



Top-line Data Demonstrate Primary Endpoint Achieved in Final Pivotal Phase 3 Study of Sufentanil NanoTab PCA System For Management of Post-Operative Pain

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- Following major orthopedic surgery, Sufentanil NanoTab-treated patients experienced significantly greater reduction in pain as measured by SPID-48 vs. placebo ($p < 0.001$) -
- Results confirm all previously reported Phase 3 trial outcomes, supporting submission of an NDA anticipated for third quarter 2013 -
- AcelRx to conduct conference call and webcast today, May 21, 8:30 a.m. EDT (5:30 a.m. PDT) -

REDWOOD CITY, Calif., May 21, 2013 /PRNewswire/ -- AcelRx Pharmaceuticals, Inc. (Nasdaq: ACRX), a specialty pharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of acute and breakthrough pain, today announced top-line data demonstrating that in a placebo-controlled Phase 3 study of its investigational sublingual Sufentanil NanoTab PCA (patient-controlled analgesia) System (NanoTab System), the primary efficacy endpoint was achieved. The study evaluated control of pain intensity compared to baseline during the 48-hour study period immediately following major orthopedic surgery, specifically knee or hip replacement, using the FDA-requested primary endpoint of Summed Pain Intensity Difference to baseline (i.e. SPID-48). Results demonstrated that patients receiving sufentanil NanoTabs realized a significantly greater SPID-48 during the study period than placebo-treated patients (+76.1 vs -11.5, $p < 0.001$). Secondary endpoint data showed that SPID at 24 hours and 72 hours was also significantly greater in the sufentanil-treated patients than in the placebo-treated patients ($p < 0.001$ in each case). Adverse events reported in the study were generally mild or moderate in nature and were similar in both placebo and treatment groups for the majority of adverse events.

"With the successful completion of this study, AcelRx has now achieved positive results in all three Phase 3 studies in which the Sufentanil NanoTab PCA System has been evaluated," said Richard King, president and CEO of AcelRx. "We remain on track for a third quarter 2013 NDA submission for the NanoTab System, a product which, if approved, will present AcelRx with an opportunity to fundamentally redefine the management of post-operative pain for tens of millions of patients both in the U.S. and around the world."

Phase 3 Orthopedic Study Design and Demographics

Utilizing a randomized, double-blind, placebo-controlled design, this pivotal Phase 3 study enrolled 426 adult patients at 34 U.S. sites for treatment of moderate-to-severe acute pain immediately following major orthopedic surgery. Seven patients did not receive study drug, resulting in 419 patients being included in the intent-to-treat (ITT) population. Patients were treated for a minimum of 48 hours, and up to 72 hours. Patients were randomized 3:1, with 315 patients randomized to sufentanil treatment and 104 to placebo treatment. Both treatments were delivered by the patient, as needed, using the NanoTab System with a 20-minute lock-out period. Patients in both groups could receive up to 2 mg morphine intravenously per hour as a rescue medication, the primary purpose of this rescue medication being to enable placebo-treated patients to stay in the study. Pain scores recorded just prior to the delivery of rescue medication were gathered and imputed forward to minimize the impact of this rescue opioid on efficacy evaluations.

As with our other Phase 3 studies, there was no upper limit on age or weight in recruitment of patients in this study. The oldest patient treated was 90 years of age, the heaviest had a BMI of 62 kg/m². Historically, older patients are more susceptible to the adverse events caused by opioids, and heavier patients tend to have greater risk of obstructive apnea, which is often worsened by opioids. This should allow the regulatory agency to review data for treating these two at-risk groups with sufentanil. Overall, patient demographics (percentage of patients) in this study were as follows:

	Male: Female	Caucasian: Non-Caucasian	BMI (kg/m ²) <30: >30	Age (yrs) <65: >65
Sufentanil	40:60	85:15	54:46	41:59
Placebo	37:63	87:13	50:50	48:52

Primary Endpoint Data

Two hundred fifteen (68.3%) sufentanil NanoTab-treated patients completed the 48-hour study period, compared to 43 (41.3%) placebo-treated patients. Primary reasons for drop-out in the sufentanil- and placebo-treated groups were adverse events (7.0% and 6.7%, respectively) and lack of efficacy (14.3% and 48.1%, respectively). The primary endpoint measure, SPID-48, was +76.1 for sufentanil-treated patients and -11.5 for placebo-treated patients ($p < 0.001$).

Key Secondary Endpoint Data

SPID separated between sufentanil- and placebo-treated patients after the first hour, and was highly significant at all timepoints thereafter as illustrated below.

Group	SPID-24	SPID-48	SPID-72
Sufentanil NanoTab	33.8	76.1	166.2
Placebo	-8.8	-11.5	-2.6
Statistical Comparison	$P < 0.001$	$P < 0.001$	$P < 0.001$

A secondary endpoint focused on Total Pain Relief measured at 48 hours (TOTPAR-48) was significantly higher in the sufentanil-treated patients than in the placebo-treated patients ($p < 0.001$). In addition, another secondary endpoint, measurement of Patient Global Assessment with Method of Pain Control at 48 hours (PGA-48) was also highly significant in favor of sufentanil-treated patients ($p < 0.001$).

