**CLE-400: A Potent Analgesic Topical Gel in Acute and Chronic Pain Pig Models**

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**Background and Aims**

- Alpha 2 (α2) adrenoceptor agonists have been in clinical use for decades, primarily in the treatment of hypertension. In recent years they have found wider application, particularly in the fields of anesthesia and pain management.
- Since α2-adrenoceptors were found to be present on nociceptors in the epidermis and dermis of the skin, treatments which may limit systemic adverse events without loss of analgesic effect, have gained interest.
- CLE-400 is a novel investigational drug that has not been approved for commercial distribution. CLE-400 is a novel topical formulation of detomidine, a potent α2-adrenoceptor agonist used for many years in veterinary medicine as a systemic medication for sedation in animals and has been developed with a proprietary topical formulation to enable maximal skin penetration while limiting systemic exposure.
- The aim of these preclinical studies was to examine the analgesic effect of CLE-400 for the management of acute post-operative pain and chronic neuropathic pain in pig models. Furthermore, studies were set to determine if there are additional protein targets regulated by detomidine, whether they are expressed in skin and thus, potentially associated with local analgesia.
- All experimental procedures were approved by an Institutional Animal Care and Use Committee in accordance with the National Institutes of Health’s Guide for the Care and Use of Laboratory Animals. Efforts were taken to minimize pain and distress of experimental animals.

**Methods**

- The validated post-operative pain pig model was selected as the preclinical model for acute pain. The pig was chosen for this study due to the notable anatomic, physiologic and neurologic resemblance between pig skin to human skin. Pigs underwent full-skin incision of 6–7 cm through the skin and fascia, keeping the muscle intact. Starting from fifteen minutes following surgery, CLE-400 at 0.1%, 0.33% and 5% strengths or placebo were administered twice daily, at a volume of 3 μl/cm² over an area of ~50 cm² for 5 consecutive days. Subcutaneous injection of neopain was used as a positive control. Mechanical sensitivity was assessed using the von Frey methodology together with General Behavior Scoring (GBS) to assess spontaneous pain and open field test to assess motor activity. These tests were performed 1 day pre-surgery (baseline), 3h, 5h, and 7h post-surgery on Day 0 and then once daily for an additional 4 days (1 hour post dose). Additionally, on Days 0 and 5 of study, blood samples and skin biopsies collected from the administration site, were taken in order to determine CLE-400 (detomidine) levels in skin and plasma.
- The validated Peripheral Neuritis Trauma (PNT) model developed in domestic pigs was chosen to evaluate CLE-400 effect on chronic neuropathic pain. Briefly, two weeks following PNT induction by partial sciatic nerve ligation, animals exhibit mechanical and tactile allodynia which are topically administered with CLE-400 at 0.1%, 0.33% and 5% strengths or placebo at 10 μl/cm² over an 80 cm² area, twice daily for 14 consecutive days on the dorsal part of the low foot - the area that is innervated by the injured sciatic nerve. Intravenous injection of Gabapentin served as a positive control.

**Results**

- Topical administration of CLE-400 demonstrated a rapid and cumulative analgesic effect in acute pain and chronic neuropathic pain pig models. CLE-400 gel formulation maintains high dermal concentrations over an extended period of time (depot effect in the skin) while maintaining limited systemic exposure. Lastly, CLE-400 may activate, in addition to α2 adrenoceptors, the histamine 4 receptors and somatostatin 4 receptor which are all expressed in skin and thus, potentially associated with the achieved local analgesia.

**Conclusion**

CLE-400 appears promising as a non-systemic, topical formulation for treating acute and chronic pain. Topical administration of CLE-400 demonstrated a rapid and cumulative analgesic effect in acute pain and chronic neuropathic pain pig models. CLE-400 gel formulation maintains high dermal concentrations over an extended period of time (depot effect in the skin) while limiting limited systemic exposure. Lastly, CLE-400 may activate, in addition to α2 adrenoceptors, the histamine 4 receptors and somatostatin 4 receptors which are all expressed in skin and thus, potentially associated with the achieved local analgesia.

**References**


**Figure 1** Analgesic efficacy in acute post-operative (POP) pig model

**Figure 2** Analgesic efficacy in PNT chronic neuropathic pain pig model

**Figure 3** Determidine targets α2A-adrenoceptor, histamine 4 receptor and somatostatin 4 receptor are expressed in pig skin