ACELRX PHARMACEUTICALS INC
Form S-1/A
December 05, 2012
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As filed with the Securities and Exchange Commission on December 5, 2012

Registration No. 333-185067

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Amendment No. 1

to FORM S-1

REGISTRATION STATEMENT

UNDER THE SECURITIES ACT OF 1933

ACELRX PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**2834**	**41-2193603**
(State or other jurisdiction of incorporation or organization)	**(Primary Standard Industrial Classification Code Number)**	**(I.R.S. Employer Identification Number)**

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)

Richard King

President and Chief Executive Officer

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Redwood City, CA 94063

(650) 216-3500

(Name, address, including zip code, and telephone number, including area code, of agent for service)

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Approximate date of commencement of proposed sale to the public: As soon as practicable after the effective date of this registration statement.

If any of the securities being registered on this form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, check the following box. ¨

If this form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

If this form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

If this form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration number of the earlier effective registration statement for the same offering. ¨

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.

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

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Proposed Maximum Aggregate Offering Price(1)(2)	Amount of Registration Fee(3)(4)
Common Stock, $0.001 par value	$50,000,000	$6,820

(1) Estimated solely for the purpose of calculating the amount of the registration fee in accordance with Rule 457(o) of the Securities Act of 1933, as amended.
(2) Includes additional shares of common stock that the underwriters have the option to purchase pursuant to their over-allotment option, if any.
(3) Calculated pursuant to Rule 457(o) based on an estimate of the proposed maximum aggregate offering price.
(4) The registrant previously paid a registration fee of $3,410 in connection with the initial filing of this registration statement. The registrant has subsequently increased the proposed aggregate maximum offering price by $25,000,000 and paid an additional $3,410 in registration fees in connection with the filing of this Amendment No. 1 to Form S-1.

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment that specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the registration statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

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The information contained in this preliminary prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell these securities and is not a soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED DECEMBER 4, 2012

PRELIMINARY PROSPECTUS

10,000,000 Shares

Common Stock

We are offering 10,000,000 shares of our common stock. Our common stock is listed on The NASDAQ Global Market under the symbol ACRX. On December 3, 2012, the last reported sale price of our common stock on The NASDAQ Global Market was $4.16 per share.

Investing in our common stock involves a high degree of risk. Please read Risk Factors beginning on page 12 of this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

	PER SHARE	TOTAL
Public Offering Price	$	$
Underwriting Discounts and Commissions [1]	$	$
Proceeds to AcelRx Pharmaceuticals before expenses	$	$

[1] See Underwriting for a description of the compensation payable to underwriters.

Delivery of the shares of common stock is expected to be made on or about , 2012. We have granted the underwriters an option for a period of 30 days to purchase an additional 1,500,000 shares of our common stock. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be $, and the total proceeds to us, before expenses, will be $.

Joint Book-Running Managers

Jefferies **Cowen and Company**

Co-Lead Manager

Canaccord Genuity

Prospectus dated , 2012

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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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We have not, and the underwriters have not, authorized anyone to provide you with information different than that contained or incorporated by reference in this prospectus and any free writing prospectus that we have authorized for use in connection with this offering. If anyone provides you with different or inconsistent information, you should not rely on it. We are not, and the underwriters are not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus, the documents incorporated by reference in this prospectus, and in any free writing prospectus that we have authorized for use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus, the documents incorporated by reference in this prospectus, and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety before making an investment decision. You should also read and consider the information in the documents to which we have referred you in the sections of this prospectus entitled Where You Can Find Additional Information and Incorporation of Certain Information by Reference.

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

ACELRX, the ACELRX logo, ARX, NANOTAB, ACCELERATE.INNOVATE.ALLEVIATE. and associated logo are trademarks of AcelRx Pharmaceuticals, Inc.

Other trademarks and trade names that are the property of their respective owners are also contained in this prospectus.

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PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere or incorporated by reference in this prospectus. This summary does not contain all the information you should consider before investing in our common stock. You should read and consider carefully the more detailed information in this prospectus, including the factors described under the heading Risk Factors in this prospectus beginning on page 11 and the financial and other information included and incorporated by reference in this prospectus, as well as the information included in any free writing prospectus that we have authorized for use in connection with this offering, before making an investment decision.

