

Cebranopadol effects on ventilatory drive, central nervous system, and pain

Simone C. Jansen¹, Antonio Pardo ², Joseph C. Grieco ², James Hackworth ², Albert Dahan ¹

1. Leiden University Medical Center (LUMC), Leiden, Zuid-Holland, Netherlands 2. Tris Pharma, Inc., Monmouth Junction, NJ

50th Annual Regional
Anesthesiology and Acute
Pain Medicine Meeting

May 1-3, 2025 | Orlando, FL

50th ANNIVERSARY
ASRA PAIN
MEDICINE

Background

- Respiratory depression is a possible life-threatening complication following opioid administration, mediated via Mu-opioid receptor (MOP) activation.
- Cebranopadol is a first-in-class dual nociceptin/orphanin FQ (NOP) and MOP receptor agonist (dual-NMR agonist) attenuating MOP related side effects.¹⁻⁴
- Cebranopadol administration leads to substantial antinociceptive effects with significantly less MOP-related abuse potential, dependence, and respiratory depression.¹⁻⁴
- Clinical trials suggest a ceiling for respiratory depression.⁴

Purpose

Our comprehensive investigation involving 30 subjects aimed to address key questions regarding cebranopadol's impact on respiratory depression compared to oxycodone, the potential presence of a ceiling effect at higher doses, and the evaluation of significant respiratory depression within the Ventilatory Response to Hypercapnia (VRH) model context.

Methods

Subjects: 30 healthy volunteers

Design: double blind, 4 way partial crossover, 2 week minimum washout period

- placebo, cebranopadol 600µg, 800µg, or 1000µg, and oxycodone 30mg or 60mg

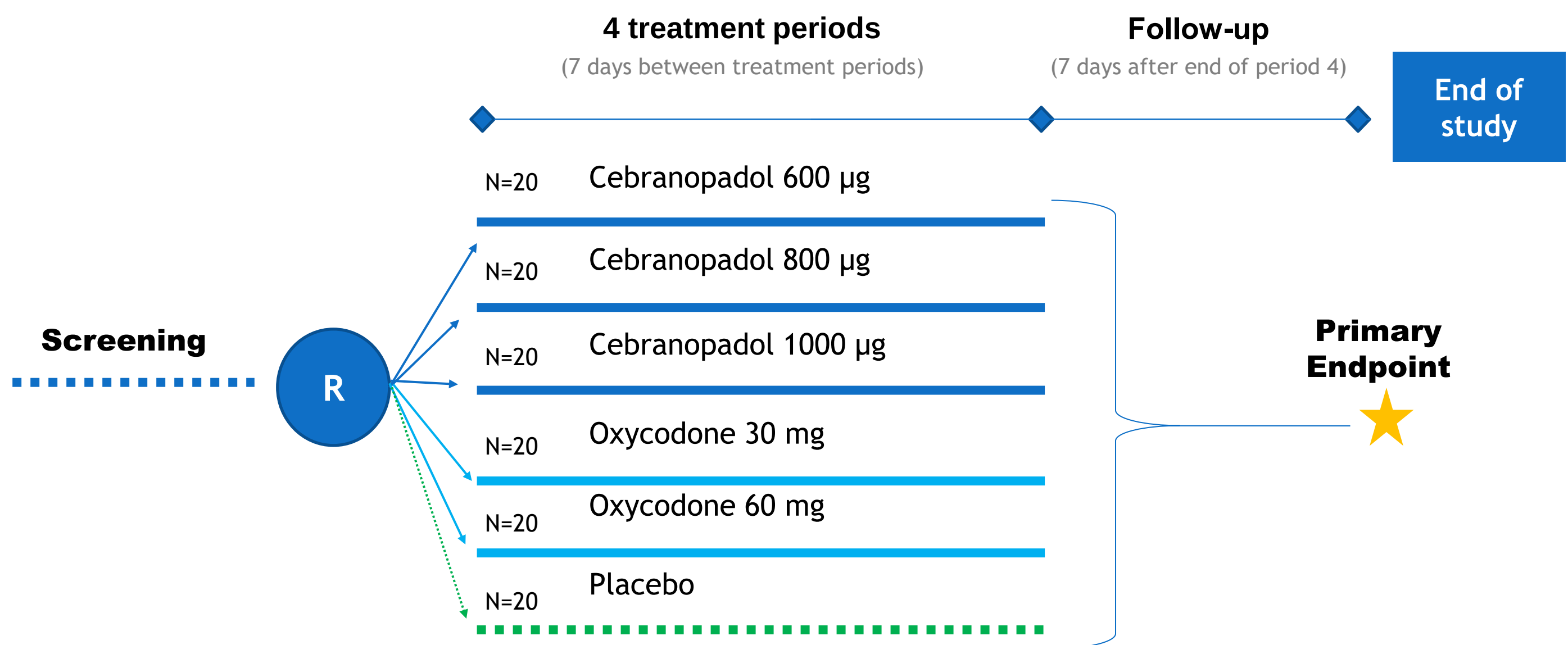
Measured:

On 12 consecutive timepoints:

