ACELRX PHARMACEUTICALS INC
Form 10-K
March 12, 2013
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# UNITED STATES

# SECURITIES AND EXCHANGE COMMISSION

**WASHINGTON, DC 20549**

# FORM 10-K

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
**For the fiscal year ended December 31, 2012**

**or**

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
**For the transition period from to**

**Commission File Number: 001-35068**

# ACELRX PHARMACEUTICALS, INC.

**(Exact name of registrant as specified in its charter)**

| Delaware | 41-2193603 |
|---|---|
| (State or other jurisdiction of incorporation or organization) | (IRS Employer Identification No.) |

**351 Galveston Drive**

**Redwood City, CA 94063**

**(650) 216-3500**

**(Address, including zip code, and telephone number, including area code, of registrant s principal executive offices)**

**Securities registered pursuant to Section 12(b) of the Act:**

| Title of Each Class | Name of Each Exchange on Which Registered |
|---|---|
| Common Stock, $0.001 par value | The NASDAQ Stock Market LLC |

**Securities registered pursuant to Section 12(g) of the Act:**

**None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ¨ No þ

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ¨ No þ

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes þ No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§-232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes þ No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§-229.405) is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. þ

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of large accelerated filer, accelerated filer, and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ¨ Accelerated filer ¨

Non-accelerated filer ¨ (Do not check if a smaller reporting company) Smaller reporting company þ

Indicate by check mark whether the registrant is a shell company (as defined in Exchange Act Rule 12b-2) Yes ¨ No þ

The aggregate market value of the voting stock held by non-affiliates of the registrant on June 29, 2012 (the last business day of the registrant s most recently completed second fiscal quarter), based upon the last sale price reported on the NASDAQ Global Market on that date, was approximately $22,421,000. The calculation excludes 15,726,270 shares of the registrant s common stock held by current executive officers, directors and stockholders that the registrant has concluded are affiliates of the registrant. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the registrant.

As of January 31, 2013, the number of outstanding shares of the registrant s common stock was 37,059,802.

**DOCUMENTS INCORPORATED BY REFERENCE**

None.

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**ACELRX PHARMACEUTICALS, INC.**

**2012 ANNUAL REPORT ON FORM 10-K**

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Unless the context indicates otherwise, the terms AcelRx, AcelRx Pharmaceuticals, we, us and our refer to AcelRx Pharmaceuticals, Inc.

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**Forward-Looking Statements**

This Annual Report on Form 10-K, or Form 10-K, contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, which are subject to the safe harbor created by that section. The forward-looking statements in this Form 10-K are contained principally under Item 1. Business, Item 1A. Risk Factors and Item 7. Management s Discussion and Analysis of Financial Condition and Results of Operations. In some cases, you can identify forward-looking statements by the following words: may, will, could, would, should, expect, intend, plan, anticipate, believe, estimate, predict, project, potential, co of these terms or other comparable terminology, although not all forward-looking statements contain these words. These statements involve risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Form 10-K, we caution you that these statements are based on a combination of facts and factors currently known by us and our projections of the future, about which we cannot be certain. Many important factors affect our ability to achieve our objectives, including:

the success, cost and timing of our product development activities and clinical trials;

our ability to obtain and maintain regulatory approval of our product candidates, and any related restrictions, limitations, and/or warnings in the label of an approved product candidate;

our ability to obtain funding for our operations, including funding necessary for the planned commercialization and manufacturing of the NanoTab System in the United States and advancement of clinical trials for other product candidates;

our plans to research, develop and commercialize our product candidates;

our ability to attract collaborators with development, regulatory and commercialization expertise;

the size and growth potential of the markets for our product candidates, and our ability to serve those markets;

our ability to successfully commercialize our product candidates;

the rate and degree of market acceptance of our product candidates;

our ability to develop sales and marketing capabilities, whether alone or with potential future collaborators;

regulatory developments in the United States and foreign countries;

the performance of our third party suppliers and manufacturers;

the success of competing therapies that are or become available;

the loss of key scientific or management personnel;

the accuracy of our estimates regarding expenses, future revenues, capital requirements and needs for additional financing; and

our ability to obtain and maintain intellectual property protection for our product candidates.