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 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 morphine, 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 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.

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 for our lead product candidate, the NanoTab System. We are also conducting two placebo-controlled efficacy and safety Phase 3 clinical trials for the NanoTab System, the first trial in patients with post-operative pain following open-abdominal surgery and the second trial in patients with post-operative pain following hip and knee replacement surgeries. We expect top-line data from both placebo-controlled efficacy and safety Phase 3 clinical trials in the first quarter of 2013.

In addition to our NanoTab System, our product candidate pipeline consists of three 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 upon additional funding or corporate partnership resources. 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 clinical trial for ARX-04 pursuant to the USAMRMC grant.

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NanoTab System Open-Label Active Comparator Phase 3 Efficacy and Safety Trial Top-Line Results

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 (1 mg/dose) for the treatment of moderate-to-severe 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.

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 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 their 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. 66.1%, 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% Cl was +3.2% to +21.6% 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 ($p=0.009$). 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 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 70.6% 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 +2.0% to +19.6% 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 ($p=0.017$). 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 8.3% of patients treated with IV PCA morphine. Additionally, 7.9% of the patients treated with the NanoTab System dropped out of the trial due to an adverse event compared to 11.1% of the IV PCA morphine patients. We observed eleven serious adverse events, or SAEs, in the trial, of which two were assessed as possibly or probably related to the trial drug, one of which was related to the NanoTab System and one of which was related to IV PCA morphine.

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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.

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 with the system.

An overview of results of the Patient and Nurse Questionnaires 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. 3.83, respectively, out of a 0 to 5 scale, with a p-value equal to 0.003).
- 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 (3.93 vs. 3.32, 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 (4.26 vs. 3.82, respectively, out of a 0 to 5 scale, with a p-value equal to 0.018).

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	0.93	1.27	0.066
Bothersome	0.54	1.09	0.006

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Our Pipeline of 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 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 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 post-operative pain following open-abdominal surgery. We expect top-line data for this trial in the first quarter of 2013.
			In August 2012, we initiated a double-blind placebo-controlled efficacy and safety Phase 3 clinical trial in patients with post-operative pain following major orthopedic surgeries. We expect top-line data for this trial in the first 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 additional funding or 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.

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The Market Opportunity for Our Product Candidates

ARX-01

According to the 2010 Decision Resources Acute Pain Report, or 2010 Decision Report, the post-operative pain market in the United States, Europe and Japan is growing steadily and is expected to reach $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 Decision Report projects that in 2013, 20.7 million in-patient procedures performed in the United States and Europe 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 in which patients experience moderate-to-severe pain in other moderate-to-high per capita healthcare expenditure nations on an annual basis.

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. Additional commissioned research in 2009 with Pharmacy and Therapeutics, or P&T, committees also indicated strong interest in the NanoTab System, with 91% of the P&T committee members interviewed indicating likely adoption to formulary.

ARX-02

According to the American Cancer Society, there were more than 1.5 million new cancer cases in the United States in 2010. It is estimated that over 625,000 of these cases result in patients who experience breakthrough pain. We estimate the prescription volume for oral transmucosal products for the management of cancer breakthrough pain to be 220,000 prescriptions per year. This suggests that less than 10% of cancer patients with cancer breakthrough pain are treated with approved transmucosal breakthrough pain medications. In addition, many physicians use immediate release oral opioids to treat cancer breakthrough pain. We believe that this market is significantly larger than the transmucosal product market.

ARX-03

Each year in the United States, more than 100 million procedures take place in a physician s office that are known to be anxiety-inducing and painful, according to commissioned market research data that was completed in 2010. These include diagnostic procedures such as breast and prostate biopsies, cosmetic procedures such as liposuction and dermal abrasions, interventional radiology procedures, and therapeutic procedures such as vasectomies and endometrial ablation procedures. IV sedative medications are typically not offered to these patients because of the high cost of the specialized personnel and monitoring equipment. Despite the high potential for pain and anxiety, most patients currently undergo these procedures with only a local anesthetic, resulting in unnecessary procedure discomfort. We believe there is significant opportunity for a fast-acting, effective and safe product that can provide mild levels of sedation, anxiety reduction and analgesia for painful procedures conducted in a physician s office without the need for specialized personnel to monitor the patient.

