Sufentanil Sublingual Tablet System for the Management of Postoperative Pain after Knee or Hip Arthroplasty

A Randomized, Placebo-controlled Study

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ABSTRACT

Background: Complications with IV patient-controlled analgesia include programming errors, invasive access, and impairment of mobility. This study evaluated an investigational sufentanil sublingual tablet system (SSTS) for the management of pain after knee or hip arthroplasty.

Methods: This prospective, randomized, parallel-arm, double-blind study randomized postoperative patients at 34 U.S. sites to receive SSTS 15 μg (n = 315) or an identical placebo system (n = 104) and pain scores were recorded for up to 72 h. Adult patients with American Society of Anesthesiologists status 1 to 3 after primary total unilateral knee or hip replacement under general anesthesia or with spinal anesthesia that did not include intrathecal opioids were eligible. Patients were excluded if they were opioid tolerant. The primary endpoint was the time-weighted summed pain intensity difference to baseline over 48 h. Secondary endpoints included total pain relief, patient and healthcare professional global assessments, and patient and nurse ease-of-care questionnaires.

Results: Summed pain intensity difference (standard error) was higher (better) in the SSTS group compared with placebo (76 [7] *vs.* −11 [11], difference 88 [95% CI, 66 to 109]; $P < 0.001$). In the SSTS group, more patients and nurses responded "good" or "excellent" on the global assessments compared with placebo ($P < 0.001$). Patient and nurse ease-of-care ratings for the system were high in both groups. There was a higher incidence of nausea and pruritus in the SSTS group.

Conclusion: SSTS could be an effective patient-controlled pain management modality in patients after major orthopedic surgery and is easy to use by both patients and healthcare professionals. **(ANESTHESIOLOGY 2015; 123:434-43)**

SOME limitations of IV patient-controlled analgesia (PCA) have been established in the literature throughout the 40-yr history of this analgesic modality. Requiring a patent IV line for analgesic delivery and physical connection to a PCA pump on an IV pole can result in reduced mobility, risk of infection, and analgesic gaps due to IV catheter infiltration or IV tubing obstruction.[1,2] Due to the programmable nature of the pump and the multiple choices of opioids and concentrations that are used with IV PCA, medication prescribing errors and pump programming errors are also well documented in the literature.[3–6] In addition, the commonly used opioids, morphine and hydromorphone, have active metabolites and slow plasma:brain equilibration half-lives, which can result in a dissociation between patient dosing and peak effect.[7,8]

In an effort to avoid the complications of IV PCA opioids, many orthopedic surgeons have used a multimodal approach to postoperative analgesia.[9] Nonopioid adjuvant analgesics and regional anesthetic blocks are often used with

What We Already Know about This Topic

- A patient-controlled sufentanil sublingual tablet system has been developed, which might remove some of the complexities and system-based adverse events in IV patient-controlled analgesia
- Large-scale investigation of efficacy in acute musculoskeletal pain has not been performed

What This Article Tells Us That Is New

- In this phase 3 trial, 426 patients were randomized to receive the sufentanil sublingual tablet system or a placebo, with IV opioid rescue after major lower extremity orthopedic surgery
- The primary outcome measure of summed pain intensity difference in the first 48 h compared with baseline was better with sufentanil than placebo although nausea and pruritus were also increased with sufentanil

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oral extended-release and immediate-release opioids in the place of IV PCA opioids. While producing sufficient postoperative analgesia, this dosing regimen is heavily nurse intensive to allow for the variable opioid analgesic requirements of different patients. This approach also sacrifices the patient-controlled nature of opioid administration, which has been shown to result in higher patient satisfaction compared with nurse-administered modalities.[10,11]

In an effort to address these issues, the sufentanil sublingual tablet system (SSTS; Zalviso; AcelRx Pharmaceuticals, Redwood City, CA), currently under review by the Food and Drug Administration, was developed. SSTS is a preprogrammed, noninvasive, patient-activated bedside system that enables patients to manage moderate-to-severe acute pain in a hospital setting. The high lipophilicity of sufentanil allows rapid sublingual uptake with a blunted peak plasma level and longer plasma half-time (time from peak plasma concentrations [C_{max}] to 50% of C_{max}) than IV-administered sufentanil.[12,13] The device has a preprogrammed 20-min lockout interval and uses a radio-frequency identification thumb tag to allow only the patient to operate the device.[14] During the SSTS set-up procedure by the healthcare professional, completed without a need for programming decisions, a small cartridge containing 40 sufentanil 15 μg tablets is inserted into the dispenser tip, which is then locked into the controller base. The system is then tethered to the bedside or other secure location (wheelchair, gurney, *etc.*). Phase 2 dose-finding studies in patients after major surgery demonstrated that sufentanil 15 μg per tablet was the optimal dosage strength resulting in analgesic efficacy and a similar adverse event profile to lower dosage strengths.[12]

The objectives of the current study were to evaluate the efficacy and safety of SSTS compared with a placebo system for the management of postoperative pain in adult patients who had undergone total knee or total hip arthroplasty. The primary null hypothesis tested was that the treatment difference in the least squares (LS) mean of the time-weighted summed pain intensity difference (SPID48) between the SSTS group and the placebo group equals zero.

