A Phase 2 Multicenter, Randomized, Placebo-Controlled Study to Evaluate the Clinical Efficacy, Safety, and Tolerability of Sublingual Sufentanil NanoTab™ in Patients Following Major Abdominal Surgery

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Abstract

Introduction: Intravenous patient-controlled analgesia (IV PCA) with morphine is the standard of care in many hospitals for the management of acute post-operative pain. However, IV PCA is associated with several limitations, including, the risk of PCA pump programming errors, reduced patient mobility secondary to the requisite IV line, and increased risk of analgesic gaps due to infiltrated and dislodged IV catheters or pump malfunction. Furthermore, while morphine is the most commonly used analgesic in this treatment modality, it can produce many undesirable side effects due to accumulation of active metabolites, especially in elderly and renally impaired patients. The Sufentanil NanoTab PCA System is a novel patient-controlled sublingual analgesia (PCSA) product candidate with a pre-programmed patient lock-out feature that is designed for use in hospital settings to provide effective, titratable, patient-controlled analgesia and reduce the risk of programming errors. The Sufentanil NanoTab PCA System also avoids the IV-related limitations of IV PCA by being designed to provide convenient and safe patient self-administration of Sufentanil NanoTabs sublingually for oral transmucosal absorption. The active drug, sufentanil, is a high therapeutic index opioid approved for intravenous and epidural administration. Although the analgesic efficacy of sufentanil has been well established, its use has been limited due to its short IV plasma half-time. In the NanoTab oral transmucosal dosage form, sufentanil demonstrates a therapeutically appropriate pharmacokinetic profile for post-operative PCA usage and has the potential for improved patient tolerability over IV PCA morphine. The primary objective of this study was to evaluate the efficacy, safety and tolerability of Sublingual Sufentanil NanoTabs in patients following major abdominal surgery.

Methods: A total of 88 patients following major lower and upper abdominal surgery were randomized to receive placebo, 10 mcg or 15 mcg doses of Sufentanil NanoTabs for post-operative pain after stabilization of pain levels in the post-operative care unit. Study drug was nurse administered sublingually as needed to treat pain at the patient's request, with a minimum re-dosing interval of 20 minutes. Patients were allowed to drop out of the study at any time. The primary efficacy endpoint was Sum of the Pain Intensity Difference SPID-12 (a cumulative measure of the difference in pain intensity over the 12-hour study compared to baseline).

Results: Patients receiving 10 mcg or 15 mcg of Sufentanil NanoTabs experienced a significant reduction in pain intensity compared to placebo for the primary endpoint SPID-12 using the three alternative imputation methods (last-LOCF, p<0.001 (10 and 15 mcg), baseline-BOCF, p=0.004 (10 mcg) and p<0.001 (15 mcg), and worst-WOCF, p<0.001 (10 and 15 mcg) observation carried forward). Furthermore, both the 10 mcg and 15 mcg dose met a key secondary endpoint, lower percentage of patient dropouts due to inadequate analgesia compared to placebo (p<0.001). There were no significant differences among treatment groups for the overall incidence of adverse events, or any specific adverse event with the exception of pruritus, which was more frequent in 15 mcg group than in the other groups. There were no serious adverse events related to study drug.

Conclusions: This Phase 2 study demonstrates analgesic efficacy, safety and tolerability of the Sublingual Sufentanil NanoTab in management of acute moderate-to-severe post-operative pain following major abdominal surgery. Future Phase 3 studies of the Sufentanil NanoTab PCA System will further delineate the safety and efficacy of this PCSA system.

