Clexio Biosciences

CLE-400
a novel non-opioid topical treatment for painful diabetic neuropathy

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SMi conference May 11th, 2021

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A clinical stage company redesigning therapies for neurological and psychiatric conditions

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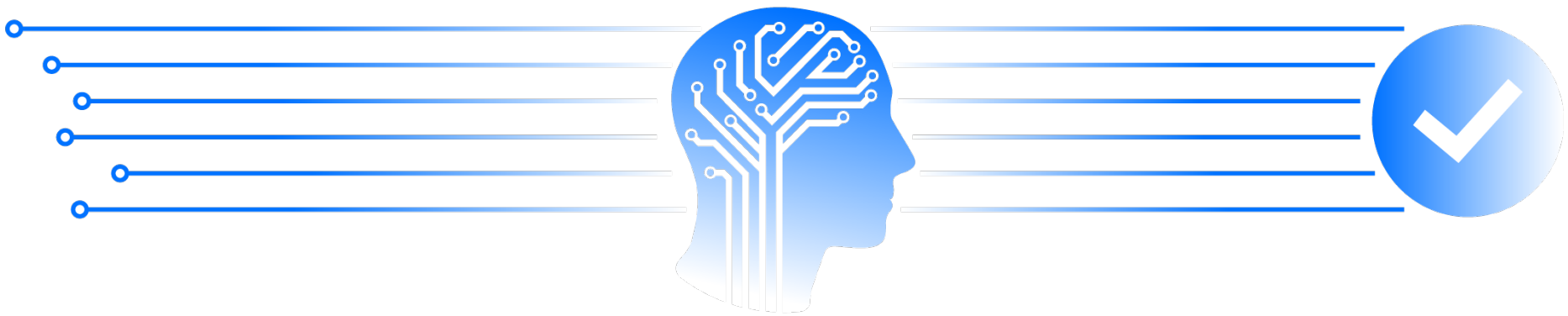
Clexio at a glance



Multi-asset pipeline

- ✓ Lead asset in Phase 2
- ✓ Additional assets in Phase 1
- ✓ Preclinical pipeline

