Clexio Biosciences

CLE-400
a Potent Analgesic Topical Gel in Acute and Chronic Pain Pig Models

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CLE-400 a Novel, Non-Opioid Topical Treatment for PDN

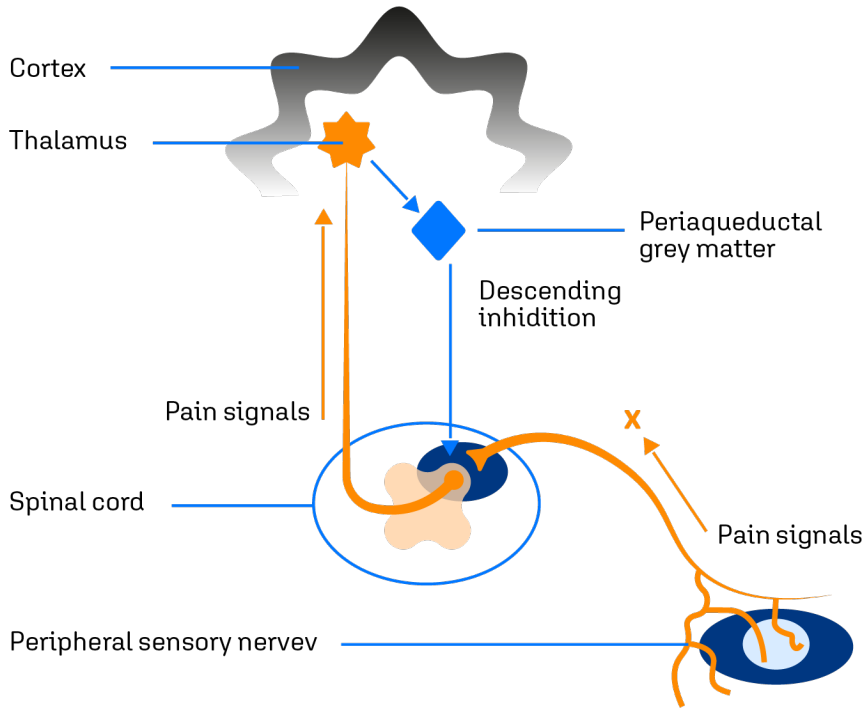
- CLE-400 is an aqueous gel of detomidine, a potent α2-adrenergic agonist activating additional potentially therapeutically relevant targets
- CLE-400 is a new investigational drug that has not been approved for commercial distribution

Targeting α2-adrenergic receptors peripherally

- Systemically administered α2-adrenergic agonists are used in pain management and anesthesia. Their use is limited to invasive RoA and may lead to systemic AEs
- Immunohistochemistry studies demonstrated that detomidine's **targets** (α2-ARs, H4R and SST4R) **are expressed in the skin**
- Activation of these receptors could produce analgesic **by inhibiting the excitability and neural signaling from the peripheral nociceptors (C-fibers) to the brain**

The technology

- CLE-400 gel formulation was developed to deliver **high dermal concentrations over extended period of time (depot effect in the skin)** while maintaining limited systemic exposure



Detomidine: A Potent α2-Adrenergic Receptor Agonist activating additional potentially therapeutically relevant targets

