

Abstract Title: 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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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.

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