Clexio Biosciences

Introducing CLE-400;

Topical Alpha-2-Adrenergic Agonist as a First-in-Class Treatment for Localized Chronic Pruritus

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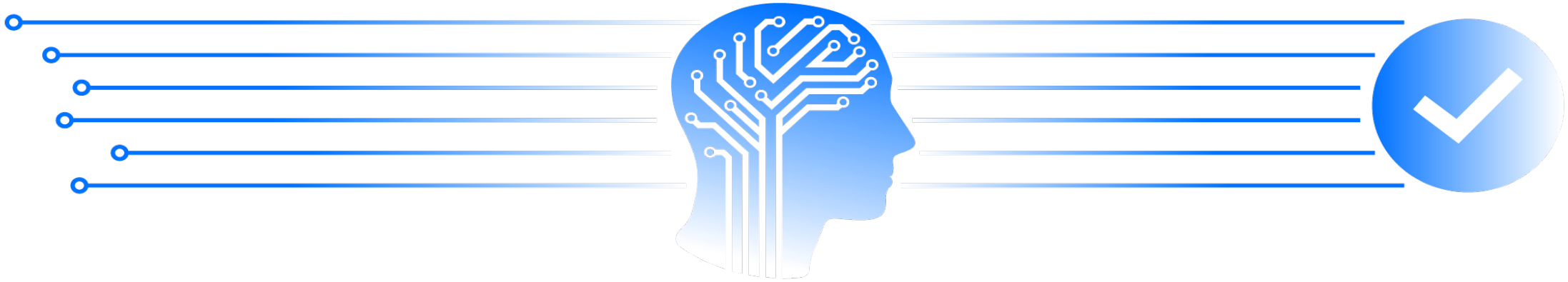
Clexio at a Glance



Multi-Asset Clinical Pipeline

- ✓ 4 clinical stage programs
- ✓ Lead asset completed Phase 2
- ✓ Advancing internally discovered preclinical pipeline

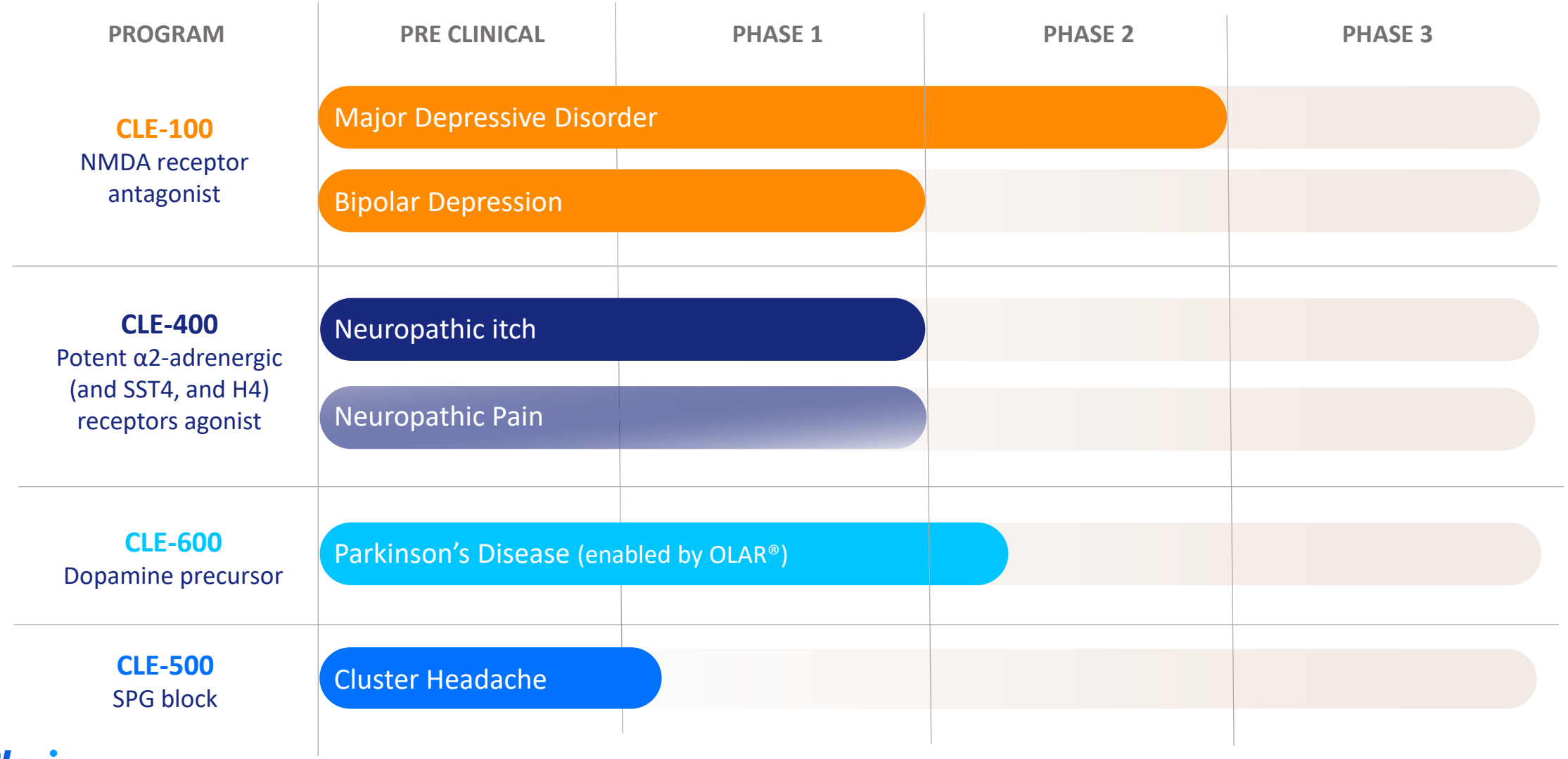
Focus on Neurological and Psychiatric conditions