Materials and Methods

This phase 3 prospective, randomized, placebo-controlled, double-blind, parallel-arm study was conducted at 34 hospitals in the United States (registered with ClinicalTrials.gov on August 7, 2012 [NCT01660763]). The study protocol and statement of informed consent were approved by a centralized Institutional Review Board, Copernicus (Research Triangle Park, North Carolina) or the local Institutional Review Board at the study site. Patients scheduled for hip or knee replacement were recruited by study staff for possible enrollment in the study and provided written informed consent before undergoing any study procedures. Male and nonpregnant female patients were eligible for inclusion if they were at least 18 yr old, with American Society of Anesthesiologists physical status 1 to 3, and scheduled to undergo total unilateral knee or hip replacement surgery under general anesthesia or with spinal anesthesia that did not include intrathecal opioids. Patients were excluded if they had previously undergone replacement of the same hip or knee or were opioid tolerant (use of > 15 mg oral morphine equivalent per day within the past 3 months). Patients were also excluded if they had sleep apnea documented by a sleep laboratory study, alcohol or drug abuse, were currently on supplemental oxygen therapy as an outpatient, or had any medical condition that would interfere with postoperative pain assessments. Because the use of any drug that may affect pain levels during the study, such as gabapentinoids, steroids, or antiinflammatory drugs were not allowed intraoperatively or postoperatively, patients with chronic pain conditions requiring the use of these medications were also excluded from the study.

During surgery, IV opioids were allowed as needed for analgesia, but the use of any other regional anesthetic technique to provide postoperative pain management, such as epidural drug administration, peripheral nerve block, or field block with local anesthetics was prohibited. Antiemetic prophylaxis (excluding intraoperative or postoperative dexamethasone) and treatment was allowed per standard hospital protocol at each site. After surgery, IV morphine, hydromorphone, or fentanyl could be administered as needed to keep the patient comfortable in the postanesthesia care unit (PACU).

Patients were randomized 3:1 to receive SSTS 15 μg or an identical system containing placebo tablets ("placebo system") using an interactive Web response system designed and implemented by PharmaNet-i3, the contract research organization for the study (Princeton, NJ). The randomization was performed in blocks of four and stratified by type of surgery (knee or hip) at each study site. The sponsor, investigator, other study center personnel, and patients were blinded to treatment group assignment. Patients were randomized in the PACU once they were awake and alert, provided they continued to meet the study entrance criteria. Pain intensity was assessed on an 11-point numerical rating scale (NRS), where 0 = no pain and 10 = worst possible pain. After randomization, but before receiving study drug, patients were required to have had a pain intensity of less than 5 at some point while in the PACU to demonstrate that their pain was manageable. They also had to have been discharged or were ready for discharge from the PACU, and finally, the patient's reported pain intensity had to escalate back above 4 on the NRS just before the first dose of study drug (recorded as the baseline pain intensity). When these conditions were met and the patient requested medication for pain, baseline vital signs, oxygen saturation, and pain intensity were assessed and the patient self-administered the first dose of study drug. Analgesia was supplied by the SSTS or placebo system for a minimum of 48 h, at which point in time the patient would be considered a completer in the trial. Sites had the option to extend the use of the system

up to 72 h if the patient continued to require strong opioid analgesia. Patients were educated about proper use of the system by study personnel using patient-training screens displayed on the graphic user interface screen on the device. This training occurred during the initial patient screening process, as well as before the first dose of study drug.

To maintain patients in both arms of the study as long as possible to minimize missing data, inadequate analgesia was treated using 2 mg IV morphine. Use of morphine was limited to use only after 10 min had passed since the dosing of the study drug, and no more than 2 mg could be used within a 60-min period. If patients were not obtaining satisfactory analgesia with the use of study drug and/or rescue IV morphine, they could drop out of the study and receive standard analgesic medications. Patients who had oxygen saturation levels that could not be maintained at 95% or greater with or without the use of supplemental oxygen, a respiratory rate less than 8 breaths/min, or excessive sedation (per healthcare professional judgment) were not allowed to have access to study drug or morphine until their vital signs had improved.

Efficacy and Safety Assessments

Efficacy was assessed by patient reports of pain intensity (based on the 11-point NRS) and pain relief (based on a 5-point scale where 0 = no relief, 1 = a little relief, 2 = moderate relief, 3 = a lot of relief, and 4 = complete relief). Patients recorded pain intensity and pain relief scores at 15, 30, 45, and 60 min, every 1 h until 12 h, every 2 h until 48 h, and every 4 h from 52 to 72 h after the first dose of study drug. Pain intensity and pain relief scores were also assessed just before dosing with IV morphine for inadequate analgesia. The primary efficacy endpoint was the time-weighted SPID (*i.e.*, SPID between each evaluation time point and baseline) over 48 h (SPID48). Secondary efficacy endpoints included SPID24 and SPID72, total pain relief (TOTPAR), and patient global assessment (PGA) and healthcare professional global assessment (HPGA) of method of pain control at 24, 48, and 72 h. The PGA and HPGA were assessed using a 4-point categorical scale, where 1 = poor, 2 = fair, 3 = good, and 4 = excellent. Validated patient and nurse ease-of-care (EOC) questionnaires were completed to assess patient and nurse impressions of the SSTS.[15,16] The patient EOC questionnaire has 23 questions; 21 of which are scored on a scale of 0 to 5 (where 0 = not at all and 5 = a very great deal) and summarized into six subscale scores (confidence with device, comfort with device, movement, dosing confidence, pain control, and knowledge/understanding) and a total EOC score. The other two questions (satisfaction with level of pain control and satisfaction with method of administration of pain medication) are scored on a 6-point scale (extremely dissatisfied to extremely satisfied) and combined into an overall satisfaction score. The nurse EOC questionnaire has 22 questions, 20 of which are scored on a scale of 0 to 5 (where 0 = not at all and 5 = a very great deal) and summarized into two subscale scores (time-consuming and bothersome) and a total EOC score. Two other questions (satisfaction with level of pain control and satisfaction with device) were scored on a 6-point scale (extremely dissatisfied to extremely satisfied) and combined into a total satisfaction score.

