Lofexidine for Treatment of Opioid Symptoms in Opioid-Dependent Adults

Introduction

• Millions of Americans meet criteria for opioid use disorder or opioid physical dependence and must discontinue the problematic opioid as the first step in the pathway to successful treatment.

• Opioid withdrawal symptoms (e.g., muscle spasms, pain, heart pounding, gastrointestinal upset, anxiety, insomnia, and extremely distressing, causing many patients to continue opioids or relapse back to opioid use, rather than undergo painful withdrawal).

• Lofexidine (LFX), a selective alpha2-adrenergic agonist, decreases norepinephrine levels that are heightened during opioid withdrawal, directly addressing the driver of withdrawal symptoms.

• The purpose of this Phase 3 trial for US Food and Drug Administration (FDA) registration was to investigate LFX for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation.

• LFX was approved by the FDA in May 2018.

Methods

• This was a double-blind, randomized, multicenter, investigator trial conducted in adults ≥18 years old seeking treatment for opioids or who relapsed back to opioid use, rather than undergo painful withdrawal.

• Key inclusion criteria: use of any opioid with half-life similar to heroin or morphine for at least 21 of 30 days prior to randomization; opioid dependence based on Mini-International Neuropsychiatric Interview criteria.

• Key exclusion criteria: self-reported use of methadone or buprenorphine; active treatment for depression or on psychotropics; specific medical conditions that would impair study participation based on Investigator judgment.

• Primary efficacy outcome: overall Short Opiate Withdrawal Scale of Gossop (SOWS-G) score differences over Study Days 1 through 7 (SOWS-G) (Table I) is a validated, subject-reported assessment of 10 common opioid withdrawal symptoms rated on a scale from none (0) to severe (3).

• Study completion rate and Clinical Opiate Withdrawal Scale (COWS, a clinician-rated assessment of 11 common opioid withdrawal signs and symptoms) were secondary outcomes.

• Subjects were randomized to placebo, LFX 0.54 mg qid (four times day) (2.16 mg study dose) or LFX 0.72 mg qid (2.88 mg study dose) treatment for 7 days after abrupt opioid discontinuation.

• Table 1: Short Opiate Withdrawal Scale of Gossop (SOWS-G).

• Table 2: Background Characteristics (mITT Population).

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• Table 3: SOWS-G and COWS Scores by Study Day (mITT Population).

• The proportion of subjects who completed through Day 7 was significantly greater for both LFX treatment groups versus placebo with odds ratio nearly twice as high in the LFX groups.

• Figure 2: Study Completion Rate (mITT Population).

Efficacy

• Both LFX dose groups were significantly superior to placebo for the primary endpoint, indicating better cumulative improvement in opioid withdrawal symptoms over the 7-day treatment period.

• Table 1, Overall SOWS-Gossop Score Differences over Study Days 1–7(mITT Population).

• Opioid withdrawal signs and symptoms were most severe on the first 5 days of the trial and were significantly reduced in the LFX groups versus placebo on SOWS-G and COWS scores.

Conclusions

• LFX, an alpha2-adrenergic agonist, significantly improved opioid withdrawal symptoms and increased completion of a 7-day opioid discontinuation treatment compared with placebo.

• AEs related to LFX’s sympatholytic activity were common but infrequently severe enough to interfere with completion of the trial.

• Successful recovery from opioid dependence requires successful treatment of opioid withdrawal symptoms, especially during the first several days of opioid withdrawal when symptom severity peaks.

• LFX provides a non-opioid treatment option that could be widely accessible to opioid-dependent patients through a variety of healthcare providers.

Disclosures

The investigator, Kristen Gullo; Mark Pirner, MD; Thomas Clincy, MD; and Thomas Clincy, MD were employees of US WorldMeds. Thomas Clincy, MD was an employee and owned ownership interest in US WorldMeds at the time of the study. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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References


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