- ✓ Targeting significant unmet needs

Using validated MOAs

- ✓ Focus on validated Mechanism of Actions
- ✓ De-risked clinical development pathways

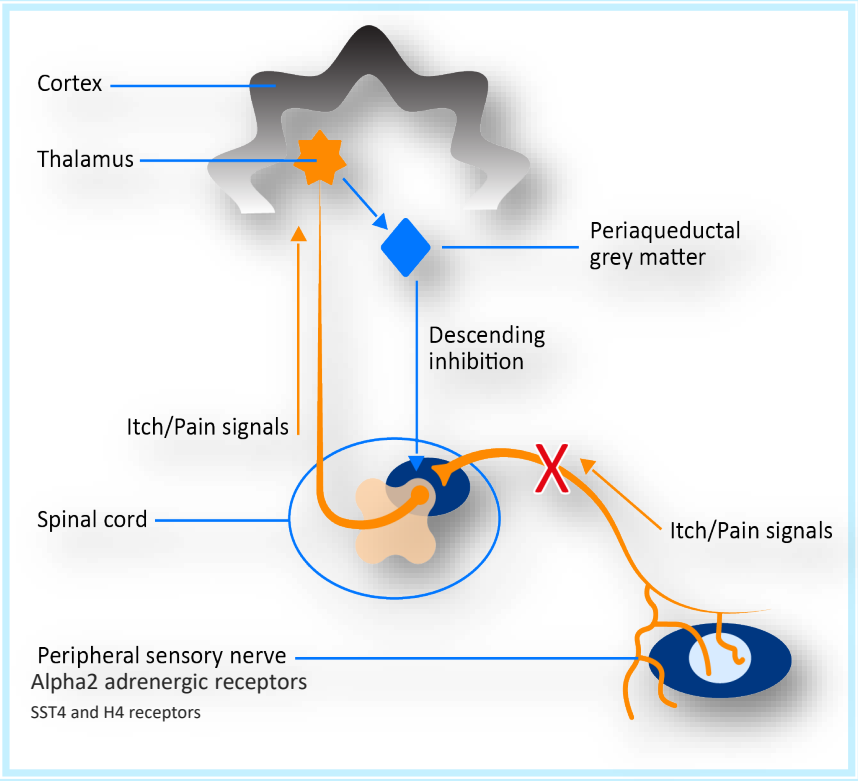
Clexio's Pipeline



CLE-400* topical gel developed for Neuropathic itch and additional localized pruritus conditions