Other key secondary endpoints included total amount of IV morphine used for inadequate analgesia over the 48-h study period and total number of study drug doses used over 24-, 48-, and 72-h study period.

Safety assessments included vital signs, continuous oxygen saturation monitoring, and treatment-emergent adverse events (*i.e.*, those that occurred during study drug administration or within 12 h after discontinuation of study drug). Patients were allowed to sleep through one vital sign assessment at a time but not two sequential assessments, and patients also were visually inspected for excessive sedation (unarousable). Patients were to be withdrawn from the study if the oxygen saturation could not be maintained more than 95% with or without supplemental oxygen, if the respiratory rate could not be maintained more than 8 breaths/min, or if excessive sedation occurred. Clinical laboratory evaluations included alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatinine, and blood urea nitrogen.

Statistical Analysis

The analyses of efficacy data were performed on the intent-to-treat population, defined as all randomized patients who received study medication. The pain intensity data collected after a patient received the first dose of study medication were included in the calculation of the primary efficacy endpoint, time-weighted SPID48. Pain intensity data collected within 1 h after IV morphine dosing for inadequate analgesia were excluded from the derivation of the efficacy endpoints based on the pain assessment data. The pain intensity and pain relief scores collected just before each dose of morphine was imputed for this 1-h time interval. The last observation carried forward method was used to impute any missing data points through the 72-h study period after termination due to reasons other than adverse event, and the worst observation carried forward method was used to impute missing data points over this same period for patients who discontinued due to an adverse event. All statistical tests were two sided and were performed at the $\alpha = 0.05$ significance level using SAS® 9.1 software (SAS Institute Inc., USA).

Demographics and baseline characteristics were compared by a two-sample *t* test for numeric variables and the Fisher exact test for categorical data. In this superiority trial, a parallel-lines analysis of covariance model was used for the analysis of the primary efficacy endpoint and continuous secondary efficacy endpoints. This model included treatment, center, and surgery type (knee and hip) factors and baseline pain intensity as a covariate. The LS mean of each treatment, SEM and 95% CI were constructed. Ordinal categorical data were analyzed using the Cochran–Mantel–Haenszel test of general association stratified by

surgery type with modified ridit scores. Dichotomous outcome data were analyzed by a two-sample Z test on two proportions between treatment groups. For time to event data, Kaplan–Meier product-limit estimators of cumulative rates of patients reaching the event (*i.e.*, termination due to inadequate analgesia and time to take first rescue medication) at follow-up time points were calculated. A log-rank test was used to compare two treatment groups. The Fisher exact test was used to compare the incidence of adverse events between treatment groups.

Using an effect size of 0.40 for the primary efficacy endpoint, a sample size of 400 patients had 90% power to show statistical difference between two treatment groups. This calculation was based on a two-sided, two-sample t test with a 3:1 sample size allocation ratio and a significance level of $\alpha = 0.05$. Assuming a 10% nonevaluable rate, 440 patients were planned for randomization in this study.

Results

This study was conducted between August 2012 and April 2013 and was stopped once the prespecified enrollment was obtained. Of the 419 patients who received study drug, 258 (61.6%) completed the 48-h study period (fig. 1); 150 patients continued in the study beyond 48 h, and 85 (56.7%) of these patients completed the 72-h study period. There were no statistically significant differences between treatment groups for any baseline or demographic variables (table 1).

Efficacy Results

The primary endpoint, LS mean (SEM) SPID48 score, was higher (better) in the SSTS group than in the placebo system group (76 [7] *vs.* −11 [11], difference 88 [95% CI, 66 to 109]; $P < 0.001$). SPID and TOTPAR scores were also higher in the SSTS group at all evaluation time points from 2 h until 72 h (fig. 2). Pain relief and pain intensity differences (PIDs) scores at each evaluation time point were higher (better) in the SSTS group than in the placebo system group as early as 45 min for pain relief (1.4 [0.1] *vs.* 1.1 [0.1], difference 0.3 [95% CI, 0.1 to 0.6]; $P = 0.009$) and 1 h for PID (1.1 [0.2] *vs.* 0.6 [0.2], difference 0.6 [95% CI, 0.1 to 1.0]; $P = 0.030$) after the first dose of study drug, and these differences were maintained for the duration of the 72-h study period. Analyses of SPID48 based on sex, age, body mass index (BMI), and type of surgery were statistically significantly greater for SSTS compared with placebo for all subgroups ($P < 0.001$; table 2).