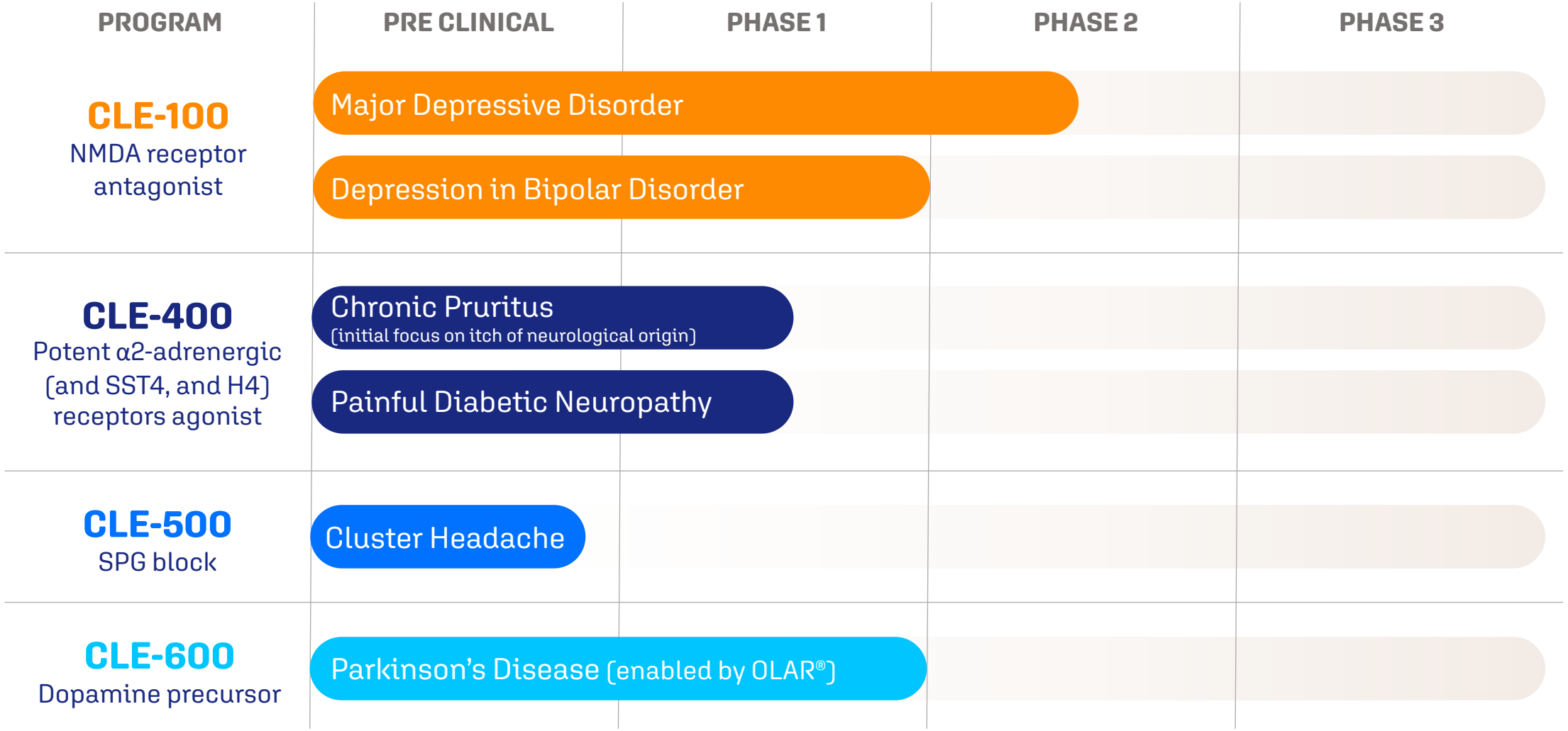
Focus on Psychiatry and Neurology

- ✓ Targeting significant unmet needs and growing markets

Technological and therapeutic innovation

- ✓ 27 patent families, 12 granted in US
- ✓ Proprietary technologies
- ✓ Internal pipeline creation capabilities

Clexio's pipeline



CLE-400

A novel non-opioid topical treatment under development for painful diabetic neuropathy and chronic pruritus

CLE-400 is a new investigational drug that has not been approved for commercial distribution

Clexio

CLE-400 novel topical agent for high unmet need

Painful Diabetic Neuropathy

2.6 million patients in the US suffer from Painful Diabetic Neuropathy (PDN)[1]

Less than **50% of patients** achieve significant benefit with any single drug [2]

Topical treatment is highly desirable for PDN patients who suffer from multiple co-morbidities

Chronic Pruritus

23-44 million patients in the US suffer from chronic pruritus due to cutaneous or systemic conditions [3]

No FDA approved treatment

Pathophysiological types:

- Dermatological
- Systemic
- Neuropathic (e.g. BRP, NP, Post-burn)

Safe and efficacious treatment options are limited for Peripheral Neuropathic conditions (both pain and itch).

1. *Painful Diabetic Neuropathy - Global Drug Forecast and Market Analysis to 2026: GDHC164PIDR Published: 1. 2018*
2. *Freynhagen R, Bennett MI. Diagnosis and management of neuropathic pain. BMJ. 2009 Aug 12;339:b3002*
3. *Mollanazar, Nicholas K., Savannah Dean Koch, and Gil Yosipovitch. "Epidemiology of chronic pruritus: where have we been and where are we going?." Current Dermatology Reports 4.1 (2015): 20-29*