Safety and Tolerability Profile

Treatment-emergent adverse events were generally mild to moderate in nature and similar for the majority of adverse events between sufentanil and placebo treated patients, despite the shorter duration of exposure in the placebo-treated patients caused by early termination due to inadequate analgesia. Adverse events of nausea (occurring in 52.7% of sufentanil-treated patients vs 33.7% of placebo-treated patients), vomiting (12.7% vs 5.8%, respectively), dizziness (6% vs 1%, respectively) and itching (6% vs 0%, respectively) were the only adverse effects that statistically separated

between sufentanil- and placebo-treated patients. Nausea, vomiting and itching are common in treatment of post-operative patients, and are easily managed with anti-emetic and anti-histamine treatment. Effective management of these symptoms is demonstrated by the low drop-out rate due to nausea (1.6% of sufentanil-treated patients vs 2.9% of placebo-treated patients), vomiting (0.6% vs 0%, respectively) and itching (0.3% vs 0%, respectively) in this study. Two patients (one each in the sufentanil group and placebo group) experienced a serious adverse event considered possibly or probably related to the study drug by the investigator.

Dr. Pamela Palmer, chief medical officer for AcelRx and an anesthesiologist said, "My primary concern with the use of opioids in the treatment of moderate-to-severe pain, especially in the elderly, is respiratory events. Each of the two Phase 3 pivotal studies has shown no statistical difference between sufentanil- and placebo- treated patients for any respiratory event. In addition, our Phase 3 head-to-head study demonstrated statistically fewer patients with oxygen desaturation events with sufentanil NanoTab than IV PCA morphine based on pulse oximetry monitoring."

Dr. David Griffin, an orthopedic surgeon at the Orthopaedic Center of Vero Beach, the first site to enroll in this study, said "The Sufentanil NanoTab PCA System eliminates the risk of programming errors and frees the patient from an IV connection which facilitates patient ambulation. These advantages, coupled with the excellent efficacy and safety of this System that we have observed in our study patients, should lead to better patient satisfaction and better patient outcomes."

Summary of Previously Reported Phase 3 Data

This study is the last of 3 successful Phase 3 studies conducted by AcelRx to support U.S. and ex-US regulatory review of the Sufentanil NanoTab PCA System. In November 2012, AcelRx announced positive top-line results for the NanoTab System in a Phase 3 open-label, active-comparator study evaluating the efficacy and safety of the NanoTab System compared to IV PCA with morphine (study IAP-309) in the management of moderate-to-severe acute pain after surgery. Results from this study demonstrated that the NanoTab System met its primary endpoint of non-inferiority in patient global assessment (PGA), with method of pain control in comparison to IV PCA with morphine at 48 hours. Additional analyses also demonstrated that the NanoTab System was statistically superior to IV PCA morphine for the PGA measurement. In addition, nurses managing patients in the study and the patients themselves reported that they had significantly greater Overall Satisfaction with the NanoTab System compared to IV PCA morphine and significantly greater Overall Ease of Care with the NanoTab System compared to IV PCA morphine using a validated assessment questionnaire. Further analyses of results from this study, presented at the ASRA meeting in May 2013 demonstrated that sufentanil delivered via the NanoTab System had a significantly greater pain intensity reduction in the first four hours after starting treatment than IV PCA morphine. In addition, there were fewer patients throughout the study that experienced oxygen desaturation events below 95% in the NanoTab System group than in the IV PCA morphine group. Oxygen saturation is a measure of a patient's respiratory function and can be affected negatively by opioids. A decrease in oxygen saturation can be linked to the serious adverse event of respiratory depression.

In March 2013, the company announced top-line results from a randomized, double-blind, placebo-controlled, pivotal Phase 3 study evaluating the ability of sufentanil NanoTabs delivered by the NanoTab System to control moderate-to-severe acute pain after major abdominal surgery compared to placebo (study IAP-310). Results demonstrated that patients receiving sufentanil NanoTabs realized a significantly greater SPID-48 during the study period than placebo-treated patients. Secondary endpoint data also showed that 24 hours and 72 hours after first dose, SPID was significantly greater in the sufentanil-treated patients than in the placebo-treated patients. Results from this study, when combined with results from the orthopedic study announced today, meet the requirements defined by the FDA to submit an application for a broad label to manage post-operative pain in the hospital setting.