ARX-04

We believe that ARX-04 could be useful in a variety of medically supervised settings, including for battlefield casualty treatment, by paramedics during patient transport, in the emergency room, or for post-operative patients, following either short-stay or ambulatory surgery, who do not require more long-term patient-controlled analgesia. According to the Centers for Disease Control and Prevention, or CDC, there were more than 136 million emergency room visits in 2009 of which it is estimated that more than 45 million were injury-related emergency room visits, and analgesics were provided or prescribed during more than 94 million of these visits. In addition, based on CDC data, there were more than 43 million ambulatory surgery procedures conducted in the U.S. in 2006.

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Our Strategy

Our strategy is to develop and commercialize a portfolio of sufentanil NanoTab-based products in specialty markets. We have designed and are developing product candidates that have clearly defined clinical development programs, target large commercial market opportunities, and require modest commercial organizations in the United States. We selectively utilize third party contractors in order to maximize the capital efficiency of our development and commercialization efforts. We plan to enter into partnerships to market our product candidates outside the United States.

Our lead product candidate, the NanoTab System, is currently in Phase 3 development. We have advanced the NanoTab System into three Phase 3 clinical trials, one of which has been completed and for which we reported positive top-line results. Contingent upon receipt of successful data from the remaining two NanoTab System Phase 3 clinical trials, which is expected in the first quarter of 2013, we intend to submit an NDA to the FDA in the third quarter of 2013 and, if approved, to commercialize the NanoTab System ourselves in the United States, and commercialize it outside the United States with a partner. Based on the availability of additional financial resources, we plan to advance ARX-02 into Phase 3 clinical trials, submit an NDA and, if approved, commercialize ARX-02 ourselves or with a partner in the United States. Further development of ARX-03 will likely depend on the identification of a partner to support this effort. Development of ARX-04 beyond the current grant-supported activities is contingent upon the successful completion of our Phase 2 clinical trial.

Intellectual Property

We have developed significant know-how regarding our manufacturing process and protect our technology through trade secrets and patents. As of October 1, 2012, we are the owner of record of one issued European patent, including national validation in ten countries, which expires in 2027, one Mexican patent which expires in 2029, four issued U.S. patents which provide coverage through at least 2027, and one issued U.S. patent which provides coverage through at least 2030. We are pursuing 15 U.S. non-provisional patent applications, one pending international Patent Cooperation Treaty application and 59 foreign national applications, including seven European Regional Phase applications directed to our product candidates.

We continue to seek and expand our patent protection for both compositions of matter and delivery devices, as well as methods of treatment related to our product candidates. In particular, we are pursuing additional patent protection for our ARX-01, ARX-02, ARX-03 and ARX-04 NanoTabs and formulations, our ARX-01 PCA device, the combination of drugs and our ARX-01 PCA device, our ARX-02, ARX-03 and ARX-04 single dose applicators, or SDAs, as well as methods of treatment using such drug and device compositions. All issued U.S. patents provide coverage for all of our development candidates, including ARX-01, ARX-02, ARX-03 and ARX-04, and provide protection for both composition of matter and methods of using NanoTabs for oral transmucosal delivery of sufentanil. Our issued U.S. Patent No. 8,252,329 includes composition of matter claims alone and in combination with key features of the ARX-01 PCA device and the ARX-02, ARX-03 and ARX-04 SDAs.

Issued European Patent No. EP2114383, including national validation in ten countries, includes composition of matter claims directed to ARX-01, ARX-02, ARX-03 and ARX-04 NanoTabs for oral transmucosal delivery of sufentanil, alone and in combination with key features of the ARX-01 PCA device, the ARX-02, ARX-03 and ARX-04 SDAs, respectively, and use of the claimed compositions in the treatment of pain.

Risks Associated with Our Business

Our business is subject to numerous risks, as more fully described in the section entitled Risk Factors immediately following this prospectus summary, beginning on page 11. You should read these risks before you invest in our common stock. We may be unable, for many reasons, including those that are beyond our control, to implement our business strategy. In particular, our risks include:

- We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.