Background and Objectives

Intravenous patient-controlled analgesia (IV PCA) with morphine is standard of care for management of acute post-operative pain. However, IV PCA has several limitations:

- Risk of PCA pump programming errors[1]
- Risk of analgesic gaps due to infiltrated or dislodged catheters or pump malfunction[2]
- Reduced patient mobility secondary to requisite IV line
- Active metabolites morphine-3-glucuronide and morphine-6-glucuronide, especially in elderly and renally mpaired patients[3,4]

The Sufentanil NanoTab PCA System:

- Preprogrammed patient lock-out eliminates the risk of programming errors
- Sublingual route of delivery avoids IV-related complications
- Sufentanil: High therapeutic index opioid[5], no active metabolites[6], approved for IV and epidural administration
- NanoTab: New oral transmucosal dosage form (3 mm in diameter) designed to minimize saliva response
  - Demonstrates high bioavailability (~80%), blunted Cmax and longer plasma half-time, which is more appropriate for post-operative PCA usage compared to IV sufentanil [7]

Objective of the Study: Evaluate the efficacy, safety and tolerability of sublingually administered Sufentanil NanoTabs in patients following major abdominal surgery

Methodology

- 92 patients following major abdominal surgery randomized to receive placebo, 10 mcg or 15 mcg doses of Sufentanil NanoTabs
- Study drug nurse-administered sublingually as needed to treat pain at patient's request, with 20-minute minimum re-dosing interval
- No rescue analgesics allowed after first 30 minutes of 12-hour study period - patient pain intensity scores required to be > 4 before study drug dosing started
- Patients allowed to drop out of study at any time
- Primary efficacy endpoint was Sum of Pain Intensity Difference SPID-12
- Secondary endpoints: pain relief scores, percentage of patients dropping out of study due to inadequate analgesia, patient global assessment of efficacy and tolerability at end of study, average hourly dosing requirements and average inter-dosing interval
- 88 patients total received study drug and included in intent-to-treat (ITT) population - patients reported pain intensity and pain relief scores using electronic diary

Results

SPID-12: Sum of Pain Intensity Difference over 12-Hour Study Period

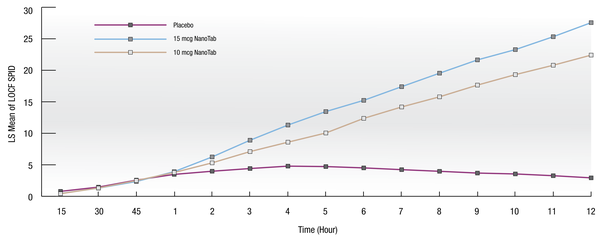
- For ITT population, statistically significant difference between treatment groups and placebo for last observation carried forward (LOCF) SPID-12 scores (p<0.001) (Figure 1)
- Least squares (LS) mean SPID-12 scores higher in both Sufentanil NanoTab groups compared to placebo group; mean (SEM) SPID-12 scores were 22.4 (3.6), 27.6 (3.5), and 2.9 (3.5) in 10 mcg, 15 mcg, and placebo groups, respectively
- LS mean difference statistically significant for both 10 and 15 mcg groups compared to placebo (p<0.001)
- Baseline observation carried forward (BOCF) and worst observation carried forward (WOCF) analyses of SPID-12 similar to LOCF analysis

SPID by Evaluation Time Point

- Statistically significant differences between Sufentanil NanoTab groups and placebo group for LS mean SPID scores at all time points from 3 to 12 hours in 15 mcg dose group (p=0.007 to p<0.001), and from 4 to 12 hours in 10 mcg dose group (p=0.048 to p<0.001), with higher mean SPID scores in active treatment groups than in placebo group

Figure 1. SPID Scores Over the 12-Hour Study Period

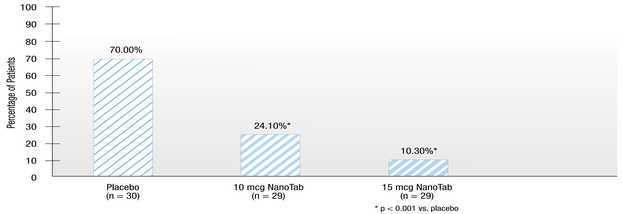
Least Squares (LS) Mean of LOCF Summed Pain Intensity Difference (SPID) by Evaluation Time Point: Intent-to-treat Population