Pruritus & pain can involve the same type of peripheral sensory neurons

(innervation of C-fibers)



CLE-400 topical application targets Peripheral α2-adrenergic receptors

- Detomidine is a potent α2-adrenergic agonist. It activates additional targets (SST4R, H4R) relevant to neuropathic conditions.
- Anti pruritic effect of α2-adrenergic agonist administered intrathecally was demonstrated in animals [(1)].
- Clexio's immunohistochemistry studies demonstrated that α2-adrenergic, SST4 and H4 receptors are expressed in the skin. Activation of these receptors could produce anti pruritic as well as analgesic effects by inhibiting the excitability and neural signaling from the peripheral nociceptors to the brain.

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

1. Alan Cowan and Gil Yosipovitch. Pharmacology of Itch. Handbook of experimental pharmacology 226, 2015. p213. SST4R – Somatostatin 4 receptor, H4R – Histamine 4 receptor

Chronic Pruritus overview

- **Chronic Pruritus** is defined as itch lasting more than 6 weeks.
- **23-44 million** patients in the US suffer from chronic pruritus.
- Pruritus may be severe and may be associated with sleep and mood disturbances, anxiety, depression and impact on quality of life [1].
- Pruritus is categorized based on the underlying etiology as **dermatological**, **systemic**, **neurological**, **psychiatric**, **multifactorial** or of **unknown causes** [2].
- There is **only one FDA approved product for chronic pruritus**, administered intravenously, for pruritus associated with chronic kidney disease (CKD-aP) in adults undergoing hemodialysis (KORSUVA™) [3] .

Safe and efficacious treatment options for Chronic Pruritus are limited

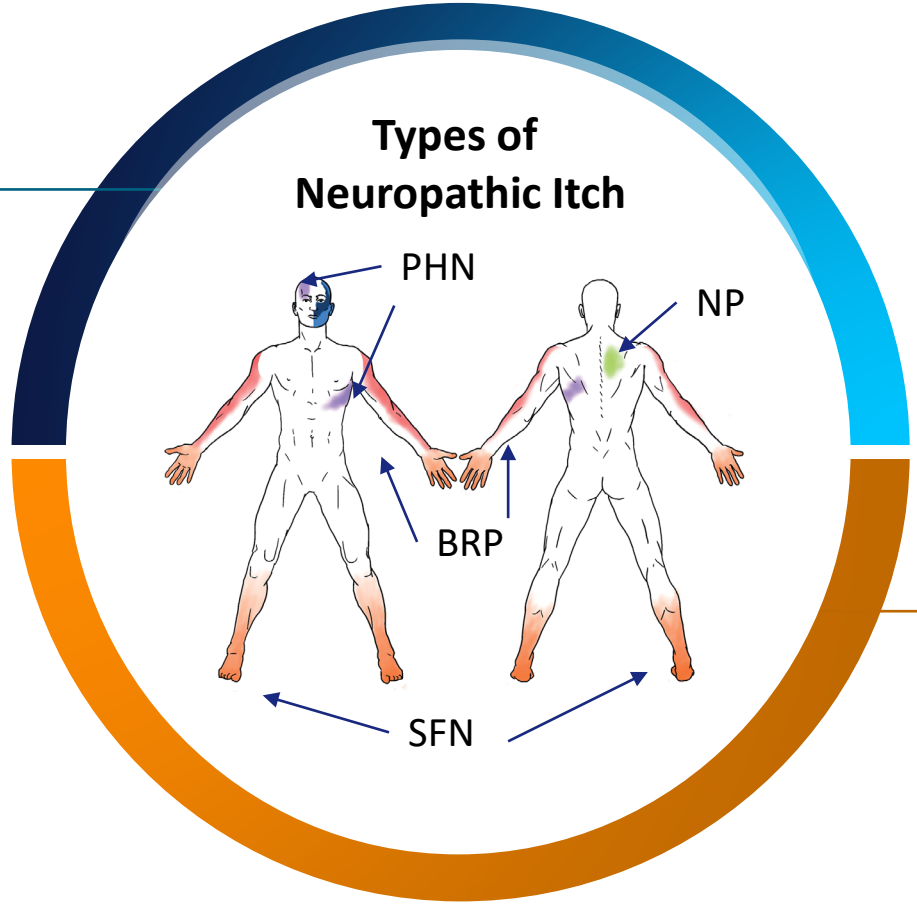
CLE-400 has the potential in alleviating itch in localized chronic pruritus conditions

