Safety and Efficacy of Sufentanil Sublingual 30 mcg Tablets for the Treatment of Acute Pain Following Outpatient Surgery

Harold Minkowitz MD[1]; Neil Singla MD[2]; Timothy Melson MD[3]; David Leiman MD[4]; Karen DiDonato MSN RN[5]; Pamela Palmer MD, PhD[5]

[1]Memorial Hermann Memorial City Medical Center, Houston, TX; [2]Lotus Clinical Research, Pasadena, CA; [3]Hellen Keller Hospital, Sheffield, AL; [4]Victory Medical Center, Houston, TX, [5]AcelRx Pharmaceuticals, Redwood City, CA

Background

Ambulatory surgery, coming to and leaving the hospital on the same day as surgery, is increasingly being adopted in Europe due to its cost effectiveness and improved quality outcomes. This considerable growth has been facilitated by the advent of minimally invasive procedures that have enabled healthcare professionals to perform multiple surgeries in a day.[1] Timely discharge demands a rapid recovery and low incidence of surgery and anesthesia related side-effects such as pain, nausea and fatigue.[2] Patients must be fit enough and symptom intensity mild enough to facilitate self-care, so there remains a clinical need for rapid-acting, potent analgesics that offer predictable offset and good tolerability. The sufentanil sublingual tablet 30mcg (SST) is in development for treatment of moderate-to-severe acute pain in medically supervised settings such as day surgery (**Figure 1**). The product is designed to leverage sufentanil's distinct pharmacodynamic properties and could offer potential analgesic advantages in short stay situations.[3-5] The primary objective of this analysis was to compare the efficacy and safety of SST by procedure type, to placebo (PT) for the management of moderate-to-severe acute post-operative pain following abdominal surgery.

Figure 1. Sufentanil Sublingual Tablet 30mcg

Methods

Study Design

- The study was multicenter, randomized, double-blind and placebo-controlled for up to 48 hours in adult patients undergoing abdominoplasty, open tension-free inguinal hernioplasty or laparoscopic abdominal (LA) surgery.
- Patients who met all inclusion and none of the exclusion criteria at screening, and following surgery, were randomly assigned at a 2:1 ratio to treatment with SST or PT.
- 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 (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).
- Key secondary endpoints included SPID over the first hour (SPID1), total pain relief (TOTPAR), early termination due to inadequate analgesia and the proportion of patients and healthcare professionals who responded "good" or "excellent" to the global assessment (PGA and HPGA).
- An a priori SPID12 subgroup analysis by type of surgery was also performed.

Safety Assessments

- Safety assessments included spontaneously reported adverse events (AEs), vital signs, including oxygen saturation, and the use of concomitant medications.

Results

Baseline Demographics and Patient Disposition

- A total of 161 patients (107 SST and 54 PT) were randomized; average age was 41 years, 68% were female.
- Baseline demographics were evenly distributed; 50%, 30% and 20% of patients, respectively, had abdominoplasty, LA surgery and hernia repair.
- Five times as many patients in the PT cohort terminated early due to 'lack of efficacy' compared to the SST cohort (18.5% vs. 3.7%).

Efficacy

- The study met it's primary endpoint with statistically significant SPID12 differences observed in favor of SST over PT (25.8 vs. 13.1; p<0.001).
- Subgroup analysis by surgery type also yielded statistically significant (abdominoplasty; 30.8 vs 17.6 [p<0.001] and LA; 21.4 vs 8.2 [p=0.019] and numerical (hernia; 18.6 vs 7.7) improvements in pain intensity for SST group compared to PT, though sample sizes were limited.
- **Figure 2** illustrates the 1 hour differences in SPID by surgery type.