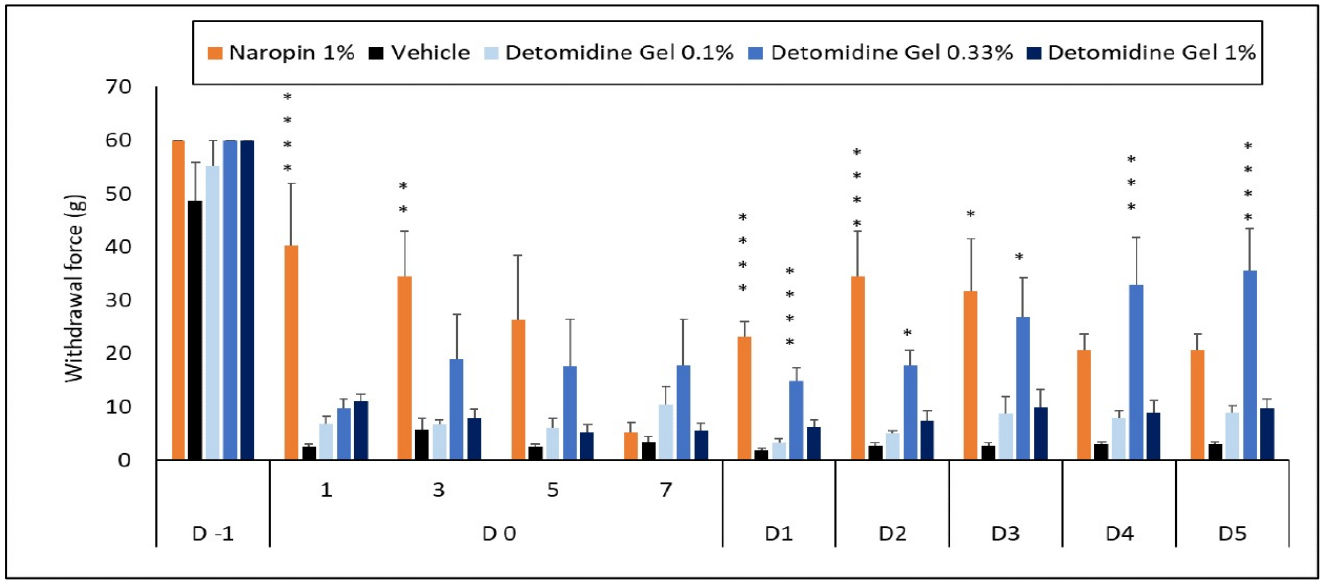
Binding and functional assays with detomidine were conducted against a wide range of molecular targets in order to better understand its MOA

- ✓ Detomidine has been confirmed to be a potent activator of α2A adrenergic receptors *in vitro*
- ✓ It was also discovered that detomidine acts as an agonist of 2 secondary targets, **histamine 4 (H4) and somatostatin 4 (sst4) receptors**

Receptor	Activity	Potency
$\alpha 2_A$ adrenergic	agonist	EC50 ~24 nM
Histamine (H4)	(partial) agonist	EC50 ~5μM
Somatostatin (sst4)	agonist	EC50 ~7μM

- ✓ Histopathological studies confirmed that detomidine's targets are expressed in the skin
- ✓ Detomidine's levels in the skin, as analyzed in pig skin, are in μM range, thus clinically relevant to all three targets

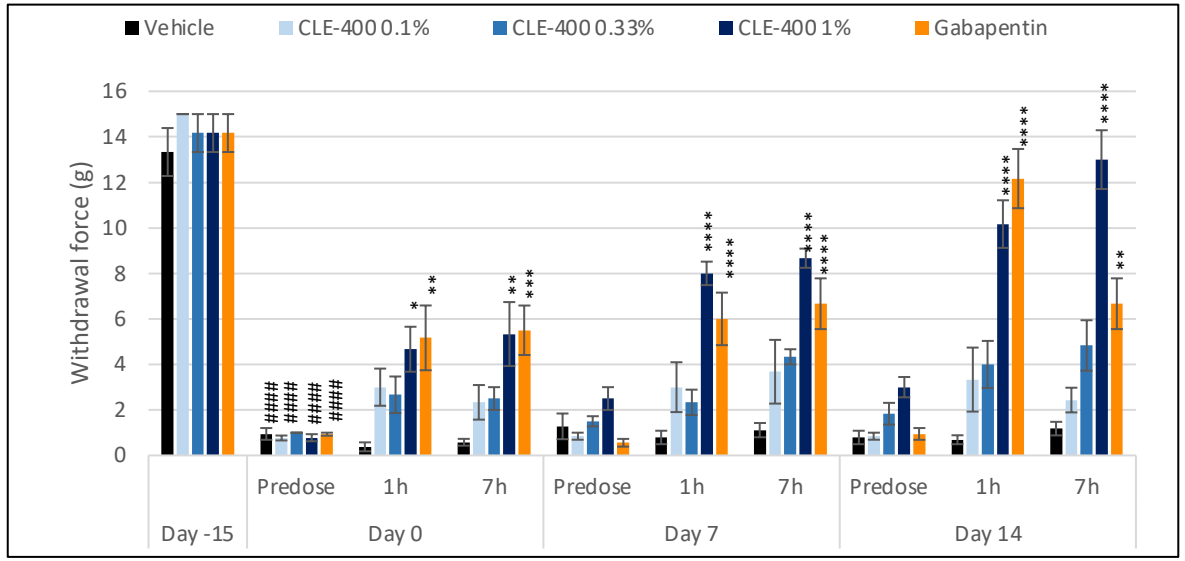
CLE-400 exhibits a substantial analgesic effect in acute post-operative pig model

