Danavorexton reverses opioid-induced respiratory depression (OIRD) and sedation

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Introduction

- The risk of postanesthesia morbidities can be influenced by several factors, including age, BMI, American Society of Anesthesiologists physical status classification, preexisting respiratory conditions, and procedural times.[1]
- Opioid-induced respiratory depression (OIRD) and sedation are associated with significant morbidity and mortality; critical postanesthesia respiratory events may include hypoxemia, hypercapnia, hypoventilation, and airway obstruction.[2-4]
- Naloxone, an opioid antagonist, is used to treat OIRD; however, adverse effects can include the reversal of analgesia.[4,5]
- The native neuropeptide orexin is a key regulator of the sleep/wake cycle and is involved in other essential functions, including respiration and metabolism, through activation of orexin receptors.[6-8]
- Danavorexton (TAK-925) is a novel, highly selective orexin type-2 receptor (OX2R) agonist that has been studied by Takeda in sleep-deprived healthy subjects and in patients with narcolepsy, idiopathic hypersomnia, and obstructive sleep apnea.[9-11] Preclinical data suggest that danavorexton directly activates neurons associated with respiratory control in the brain.[12,13]
- Prevention of OIRD during postanesthesia recovery remains a key unmet need in the postanesthesia care setting that may be addressed by intravenous administration of danavorexton.

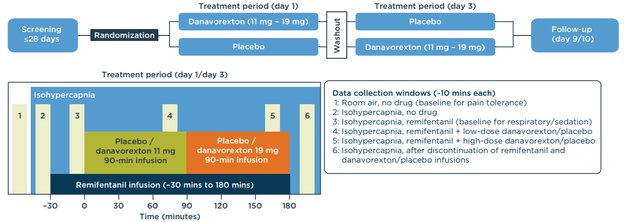
Objective

- To assess the safety, tolerability, and pharmacodynamics of danavorexton administered in healthy subjects undergoing OIRD.

Methods

- A phase 1, randomized, double-blind, placebo-controlled, 2-way crossover trial (ISRCTN63027076) was conducted in healthy male volunteers from a single site in the Netherlands.
- Subjects were randomized to receive danavorexton low dose (11 mg) and high dose (19 mg) (day 1) followed by placebo (day 3), or vice versa, separated by a ≥36-hour washout period (**Figure 1**).
  - Danavorexton 11 mg and 19 mg and placebo were administered as 2 sequential 90-minute infusions within each treatment period.
  - Remifentanil was administered over 210 minutes under isohypercapnic conditions (induced by dynamic end-tidal forcing technique) throughout danavorexton/placebo infusion, and titrated to achieve 30–40% respiratory depression.
- Assessments included monitoring of treatment-emergent adverse events (TEAEs), ventilation, sedation (visual analog scale [VAS] and Richmond Agitation Sedation Scale [RASS]), and pain tolerance.
- Descriptive statistics were used to summarize all variables.

Figure 1. Study design



Results

Participants

- 13 healthy male volunteers aged 23–30 years were randomized and 12 completed both placebo and danavorexton treatment sequences.

TEAEs

- Danavorexton was well tolerated with no serious adverse events or deaths.
- 1 subject withdrew consent from the study after experiencing an influenza-like illness during treatment that was determined to be not related to the study drug.
- 4 subjects (30.8%) experienced a total of 6 TEAEs during danavorexton infusion, all of which were mild (**Table 1**).
- Only the TEAE of insomnia was considered related to danavorexton.

Table 1. Summary of TEAEs

	Placebo (n=12)		Danavorexton (n=13)	
	Events	Subjects, n (%)	Events	Subjects, n (%)
Unrelated TEAE, mild	1	1 (8.3)	6	4 (30.8)
Headache	1	1 (8.3)	2	2 (15.4)
Nausea	0	0	1	1 (7.7)
Vomiting	0	0	1	1 (7.7)
Influenza-like illness*	0	0	1	1 (7.7)
Related TEAE	0	0	1	1 (7.7)
Insomnia	0	0	1	1 (7.7)

TEAE, treatment-emergent adverse event.
*Event determined to not be related to study drug and led to voluntary withdrawal from study.