Discontinuation Due to Inadequate Analgesia

- Statistically significant differences between each Sufentanil NanoTab group and placebo group for proportion of subjects who discontinued study due to inadequate analgesia (p<0.001)
- 21 (70.0%) patients in placebo group discontinued due to inadequate analgesia
- 7 (24.1%) and 3 (10.3%) patients, respectively, in 10 and 15 mcg groups (Figure 2)
- Kaplan-Meier analysis of cumulative event-free rates for time to termination due to inadequate analgesia showed significant difference between each Sufentanil NanoTab group and placebo group (p<0.001)

Figure 2. Discontinuation Due to Inadequate Analgesia

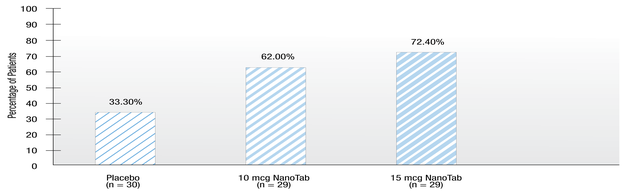


Patient Global Evaluation of Pain Relief

- For ITT population, significant differences among treatment groups for all responses on patient global evaluation of pain relief (p=0.005) and for proportion of patients who responded 'very good' or 'excellent' on patient global evaluation of pain relief (p<0.001)
- 18 (62.0%) patients in 10 mcg group and 21 (72.4%) patients in 15 mcg group responded 'good,' 'very good' or 'excellent' on patient global evaluation of pain relief, compared with 10 (33.3%) patients in placebo group (Figure 3)

Figure 3. Patient Global Evaluation of Pain Relief

Proportion of Patients that responded 'good, 'very good' or 'excellent' in Patient Global Evaluation of Pain Relief: Intent-to-treat Population



Median Time to First Re-Medication

- For ITT population: 36 and 37 minutes in Sufentanil NanoTab 10 and 15 mcg groups, respectively

Total Number of Doses Used and Inter-Dosing Interval for Completers

- LS mean (range) total number of doses used was 8.6 (2 – 21) and 8.6 (1 – 15) in 10 and 15 mcg groups, respectively
- Mean inter-dosing interval was 118.9 and 100.7 minutes in 10 and 15 mcg groups, respectively

Safety Results

- No significant differences among treatment groups for overall incidence of adverse events or any specific adverse event, with the exception of pruritus, which was more frequent in 15 mcg group than in other groups
- No serious adverse events related to study drug
- No reports of oral mucosa irritation

Adverse Events	Placebo n=30	10 mcg n=29	15 mcg n=29	IV PCA [8,9]
Nausea	14 (47%)	16 (55%)	19 (65%)	25 - 53%
Vomiting	2 (7%)	2 (7%)	0 (0%)	20 - 34%
Pruritus	1 (3%)	2 (7%)	6 (21%)	15%
Somnolence	0 (0%)	0 (0%)	0 (0%)	56%
Oxygen Desaturation	0 (0%)	0 (0%)	0 (0%)	11.5%
Respiratory Depression	0 (0%)	0 (0%)	0 (0%)	1.2 - 1.9%

Conclusions

- Sufentanil NanoTab 10 mcg and 15 mcg were effective, safe, and well-tolerated for treatment of acute post-operative pain in patients after major abdominal surgery
- Both dosage strengths significantly more effective than placebo for all measures of pain intensity and pain relief in this study
- Treatment with Sufentanil NanoTab was well tolerated - most common AE was nausea, but this occurred with similar frequency in all treatment groups
- No clinically significant changes in laboratory variables, vital signs, or oxygen saturation during the study
- Interdosing interval for Sufentanil NanoTabs that ranges between 100.7 – 118.9 minutes is longer than typical interdosing interval with IV PCA (calculated to be between 20-40 minutes[10,11]), and correlates well with Phase 1 sublingual pharmacokinetic profile for study drug

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Acknowledgements: The authors wish to thank the study subjects, Trio Clinical Research, and the investigators and research coordinators for their contribution. Study supported by AcelRx Pharmaceuticals, Inc., Redwood City, CA.