In addition, you should refer to Item 1A. Risk Factors in this Form 10-K for a discussion of these and other important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Form 10-K will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. Also, forward-looking statements represent our estimates and assumptions only as of the date of this Form 10-K. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

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**PART I**

**Item 1. Business**

**Overview**

We are a development stage specialty pharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of acute and breakthrough pain. Our lead product candidate, the Sufentanil NanoTab PCA System, or the NanoTab System or ARX-01, is designed to improve the management of moderate-to-severe acute post-operative pain in patients in the hospital setting. Although widely used, the current standard of care for patients with post-operative pain, intravenous patient-controlled analgesia, or IV PCA, has been shown to cause harm and inconvenience to patients following surgery because of the side effects of commonly used IV PCA opioids, the invasive IV needle route of delivery and the inherent potential for programming and delivery errors associated with the complexity of infusion pumps.

*The Sufentanil NanoTab PCA System*

The Sufentanil NanoTab PCA 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:** The 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 eliminating the risk of IV-related analgesic gaps and IV complications, such as catheter-related infections. In addition, because patients are not tethered to IV tubing and a pump for pain relief, the NanoTab System allows for ease of patient mobility.

**A simple, pre-programmed PCA solution:** The NanoTab System is a pre-programmed PCA system designed to eliminate the risk of pump programming errors.

Our Phase 3 clinical program for the NanoTab System consists of two placebo-controlled efficacy and safety trials and an open-label active comparator trial, in which the NanoTab System was compared to IV PCA. A summary of Phase 3 trials and results to date is as follows:

In March 2013, we reported top-line data showing that the primary endpoint was achieved in a pivotal, double-blind, placebo-controlled, Phase 3 trial of the NanoTab System for acute post-operative pain in major open abdominal surgery patients.

In November 2012, we reported top-line data showing that the primary endpoint of non-inferiority was met in an open-label active-comparator Phase 3 clinical trial.

In the second quarter of 2013, we expect data from our final planned Phase 3 trial, a pivotal, double-blind, placebo-controlled efficacy and safety trial in patients with acute post-operative pain following hip and knee replacement surgeries.

*ARX-04*

We are also developing a Sufentanil Single-Dose NanoTab, or ARX-04, for the treatment of moderate-to-severe acute pain on the battlefield, in the emergency room or in ambulatory care facilities. In May 2011, we announced that the U.S. Army Medical Research and Materiel Command, or USAMRMC, awarded us a $5.6 million grant to support the development of ARX-04 for the treatment of moderate-to-severe acute pain. In November 2012, we initiated a Phase 2 placebo-controlled, dose-finding trial and, in February 2013, dosing of the last patient in this trial was

completed. This trial enrolled 101 patients and top-line results from the trial are expected during the second quarter of 2013.

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In addition to our NanoTab System and ARX-04, our product candidate pipeline consists of two other sufentanil-based product candidates. The Sufentanil NanoTab BTP Management System, or ARX-02, is a pain management system for the treatment of cancer patients who suffer from breakthrough pain, or BTP. The Sufentanil/Triazolam NanoTab, or ARX-03, is a single, fixed-dose product designed to provide mild sedation, anxiety reduction and pain relief for patients undergoing painful procedures in a physician s office. We have successfully completed Phase 2 clinical trials for ARX-02 and ARX-03. Future development of ARX-02 and ARX-03 is contingent on identification of corporate partnership resources.

We were originally incorporated as SuRx, Inc. in Delaware on July 13, 2005. We subsequently changed our name to AcelRx Pharmaceuticals, Inc. on August 13, 2006.

