Efficacy and safety study of ALO-02 (extended-release oxycodone surrounding sequestered naltrexone) for moderate to severe chronic low back pain treatment

SCIENCE
Clinical Research

Key Take-Away:
ALO-02 has been demonstrated to provide significant reduction of pain in patients with chronic low back pain (CLBP) and has a safety profile similar to other opioids.

Chronic pain was estimated to affect 100 million Americans in 2008 and is conservatively estimated to cost between $560 and 635 billion (2008 dollars). Chronic pain is commonly treated with opioids, especially when other forms of therapy are ineffective. Increasing abuse, misuse, and diversion of prescription opioids recognized in the United States have led the U.S. Food and Drug Administration to suggest that the development of opioids formulated to deter abuse be a high public health priority.

ABSTRACT:
Background:
Chronic pain was estimated to affect 100 million Americans in 2008 and is conservatively estimated to cost between $560 and 635 billion (2008 dollars). Chronic pain is commonly treated with opioids, especially when other forms of therapy are ineffective. Increasing abuse, misuse, and diversion of prescription opioids recognized in the United States have led the U.S. Food and Drug Administration to suggest that the development of opioids formulated to deter abuse be a high public health priority.

ALO-02 capsules contain pellets of extended-release oxycodone hydrochloride (HCl) surrounding sequestered naltrexone HCl. This investigational formulation is designed to enable absorption of oxycodone HCl without release of naltrexone when taken as directed. Physicians may consider incorporating these abuse-deterrent formulations into an overall opioid risk management approach while appropriately weighing the benefits and risks for each patient who would benefit from opioid analgesia.

Rationale behind research
i. Epidemiological data illustrate the close relationship between increasing availability of prescription opioids and increasing rates of abuse, diversion, and negative outcomes
ii. One of the ways to deter abuse is by discouraging common methods of tampering to rapidly release the full opioid dose in extended-release formulations

Objective
To assess the efficacy and safety of ALO-02 in managing pain in patients with moderate to severe CLBP who require continuous around-the-clock opioid therapy.
NOTE: This double blind, placebo controlled, enriched-enrollment randomized withdrawal study (EERW) consisted of 4 phases: a screening period, an open label conversion and titration period, a double-blind treatment period and double-blind post treatment period.

- **Study outcomes**
  - Primary outcomes: mean change in weekly average diary numeric rating scale (NRS)-pain scores
  - Secondary outcomes: changes in roland morris disability questionnaire (RMDQ), Patient’s global assessment (PGA) of low back pain, 5 point categorical satisfaction with treatment (1, very dissatisfied to 5, very satisfied) and assessment of safety due to reported Adverse events (AEs)

- **Time Points**
  - **Primary outcomes**: baseline to final 2 weeks of double-blind treatment period
  - **Secondary outcomes**: baseline to week 12/Early Termination (ET)

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Results:

Outcomes

- **Baseline**: Overall characteristics between the randomized groups were similar.
- **Open-label conversion titration period**: During the open-label period, the median starting daily dose of ALO-02 was 20 mg, which rose to 60 mg as the final daily dose over the course of an average of 31 days. For patients randomized into the double-blind treatment period, the mean weekly NRS-Pain score decreased from 7.0 at screening to 3.1 at the end of the open-label period (randomization baseline).
- **Randomized double-blind treatment period**: For the final 2 weeks of the treatment period, these scores increased to 4.3 for placebo and 3.6 for ALO-02. The mean difference in NRS-Pain scores from randomization baseline to the final 2 weeks, the primary efficacy end point, was significantly superior for ALO-02 compared with placebo \( P = 0.0114 \).

Figure 1: Mean change from randomization baseline to the final 2 weeks of double blind treatment period in weekly NRS-pain scores

- Roland Morris Disability Questionnaire and PGA did not show significant treatment differences during the double-blind treatment period. At the end of week 12/ET, the percentage of patients reporting “very good,” “good,” or “fair” tended to be higher for ALO-02 than placebo. The treatment difference in category shift from randomization baseline to the end of week 12/ET between ALO-02 and placebo was not statistically significant \( P = 0.1272 \).
- Other secondary end points related to pain favored ALO-02. Fifty-nine (44.0%) patients in the placebo group and 84 (57.5%) patients in the ALO-02 group of the double-blind treatment period reported ≥30% decrease in weekly average NRS-Pain scores from screening to the final 2 weeks of the double-blind treatment period, which was statistically significant \( P = 0.0248 \); 40 (29.9%) patients in the placebo...
group. Fifty eight (39.7%) patients in ALO-02 group showed 50% decrease in the weekly average NRS-Pain scores during the same period favoring ALO-02 but not statistically significant (P 5 0.0874).

- Acetaminophen was used as a rescue medication by 58 (43.3%) patients in the placebo group compared with 51 (34.9%) patients in the ALO-02 group during the double-blind treatment period.
- In the double blind treatment period, 56.8% of patients in the ALO-02 group and 56.0% of the patients in the placebo group experienced a treatment emergent adverse event (TEAE). The most common treatment-related TEAEs for ALO-02 during the treatment were nausea, vomiting, and constipation consistent with opioid therapy.

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**Conclusion:**

This study shows that ALO-02 is effective in the treatment of CLBP in the patient population. The safety profile of ALO-02 is also consistent with that of other opioids. The abuse-deterrent feature of the formulation did not alter the effect on pain or add to the concerns of withdrawal.

The safety results of this study are consistent with the findings of an expert panel, which reported that the most frequent opioid related AEs were constipation, nausea and vomiting, sedation or clouded mentation and pruritus or myoclonus. Nausea, vomiting and sedation tend to wane over time. Overall, the observed safety results were consistent with the use of opioids and confirmed the observed safety profile of a long-term safety study of ALO-02 in adults with moderate-to-severe chronic non-cancer pain.

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Therapeutic, oxycodone, naltrexone, Low Back Pain, Spine, Chronic, Opioid, opiate antagonists, Double Blind, Placebo Controlled, Enriched-Enrollment Randomized Withdrawal Study, Efficacy, Safety, numeric rating scale (NRS), Roland Morris Disability Questionnaire (RMDQ), Patient’s Global Assessment (PGA)