Statistically significant differences between treatment groups for time-weighted SPID48 were also observed after the performance of sensitivity analyses calculated using last observation carried forward, worst observation carried forward, and baseline observation carried forward imputation methods for missing posttermination pain intensity data, with higher mean SPID48 scores in the SSTS group than in the placebo group for all imputation methods ($P < 0.001$ for all). Pain intensity NRS scores for completers in the SSTS and placebo groups (this analysis avoids imputed scores for missing data due to drop-outs) averaged

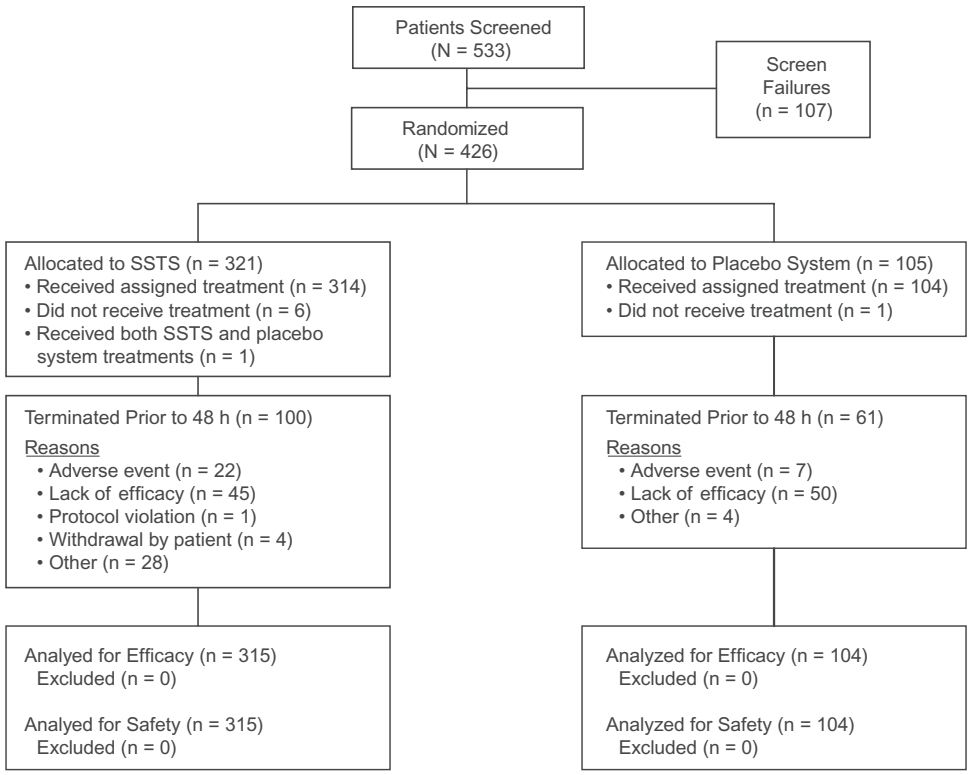

Fig. 1. Patient disposition (CONSORT flow diagram). SSTS = sufentanil sublingual tablet system.

Table 1. Demographics and Baseline Characteristics: Intent-to-treat Population

	SSTS (n = 315)	Placebo System (n = 104)	Total (N = 419)
Age, yr			
< 65, n (%)	129 (41.0)	50 (48.1)	179 (42.7)
≥ 65, n (%)	186 (59.0)	54 (51.9)	240 (57.3)
Mean (SD)	66.6 (10.8)	65.0 (10.5)	66.2 (10.7)
Minimum, maximum	26.0, 90.0	33.0, 87.0	26.0, 90.0
Sex, n (%)			
Male	127 (40.3)	38 (36.5)	165 (39.4)
Female	188 (59.7)	66 (63.5)	254 (60.6)
Race, n (%)			
White	277 (87.9)	91 (87.5)	368 (87.8)
Black or African American	34 (10.8)	12 (11.5)	46 (11.0)
Asian	2 (0.6)	1 (1.0)	3 (0.7)
Other	2 (0.6)	0 (0.0)	2 (0.5)
Ethnicity, n (%)			
Hispanic or Latino	8 (2.5)	1 (1.0)	9 (2.1)
Not Hispanic or Latino	307 (97.5)	103 (99.0)	410 (97.9)
BMI, kg/m^2			
< 30, n (%)	170 (54.1)	52 (50.5)	222 (53.2)
≥ 30, n (%)	144 (45.9)	51 (49.5)	195 (46.8)
Mean (SD)	30.5 (6.9)	31.0 (6.0)	30.6 (6.7)
Minimum, maximum	12.6, 62.0	20.0, 55.1	12.6, 62.0
Surgery, n (%)			
Knee	152 (48.3)	49 (47.1)	201 (48.0)
Hip	163 (51.7)	55 (52.9)	218 (52.0)

BMI = body mass index; SSTS = sufentanil sublingual tablet system.