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

A New Molecule for PDN

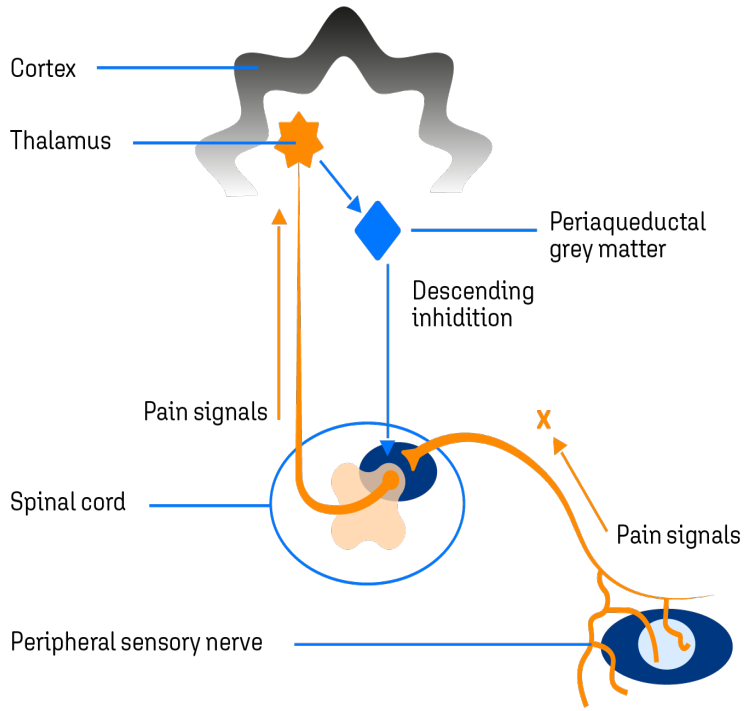
- Detomidine, a potent α2-adrenergic receptor agonist activating additional potentially therapeutically relevant targets (SST4R, H4R)
- Approved as a systemic medication for veterinary use. Never developed for human.

Targeting α2-adrenergic receptors peripherally

- Systemically administered α2-adrenoceptor agonists are used in pain management and anesthesia. Their use is limited to invasive RoA and may lead to systemic AEs
- Clexio's Immunohistochemistry studies demonstrated that **α2-ARs, H4R and SST4R are expressed in the skin**
- Activation of these receptors could produce analgesia **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



CLE-400 – highlights on development

A potent α2-adrenoceptor agonist
activating additional relevant targets (SST4R, H4R)

+

Peripheral effect
Targeting peripheral nociceptors,
limiting systemic exposure

+

Long lasting effect
depot effect in the skin,
once daily administration

Significant effect demonstrated in two Pain pharmacological models:

- Onset within 1hr of treatment (PNT)
- Cumulative analgesic effect

Significant effect demonstrated in pre-clinical Pruritus pharmacological model:

- Significantly suppressed chloroquine-induced scratching behaviors

Completed successfully FIH SAD study, 3 doses tested

- Dose linearity
- PK: suitable for QD administration
- Safety supports proceeding to MAD with all doses

Starting MAD, preparing Ph2 in neuropathic itch and in PDN

Proposed Mechanism of Action

Potential Multi-Modal MOA of Detomidine

α2A adrenoceptor agonist (EC_{50} ~24 nM)

- The systemic analgesic effect of another α2 adrenoceptor agonist (clonidine) has been demonstrated in pain.
- α2 adrenoceptors have been shown to be expressed on nociceptors in skin epidermis [1]
- Topical administration of α2 adrenoceptor agonist may inhibit abnormal nociceptor excitability associated with pain.