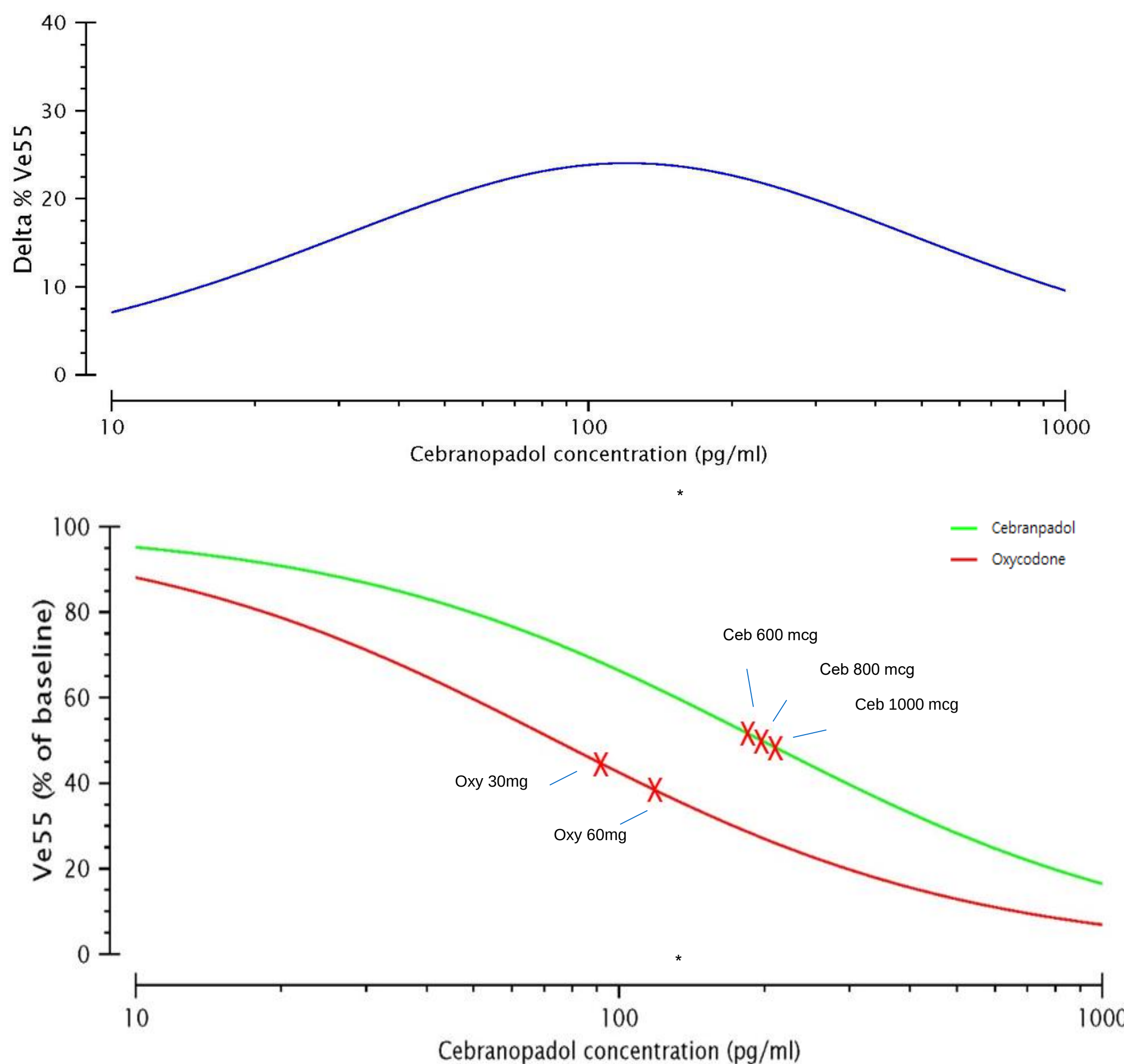
- Ventilatory response to hypercapnia (Ve55)⁵
- Electrical pain tolerance threshold
- Pupil diameter
- Pharmacokinetic venous blood samples

Analysis: A population PK/PD model in NONMEM. For the pharmacodynamic models the following parameters were used; the Ve55, the pupil diameter, and the electrical pain tolerance threshold. This model allowed us to compare the respiratory effects of cebranopadol to oxycodone at equi-analgesic plasma concentrations.