(3.9 [0.2] *vs.* 5.1 [0.4], difference −1.2 [95% CI, −2.0 to −0.5]; $P = 0.002$) at 24 h, (2.5 [0.2] *vs.* 3.6 [0.3], difference −1.0 [95% CI, −1.8 to −0.3]; $P = 0.005$) at 48 h, and (2.2 [0.2] *vs.* 2.7 [0.4], difference −0.5 [95% CI, −1.2 to 0.3]; $P = 0.22$) at 72 h.

More patients in the placebo system group compared with the SSTS group discontinued the study before 48 h due to inadequate analgesia (48 *vs.* 14%; $P < 0.001$) and required at least one dose of rescue IV morphine during this time period (73 *vs.* 51%; $P < 0.001$). Kaplan–Meier analysis of time to discontinuation due to inadequate analgesia and time to take the first rescue IV morphine dose demonstrated that both occurred earlier in the placebo system group than in the SSTS group ($P < 0.001$; fig. 3). The mean total number of IV morphine doses was lower in the SSTS group compared with the placebo system group (2.3 doses [4.6 mg] *vs.* 4.0 doses [8.0 mg]; $P < 0.001$). The median (range) of sufentanil doses used for study completers in the SSTS group was 21 (1 to 55) tablets in the first 24 h, 11 (0 to 45) tablets in 24 to 48 h, and 6.5 (0 to 31) tablets in the 48- to 72-h study period.

More patients reported success (*i.e.*, responded "good" or "excellent") in the SSTS group compared with patients in the placebo group on the PGA at 24 h (66 *vs.* 33%), 48 h (70 *vs.* 29%), and 72 h (71 *vs.* 32%) ($P < 0.001$ for all). More healthcare professionals reported success on the HPGA at 24 h (70 *vs.* 34%), 48 h (70 *vs.* 28%), and 72 h (71 *vs.* 29%) ($P < 0.001$ for all) than in the placebo system group.

Overall, both patients and nurses rated the overall EOC of the system as greater than 4 on the 0- to 5-point scale. Patient EOC questionnaire results were similar in both treatment groups, except, as expected, SSTS group results showed better scores for questions related to pain control than the placebo system group results (table 3). Because nurses set up both active and placebo systems and were blinded to the treatment groups when completing these questionnaires, the nurse EOC results were compared for nurses with less than 1 yr of experience setting up IV PCA pumps *versus* nurses with more than 1 yr of experience. Overall nurses' subscale scores for bothersome and time consuming were low (*i.e.*, minimally bothersome and minimally time consuming). Nurses with more than 1 yr experience using IV PCA rated a higher overall satisfaction score for the sublingual system compared with nurses with less than 1 yr experience with IV PCA ($P = 0.043$).

Safety Results

A higher proportion of patients in the SSTS group had at least one adverse event related to study drug (54 *vs.* 34%; $P < 0.001$). There was a higher incidence of nausea and pruritus in the SSTS group compared with the placebo group for adverse events considered possibly or probably related to study drug (table 4). Given the 3:1 randomization of active to placebo, more patients in the SSTS group experienced adverse events in general. Seven patients (6 SSTS and 1 placebo) had one or more treatment-emergent serious

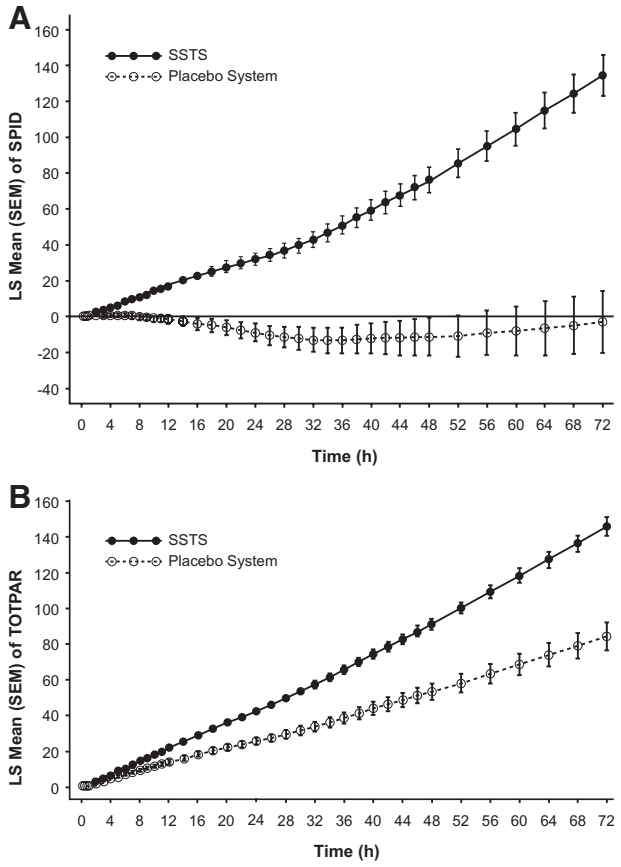

Fig. 2. Least squares (LS) mean (SEM) of (*A*) time-weighted summed pain intensity difference (SPID) and (*B*) total pain relief (TOTPAR) by evaluation time point (intent-to-treat population). Significant differences occurred between treatment groups at all time points from 2 to 72 h ($P < 0.001$). SSTS = sufentanil sublingual tablet system.

