A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Clinical Efficacy, Safety, and Tolerability of ARX-03 Sublingual Sufentanil/Triazolam 15 mcg/200 mcg NanoTab® in Patients Undergoing an Elective Abdominal Liposuction Procedure

AcelRx Pharmaceuticals, Inc.
575 Chesapeake Drive
Redwood City, CA 94063
ppalmer@acelrx.com

Neil K. Singla, MD[1]; Shankar Lakshman, MD[1]; Mark A. Evashenk[2]; Martha E. Neubauer[2]; Pamela P. Palmer, MD, PhD[2]

[1]Lotus Clinical Research, Pasadena, CA (USA); [2]AcelRx Pharmaceuticals, Redwood City, CA (USA)

Abstract

Many patients are anxious and uncomfortable during office-based aesthetic, diagnostic and therapeutic procedures, which can negatively impact both the patient and the surgeon. ARX-03 is a new sublingual product combining sufentanil with triazolam and is in development to provide mild sedation, anxiolysis and analgesia with rapid onset of action for painful office-based procedures. Since ARX-03 is designed for Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) Level 1 sedation (minimal sedation), administration of ARX-03 will not require the level of staff monitoring mandated for intravenous sedation. In this randomized Phase 2 study, 40 patients undergoing low-volume liposuction received either a single sublingual dose of ARX-03 (sufentanil 15 mcg/triazolam 200 mcg NanoTab) or placebo prior to injection of a local anesthetic. The primary endpoint was mild sedation during the procedure, as assessed using the validated, objective Richmond Agitation-Sedation Scale (RASS). The summed RASS score over the 4-hour study period showed significantly greater sedation for ARX-03 than for placebo ($p < 0.001$) and a separation from placebo was seen as early as 30 minutes post-dosing ($p = 0.046$). The summed anxiety score (patient-reported 11-point scale) over 4 hours was also significantly lower for ARX-03 than for placebo ($p = 0.004$), with separation from placebo occurring at 15 minutes post-dosing ($p = 0.034$). Both physician and patient global evaluations of effectiveness and tolerability were significantly higher in the active versus placebo groups ($p < 0.001$ and $p = 0.028$, respectively) and all patients were ready for discharge immediately following the procedure, as measured by the modified Aldrete score. Adverse events were minimal and no respiratory depression was observed. The ARX-03 Sufentanil/Triazolam NanoTab demonstrated effectiveness and high tolerability in providing mild sedation with rapid onset for office-based procedures. Future studies of the Sufentanil/Triazolam NanoTab will further delineate the safety and efficacy of this novel product.

Background and Objectives

Background: Sedation for painful office-based procedures is often problematic. Intravenous delivery provides rapid onset of action but requires sedation-trained personnel for delivery of benzodiazepines with opioids or other IV sedatives, such as dexmedetomidine, propofol or fospropofol. Oral pills or liquid formulations have a slow and erratic onset of action, therefore possibly delaying the procedure, since sedatives must be dosed after informed consent is obtained.

The non-invasive sublingual Sufentanil/Triazolam 15 mcg/200 mcg NanoTab combines a sedative with an opioid to provide rapid onset mild sedation for painful office-based procedures:

- Sufentanil: High therapeutic index opioid[1], no active metabolites[2], highly lipophilic[3] to allow rapid transmucosal uptake
- Triazolam: Short-acting benzodiazepine with no active metabolites[4], highly lipophilic[5] to allow rapid transmucosal uptake

Objective of the Study: To evaluate the efficacy and safety of sublingually administered Sufentanil/Triazolam NanoTabs in patients undergoing elective abdominal liposuction.

Methodology

- 40 patients randomized to double-blind treatment consisting of one Placebo NanoTab or one ARX-03 Sufentanil/Triazolam 15 mcg/ 200 mcg NanoTab administered by the site staff in the clinic just prior to the procedure
- The primary efficacy endpoint was the summed Richmond Agitation-Sedation Scale (RASS) score over the 4-hour study period (SRS-4) as assessed by the 10-point RASS, where unarousable is graded as minus 5 (- 5) and combative is graded as plus 4 (+ 4).
- Secondary endpoints included: RASS score at multiple time points, summed anxiety difference over the 4 hour study period (SAND-4), procedural anxiety at each evaluation time point, summed pain intensity over the 4-hour study period (SPI-4), pain intensity at each evaluation time point, patient and physician global satisfaction of effectiveness and tolerability, patients who terminated prematurely due to lack of efficacy, and time to readiness for discharge from clinic based on total modifed Aldrete score.
- Safety was monitored by regular measurements of vital signs and continuous monitoring of oxygen saturation, as well as assessment of adverse events (AEs) and the use of concomitant medications.
- Patients reported anxiety, pain intensity and global satisfaction scores using paper diaries via verbal report recorded by site staff

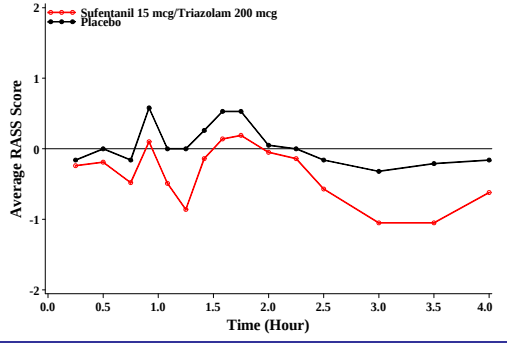
Results

All 40 patients received treatment and completed the study and were included in the intent-to-treat (ITT) population analyses.