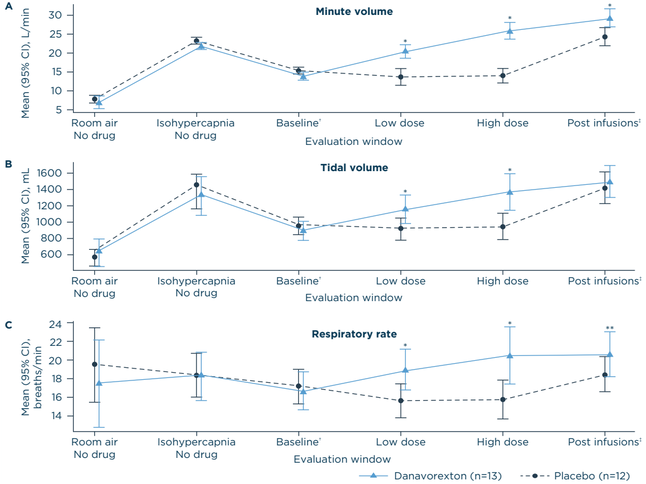
Vital signs and laboratory parameters

- There were no notable changes in serum chemistry, hematology, and urinalysis during the study period.
- Transient increases in blood pressure were observed during study drug administration.
- Mean systolic and diastolic blood pressure returned to near baseline by 4–6 hours following administration of danavorexton.
- No subject experienced hypertension as a TEAE.

Ventilation measurements

- Greater increases in minute volume were observed with danavorexton versus placebo.
- Compared with placebo, adjusted least squares (LS) mean (standard error [SE]) minute volume was increased by 7.3 (1.51) L/min with low-dose danavorexton and by 12.4 (1.51) L/min with high-dose danavorexton (**Figure 2A**).
- The improvement in minute volume was attributed to increases in both tidal volume (**Figure 2B**) and respiratory rate (**Figure 2C**), and was sustained even after danavorexton infusion was discontinued.

Figure 2. Effect of danavorexton on minute volume, tidal volume, and respiratory rate

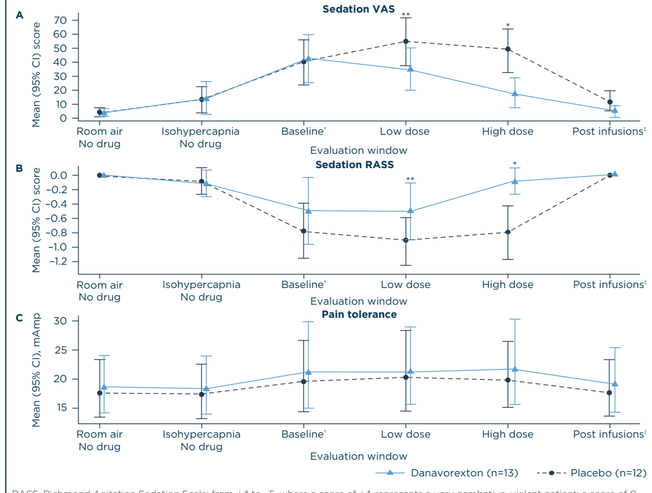


Minute volume = (tidal volume × respiratory rate)/1000. *P≤0.001. **P<0.01 from prespecified mixed-effects model testing change from period baseline, accounting for baseline, treatment, time window, subject. There was no adjustment for multiplicity, and these values are nominal.†Under isohypercapnia with remifentanil infusion, pre danavorexton/placebo. ‡Under isohypercapnia after discontinuation of remifentanil and danavorexton/placebo infusions.

Sedation and pain measurements

- A greater reduction in sedation was observed with danavorexton versus placebo.
- Adjusted mean (SE) sedation on the VAS decreased by 19.9 mm (6.83 mm) with low-dose and by 30.8 mm (6.89 mm) with high-dose danavorexton versus placebo (**Figure 3A**).
- LS mean (SE) change in RASS scores from baseline were 0.4 (0.14) with low-dose and 0.7 (0.14) with high-dose danavorexton versus placebo (**Figure 3B**).
- Pain tolerance did not differ significantly between placebo and treatment sessions under comparable remifentanil concentrations (**Figure 3C**).

Figure 3. Effect of danavorexton on sedation and pain tolerance



RASS, Richmond Agitation Sedation Scale: from +4 to −5, where a score of +4 represents a very combative, violent patient; a score of 0 represents an alert and calm patient; and a score of −5 represents an unarousable patient. VAS, visual analog scale: subjective questionnaire about the degree of sedation – visual rating scale from 0 to 100 mm, where 0 = no sedation and 100 = maximum sedation. *P≤0.001. **P<0.01 from prespecified mixed-effects model testing change from period baseline, accounting for baseline, treatment, time window, subject. There was no adjustment for multiplicity, and these values are nominal. †Under isohypercapnia with remifentanil infusion, pre danavorexton/placebo. ‡Under isohypercapnia after discontinuation of remifentanil and danavorexton/placebo infusions.

Conclusions

- **Danavorexton, a novel and highly selective OX2R agonist, significantly improved respiration and reduced sedation in an OIRD setting under isohypercapnic conditions, without affecting pain tolerance**
- **Danavorexton administered intravenously may optimize postanesthesia respiratory function**
- **The safety and tolerability of a single administration of danavorexton was consistent with that of other danavorexton studies with single administration**
- **These findings suggest that OX2R activation may reverse OIRD and sedation without reversing analgesia**

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