Table 2. Subgroup Analysis of Summed Pain Intensity Difference over 48 h (SPID48)

	SPID48*	
Subgroup	SSTS	Placebo System
Sex		
Male	84 (9)	–27 (15)
Female	70 (7)	–5 (12)
Age, yr		
< 65	57 (9)	–8 (14)
≥ 65	88 (7)	–17 (12)
BMI		
< 30	78 (8)	–32 (14)
≥ 30	68 (8)	5 (13)
Surgery type		
Knee	40 (9)	–50 (15)
Hip	110 (7)	24 (12)

* SSTS SPID48 values are statistically superior to placebo SPID48 values for all subgroup analyses ($P < 0.001$ for all values listed). All values are expressed as least squares mean (SEM).

BMI = body mass index; SPID48 = time-weighted summed pain intensity difference to baseline over 48 h; SSTS = sufentanil sublingual tablet system.

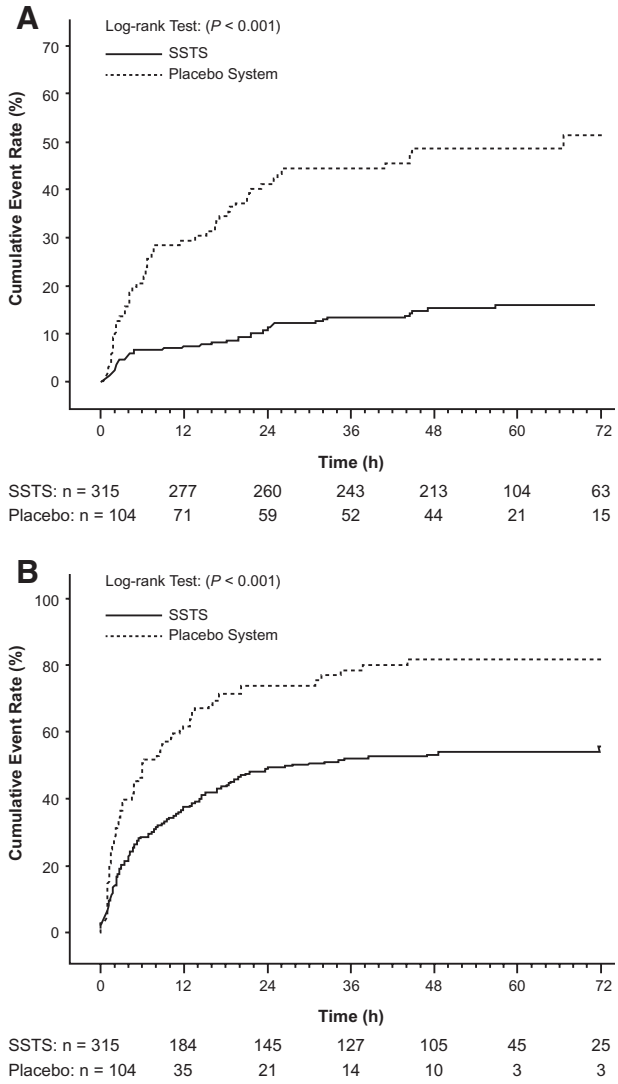

Fig. 3. Kaplan–Meier cumulative event rates for (*A*) time to termination from the study due to inadequate analgesia and (*B*) time to take first rescue medication due to inadequate analgesia (intent-to-treat population). Numbers below x axis indicate the number of patients followed at each time point. SSTS = sufentanil sublingual tablet system.

adverse events (SAEs). Four of these SAEs (atrial fibrillation in the placebo system group and oxygen saturation decreased, sinus tachycardia, and confusional state in the SSTS group) were considered possibly or probably related to study drug. All SAEs in the SSTS group were resolved by the end of the study. Twenty-nine patients (22 SSTS and 7 placebo) had a total of 34 adverse events that caused discontinuation of study drug before 48 h. The most frequent events were nausea (eight patients) and sedation (four patients). Most events were mild or moderate in severity.

There were no statistical differences between the groups for changes in laboratory parameters compared with baseline. At a few evaluation time points throughout the study, there were statistically significant differences

Table 3. EOC Questionnaire Results

	SSTS (n = 302)	Placebo System (n = 100)
Patient EOC subscale results, mean (SD)		
Confidence with device	4.70 (0.53)	4.74 (0.47)
Comfort with device	4.46 (0.67)	4.39 (0.64)
Movement	4.79 (0.65)	4.78 (0.63)
Dosing confidence	4.78 (0.58)	4.76 (0.64)
Pain control*	3.44 (1.38)	2.72 (1.50)
Knowledge/understanding	4.18 (1.23)	4.36 (1.10)
Patient EOC, total, mean (SD)	4.39 (0.51)	4.29 (0.46)
Satisfaction scores		
Level of pain control, %*		
Extremely dissatisfied—dissatisfied	16.9	51.0
Satisfied—extremely satisfied	83.1	49.0
Drug administration, %		
Extremely dissatisfied—dissatisfied	4.6	10.0
Satisfied—extremely satisfied	95.4	90.0
Overall patient satisfaction, mean (SD)*	3.94 (1.04)	3.16 (1.15)
	IV PCA Experience < 1 Yr (n = 39)	**IV PCA Experience > 1 Yr (n = 38)**
Nurse EOC subscale results, mean (SD)		
Time consuming†	0.85 (0.99)	0.63 (0.54)
Bothersome†	0.42 (0.44)	0.42 (0.48)
Nurse EOC, total, mean (SD)	4.41 (0.53)	4.47 (0.49)
Satisfaction scores, %		
Pain control		
Extremely dissatisfied—dissatisfied	7.7	7.9
Satisfied—extremely satisfied	92.3	92.1
Device Satisfaction		
Extremely dissatisfied—dissatisfied	5.2	0
Satisfied—extremely satisfied	94.8	100
Overall nurse satisfaction, mean (SD)‡	3.65 (0.93)	4.07 (0.82)