**Sufentanil NanoTabs**

Sufentanil, a high therapeutic index opioid, which has no active metabolites, is 5 to 10 times more potent than fentanyl and is used intravenously as a primary anesthetic to produce balanced general anesthesia for surgery, and for epidural administration during labor and delivery. Sufentanil has many pharmacological advantages over other opioids. Published studies demonstrate that sufentanil produces significantly less respiratory depressive effects relative to its analgesic effects compared to other opioids, including morphine, alfentanil and fentanyl. These third party clinical results correlate well with preclinical trials demonstrating sufentanil s high therapeutic index, or the ratio of the toxic dose to the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment. Accordingly, we believe that sufentanil can be developed to provide an effective and well-tolerated treatment for acute and breakthrough pain. The following table illustrates the difference between the therapeutic index of different opioids.

| Opioid | Therapeutic Index |
|---|---|
| Meperidine | 5 |
| Methadone | 12 |
| Morphine | 71 |
| Hydromorphone | 232 |
| Fentanyl | 277 |
| Sufentanil | 26,716 |

In addition, the pharmaceutical attributes of sufentanil, including lipid solubility and ionization, result in rapid cell membrane penetration and onset of action, which we believe make sufentanil an optimal opioid for the treatment of both acute pain and breakthrough pain.

Although the analgesic efficacy and safety of sufentanil have been well established, the product s use has been historically limited due to its short duration of action when delivered intravenously. We believe that sublingual delivery of sufentanil avoids the high peak plasma levels and short duration of action of IV administration.

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Our portfolio of product candidates leverages the inherent advantages of sufentanil that are underutilized in medical practice. We believe our non-invasive, proprietary NanoTab sublingual dosage form overcomes the limitations of the current treatment options available for both acute and breakthrough pain.

None of our product candidates have been approved by the United States Food and Drug Administration, or FDA. We have not generated any revenue from the sale of any of our product candidates.

***Sublingual Delivery of Sufentanil: Summary of Phase 1 Clinical Studies Results***

We have completed four Phase 1 PK studies with our proprietary sublingual sufentanil NanoTabs to support our four product candidates under development. These studies demonstrated desirable and consistent PK parameters, including:

- relatively high bioavailability via the oral mucosa and very low gastrointestinal, or GI, bioavailability;
- prolonged plasma levels relative to IV delivery;
- PK parameters proportional to dose across a wide range of doses (2.5 mcg to 80 mcg);
- lower peak plasma concentration, or $C_{max}$, than IV delivery;
- time to maximum plasma concentrations, or $T_{max}$, range from 30 to 90 minutes;
- relatively low patient to patient variability in $T_{max}$ and $C_{max}$; and
- repeat dosing PK that supports a 20 minute minimum re-dosing interval.

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The chart below illustrates the PK profile of sublingual sufentanil NanoTab compared to IV delivery of sufentanil from one of our completed Phase 1 PK studies.

We have demonstrated that sublingual delivery of sufentanil avoids the high peak plasma levels and short duration of action of IV administration, enabling potential for broader use. Our proprietary NanoTab dosage form is a very small disc-shaped tablet with a bioadhesive excipient, or inactive ingredient, that enables the NanoTab to adhere to mucosal tissues. This allows sublingual delivery of sufentanil from the NanoTab by adherence to the sublingual mucosa, or tissues under the tongue. The NanoTab adheres within seconds after administration and full disintegration occurs within minutes. The small size of the NanoTab, pictured above, is designed to minimize the saliva response and amount of sufentanil swallowed, resulting in high oral transmucosal uptake, whereby a majority of the drug is absorbed via the oral tissues directly into the bloodstream, and consistent pharmacokinetics.

We have completed three additional definitive PK studies that will be included in the NDA, as follows:

IAP101 (single vs. multiple dose) Study IAP101 was conducted with the Sufentanil NanoTab PCA System and was designed to characterize the plasma concentration profile of the Sufentanil NanoTab after repeated dosing. Subjects self-administered a single dose from the NanoTab PCA System and, after a washout period, 40 consecutive doses every 20 minutes. Plasma concentration profiles and pharmacokinetic parameters after the single and multiple dosing were compared.

IAP102 (route of delivery) Study IAP102 was conducted to characterize the plasma concentration profile of the Sufentanil NanoTab after transmucosal (sublingual and buccal) and oral administration. The absolute bioavailability of the Sufentanil NanoTab was also calculated.

IAP104 (drug interaction study) Study IAP104 was conducted to determine whether there is a change in the Sufentanil NanoTab plasma concentration profile when a subject is concomitantly receiving a CYP3A4 inhibitor.