Summed RASS Score Over the 4-hour Study Period (SRS-4)

- For the ITT population, the least squares (LS) mean SRS-4 score was statistically significantly lower (i.e. greater sedation) in the ARX-03 treatment group compared to the placebo treatment group; the LS mean (SEM) SRS-4 scores were -5.44 (0.82) and 0.79 (0.86) for the ARX-03 treatment and placebo treatment groups, respectively ($p < 0.001$).
- The RASS scores at each time point are shown in Figure 1.

Figure 1. Average RASS Scores by Evaluation Time Point

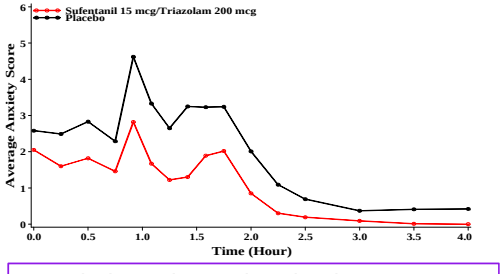


Results (continued)

Summed Anxiety Difference Over 4 Hours (SAND-4)

- The mean SAND-4 was statistically significantly greater in the ARX-F03 treatment group compared to the placebo treatment group ($p = 0.004$).
- ARX-03-treated patients had lower anxiety scores as early as 15 minutes following NanoTab dosing ($p < 0.05$).

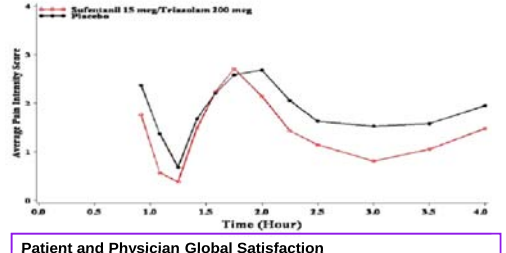
Figure 2. Average Anxiety Score by Evaluation Time Point



Summed Pain Intensity over 4-hours (SPI-4)

- The SPI-4 score of the ARX-03 treatment group and placebo treatment group were not significantly different but the average PI scores for the ARX-03 treatment group at most evaluation time points were consistently numerically lower than the placebo treatment group (see Figure 3).
- The LS mean (SEM) SPI-4 was 17.19 (3.44) for the ARX-03 treatment group and 22.32 (3.62) in the placebo group ($p = 0.311$).

Figure 3. Average Pain Intensity Score by Evaluation Time Point



Patient and Physician Global Satisfaction

- The ARX-03 treatment group had a higher percentage of patients who rated the treatment very good or excellent on the global assessment of effectiveness and tolerability (71.4%) than the placebo treatment group (36.8%) ($p < 0.028$).
- The ARX-03 treatment group had a higher percentage of patients rated by the surgeon as very good or excellent for the global assessment of effectiveness and tolerability (61.9%) than the placebo treatment group (5.3%) ($p < 0.001$).

Results (continued)

Readiness for Discharge

- The minimum Modified Aldrete Score for any patient was an 8, a score which indicates a patient is ready for discharge. All patients in both the ARX-03 treatment and placebo treatment groups, were ready for discharge beginning with the first assessment at 120 minutes after dosing and continuing through the final assessment at 240 minutes after dosing.

Safety Results

- A total of 10 patients had one or more AEs during the study. The most common AE was dizziness which occurred in 2 patients in the ARX-03 treatment group and 2 patients in the placebo group.
- There were no clinically significant changes in blood pressure, heart rate, respiratory rate or oxygen saturation during the study.
- There were no significant differences between the two treatment groups for the overall incidence of AEs, the incidence of any class of AEs, or any specific AE.
- No serious AEs were reported throughout the study.
- No reports of oral mucosa irritation were noted.

Conclusions

- **ARX-03 Sufentanil/Triazolam NanoTab was effective, safe, and well-tolerated in patients undergoing elective low-volume abdominal liposuction**
- **ARX-03 was superior to placebo based on the primary efficacy endpoint of summed RASS over the 4-hour study period**
- **ARX-03 was significantly more effective than placebo as measured by the summed anxiety difference over the 4-hour study period, physician global assessment and patient global assessments**
- **ARX-03 was well tolerated. The most common AE was dizziness but this occurred with similar frequency in the placebo treatment group**
- **ARX-03 did not delay patient discharge compared to the placebo treatment group**

References

1. Mather LE: Clin Exp Pharmacol Physiol 1995;22:833-6.
2. Sufenta® package insert
3. Bernards CM: Opioids in Pain Control (ed. Christoph Stein) 1999; pp 166-87.
4. Halcion® package insert
5. Arendt RM, Greenblatt DJ, Liebisch DC, Luu MD Paul SM: Psychopharmacology 1987;93:72-6.

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