Safety

- Nausea, headache and vomiting were the most common treatment-emergent AEs across both treatment arms
- **Table 1** includes AEs by type of surgery "possibly" or "probably" related to study drug and reported by ≥ 3 patients in any treatment arm

Figure 2.SPID over the First Hour of Treatment (LS Mean)

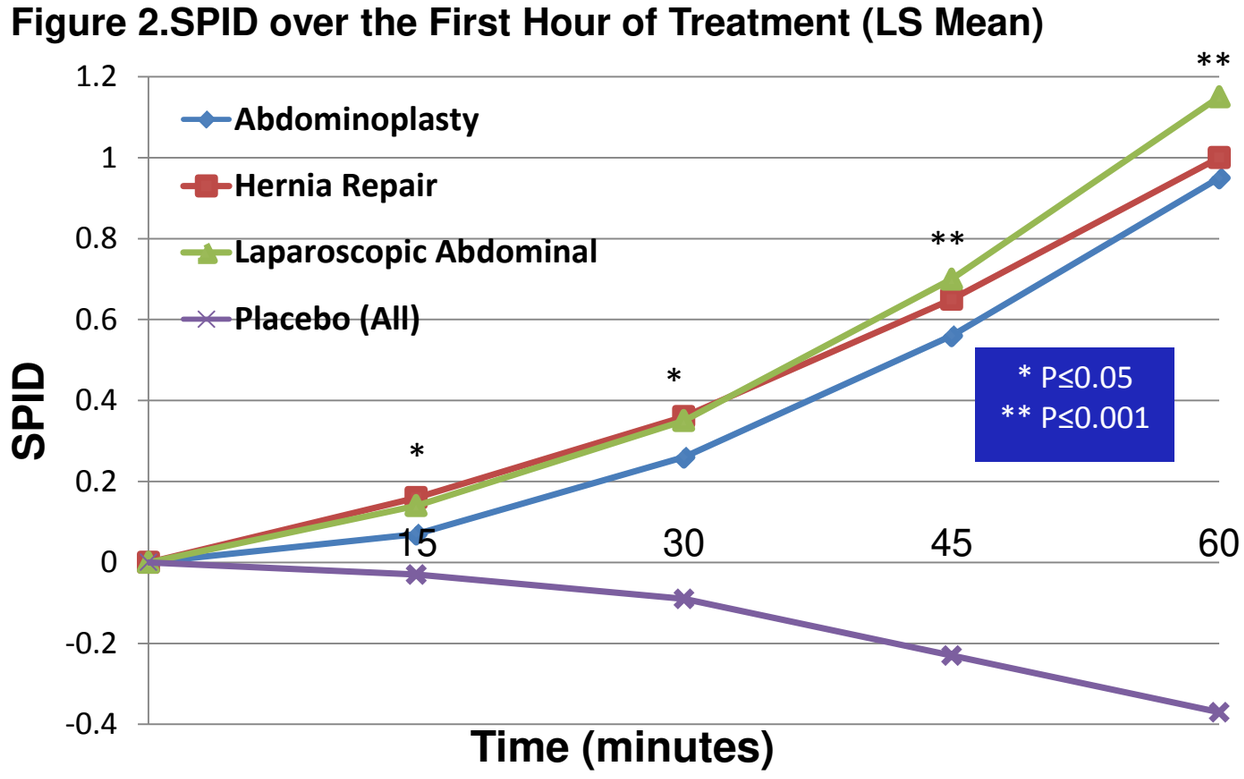

Table 1. Related Adverse Events by Surgery Type (≥3 patients)

Adverse Event N (%)	Abdominoplasty		Lap Abdominal		Hernia Repair	
	SST n=52	Placebo n=28	SST n=32	Placebo n=16	SST n=23	Placebo n=10
Nausea	22 (42)	7 (25)	3 (9)	4 (25)	6 (26)	1 (10)
Headache	10 (19)	5(18)	2 (6)	1 (6)	1 (4)	0
Vomiting	4 (8)	1 (4)	1 (3)	0	1 (4)	0
Dizziness	6 (12)	2 (7)	0	0	0	0
Somnolence	3(6)	2 (7)	0	0	0	0
Hypotension	5 (10)	2 (7)	0	0	0	0

Conclusion

- **Efficacy and tolerability results from this study suggest that the sufentanil sublingual tablet 30mcg may offer a viable alternative to IM or IV dosing across a variety of ambulatory surgical procedures**
- **Nausea and headache were the most commonly reported AEs across all surgery types**

References

1. Deshmukh, S. Rising number of day surgeries due to advent of minimally invasive surgeries in European market. *Europlat.org* Feb 2015.
2. Jakobsson J. Pain Management in Ambulatory Surgery-A Review. *Pharmaceuticals 2014;7:850-865*
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):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.