Histamine H4R agonist (EC_{50} ~5 μM)

- H4 receptor is expressed in immune cells, dermal fibroblasts and keratinocytes, CNS, DRG and in peripheral afferent nerve fibers.
- Systemic administration of H4 receptor agonists has been shown to **alleviate painful peripheral neuropathy in multiple rodents models [2].**

Somatostatin SST4R agonist (EC_{50} ~7 μM)

- SST4 receptors are localized in the CNS, peripheral immune cells, DRG and skin epidermis.
- Systemic administration of SST4 agonists exhibited **analgesic effects in various rodent pain models, including inflammatory pain, back pain, cancer pain and neuropathic pain [3].**

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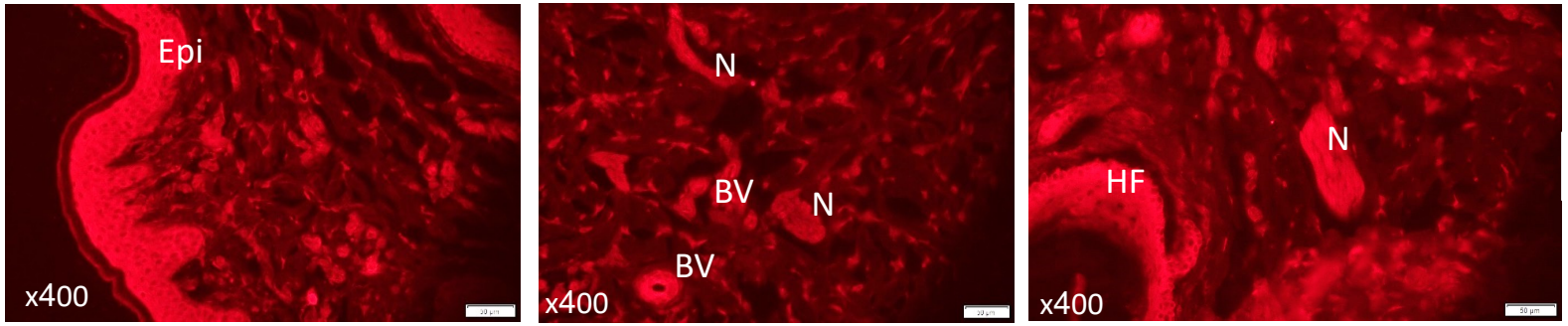
1. Riedl et al, Comp Neurol. 2009 April 1; 513(4): 385–398.
2. Sanna et al, Pain, 2015 Dec;156(12):2492-2504
3. Pinter et al, Naunyn-Schmiedeberg's Archives of pharmacology 2002 Aug;366(2):142-50.

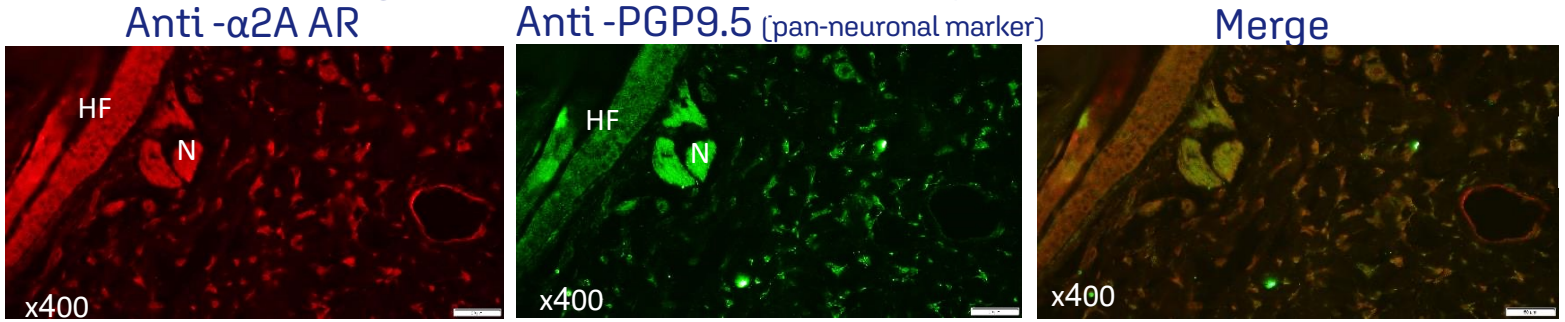
α2A-Adrenergic Receptor expression in the skin of Peripheral Neuritis Trauma (PNT) pigs

