Efficacy and Safety of Sublingual Sufentanil for the Management of Acute Pain Following Bunionectomy

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My disclosure is in the final AOFAS Mobile App.

I have a potential conflict with this presentation due to:
Employee of AcelRx Pharmaceuticals
Introduction

• Pain in the immediate post-operative period remains a primary concern of those considering surgery, and with HCAHPS surveys now being implemented at the level of Ambulatory Surgery Centers,¹ appropriate and timely management of pain has become not just a clinical goal, but a business necessity.

• There remains a need for rapid-acting, potent analgesics that do not require an invasive route of delivery and possess a predictable off-set, specifically for minor surgery patients appropriate for same-day discharge.

• A sufentanil tablet dosed sublingually by a healthcare professional (HCP) via a single-dose applicator is under development for treatment of moderate-to-severe acute pain in a medically supervised setting.

Introduction (Cont)

• The product is designed to leverage sufentanil’s unique PK characteristics and could offer potential analgesic advantages in an ambulatory care or acute trauma setting.

• Sufentanil possesses a high therapeutic index in animal models (>26,000 vs 71 for morphine) and as a result of its lipophilic nature, demonstrates rapid equilibration between plasma and CNS ($t_{1/2 ke0} = 6$ min vs. 2.8 hrs for morphine).³⁴.

<table>
<thead>
<tr>
<th>Common Opioids</th>
<th>Therapeutic Index</th>
<th>$t_{1/2 ke0}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>71²</td>
<td>168³*</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>232⁵</td>
<td>46⁶</td>
</tr>
<tr>
<td>Meperidine</td>
<td>5²</td>
<td>10⁶</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>277²</td>
<td>6.6⁴</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>26,716²</td>
<td>6.2⁴</td>
</tr>
</tbody>
</table>

Objective

• The primary objective of this phase 2, double-blind, dose-finding study was to demonstrate the repeat-dose efficacy, safety and tolerability of sufentanil 20mcg [ST20] and 30mcg [ST30] sublingual tablets compared to placebo for the management of moderate-to-severe acute pain following bunionectomy surgery as determined by the time-weighted sum of pain intensity differences (SPID) to baseline over the 12-hour study period (SPID12).
  • Pain Intensity values were generated from a validated numerical rating scale (NRS) where 0 = no pain and 10 = worst possible pain.
Methods - Design

• This was a multi-center, randomized, double-blind, placebo-controlled trial for 12 hours in patients who were undergoing bunionectomy alone or with ipsilateral hammertoe repair under Mayo block local analgesia and IV sedation.

• Patients who met all eligibility criteria were randomly assigned at a 2:2:1 ratio to ST20, ST30 or placebo, administered sublingually prn to manage pain, but not more frequently than q1 hour.
  • Before study staff could administer the first dose of study drug, the patient must have reported a pain score of 4 or higher on an 11-point rating scale.

• Patients with inadequate analgesia were encouraged to remain in the study and were permitted access to rescue medication (Vicodin® [5 mg hydrocodone/500 mg acetaminophen]).
  • Rescue medication could only be administered after at least 10 minutes had passed since dosing with study drug and not more frequently than q4 hours.
Methods - Assessments

• The primary efficacy variable was the time-weighted summed Pain Intensity (PI) differences to baseline over the 12-h study period (SPID12), generated from a validated numerical rating scale (NRS) where 0 = no pain and 10 = worst possible pain.

• Key secondary efficacy variables included:
  • SPID over the first hour (SPID1)
  • Total pain relief over the 12-hour study period (TOTPAR12)
  • Time to perceived pain relief
  • Time to meaningful pain relief
  • Patient global assessment of method of pain control (PGA)
  • Use of rescue medication

• Safety assessments included vital signs, oxygen saturation, spontaneously reported adverse events (AEs) and the use of concomitant medications.
Results – Demographics and Disposition

• A total of 100 patients were randomized and received study drug (40 ST20, 40 ST30 and 20 PBO) and were included in the intent-to-treat (ITT) population.

• Baseline demographics were equally distributed across treatment arms with 91 (91%) patients completing the 12-hour study.
  • The mean age was 42.5 years with 96% of patients under age 65 years.
  • The most common reasons for early termination included lack of efficacy (6.0%) and adverse event (2.0%).
  • A higher proportion of patients in the ST30 group discontinued the study due to lack of efficacy (7.5%) than in the ST20 group (5.5%) and the placebo group (5.0%), but the differences were not statistically significant.
Results – Efficacy

• The ST30 group was superior to placebo (p = 0.003) for the time-weighted SPID12 with LS mean (SEM) scores of 6.53 (2.56) vs. -7.12 (3.64), respectively.

• For the time-weighted sum of PR scores over the 12h study period, there were statistically significant differences in favor of the ST30 group over placebo (9.73 [0.98] vs 4.37 [1.38], respectively; p = 0.002).

• Pain intensity differences compared to baseline for evaluation time points over the first hour of the study, demonstrated statistically significant differences as early as 30 minutes.

• Statistically significant differences favoring the ST30 compared to the ST20 were also observed for the time to perceived PR (p = 0.023) and time to meaningful PR (p = 0.010), with median times of 24 and 74 minutes, respectively. The placebo group never achieved either endpoint.
Results – Efficacy

Figure: Least Squares (LS) Mean of Time-weighted SPID by Evaluation Time Point (ITT Population)
Results – Efficacy

Pain Intensity Difference to Baseline in the First Hour
Safety

- Two patients (2.0%) prematurely discontinued the study due to AE: anxiety/chest pain (unrelated) and somnolence/respiratory depression (possibly related), both in the ST30 group.

- Two (2.0%) patients experienced SAEs, reported 8 days (severe osteomyelitis) and 11 days (moderate cellulitis) after the 12h study period, respectively. Neither were considered related.

- Nausea, vomiting, dizziness and somnolence were the most frequently reported AEs

<table>
<thead>
<tr>
<th></th>
<th>ST20</th>
<th>ST30</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>14 (35%)</td>
<td>23 (57.5%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (15%)</td>
<td>11 (27.5%)</td>
<td>0</td>
<td>0.021</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (7.5%)</td>
<td>8 (20%)</td>
<td>1 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (5%)</td>
<td>8 (20%)</td>
<td>0</td>
<td>0.027</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (5%)</td>
<td>3 (7.5%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>3 (7.5%)</td>
<td>1 (2.5%)</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>
Conclusions

- The sublingual sufentanil 30mcg tablet was the dosage strength that was associated with the largest reduction in pain intensity in this study of bunionectomy surgery patients.
- The median time to perceived pain relief for the 30 mcg dose was 24 minutes; more rapid than the 20 mcg dose or placebo.
- The type and frequency of adverse events observed were typical of opioids in a post-operative setting with reports of nausea, vomiting and somnolence more common in the active drug cohorts.
- Additional studies of sublingual sufentanil 30 mcg are indicated to assess efficacy and tolerability in broader patient populations.