Design



Results



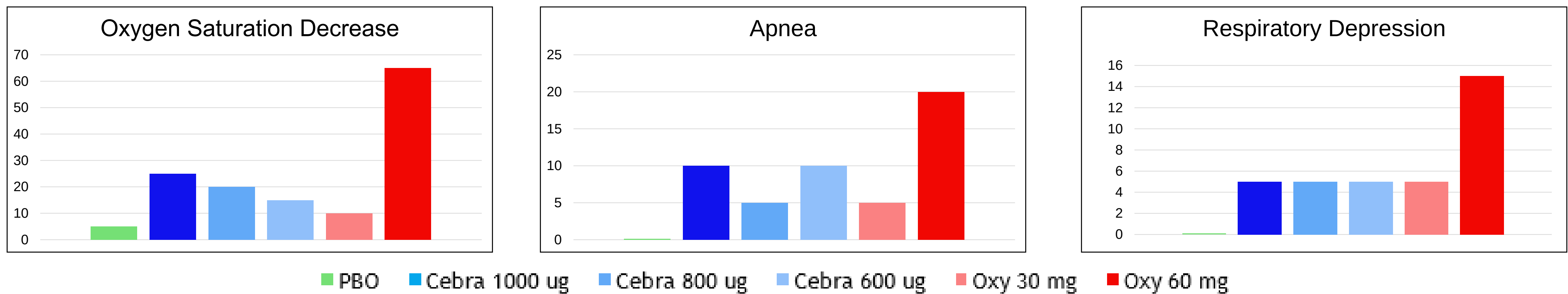
At equianalgesic efficacy, cebranopadol produces **~25% less respiratory depression** compared to oxycodone

Cebranopadol presents a **longer time to impact on respiratory parameters** compared to oxycodone

Cebranopadol featured **prolonged analgesic effects, with gradual onset and offset**

*The X-axis is demonstrating analgesia normalized to cebranopadol concentrations

Safety



Preferred Term	Placebo (N=20)		Cebranopadol 1000 ug (N=20)		Cebranopadol 800 ug (N=20)		Cebranopadol 600 ug (N=20)		Oxycodone 30 mg (N=20)		Oxycodone 60 mg (N=20)		All Subjects (N=30)	
	Subjects N (%)	Events N	Subjects N (%)	Events N	Subjects N (%)	Events N	Subjects N (%)	Events N	Subjects N (%)	Events N	Subjects N (%)	Events N	Subjects N (%)	Events N
Apnea	0	0	2 (10.0%)	3	1 (5.0%)	1	2 (10.0%)	3	1 (5.0%)	1	4 (20.0%)	5	6 (20.0%)	13
Respiratory depression	0	0	1 (5.0%)	1	1 (5.0%)	1	0	0	1 (5.0%)	1	3 (15.0%)	3	5 (16.7%)	6
Oxygen saturation decreased	1 (5.0%)	1	5 (25.0%)	47	4 (20.0%)	8	3 (15.0%)	19	2 (10.0%)	7	13 (65.0%)	80	17 (56.7%)	162

(AESI) Adverse Event of Special Interest, (Apnea) = No Breathing for >10s, (O₂ Desaturation) = <90%

Conclusions

Cebranopadol produces **potent long-lasting analgesia**

- This study confirms that cebranopadol produces potent analgesia that will persist for longer and will be associated with less respiratory depression when compared to equianalgesic doses of oxycodone.
- The delayed onset of respiratory effects is a noteworthy clinical benefit of cebranopadol, allowing for the gradual accumulation of arterial CO₂, thereby mitigating the full manifestation of respiratory depression.
- This characteristic of cebranopadol both gives the body time to adjust its breathing and gives healthcare providers a more extended timeframe for appropriate interventions, strengthening its overall safety in clinical use.
- Taken together, the results of this and previous clinical studies, as well as results from preclinical models, provide evidence to support the likelihood a ceiling of respiratory depression exists in humans. However, these data lead us to conclude further studies are needed to fully characterize the ceiling of respiratory effects cebranopadol may exhibit.

Cebranopadol is a first-in-class dual-NMR agonist that is able to **significantly attenuate MOP related side-effects including respiratory depression**

References

- Ding H, Trapella C, Kiguchi N, Hsu FC, Caló G, Ko MC. Functional Profile of Systemic and Intrathecal Cebranopadol in Nonhuman Primates. Anesthesiology. Sep 1 2021;135(3):482-493. doi:10.1097/ain.0000000000003848
- Koch ED, Kapanadze S, Eerdeken MH, et al. Cebranopadol, a Novel First-in-Class Analgesic DrugCandidate: First Experience With Cancer-Related Pain for up to 26 Weeks. J Pain Symptom Manage. Sep2019;58(3):390-399. doi:10.1016/j.jpainsymman.2019.05.012
- Linz K, Schröder W, Frosch S, Christoph T. Opioid-type Respiratory Depressant Side Effects of Cebranopadol in Rats Are Limited by Its Nociceptin/Orphanin FQ Peptide Receptor Agonist Activity. Anesthesiology. 2017;126(4):708-715. doi:10.1097/ALN.0000000000001530
- Dahan A, Boom M, Sarton E, et al. Respiratory Effects of the Nociceptin/Orphanin FQ Peptide and Opioid Receptor Agonist, Cebranopadol, in Healthy Human Volunteers. Anesthesiology. Apr2017;126(4):697-707. doi:10.1097/ALN.0000000000001529
- Hellinga M, Algera MH, van der Schrier R, et al. A biomarker of opioid-induced respiratory toxicity in experimental studies. iScience. Apr 21 2023;26(4):106520. doi:10.1016/j.iisci.2023.106520

Copyright © 2025 Tris Pharma, Inc. This study was sponsored by Tris Pharma, Inc.