Objectives

• The primary objective of the phase 3 study was to compare the efficacy and safety of the Sublingual Sufentanil Tablet System (SSTS) to placebo in the management of post-operative pain after open abdominal surgery (including laparoscopic-assisted surgery) under general or spinal anesthesia that did not include intrathecal opioids.

• The primary objective of the phase 2 dose-finding study was to demonstrate the repeat-dose efficacy of sufentanil 20 mcg (ST20) and 30 mcg (ST30) compared to placebo for the management of post-operative acute pain in patients undergoing bunionectomy alone or with hammer toe repair.

Introduction / Description of Technology

Sublingual Sufentanil for the Management of Acute Pain

Abstract

Methods/Materials

Study Design

• Both studies were multi-center, randomized, double-blind and placebo-controlled.

• Following IRB approval and patient informed consent, patients who met all eligibility criteria were randomly assigned at a 2:1 ratio to sufentanil tablet or placebo administered sublingually prn to manage pain.

• Before study staff could administer the first dose of study drug, the patient must have reported a pain score of 4 or higher on a validated, 11-point numerical rating scale (NRS) where 0 = no pain and 10 = worst possible pain.

• Patients with inadequate analgesia were encouraged to remain in the study and were permitted access to rescue medication (2mg IV morphine in the phase 3 study and Vicodin® (5 mg hydrocodone/500 mg acetaminophen) in the phase 2 study).

Efficacy Assessments

• The primary efficacy variable in the phase 3 study was the time-weighted averaged Pain Intensity Difference (SPID) to baseline over the 48-hour study period (SPID48).

• The primary efficacy variable in the phase 2 study was the time-weighted averaged Pain Intensity Difference (PI) to baseline over the 12-hour study period (SPID12).

• A double stop-watch technique was also used in the bunionectomy trial to assess onset of perceived and meaningful PR following T0.

• Additional key secondary endpoints included Pain Relief (PR), percentage of patients requiring rescue analgesics, early termination due to inadequate analgesia and patient global assessment.

Safety Assessments

• Safety assessments for both studies included vital signs, oxygen saturation, spontaneously reported adverse events (AEs) and the use of concomitant medications.

Results

Baseline Demographics and Patient Disposition

• A total of 214 patients were screened in the phase 3 SSTS study with 178 randomized (119 active vs 59 placebo).

• In the phase 2 study, 100 patients were randomized and received study drug (40 ST20, 40 ST30 and 20 Placebo) and were included in the intent-to-treat (ITT) population.

• Average patient age (years) in the phase 3 abdominal study was 55.2 compared to 42.5 for the bunionectomy trial.

Efficacy

• Both studies met their respective primary endpoints demonstrating superiority of Sublingual Sufentanil over placebo for management of post-operative pain.

• SSTS was superior to placebo for the SPID48 primary endpoint (least squares [LS] mean 6.53 vs. -7.12, p = 0.003)

• The ST30 group was superior to placebo (p = 0.003) for the time-weighted SPID12 in the phase 2 trial, with LS mean (SEM) scores of 6.53 (2.56) vs. -7.12 (3.64), respectively. Figure 3 demonstrates pain intensity differences compared to baseline for evaluation time points over the first hour of the study, with statistically significant differences observed as early as 30 minutes.

Figure 2. Kaplan-Meier Cumulative Event Rates for Time to Termination due to inadequate analgesia [A] and Time to First Rescue [B] (ITT Population)

Table 1. Frequent Treatment-Emergent Adverse Events (greater than 5% in any group)

<table>
<thead>
<tr>
<th>Event</th>
<th>Phase 3 Study</th>
<th>Phase 2 Study</th>
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<tbody>
<tr>
<td></td>
<td>SSTS (n = 114)</td>
<td>Placebo (n = 58)</td>
</tr>
<tr>
<td>Nausea</td>
<td>35 (31)</td>
<td>24 (41)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (9)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17 (15)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>O2 Sat Decreased</td>
<td>7 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (4)</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

Conclusions

• Sufentanil tablets dispensed sublingually with a handheld PCA device (15mcg) or via single-dose applicator (30mcg) from a healthcare professional are in late-stage development for treatment moderate to severe acute pain.

• When administered sublingually, sufentanil’s fast onset of analgesia, non-invasive route of delivery and favorable patient satisfaction ratings make it a potential alternative to IM or IV dosing.

• The type and frequency of adverse events observed in the studies were typical of opioids in a post-operative setting with reports of nausea, vomiting and somnolence more common in the active drug cohorts.

References