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**Our Product Candidates**

The following table summarizes key information about our existing product candidates for which we currently hold worldwide commercialization rights.

| Product Candidate | Description | Target Indication | Development Status |
|---|---|---|---|
| ARX-01 | Sufentanil NanoTab PCA System | Moderate-to-severe acute post-operative pain | Three Phase 3 clinical trials were initiated in 2012 as follows: |
| | | | In April 2012, we initiated an open-label active comparator Phase 3 clinical trial comparing ARX-01 to the current standard of care, IV PCA morphine, in patients with acute post-operative pain following open-abdominal surgery or major orthopedic surgery. In November 2012, we reported that this trial met its primary endpoint of non-inferiority. |
| | | | In March 2012, we initiated a double-blind placebo-controlled efficacy and safety Phase 3 clinical trial in patients with acute post-operative pain following open-abdominal surgery. In March 2013, we reported that this trial met its primary endpoint. |
| | | | In August 2012, we initiated a double-blind placebo-controlled efficacy and safety Phase 3 clinical trial in patients with acute post-operative pain following major orthopedic surgeries. We expect top-line data for this trial in the second quarter of 2013. |
| ARX-02 | Sufentanil NanoTab BTP Management System | Cancer breakthrough pain | Phase 2 clinical trial and End of Phase 2 meeting successfully completed. |
| | | | Future development contingent upon identification of corporate partnership resources. |
| ARX-03 | Sufentanil/Triazolam NanoTab | Mild sedation for painful procedures in a physician s office | Phase 2 clinical trial and End of Phase 2 meeting successfully completed. |
| | | | Future development contingent upon identification of corporate partnership resources. |
| ARX-04 | Sufentanil Single-Dose NanoTab | Moderate-to-severe acute pain | Phase 2 clinical trial initiated in November 2012 pursuant to grant from USAMRMC. In February 2013, we completed enrollment of this trial and we expect top-line data in the second quarter of 2013. |

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**ARX-01 Sufentanil NanoTab PCA System**

This product candidate has not been approved by the FDA. We have not generated any revenue from the sale of any of our product candidates.

***The Market Opportunity for the NanoTab System***

According to the 2010 Decision Resources Acute Pain Report, or 2010 DR Report, the post-operative pain market in the United States, Europe and Japan is growing steadily and is expected to reach approximately $6.5 billion by 2018. Despite its size, this market remains underserved. Studies report that up to 75% of patients experience inadequate pain relief after surgery. Inadequate pain relief can lead to decreased mobility, which increases the risks of other medical complications, including deep vein thrombosis and partial lung collapse, and can result in extended hospital stays. The 2010 DR Report projects that in 2013, 20.7 million in-patient procedures performed in the United States and the five largest European Union member state markets will require post-operative treatment of pain, growing at a rate of approximately 1% per annum. Additionally, based on an analysis of data published in 2008 from the World Health Organization, we estimate that there are approximately 27 million surgical procedures annually in other moderate-to-high per capita healthcare expenditure nations in which patients experience moderate-to-severe pain.

Commissioned market research targeting surgeons and anesthesiologists has identified a consistent positive response to the attributes of the NanoTab System and indicates an interest in using the NanoTab System in at least 75% of their eligible patients. Additional market research indicated that physicians expressed interest in using the NanoTab System for patients who stay in the hospital for less than 24 hours and are not traditionally treated with IV PCA. Pharmacy and Therapeutics, or P&T, committees also indicate strong interest in the NanoTab System, with 91% of the P&T committee members interviewed indicating likely adoption to formulary.

***How the NanoTab System Addresses the Unmet Medical Need in Post-Operative Pain Management***

There are many deficiencies associated with the current use of IV PCA, including:

- side effects associated with the most commonly used opioid, morphine, and its active metabolites;
- infection risk, analgesic gaps and decreased mobility associated with the invasive nature of IV delivery; and
- medication errors, which in some instances may be fatal, due to the complexity of IV PCA pumps, many of which arise from programming errors.