1. *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*
2. *Periera MP et al. Itch (2017) 2:e06, p1-6*
3. *KORSUVA label.*

Neuropathic itch overview

- **Neuropathic itch** accounts for **8% to 19%** of patients affected by chronic pruritus treated in itch centers[1]

- **Lesions of the peripheral nervous systems** are the most common cause of Neuropathic Itch



No FDA-approved drugs for neuropathic itch

Limited off-label options

- Topical capsaicin patch 8% – no proven efficacy
- Systemic treatments (eg, Pregabalin, gabapentin) may be effective but may not be well tolerated

1. Rosen et al. *Derm.Clin*. 2018;36:213-224.
BRP=Brachioradial pruritus; NP=notalgia paresthetica; PHN=postherpetic neuralgia; SFN= small fiber neuropathy.

Neuropathic Itch conditions presumably associated with nerve entrapment

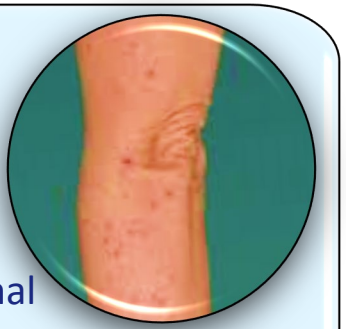
Notalgia Paresthetica (NP) and Brachioradial Pruritus (BRP)

- Most patients suffer from daily itch [1].
- Pruritus is accompanied by paraesthetic and dysaesthetic symptoms [2].
- Patients' sleep, mood and self-care activities are negatively impacted by this condition [3].
- Patients often seek relief through the application of cold to the skin (ice-pack sign) [2].
- Underdiagnosed condition.

Notalgia Paresthetica

- Localized pruritus to the mid-to-upper portion of the back, typically unilateral. May be associated with hyperpigmented skin patches [4]
- Caused by damage to the thoracic nerves (T2-T6) most frequently from vertebrae degeneration, disc herniation or musculoskeletal compression [4].

Brachioradial Pruritus



- Typically bilateral pruritus in the forearms.
- Caused by compression of the cervical spinal cord or spinal ganglia at the C5/C6 level [1].

1. Lipman et al. JAAD Int. 2021 Mar; 2: 96–97.
2. Perieria MP et al. Acta Derm Venereol 2018; 98: 82–88
3. Howard et al. International Journal of Dermatology 2017, p1-5
4. Bacci E. et al. JAAD Int 2022;8:94-101

