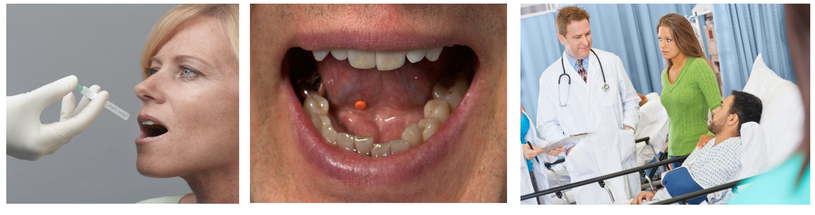
A PHASE 3 OPEN-LABEL STUDY OF THE SUFENTANIL SUBLINGUAL TABLET 30 MCG FOR TREATMENT OF ACUTE POST-OPERATIVE PAIN

Harold Minkowitz, MD[1]; David Leiman, MD[2]; Karen DiDonato, MSN, RN[3], Pamela Palmer, MD, PhD[3]
[1]Memorial Hermann Memorial City Medical Center, Houston, TX; [2]Hermann Drive Surgical Hospital, Houston, TX; [3]AcelRx Pharmaceuticals Medical Affairs, Redwood City, CA

Background

Short-stay surgery is increasingly being adopted for more invasive surgeries and in older patients.[1] The number of outpatient surgery visits in the United States increased from 20.8 million in 1996 to 34.7 million in 2006, with patients aged 45 to 64 years making up the largest cohort of procedures by number, followed by ages 15-44 years and 65-74 years, respectively.[2] Early discharge demands a rapid recovery and low incidence and intensity of surgery and anesthesia related side-effects such as pain, nausea and fatigue, so there remains a clinical need for rapid-acting, potent analgesics that offer predictable offset and good tolerability across all age groups. A sufentanil sublingual tablet (SST) 30 mcg, dispensed using a single-dose applicator, is in development for treatment of moderate-to-severe acute pain in a medically supervised setting (**Figure 1**). The product is designed to leverage sufentanil's unique pharmacodynamic properties, such as high lipophilicity, a high therapeutic index and a plasma:brain equilibration of 6 minutes compared to 2.8 hours for morphine and 46 minutes for hydromorphone. [3-5] These characteristics could offer potential analgesic advantages in ASCs or other venues requiring non-invasive, acute pain management. The primary objective of this study was to evaluate the safety and efficacy of the SST 30 mcg in older patients and patients with co-morbidities, such as organ impairment, in the first 12 hours after surgery, which is the most critical timeframe for short-stay surgeries.

Figure 1. Sufentanil Sublingual Tablet 30 mcg



Methods

Study Design

- This is a multicenter, open-label, single-arm study to evaluate up to 150 adult patients following surgery who were aged 40 years or older with an emphasis on enrolling patients with comorbidities.
- Upon meeting all entrance criteria, patients were administered the SST 30 mcg by a healthcare professional (HCP) no more frequently than hourly as needed to manage the patient's pain. Rescue IV morphine 1 mg was available on request.
- Before study staff could administer the first dose of study drug, patients must have reported a pain score of 4 or higher on a validated, 11-point numerical rating scale (NRS 0-10).

Efficacy Assessments

- The primary efficacy variable (endpoint) was the time-weighted summed pain intensity difference to baseline over the 12-hour study period (SPID12).

Methods (Cont)

Safety Assessments

- Safety assessments included spontaneously reported adverse events (AEs), vital signs (blood pressure, heart rate, and respiratory rate), and oxygen saturation values.
- Screening laboratory analysis of BUN, creatinine, ALT, AST and total bilirubin were analyzed to classify patients regarding renal and liver impairment status.