According to published literature, the estimated annual error rate is 407 errors per 10,000 people treated with IV PCA in the United States. Published analysis of Medmarx from 2000 to 2005 reveals that IV PCA errors represent a four-fold higher relative risk of harm compared to all other medication errors. The most recent published analysis of the FDA MAUDE database reports that 5% of IV PCA operator errors reported during a two-year index period, from 2002 to 2003, resulted in patient deaths. Approximately 56,000 adverse events were reported to the FDA between 2005 and 2009, prompting 70 Class II infusion pump recalls of devices that could cause temporary or reversible adverse effects and 14 Class I infusion pump recalls of devices that could cause serious injury or death. These issues with infusion pumps have resulted in the issuance of new draft guidance by the FDA, significantly increasing the data required to be submitted by IV PCA pump manufacturers to address safety problems.

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The NanoTab System has the potential to address many of the key disadvantages of IV PCA, including:

- reducing the incidence of drug related side effects;
- eliminating the risk of IV PCA related infections, reducing analgesic gaps and enhancing mobility; and
- eliminating the risk of programming errors.

We believe that the NanoTab System will provide a favorable safety, efficacy and tolerability profile, enabling the NanoTab System to become the new standard of care for PCA. Further, we believe use of the NanoTab System will result in increased patient satisfaction and reduced overall healthcare costs.

***The NanoTab System Description***

The NanoTab System allows patients to self-administer sublingual Sufentanil NanoTabs as needed to manage their post-operative pain in the hospital setting, and provides the record-keeping attributes of a conventional IV PCA pump while avoiding some of the key issues, such as programming errors, associated with conventional IV PCA use.

Our NanoTab System consists of three components:

- sufentanil, a high therapeutic index opioid;
- NanoTabs, our proprietary, non-invasive sublingual dosage form; and
- our novel, pre-programmed, handheld PCA device that enables simple patient-controlled delivery of NanoTabs in the hospital setting and eliminates the risk of programming errors.

The NanoTab System utilizes sufentanil, which has one of the highest therapeutic indices of all commercially available opioids, making it an attractive candidate for the management of post-operative pain. Formulated in our proprietary sublingual NanoTab dosage form, sufentanil provides for relatively high bioavailability, with lower peak drug levels and a longer duration of action compared to IV delivery.

Our NanoTab System consists of the following components: a disposable dispenser tip (Figure A); a disposable dispenser cap (Figure B); an adhesive thumb tag (Figure C); a stack of 40 sufentanil 15 mcg NanoTabs (approximately a two-day supply) in a disposable radio frequency identification and bar-coded cartridge (Figure D); a reusable, rechargeable handheld controller (Figure E); a tether (Figure F); and an authorized access card (Figure G).

This product candidate has not been approved by the FDA. We have not generated any revenue

from the sale of any of our product candidates.

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Our novel handheld PCA device has the following safety features:

- an authorized access card, which is a wireless system access key for the healthcare professional;
- a wireless, electronic, adhesive thumb tag that acts as a single-patient identification key;
- pre-programmed 20-minute lock-out to avoid overdosing;
- NanoTab singulation, or dispensing, motion that eliminates runaway motor delivery risk;
- a security tether that is designed to prevent theft and misuse; and
- fully automated inventory record of NanoTabs usage.

To set up the handheld PCA device, the nurse or healthcare professional turns on the controller and follows the simple step-by-step instructions on the color graphical user interface screen described below:

- retrieve the NanoTab cartridge from secure drug storage;
- lock the cartridge and dispenser into the controller; and
- set up the secure patient access system, which is comprised of a security tether and a wireless, electronic, adhesive thumb tag that acts as a single-patient identification key.

To use the NanoTab System, the patient would:

- confirm that the green indicator light is illuminated, meaning the device is available to dose;
- place dispenser tip under tongue and push the large button on the controller, which dispenses a single NanoTab;
- remove the device from mouth upon hearing a tone confirming delivery of the NanoTab; and
- see the blue indicator light illuminate, indicating no new dose can be dispensed for the next 20 minutes.

***NanoTab System Clinical Program***

*Summary*

Our Phase 3 program for the NanoTab System consists of three Phase 3 clinical trials. We have reported top-line results from two of these three clinical trials and expect to report top-line data from the final planned Phase 3 trial in the second quarter of 2013. Prior to our Phase 3 program, we completed three successful Phase 2 clinical trials of sufentanil NanoTabs in the post-operative setting. These Phase 2 clinical trials demonstrated analgesic efficacy, a low adverse event profile and excellent device functionality. During our End of Phase 2 meeting with the FDA, the FDA stated that the demonstration of efficacy versus placebo in two Phase 3 clinical trials with a total safety database of at least 600 patients exposed to the active drug should suffice to support a new drug application, or NDA. We have designed our Phase 3 clinical trials based on the feedback from the FDA.