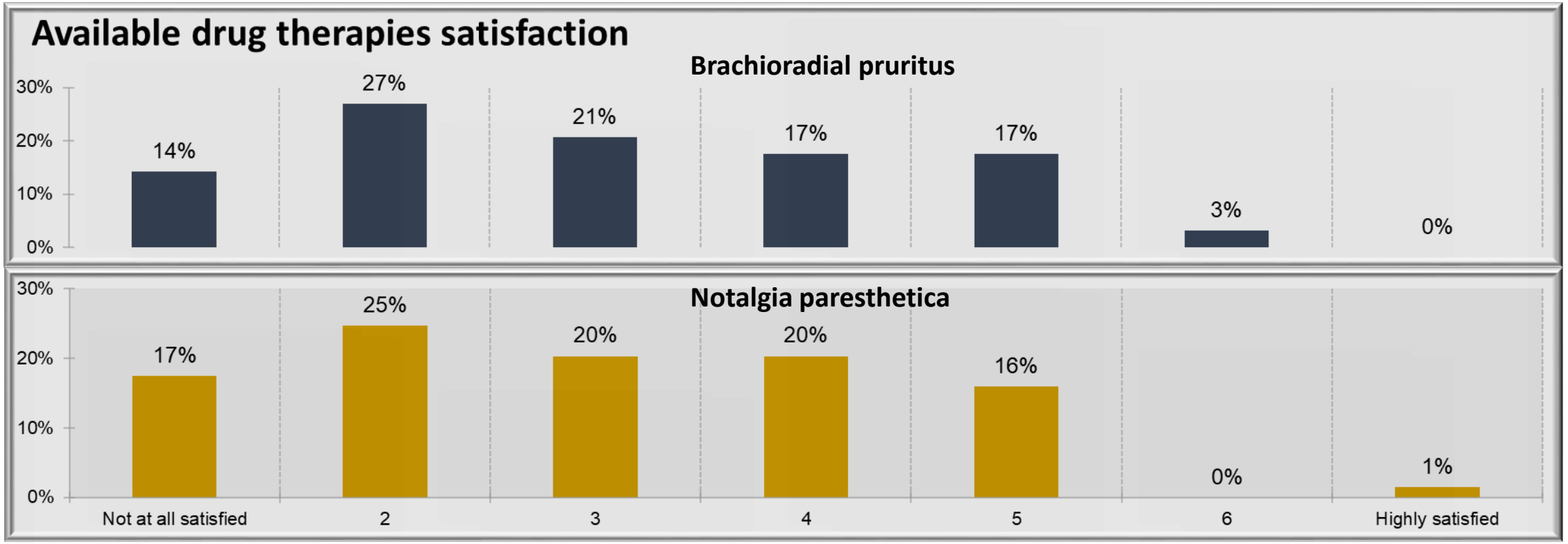
Insights from US physicians survey [1] : a significant unmet need

- Brachioradial pruritus (BRP) and Notalgia Paresthetica (NP) are treated almost exclusively by dermatologists
- Estimated prevalence in the US: 3.5 million patients suffering from NP and BRP , Out of which: only 860 thousand patients are drug-treated
- Clinicians estimate more than half of BRP and NP patients to have moderate to severe pruritus (60% and 53%, respectively)
- Topical steroids are the mainstay of treatment, and unmet need is high