* $P < 0.001$; † for nursing subscale scores, lower is better (*i.e.*, less time consuming); however, these values are converted back to the 0–5 scale (where 5 is the highest score) for the nurse EOC total score; ‡ $P < 0.05$.

EOC = ease of care; IV PCA = intravenous patient-controlled analgesia; SSTS = sufentanil sublingual tablet system.

Table 4. Possibly or Probably Related Adverse Events (> 2% in Either Treatment Group)

Preferred Term	SSTS (n = 315)	Placebo System (n = 104)
Any related adverse event*	171 (54.3%)	35 (33.7%)
Nausea†	110 (34.9%)	23 (22.1%)
Vomiting	34 (10.8%)	6 (5.8%)
Oxygen saturation decreased	22 (7.0%)	3 (2.9%)
Dizziness	16 (5.1%)	1 (1.0%)
Constipation	15 (4.8%)	1 (1.0%)
Pruritus†	15 (4.8%)	0
Headache	13 (4.1%)	6 (5.8%)
Insomnia	13 (4.1%)	3 (2.9%)
Hypotension	12 (3.8%)	2 (1.9%)
Confusional state	8 (2.5%)	1 (1.0%)

Adverse event mapping based on the MedDRA Version 11.0 thesaurus.[23] A patient could be reported in more than one category. Includes all possibly or probably related adverse events occurring while patients were taking study drug or within 12 h after the discontinuation of study drug.

* $P < 0.001$; † $P < 0.05$.

SSTS = sufentanil sublingual tablet system.

for mean systolic (3 of 39 evaluations) and diastolic blood pressures (4 of 39 evaluations) from baseline between the groups, with a slight lowering of blood pressure values in the SSTS group compared with the placebo group. None of the changes in blood pressure were considered to be medically meaningful, and reports of hypotension were low and statistically similar between the treatment arms (table 4). At three evaluation time points, there were small, but statistically significant, increases in heart rate in the placebo group compared with the SSTS group, with no difference in reports of tachycardia between the groups (1% for both groups). Changes from baseline for respiratory rate were only significant at one evaluation and was due to a slightly larger mean increase in breaths/min in the placebo group compared with the SSTS group. There were no statistically significant differences between treatment groups for mean oxygen saturation values during the study, and the same proportion of patients (15%) in each group experienced a desaturation below 93% at some point throughout the study.

Discussion

The findings from this phase 3 study demonstrate the efficacy of the SSTS in the treatment of postoperative pain in patients after total knee and total hip arthroplasty and suggest that a single cartridge of 40 tablets would provide analgesia for at least 48 h in most patients. Pain intensity reduction in the SSTS group compared with the placebo group was superior across the different sex, age, BMI, and surgical subpopulations. This study was not conducted using multimodal analgesia, and the subgroup analysis shows that younger patients and patients receiving knee replacements had the lowest SPID48 values, demonstrating the importance of adjuvant analgesics in these populations. The SSTS group had mean pain relief and PID assessments that were greater than that in placebo as early as 45 and 60 min, respectively. This rapid onset of action is possibly due to the high lipophilicity of sufentanil (octanol:buffer partition coefficient of 1,757:1) as well as a 20% nonionized fraction (at pH of 7.4).[17] Lipophilic, nonionized drug molecules rapidly transit to the μ-opioid effector site in the central nervous system (CNS) (plasma:CNS equilibration half-life [$t_{1/2}k_{e0}$] = 6.2 min for sufentanil).[18] Morphine and hydromorphone are not lipophilic (octanol:buffer partition coefficient of 1:1 and 1.28:1) and, therefore, even when delivered IV, these opioids have delayed transit times to the CNS ($t_{1/2}k_{e0}$ = 2.8 h and 46 min, respectively).[17,19] Opioid analgesics absorbed *via* the gastrointestinal route have relatively slow onset, in addition to erratic absorption after surgery due to gastric stasis. Nurse-administered analgesics have the additional delay of acquisition and administration time.