Results

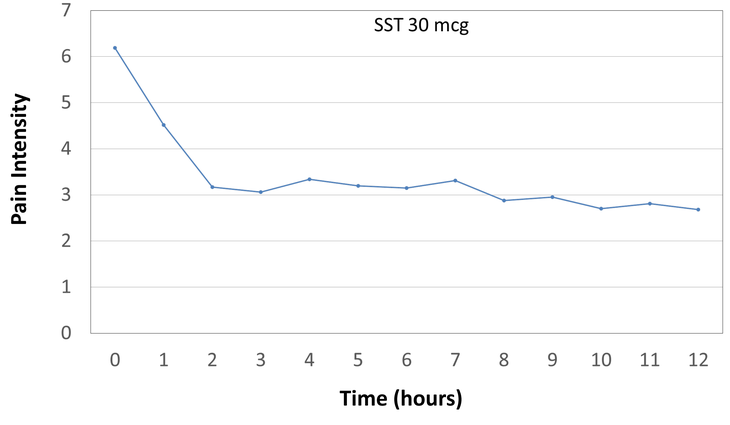
Baseline Demographics and Patient Disposition

- A total of 140 patients were enrolled across 9 sites in the US.
- Mean age 54.7 years with a range of 40 – 84 years; 54% female
- 112 patients had abdominal or other surgery while 28 patients had orthopedic surgery
- 34, 2 and 1 patients, respectively, had mild, moderate and severe hepatic impairment and 5 patients each had mild or moderate renal impairment
- Average inter-dosing interval for SST 30 mcg was 193 minutes

Efficacy

- Mean SPID12 for all patients was 36.04, with higher values observed in abdominal patients (39.27) compared to orthopedic patients (22.18).
    - Decreases in mean PI were apparent by 30 minutes after the initiation of study drug (**Figure 2**) and increases in mean pain relief (PR) measured on a 0-4 scale, were apparent by 15 minutes.
    - 14% of patients requested rescue medication
- Overall, 118/135 (87.4%) patients and 111/123 (90.2%) HCPs responded "good" or "excellent" on the Global Assessment of method of pain control.

Figure 2. Mean Pain Intensity over the 12 Hours of Treatment



Results (Cont)

Safety

- 63% of patients had no adverse events. Adverse events are listed in **Table 1.**
- AEs in general were mild to moderate in severity with nausea (27%) and headache (6%) the most common.
- There were no clinically relevant mean changes from baseline in any vital sign throughout the study.

Table 1. Adverse Events

Adverse Events (≥ 2% frequency)	Sublingual Sufentanil 30mcg Total n=140
No adverse event	**63%**
Nausea	27%
Headache	6%
Dizziness	4%
Pruritus	3%
Hypotension	2%
Oxygen Saturation Decreased	2%

Conclusion

- **Results from this study in patients 40 years of age or older, many with comorbidities including organ impairment, suggest SST 30 mcg is well-tolerated and effective in treating moderate-to-severe pain after surgery**
- **The majority of patients experienced no adverse events throughout the study**
- **Global Assessment results show patients and HCPs give high ratings to the SST 30 mcg as a method of pain control in this postoperative setting.**

References

1. Jakobsson J. Pain Management in Ambulatory Surgery-A Review. *Pharmaceuticals 2014;7:850-865*
2. Centers for Disease Control and Prevention (CDC) National Center for Health Statistics Report on Ambulatory Surgery in the United States, 2006, revised.
3. Mather LE. Opioids: a pharmacologist's delight! *Clin Exp Pharmacol Physiol* 1995; 22:833-6.
4. Lötsch J. Pharmacokinetic-pharmacodynamic modeling of opioids. *J Pain Symptom Manage* 2005; 29(5 Suppl):S90-S103.
5. Scott JC, Cooke JE, Stanski DR. Electroencephalographic quantitation of opioid effect: comparative pharmacodynamics of fentanyl and sufentanil. *Anesthesiol* 1991; 74:34–42.

Poster presentation at American Society of Regional Anesthesia and Acute Pain Medicine Fall 2016, November 17-19; San Diego, CA.

Acknowledgements: AcelRx Pharmaceuticals (Redwood City, CA), the study sponsor, wishes to thank the study subjects, PRA Health Sciences, the Research Coordinators and the Investigators.