*Phase 3 Clinical Trials for the NanoTab System*

*Active comparator trial (IAP 309)*

In November 2012, we reported top-line data showing that the NanoTab System had met its primary endpoint of non-inferiority in the Phase 3 open-label active comparator trial designed to compare the efficacy and safety of the NanoTab System (15 mcg/dose) to IV PCA with morphine (1mg/dose) for the treatment of moderate-to-severe acute post-operative pain. Utilizing a randomized, open-label, parallel group design, this trial enrolled 359 adult patients at 26 U.S. sites for the treatment of pain immediately following open-abdominal or major orthopedic surgery (hip and knee replacement). Patients were randomized 1:1 to treatment with the NanoTab System or IV PCA morphine and were treated for a minimum of 48 hours and up to 72 hours.

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The primary endpoint for the trial was a comparison of the patient s response using the Patient Global Assessment, or PGA, of method of pain control over the 48-hour trial period between the patients treated with the NanoTab System and IV PCA morphine. The PGA uses a 4-point scale of poor, fair, good or excellent to rate each method of pain control. The primary endpoint was determined by measuring the proportion of patients who responded good or excellent using the PGA to rate their method of pain control. An overview of the top-line primary endpoint results of this Phase 3 clinical trial demonstrates that:

- For the primary comparison, the NanoTab System was non-inferior ($p<0.001$) to IV PCA morphine for the primary endpoint of PGA comparison over the 48-hour study period as determined by the combined percentage of patients with PGA ratings of good or excellent (78.5% vs. 65.6%, respectively). A p-value is a probability with a value ranging from 0 to 1, which indicates the likelihood that a clinical trial is different between treatment and control groups. P-values below 0.05 mean that there is a 95% or greater chance that there is a true difference between the groups, and are typically referred to as statistically significant.

- The assessment of non-inferiority was based on a lower limit of 15% for the 95% confidence interval, or CI, around the difference between these percentages. Because the 95% CI was +3.7% to +22.1% for the 48 hour PGA and therefore did not cross the zero difference line, a secondary comparison of the primary endpoint, specifically a statistical analysis of superiority could be performed. In this trial, the NanoTab System was statistically superior to IV PCA morphine for the PGA endpoint ($p=0.007$). Statistically superior PGA was also seen at the 24 hour and 72 hour timepoints.

A number of secondary endpoints were also evaluated, including comparison of individual PGA ratings, a Healthcare Professional Global Assessment, or HPGA, of method of pain control, drop outs from the trial due to inadequate analgesia and adverse events, and Patient and Nurse Ease of Care Questionnaires using a validated questionnaire methodology specifically to evaluate patient-controlled analgesia systems. The NanoTab System achieved a PGA rating of excellent in 42.9% of treated patients, compared to 30.6% for IV PCA with morphine, with a p-value of 0.016.

The HPGA was measured at 24, 48 and 72 hours, and produced similar results to the Patient Global Assessment. HPGA ratings of good or excellent at 48 hours were 81.4% for the NanoTab System compared to 70.0% for IV PCA morphine. An assessment of non-inferiority was conducted and demonstrated that the NanoTab System was non-inferior to IV PCA morphine ($p < 0.001$) in the trial. Because the 95% CI was +2.6% to +20.2% for the 48 hour HPGA and therefore didn t cross the zero difference line, a statistical analysis for superiority could be performed, which demonstrated that for this trial, the NanoTab System was statistically superior to IV PCA morphine for the HPGA endpoint at 48 hours ($p=0.012$). Statistically superior HPGA was also seen at the 24 hour and 72 hour timepoints.

Throughout the course of the trial, 7.3% of patients treated with the NanoTab System dropped out of the trial prematurely due to lack of efficacy compared to 8.9% of patients treated with IV PCA morphine. Additionally, 7.3% of the patients treated with the NanoTab System dropped out of the trial due to an adverse event compared to 10.0% of the IV PCA morphine patients. We observed 13 patients who experienced serious adverse events, or SAEs, in the trial, of whom three patients experienced serious adverse events assessed as possibly or probably related to the trial drug, one was related to the NanoTab System and two were related to IV PCA morphine.