A close association between patient dosing and peak CNS effect of the opioid is critical to avoid dose stacking, along with a lockout interval that is similar to the opioid T_{max} with repeated dosing. With slow-equilibrating opioids, multiple doses administered during the initial period of inadequate analgesia will be followed by a delayed wave of opioid equilibrating with the brain μ-opioid receptors, possibly producing adverse events. Further complicating this dose-stacking phenomenon is the delayed production of active morphine and hydromorphone metabolites by the liver. The active metabolite of morphine, morphine-6-glucuronide, has an even longer equilibration time with the CNS ($t_{1/2}k_{e0}$ = 6.4 h).[19] For sufentanil, the median time to peak plasma concentration (T_{max}) of 18 min after repeated sublingual administration matches the lockout for the SSTS device,[13] and together with the rapid $t_{1/2}k_{e0}$ of sufentanil and the lack of active metabolites allows a very close association between dosing and peak effects and minimizes the risk of dose stacking. Adverse events suggestive of dose stacking (*i.e.*, excessive sedation) were rare in the SSTS phase 3 program.[14,20] As with most drugs administered in postoperative patients, various comorbidities may result in a prolonged T_{max} and possible overdose *via* could occur under these conditions.

Minimal dosing of IV morphine for inadequate analgesia was used in the SSTS group (a total of 2.3 doses = 4.6 mg IV morphine) over the duration of the study. The placebo group used statistically more IV morphine (8 mg); however, this amount is still surprisingly low. Although this can partially be accounted for by the earlier and higher drop-out rate of placebo patients (58.7% before 48 h) in that they had less time in the study in which to use IV morphine, it suggests that there was a relatively high placebo-responding rate in this trial. It is possible that the novelty of the device attributed to this robust placebo response. Analgesia resulting from use of IV morphine was not included in the pain scores because premorphine pain intensity and pain relief scores were imputed forward for 1 h after morphine dosing; however, given the low use of IV morphine, this imputed data would have little effect on the overall SPID values over the 2- to 3-day study.

Approximately 14% of patients in the SSTS group dropped out of the study due to inadequate analgesia, possibly caused by insufficient analgesic response to the study drug, study drug dose, and/or lockout interval. This percentage was significantly less than the placebo group, and the drop-outs occurred later in the SSTS group. This study allowed no adjuvant analgesics, and the blinded nature of the study meant patients were unsure as to whether they were receiving active study drug and may have tended to drop-out to guarantee access to analgesics. Additional study limitations include a disproportionate number of white patients and female patients in both treatment groups, which is not surprising given that these are common demographics receiving knee and hip replacements.

Patient and HPGAs, as well as the EOC questionnaire ratings, all demonstrate that both patients and healthcare professionals found the system to be easy to set up and use and to provide the patient with significant analgesia over placebo. For patients randomized to either active or placebo (the same device was used in both groups), EOC scores of the system were high, with the exception of pain relief, which was appropriately lower in the placebo system group. In an open-label, randomized study of SSTS compared with IV PCA morphine in patients after either open abdominal surgery or major joint replacement surgery, patient and nurse EOC scores were higher for the SSTS compared with IV PCA for both the total EOC score and each subscale score.[14] The SSTS device is novel and offers patients a much greater degree of sensory feedback (*i.e.*, lockout mode notification, flashing lights, positive/negative dosing sounds, and vibration of motor during dispensing) than IV PCA, which not only may have contributed to the significantly higher patient EOC ratings, but also may have enhanced the reported analgesic response, such as SPID and TOTPAR, in both the active and placebo groups.

There were no clinically relevant differences in vital signs between active and placebo groups. The adverse events were

typical of postoperative patients, and nausea and pruritus were the only two related adverse events that were statistically greater for the SSTS group. The SSTS-related occurrence rate of many of the adverse events in table 4 is lower than reported in meta-analyses for postoperative IV PCA opioids in the literature.[21,22]

To reflect a typical surgical population, the protocol did not limit enrollment by age or BMI, resulting in an age range of 26 to 90 yr with 57% of the patients at least 65 yr old. The patients' BMIs ranged from 12.6 to 62, and 47% of the study population was obese (BMI > 30). The similar safety profiles of SSTS compared with placebo is encouraging for the use of this product in an at-risk population, but given the limited number of patients in this study (< 500), the relatively healthy patient population and the exclusion of sleep laboratory–documented sleep apnea patients, additional postmarket studies and experience are indicated.

In summary, the SSTS is an investigational system for the management of moderate-to-severe acute pain in a hospital setting. The system is preprogrammed and noninvasive, overcoming some of the issues with IV PCA, but allows patient control over dosing, thereby possibly enhancing patient satisfaction over nurse-administered analgesics. This study, conducted without the benefit of multimodal analgesia, demonstrated that SSTS is effective in a broad demographic profile of patients after total knee or hip arthroplasty. Optimally, in the treatment of moderate-to-severe postoperative musculoskeletal pain, SSTS would be used in conjunction with nonopioid adjuvant analgesics to afford a more balanced postoperative analgesic regimen.

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Competing Interests

Dr. Jove received research funding from AcelRx Pharmaceuticals (Redwood City, California) for conducting this study. Dr. Griffin received research funding from AcelRx Pharmaceuticals for conducting this study and is a speaker for AcelRx Pharmaceuticals (received honoraria from AcelRx Pharmaceuticals). Dr. Minkowitz received research funding from AcelRx Pharmaceuticals for conducting this study and is an advisory board member for AcelRx (received fees from AcelRx Pharmaceuticals). Dr. Ben-David received research funding from AcelRx Pharmaceuticals during this study. Drs. Evashenk and Palmer were salaried employees of AcelRx Pharmaceuticals with stock options.

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