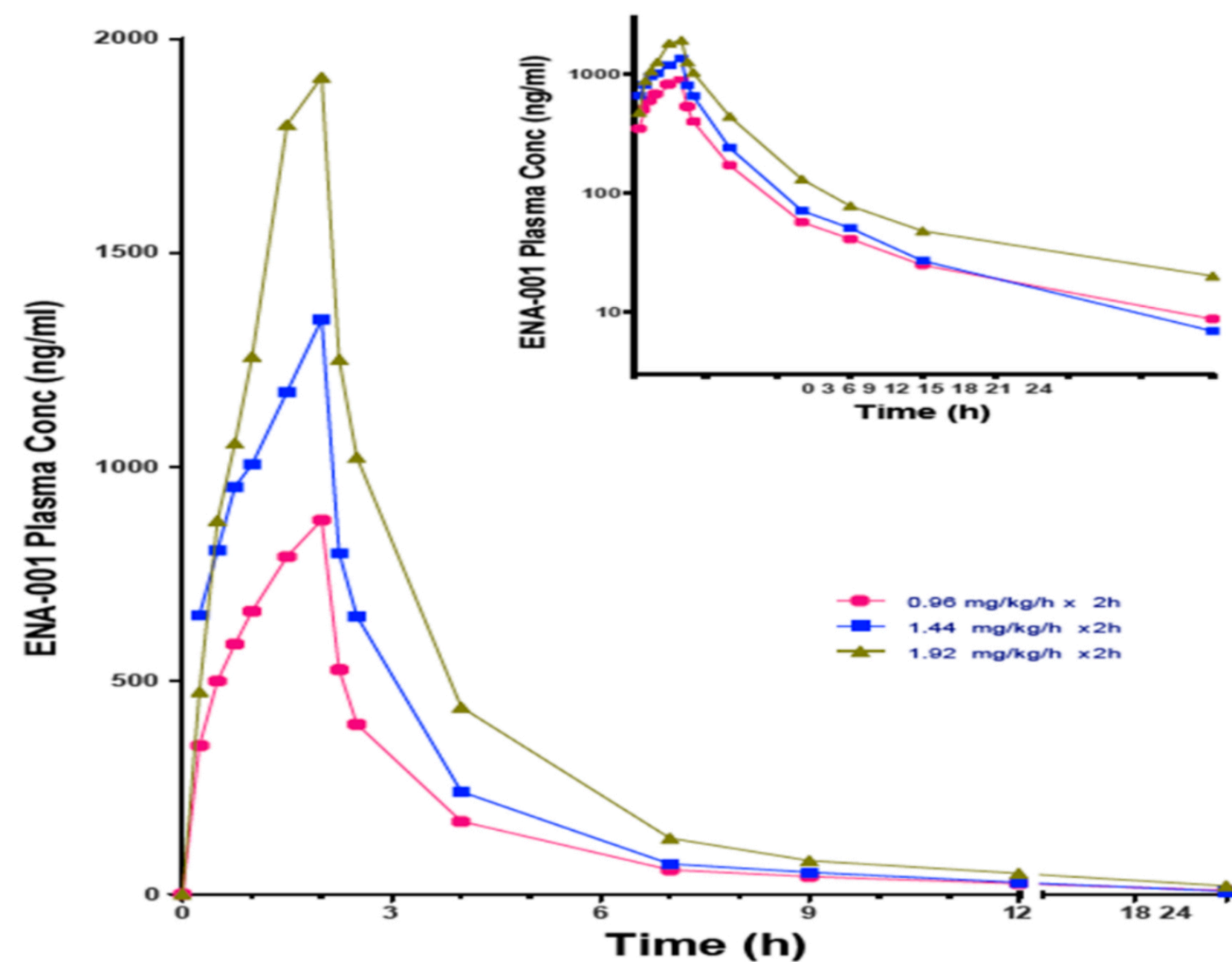


Figure 4: Mean plasma concentration-time profiles of ENA-001 following intravenous infusion



Designed by *Morgan Wagner*