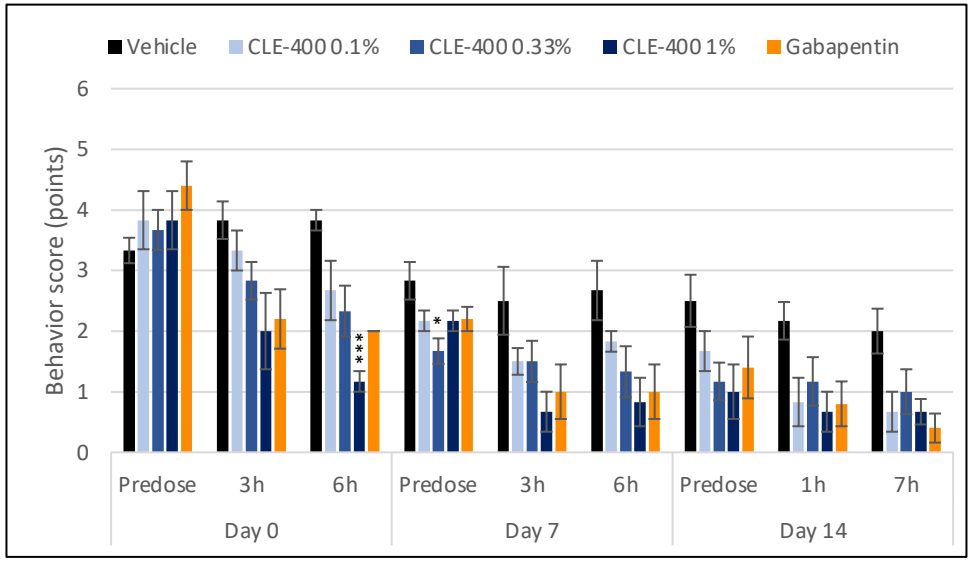


CLE-400 was administered twice daily, for 6 consecutive days. Mean (± SEM) group withdrawal response (g) following von Frey stimulation. *P<0.05; **P<0.01; ***p<0.001; ****p<0.0001 vs. placebo.

- ✓ Topical application of CLE-400 0.33% for 6 days resulted in a statistically significant increase in pain threshold as soon as Day 1 (2nd day of treatment); this effect gradually increased up to Day 5
- ✓ CLE-400 gel had no significant effect on locomotor activity, indicative of a lack of systemic toxicity (i.e. sedation)

CLE-400 exhibits a significant, dose dependent, analgesic effect in Peripheral Neuritis Trauma (chronic neuropathic pain) pig model





CLE-400 was administered twice daily, for 14 consecutive days. (A) Group withdrawal response (g) following von Frey stimulation. Mean (± SEM). #### p<0.0001 vs. baseline. *p<0.05; **p<0.01; ***p<0.001 ****p<0.0001 vs. Vehicle. **(B) General behavior score.** Mean (± SEM).*p<0.05; ***p<0.001 vs. Vehicle.

- ✓ CLE-400 exhibited a dose-dependent analgesic effect as early as 1 hour post application. Repeated dosing enhanced the analgesic effect up to Day 14
- ✓ CLE-400 resulted in a dose-dependent decrease in the behavior score starting several hours post treatment and throughout the entire study
- ✓ No sedation was observed

Conclusions

- Topical administration of **CLE-400** demonstrated a robust pharmacological effect in an acute post-operative pig model and in a chronic neuropathic pain (PNT) pig model
- Detomidine has been confirmed to potently activate α2A adrenergic receptors in vitro, with additional modalities that might contribute to **CLE-400** efficacy, presenting a possible multi-modal MOA
- Main and secondary targets of detomidine have been shown to be expressed in the skin, strengthening the proposition of local activity of **CLE-400**
- **CLE-400** is generally well tolerated locally and systemically in efficacy and safety/toxicology studies

Thank you

You are welcome to contact us

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