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CLE-400: Topical α2-Adrenergic Agonist Being Developed as a Novel Mechanism for Treating Chronic Pruritus Associated with Notalgia Paresthetica

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Introduction & Objectives:

Notalgia paresthetica (NP) is a chronic peripheral neuropathy primarily characterized by localized back pruritus and possibly associated dysesthesias, including sensations of pain, numbness, and tingling. The symptoms of NP are typically unilateral and located medial or inferior to the scapula within the middle-upper back. NP is an often overlooked and underdiagnosed condition(1), and there are no approved treatments for it(2).

CLE-400 is a topical gel, comprising detomidine, an α2 adrenergic agonist, being developed to alleviate itch in localized chronic pruritus conditions. The activation of the α2 adrenergic receptors in the skin could produce anti pruritic and analgesic effects by inhibiting the excitability and neural signaling from the peripheral nociceptors to the brain. Our aim is to evaluate the efficacy and safety of CLE-400 in preclinical models and in clinical studies.

Materials & Methods:

CLE-400 antipruritic effect was examined in the chloroquine-inducted itch model in mice. Three doses of CLE-400 were administered topically once daily for 5 days, and the number of scratches was recorded for 30 min following chloroquine injection on the 5th day.

CLE-400 effect in peripheral neuropathy was tested in the peripheral neuritis trauma (PNT) model in pigs. In this study 3 doses were administered topically BID for 14 days and mechanical sensitivity in the affected skin area was measured using the Von Frey (VF) assessment.

The safety, tolerability, and pharmacokinetics of CLE-400 was evaluated in Phase 1 Single-Ascending-Dose and Multiple-Ascending-Dose studies in healthy volunteers. Currently, a phase 2 study in patients with NP is ongoing in the US, to study the efficacy, safety and tolerability of 4 weeks of treatment with CLE-400.

Results:

Topical application of CLE-400 significantly suppressed chloroquine-induced scratching behaviors in mice at all dose levels. In addition, CLE-400 exhibited a dose-dependent analgesic effect in the PNT model, that started as early as 1 hour post-dose, and was enhanced following repeated dosing during treatment period.

Phase 1 studies have shown that detomidine exposure increases proportionally with the dose, and the PK profile supports once daily administration. CLE-400 was safe and well tolerated, supporting proceeding to Phase 2.

Conclusion:

CLE-400 has demontrated anti pruritic and analgesic effects in preclinical models. Phase 1 study results supported proceeding to Phase 2, to further assess the efficacy and safety of CLE-400 in Notalgia Paresthetica patients.

While α2 adrenergic agonists are well established as systemic treatment of cardiovascular and psychiatric disorders , this trial of CLE-400 for Notalgia Parasthetica represents the first clinical study of this mechanism of action for the topical treatment of chronic, localized pruritus.

References:

1. Robinson C et al. Clin. Pract. Vol 13, p315–32, 2023
2. Bacci ED et al. JAAD Int. Vol 8, p94-101, 2022