Immunostaining with anti –α2a adrenoceptor (α2A AR)



α2A-AR expression in epidermis, dermal nerves, blood vessels and hair follicles

Immunostaining with anti –α2a adrenoceptor and neuronal marker



α2A-AR is expressed in the skin peripheral nerves

Legend: N- nerve, BV- blood vessel, Epi- epidermis, HF- hair follicles

Clexio confirmed α2A expression in pig skin (epidermis, dermal nerves, blood vessels and hair follicles) using immunohistochemistry staining, supporting the hypothesis of CLE-400 peripheral activity

Clexio evaluation of CLE-400 in relevant Pain preclinical models

- Peripheral Neuritis Trauma (PNT)
- Post Operative Pain (POP)

Peripheral Neuropathic Pain Pig Model

- Peripheral neuritis trauma (PNT) model was developed in domestic pigs* to understand the pathophysiology of chronic neuropathic pain
- Pig is considered an excellent model for topical application due to their skin resemblance to humans skin and potential better clinical translation than rodents
- Gabapentin and Morphine have shown efficacy in this model (inhibited evoked and spontaneous pain)
- PNT in pigs serves as a valid preclinical model for the study of the chronification of peripheral nerve injury and for investigation of new pain therapies

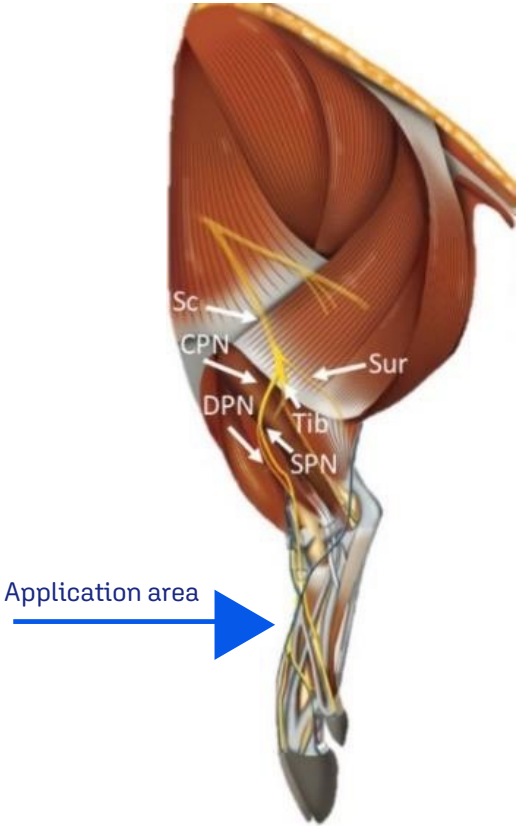
*Castel D. *et al.* The Journal of Pain, Vol 17, No 1 (January), 2016: pp 36-49
Rice FL, *et al.* Neurobiology of Pain, 5 (2019) 100021

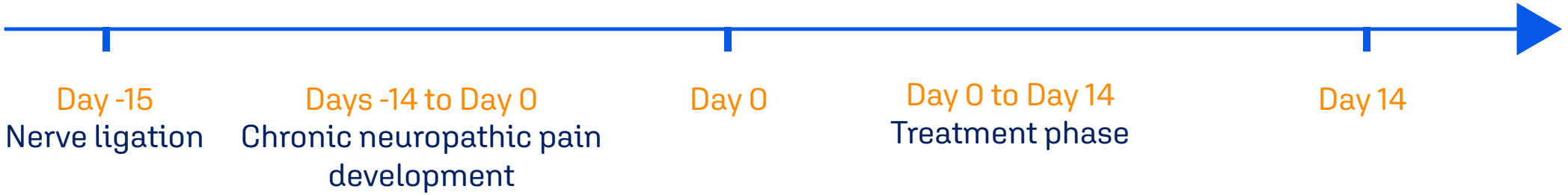
Induction of Neuropathic Pain

1. Animals are anaesthetized and an incision is made through the skin and fascia on the left side of the lower back, approximately 1 cm lateral and parallel to the spine line of the pig. The muscles are then retracted, and the sciatic nerve exposed.