1. *Clexio-sponsored research in the US with 111 dermatologists - Jan 2022*

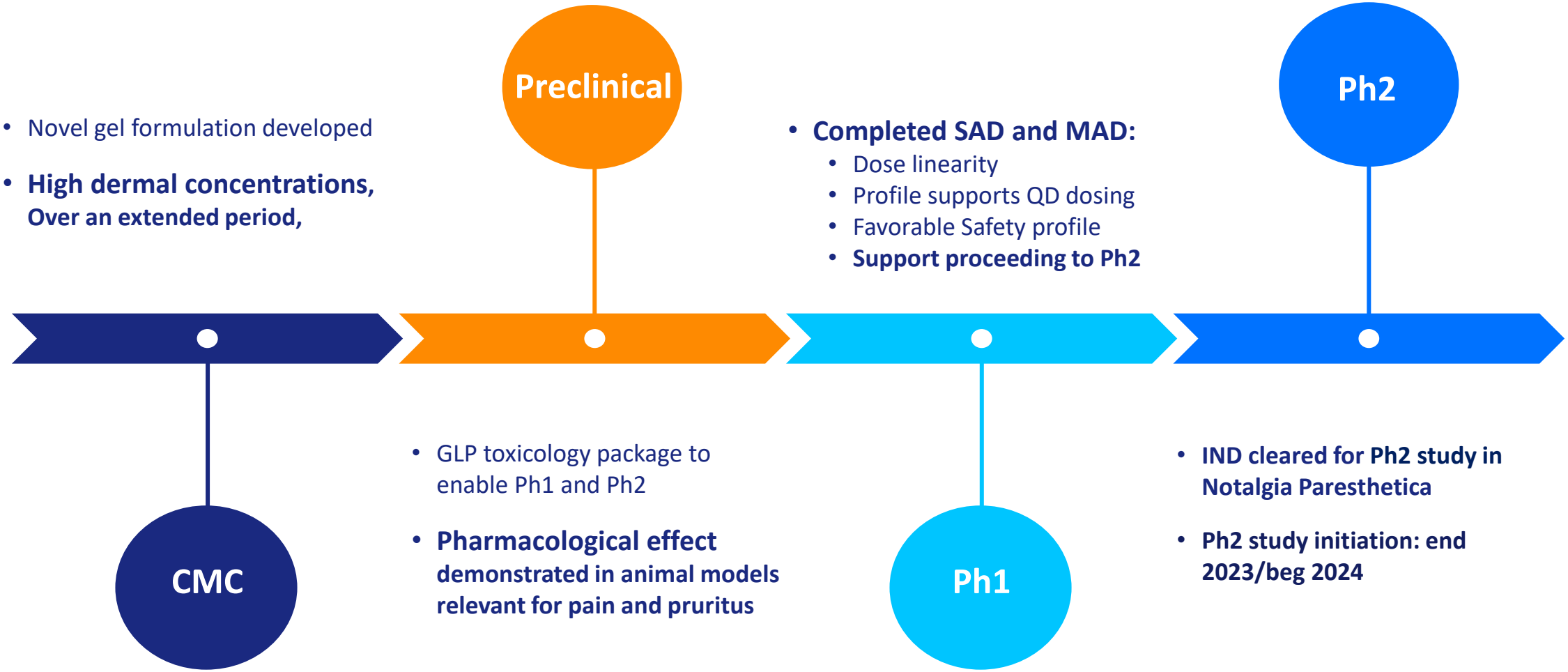
Unmet Need: Dermatologists are dissatisfied with the available drugs to treat BRP and NP[1]