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We have never generated any product or commercial revenue and may never be profitable.

We will require substantial additional capital following this offering and may be unable to raise capital, which would force us to delay, reduce or eliminate our product development programs and could cause us to cease operations. We cannot be certain that funds will be available and, if they are not available, we may not be able to continue as a going concern which may result in actions that could adversely impact our stockholders.

We depend substantially on the success of our NanoTab System, which is still under clinical development, and may not receive regulatory approval or be successfully commercialized.

We depend substantially on the successful completion of Phase 3 clinical trials for our product candidates. The positive clinical results obtained to date for our product candidates may not be repeated in the future.

Delays in clinical trials are common and have many causes, and any delay could result in increased costs to us and jeopardize or delay our ability to obtain regulatory approval and commence product sales.

Our product candidates may cause adverse effects or have other properties that could delay or prevent their regulatory approval or limit the scope of any approved label or market acceptance.

Our designs for the PCA device components of our NanoTab System for Phase 3 clinical trials may not be fully functional or commercially viable.

The commercial success of the NanoTab System and our other product candidates will depend upon the acceptance of these products by the medical community, including physicians, nurses, patients and pharmacy and therapeutics committees.

If we cannot defend our issued patents from third party claims or if our pending patent applications fail to issue, our business could be adversely affected.

Corporate Information

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. Our principal executive offices are located at 351 Galveston Drive, Redwood City, California 94063, and our telephone number is (650) 216-3500. Our website address is www.acelrx.com. The information contained in or that can be accessed through our website is not part of this prospectus.

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THE OFFERING

Common stock offered by us in this offering	10,000,000 shares
Common stock outstanding after the offering	32,646,773 shares
Over-allotment option	We have granted the underwriters an option to purchase up to 1,500,000 additional shares of our common stock. This option is exercisable, in whole or in part, for a period of 30 days from the date of this prospectus.
Use of proceeds	We intend to use the net proceeds from this offering to fund continued development of the NanoTab System, including completion and submission of a planned NDA to the FDA, and for working capital and other general corporate purposes. See Use of Proceeds on page 37.
NASDAQ Global Market listing	Our common stock is listed on The NASDAQ Global Market under the symbol ACRX.
Risk factors	Investing in our common stock involves a high degree of risk. See Risk Factors beginning on page 11 of this prospectus.

Entities affiliated with Three Arch Partners, our largest stockholder, have indicated an interest in purchasing up to approximately 20% of the shares of common stock offered in this offering, at the price offered to the public. However, because indications of interest are not binding agreements or commitments to purchase, the underwriters may determine to sell more, less or no shares in this offering to any of these entities, or any of these entities may determine to purchase more, less or no shares in this offering.

Outstanding Shares

The number of shares of common stock outstanding immediately after this offering is based on 22,646,773 shares of common stock outstanding as of September 30, 2012. This number excludes:

- 3,136,300 shares of common stock issuable upon the exercise of warrants outstanding as of September 30, 2012, at a weighted average exercise price of $3.42 per share;
- 3,321,038 shares of common stock issuable upon the exercise of options outstanding as of September 30, 2012, at a weighted average exercise price of $3.18 per share;
- 161,096 shares of common stock issuable upon the vesting of restricted stock units outstanding as of September 30, 2012;
- up to 539,267 shares of common stock that we may, subject to certain conditions and limitations, issue upon our election to convert up to $3.0 million of principal amount into shares of our common stock under outstanding promissory notes that we issued to Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc.; and
- 1,392,284 additional shares of common stock reserved for future issuance under our 2011 Equity Incentive Plan, or 2011 Plan, and our 2011 Employee Stock Purchase Plan, or Purchase Plan, as of September 30, 2012, plus any annual increases in the number of shares of common stock reserved for future issuance under the 2011 Plan and the Purchase Plan pursuant to evergreen provisions and any other shares that may become issuable under the 2011 Plan or the Purchase Plan pursuant to their terms.