2. Following sciatic nerve exposure, PNT is induced by silk threads, immersed in complete Freund's adjuvant overnight to induce inflammation. The threads are used to create 3 loose ligations surrounding the lateral half of the sciatic nerve bundle.

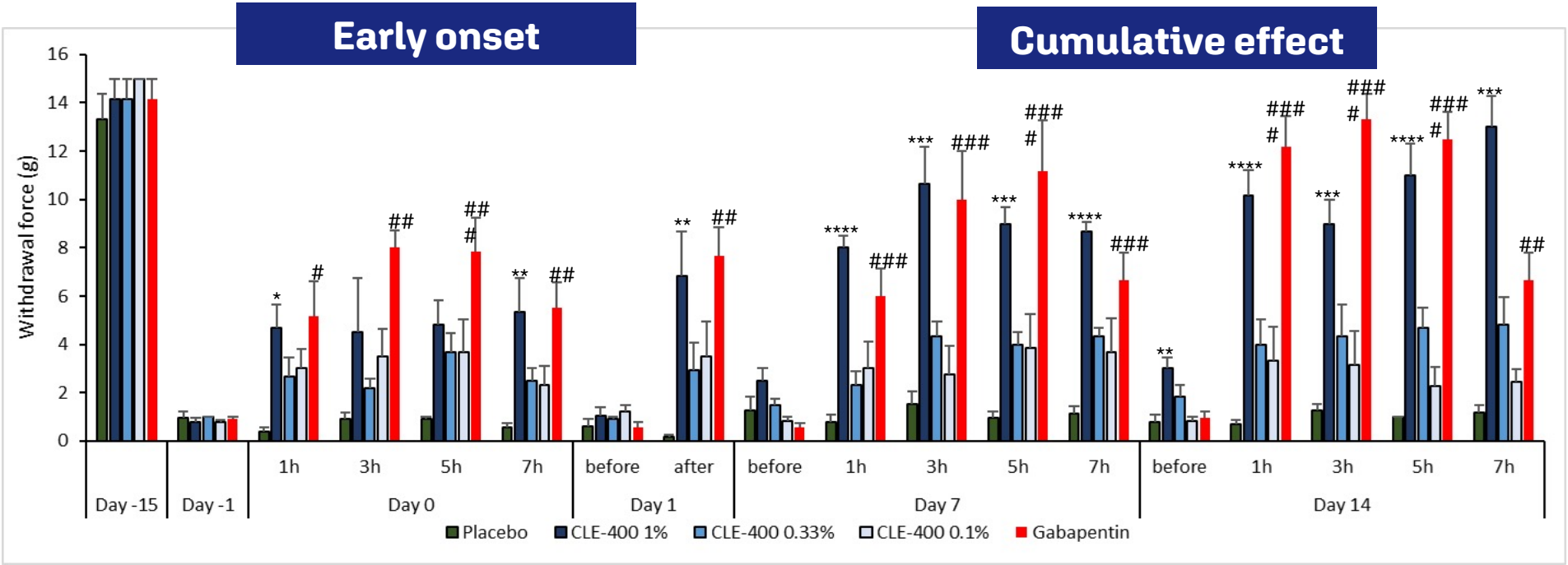
3. 2 weeks after surgery, once chronic neuropathic pain is established, CLE-400 was topically applied twice daily for 2 weeks on the outer area of the leg that is innervated by the injured sciatic nerve.





CLE-400 results in pig PNT (Peripheral Neuritis Trauma) model

The analgesic activity of CLE-400 at 3 doses administered topically (BID) for 14 days was evaluated on PNT-induced neuropathic pain in pigs. Von Frey (VF) assessment was used to evaluate mechanical sensitivity. A lower withdrawal force threshold indicates severe pain.