- BRP and NP treatments satisfaction is similar

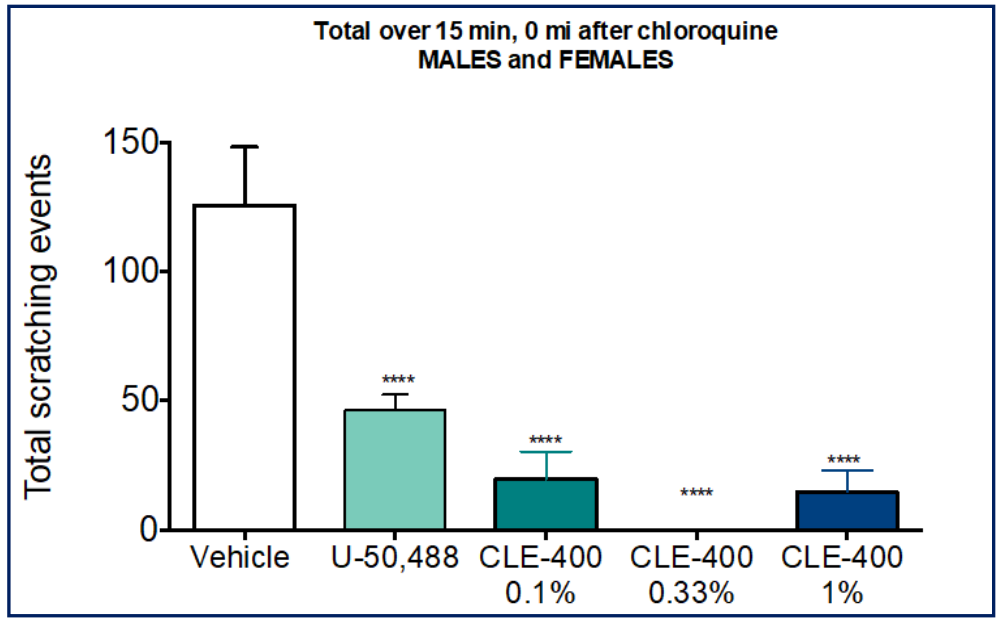


1. *Clexio-sponsored research in the US with 111 dermatologists - Jan 2022*

CLE-400 development status – completed MAD, Ph2 ready



CLE-400: results in mice chloroquine-induced itch model



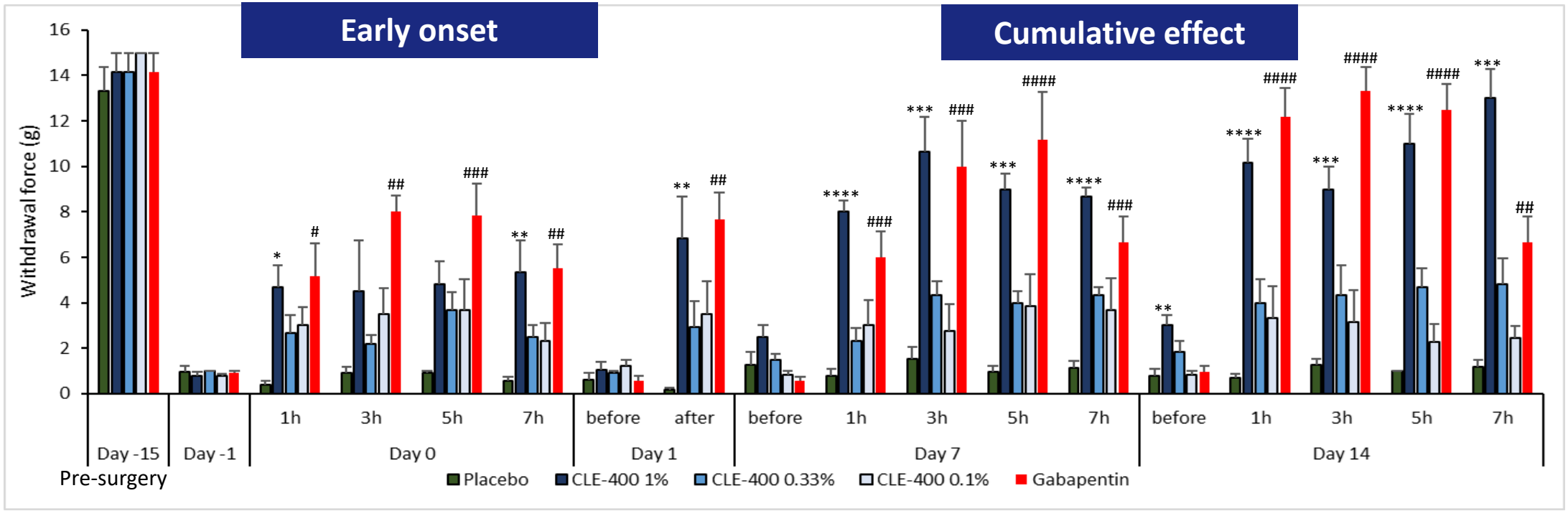
****P < 0.0001 compared to vehicle-treated group. N=7-8 per group.
One-way ANOVA with Fisher's LSD test

- 3 doses of CLE-400 administered topically once daily for 5 days (last application 30 min prior to chloroquine challenge)
- Positive control: U-50,488 (Kappa-opioid receptor agonist, short-acting antipruritic agent), injected IP once 30 min prior to chloroquine challenge

Topical application of CLE-400 significantly suppressed chloroquine-induced scratching behaviors at all dose levels

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

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 allodynia. A lower VF 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.