A comparison of efficacy measures below, including SPID-48, TOTPAR-48 and percent of patients reporting "good" or "excellent" PGA-48 demonstrates the consistency of effect using the NanoTab System across the various patient populations studied in Phase 3 (major abdominal and major orthopedic surgery patients):

Study	SPID-48	TOTPAR-48	PGA-48
IAP-309 - Abdominal	108.2	102.4	81.1%
IAP-309 – Orthopedic	79.6	99.8	77.9%
IAP-310 – Abdominal	105.6	93.3	67.8%
IAP-311 – Orthopedic	76.5	91.3	70.2%

About Post-Operative Pain

Acute pain management in the hospital, in particular post-operative analgesia, remains a challenge for healthcare providers with up to 75% of patients reporting inadequate pain relief following surgery. Inadequate treatment of post-surgical pain can lead to decreased mobility, which increases the risks for serious medical complications, including deep vein thrombosis and partial lung collapse, potentially resulting in extended hospital stays. More than 30 million surgical procedures per year result in moderate to severe pain in the U.S. and EU, with an additional 27 million procedures in countries with moderate to high per capita healthcare expenditures. The U.S., 5 main EU countries and Japan represented \$5.1 billion of acute pain treatment product sales in 2008. Currently patients experiencing post-operative pain in the hospital may have IV PCA treatment, typically utilizing morphine or hydromorphone. However, there are deficiencies associated with the current use of IV PCA that can negatively impact patient safety, well-being and recovery. These include drug-related side effects associated with morphine or hydromorphone, complications associated with IV delivery, and medication delivery errors typically associated with misprogramming of the complex IV PCA pumps.

About the Sufentanil NanoTab PCA System

The NanoTab System is an investigational pre-programmed, non-invasive, handheld system that allows post-operative patients to self-dose with sublingual Sufentanil NanoTabs to manage their post-operative pain. The NanoTab System is designed to address the limitations of IV PCA by offering:

- A high therapeutic index opioid: NanoTab System uses the high therapeutic index opioid sufentanil; it offers post-operative pain patients the potential for effective patient-controlled analgesia with a low incidence of drug-related side effects.
- A non-invasive route of delivery: The sublingual route of delivery used by the NanoTab System provides rapid onset of analgesia, therefore reducing the risk of IV-related analgesic gaps and IV complications, such as catheter-related infections. In addition, because patients are not physically connected via IV tubing to a pump for pain relief, the NanoTab System allows for ease of patient mobility.
- A simple, pre-programmed PCA solution: NanoTab System is pre-programmed that eliminates the risk of pump programming errors by the healthcare providers.

Conference Call

AcelRx will conduct a conference call and webcast today, May 21, 2013, at 8:30 a.m. Eastern time (5:30 a.m. Pacific time) to discuss the orthopedic

postoperative pain Phase 3 top-line results. To listen to the conference call, dial in approximately ten minutes before the scheduled call to 1-800-860-2442 for domestic callers, 1-866-605-3852 for Canadian callers, or 1-412-858-4600 for international callers. Those interested in listening to the conference call live via the Internet may do so by visiting the Investors/Upcoming Events section of the company's website at www.acelrx.com. A webcast replay will be available on the AcelRx website for 90 days following the call by visiting the Investors section of the company's website at www.acelrx.com.

About AcelRx Pharmaceuticals, Inc.

AcelRx Pharmaceuticals, Inc. is a specialty pharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of acute and breakthrough pain. AcelRx's lead product candidate, the Sufentanil NanoTab PCA System, is designed to solve the problems associated with post-operative intravenous patient-controlled analgesia which has been shown to cause harm to patients following surgery because of the side effects of morphine, the invasive IV route of delivery and the complexity of infusion pumps. The NanoTab System has successfully completed all three of its planned Phase 3 clinical trials and a New Drug Application submission is planned for the third quarter of 2013. AcelRx has announced positive top-line results for a Phase 2 trial for ARX-04, a sufentanil formulation for the treatment of moderate-to-severe acute pain, funded through a grant from U.S. Army Medical Research and Materiel Command. The company has two additional pain treatment product candidates, ARX-02 and ARX-03, which have completed Phase 2 clinical development. For additional information about AcelRx's clinical programs please visit www.acelrx.com.

Forward Looking Statements

This press release contains forward-looking statements, including, but not limited to, statements related to the process and timing of anticipated future clinical development of AcelRx Pharmaceuticals' product candidates, including the release of the top-line clinical data in the final pivotal Phase 3 study of NanoTab System, the potential submission of an NDA for NanoTab System and the timing thereof, therapeutic and commercial potential of NanoTab System and the anticipated timing and therapeutic and commercial potential of other AcelRx Pharmaceuticals' product candidates. These forward-looking statements are based on AcelRx Pharmaceuticals' current expectations and inherently involve significant risks and uncertainties. AcelRx Pharmaceuticals' actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks related to: the possibility that subsequent analyses of the data may lead to different (including less favorable) interpretations of the results than the analyses conducted to date or may identify important implications of the study that are not reflected in these statements, or be subject to differing interpretations by the regulatory agencies; the success, cost and timing of all product development activities; any delays or inability to obtain and maintain regulatory approval of its product candidates in the United States and Europe; its ability to attract funding partners or collaborators with development, regulatory and commercialization expertise; its ability to obtain sufficient financing to complete registration of its product candidates in the United States and Europe; the market potential for its product candidates; and other risks detailed in the "Risk Factors" and elsewhere in AcelRx Pharmaceuticals' U.S. Securities and Exchange Commission filings and reports, including its Quarterly Report on Form 10-Q filed with the SEC on March 8, 2013. AcelRx Pharmaceuticals undertakes no duty or obligation to update any forward-looking statements contained in this release as a result of new information, future events or changes in its expectations.

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