Mean (± SEM) group withdrawal response (g) following von Frey stimulation:
*P<0.05; **P<0.01; ***p<0.001; ****p<0.0001 CLE-400 1% vs. placebo using one-way Anova followed by Tukey test
#P<0.05; ##P<0.01; ###p<0.001; ####p<0.0001 Gabapentin vs. placebo using one-way Anova followed by Tukey test

CLE-400 exhibited a dose-dependent analgesic effect as early as 1hr.
Repeated dosing enhanced the analgesic effect.

PNT model – Conclusions

- Topical administration of CLE-400 twice daily for 14 days exhibited a **dose-dependent** analgesic effect, with CLE-400 1% alleviating pain in a **statistically significant** manner as soon as 1 hr after the first treatment.
- Cumulative analgesic effect with repeated administrations of CLE-400.
- Effect is achieved when gel is applied on the dermatome and not on lesion area itself.
- No motor impairment/sedation were observed (tested in open field apparatus)

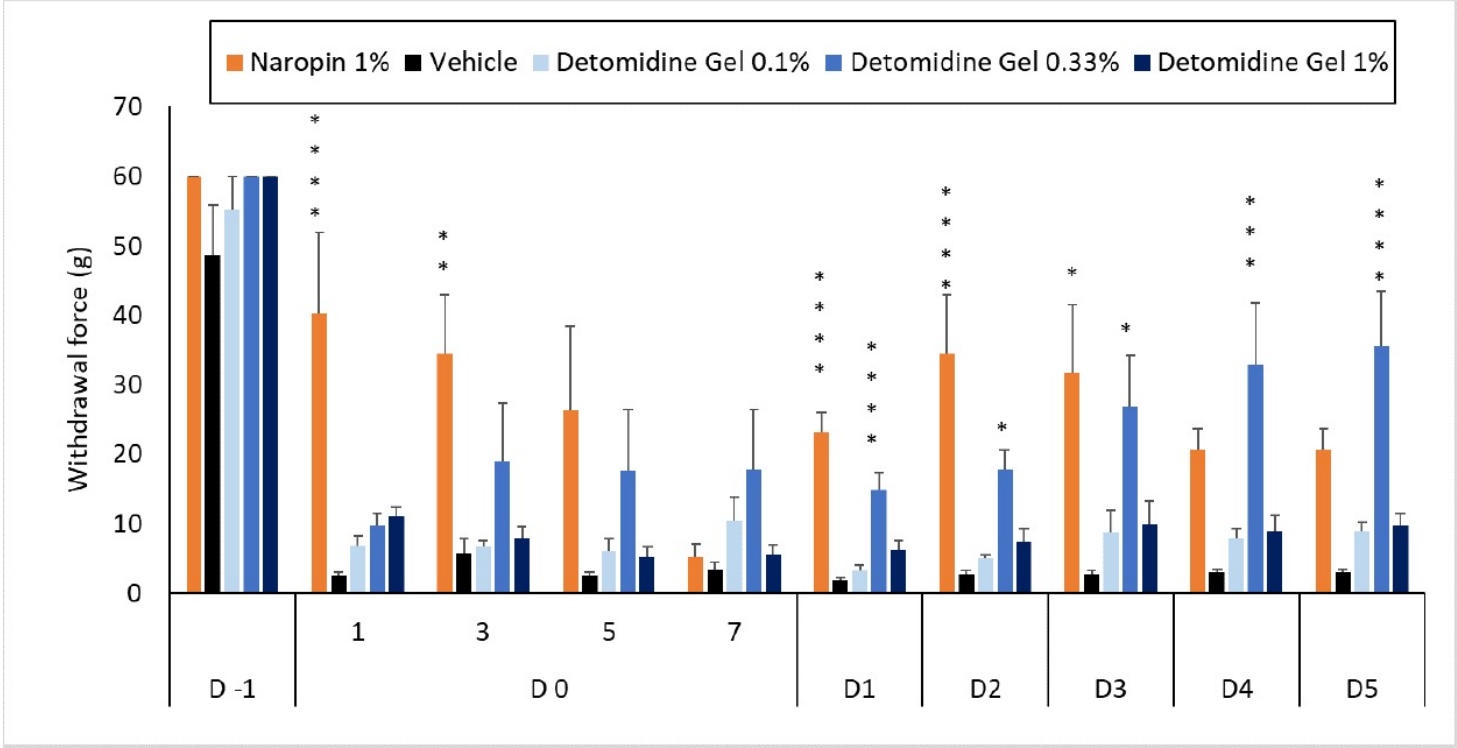
Acute Post-Operative Pain (POP) Model

Acute Post-Operative Pain (POP) Pig Model

- A validated model of POP in pigs was used to assess the topical analgesic effects of CLE-400.
- The pig model of incisional pain provides greater translational relevance for validating new topical and localized pain treatments in humans* as pigs skin bares notable similarity to human anatomy.
- The anesthetized animals are undergoing a 6-7 cm long skin and fascia incision in the left flank, keeping the muscle intact. The skin incision is then closed using a sterile suture.
- CLE-400 was applied twice daily for 6 days (Day 0 to Day 5) starting 15 min following surgery on Day 0, on the skin area surrounding the incision (left flank).
- Analgesic effects of CLE-400 (0.1 to 1.0%) post-surgery were evaluated on Days 0-5 by measuring withdrawal threshold to von Frey filaments (as a measure of pain).

*Castel D. *et al.* Eur J of Pain, Vol 18, 2014: pp496-505

CLE-400 results in pig POP model – Mechanical Sensitivity
(measured by Von Frey assessment)



Mean (± SEM) group withdrawal response (g) following von Frey stimulation:
*P<0.05; **P<0.01; ***p<0.001; ****p<0.0001 vs. placebo using one-way Anova followed by Tukey test Von Frey assessment on D1-D5 was performed 1 hour post morning application of CLE-400

