PRURITUS

OPIOID RECEPTOR MODULATION AS NOVEL THERAPY TARGET IN CHRONIC PRURITUS

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Chronic pruritus (CP) is a highly prevalent symptom of dermatoses and systemic diseases. Novel therapies are lacking but are urgently needed as this symptom places a high burden on patients. In many patients, CP is associated with an itch-scratch cycle that evolves from the abnormal neuronal sensitization to itch. Signaling from periphery to spinal cord to brain involves mu and kappa opioid receptors at all transition points (i.e. opiate gating circuitry). Therefore, targeting opioid receptors via Nalbuphine (NAL), the novel mu-competitive antagonist/kappa agonist, is a promising approach to modulating the central sensation of itch, including those signals initiated in the skin. NAL Extended Release (NAL-ER) tablets have been formulated and investigated in 2 CP conditions.
In chronic kidney disease (CKD) associated-pruritus, subjects with end-stage renal disease undergoing hemodialysis, the 8 weeks NAL-ER 120mg BID therapy group (N=120; mean baseline Worst Itch NRS (WI-NRS) 6.94) demonstrated a statistically significant reduction (p=0.017) by 3.5 [2.4] compared to 2.8 [2.2] in the placebo group (N=123; mean baseline WI-NRS 6.75). In a prurigo nodularis (PN) phase 2 study (baseline mean 7-day WI-NRS ≥5), 6 of 12 subjects completing 10 weeks of NAL-ER 162mg BID reported ≥50% itch reduction as compared to 4 of 20 (20%) in placebo. In the long-term PN extension study, over 50% of subjects who maintained treatment for ≥6 months showed ≥1 improvement in the PN lesions based on clinician assessment.
The safety profile observed for NAL-ER showed primarily mild to moderate CNS (dizziness, somnolence) and gastrointestinal (nausea) adverse events that are self-limiting and occur in the first 2 weeks of drug initiation. A PN phase 3 study is currently enrolling.
Targeting opioid receptors in the skin and CNS is a promising approach in CP related to dermatoses and systemic diseases as these studies in PN and CKD suggest.