CLE-400 Phase 1 SAD/MAD results

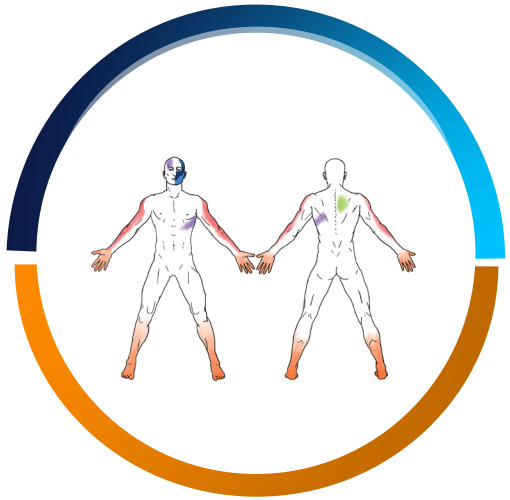
Completed successfully FIH Single Ascending Dose (SAD) study, 3 doses tested

- A Placebo-controlled, Randomized, Double-blind Phase 1 study to Assess Safety, Tolerability, and Pharmacokinetics of Single Escalating Topical Doses of CLE-400 applied once daily in Healthy Subjects
- Dose linearity (absorption) - Detomidine exposure increases proportionally with dose
- PK: **supports once daily administration**
- Safety: supports proceeding to multiple ascending dose (MAD) study

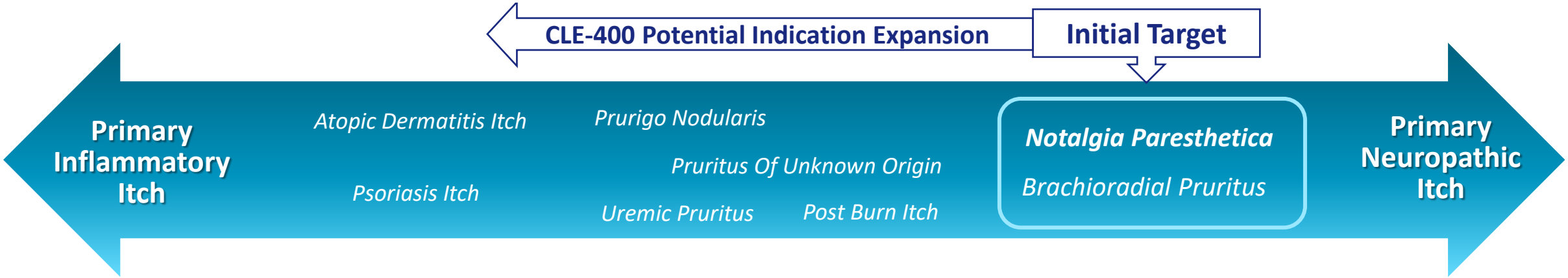
Completed successfully Multiple Ascending Dose (MAD) study, 3 doses tested

- A Placebo-controlled, Randomized, Double-blind Phase 1 Study to Assess Safety, Tolerability, and Pharmacokinetics of Multiple Escalating Topical Doses of CLE-400 (3 doses tested) applied once daily in Healthy Subjects for a week
- No severe adverse events, serious adverse events, or deaths were reported
- Overall, CLE-400 was safe and well tolerated. **The safety findings from Phase 1 supports proceeding to Phase 2 PoC study in Neuropathic itch**

Clinical development strategy: Target neuropathic itch initially, then expand to other types of chronic itch



- **First:** Phase 2 POC planned in Notalgia Paresthetica, randomized, vehicle-controlled, double-blind study, including 4 weeks treatment period, 2 weeks follow up.
- **Then:** Run phase 2/3 in neuropathic itch **as well as additional studies in other itch indications to realize the program's full potential. Atopic Dermatitis Itch as a potential follow on**



THANK YOU!

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