Topical application of CLE-400 0.33% for 6 days resulted in statistically significant increase in pain threshold as soon as Day 1 (2nd day of treatment) and this effect increased gradually up to Day 5

POP model – Conclusions

- Following the procedure, placebo-treated pigs developed high sensitivity to mechanical stimulation, detectable spontaneous behavioral changes and had minor to nonexistent motor dysfunction, demonstrating validity of the model.
- **Twice daily topical application of CLE-400 0.33% for 6 days resulted in statistically significant analgesic effects as soon as Day 1 (Day 0 is defined as the 1st dosing day) and this effect increased gradually up to Day 5, indicative of a cumulative effect with repeated dosing.**
- The total walking distance in the open field apparatus was not affected by CLE-400 at any dose level, suggesting that no motor impairment/sedation were observed.

Phase 1 studies

CLE-400 Phase 1 studies - SAD

Single Ascending Dose (SAD) study completed successfully (Germany, Oct 2020)

Study design

- A Placebo-controlled, Randomized, Double-blind Phase 1 Study to Assess Safety, Tolerability, and Pharmacokinetics of Single Escalating Topical doses of CLE-400 (3 strengths) in Healthy Subjects
- 10 subjects per cohort (total of 30 subjects): 8 subjects received CLE-400, 2 received placebo on Day 1, followed up to 8 days after dosing

Safety

- All 3 cohorts were completed successfully
- **The safety results support proceeding with clinical development**

PK

- Dose proportionality was demonstrated
- **PK profile supportive of once daily administration**

CLE-400 ongoing studies and next steps

- **Ongoing Multiple Ascending Dose (MAD) study:**
  A Placebo-controlled, Randomized, Double-blind Phase 1 Study to Assess Safety, Tolerability, and Pharmacokinetics of Multiple Escalating Topical Doses of CLE-400 applied once daily in Healthy Subjects

- **Preparing for Ph2 POC studies in PDN and in Neuropathic itch**

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Thank you

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