The Patient Ease of Care Questionnaire, or Patient Questionnaire, asked patients to respond to 21 questions regarding aspects of analgesia and PCA systems using a zero to five rating scale, including statements such as, but not limited to, pain woke me up from my sleep , the device was easy to use , and the device interfered with my ability to get out of bed and walk around. Answers to the Patient Questionnaire were combined for an Overall Patient Ease of Care score. These Patient Questionnaire statements were also grouped into six validated subscales, such as comfort with device , impact on movement , and knowledge and understanding. Patients were also asked in this Patient Questionnaire to rate their Overall Satisfaction with the level of pain control and with the way in which the medication was administered during the trial.

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The Nurse Ease of Care Questionnaire, or Nurse Questionnaire, asked nurses to respond to 21 questions regarding aspects of analgesia and PCA systems using a zero to five rating scale, including statements regarding the set-up and management of the systems and management of the patients. Answers to the Nurse Questionnaire were combined for an Overall Nurse Ease of Care score. These Nurse Questionnaire statements were grouped into two validated subscales entitled time-consuming and bothersome . Nurses were also asked in this Nurse Questionnaire to rate their Overall Satisfaction based on the level of pain control and with their overall satisfaction of the system.

An overview of results of the Patient and Nurse Questionnaires results includes:

- Patients in the trial reported that they had significantly greater Overall Satisfaction with the NanoTab System compared to IV PCA morphine (4.15 vs. 3.84, respectively, out of a 0 to 5 scale, with a p-value equal to 0.004).

- Patients in the trial reported that they had greater Overall Ease of Care with the NanoTab System compared to IV PCA morphine (4.45 vs. 4.07, respectively, out of a 0 to 5 scale, with a p-value less than 0.001).

- Nurses managing patients in the trial reported they had significantly greater Overall Satisfaction with the NanoTab System compared to IV PCA morphine (3.92 vs. 3.35, respectively, out of a 0 to 5 scale, with a p-value less than 0.001).

- Nurses managing patients in the trial reported they had greater Overall Ease of Care with the NanoTab System compared to IV PCA morphine (4.27 vs. 3.82, respectively, out of a 0 to 5 scale, with a p-value equal to 0.017).

As noted above, additional subscale analyses were performed related to the Overall Ease of Care with the NanoTab System as reported by both nurses and patients. The results, as detailed in the tables below, demonstrate that all Patient Ease of Care subscales were significantly higher for the NanoTab System than for IV PCA morphine in the trial. For the Nurse Ease of Care subscales, nurses rated the NanoTab System significantly less bothersome than IV PCA morphine and there was a trend towards the NanoTab System being less time consuming than IV PCA morphine.

*Patient Ease of Care*

| **Subscale (0-5 scale)** | **NanoTab System** | **IV PCA morphine** | **P Value** |
|---|---|---|---|
| Confidence with Device | 4.69 | 4.51 | 0.015 |
| Comfort with Device | 4.47 | 4.33 | 0.041 |
| Impact on Movement | 4.73 | 3.88 | <0.001 |
| Dosing Confidence | 4.74 | 4.47 | 0.003 |
| Pain Control | 3.58 | 3.16 | 0.004 |
| Knowledge and Understanding | 4.47 | 4.05 | <0.001 |

*Nurse Ease of Care*

| **Subscale (0-5 scale)** | **NanoTab System** | **IV PCA morphine** | **P Value** |
|---|---|---|---|
| Time consuming | 0.92 | 1.24 | 0.076 |
| Bothersome | 0.54 | 1.09 | 0.006 |

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*Double-blind, placebo-controlled, abdominal surgery trial (IAP 310)*

In March 2013, we reported top-line data results demonstrating that the NanoTab System met its primary endpoint in a pivotal Phase 3 trial designed to compare the efficacy and safety of the NanoTab System to placebo in the management of acute post-operative pain after major open abdominal surgery. Adverse events reported in the trial were generally mild or moderate in nature and similar in both plac