In addition, the number of shares outstanding immediately after this offering does not include shares of common stock that we may sell pursuant to an At Market Issuance Sales Agreement, or the Sales Agreement,

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that we entered into with MLV & Co. LLC, or MLV, on August 31, 2012. Under the Sales Agreement, we may issue and sell shares of our common stock from time to time after the expiration of the 90-day lock-up period described under the section of this prospectus entitled Underwriting in such amounts as we may determine, subject to certain limitations under applicable securities laws.

Except as otherwise indicated, all information in this prospectus gives effect to a 1-for-4 reverse stock split of our capital stock that became effective on January 28, 2011 and assumes no exercise by the underwriters of their over-allotment option.

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SUMMARY FINANCIAL DATA

The following table summarizes our financial data. We have derived the following summary financial data for the years ended December 31, 2009, 2010 and 2011 from our audited financial statements. The summary financial data for the nine months ended September 30, 2012 and 2011 and the balance sheet data as of September 30, 2012 have been derived from our unaudited interim financial statements. The unaudited interim financial results have been prepared on the same basis as the audited financial statements and reflect all adjustments necessary to fairly reflect our financial position as of September 30, 2012 and results of operations for the nine months ended September 30, 2012 and 2011. Our historical results are not necessarily indicative of the results that may be expected in the future. The following summary financial data should be read in conjunction with Management s Discussion and Analysis of Financial Condition and Results of Operations and our financial statements and related notes incorporated by reference in this prospectus. For more details on how you can obtain the documents incorporated by reference in this prospectus, see Where You Can Find Additional information and Incorporation of Certain Information by Reference.

	Year Ended December 31,			Nine Months Ended September 30,	
	2009	2010	2011	2011	2012
				(Unaudited)	
	(in thousands, except share and per share data)				
Operations Data:					
Research grant revenue	$	$	$ 1,072	$ 448	$ 719
Operating Expenses:					
Research and development	$ 15,502	$ 8,193	$ 13,624	$ 8,922	$ 17,113
General and administrative	3,529	3,993	6,800	5,086	5,290
Total operating expenses	19,031	12,186	20,424	14,008	22,403
Loss from operations	(19,031)	(12,186)	(19,352)	(13,560)	(21,684)
Interest income	33	4	52	38	37
Interest expense	(1,242)	(1,397)	(2,309)	(1,891)	(1,765)
Other income (expense), net	121	(765)	1,508	1,684	571
Net loss	$ (20,119)	$ (14,344)	$ (20,101)	$ (13,729)	$ (22,841)
Net loss per share of common stock, basic and diluted	$ (34.93)	$ (21.84)	$ (1.16)	$ (0.83)	$ (1.09)
Shares used in computing net loss per share of common stock, basic and diluted	576,021	656,650	17,344,727	16,594,051	20,961,886

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The following table presents summary balance sheet data:

on an actual basis; and

on an as adjusted basis to give effect to the sale of the 10,000,000 shares of our common stock that we are offering at an assumed public offering price of $4.16 per share (the last reported sale price of our common stock as reported on The NASDAQ Global Market on December 3, 2012), after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

	As of September 30, 2012	
	Actual	As Adjusted [1]
	(Unaudited) (in thousands)	
Balance Sheet Data:		
Cash, cash equivalents and short-term investments	$ 23,375	$ 61,929
Working capital	13,070	51,624
Total assets	28,151	66,705
Total debt	17,682	17,682
Total stockholders equity (deficit)	(327)	38,227

[1] Each $0.50 increase (decrease) in the assumed public offering price of $4.16 per share, the last reported sale price of our common stock on The NASDAQ Global Market on December 3, 2012, would increase (decrease) the as adjusted amount of cash, cash equivalents and short-term investments, working capital, total assets and total stockholders equity (deficit) by approximately $4.7 million, assuming the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. We may also increase or decrease the number of shares we are offering. Each increase (decrease) of 1,500,000 shares in the number of shares offered by us would increase (decrease) the as adjusted amount of cash, cash equivalents and short-term investments, working capital, total assets and total stockholders equity (deficit) by approximately $5.9 million, assuming that the assumed public offering price remains the same, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. The as adjusted information discussed above is illustrative only and will be adjusted based on the actual public offering price and other terms of this offering determined at pricing.

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RISK FACTORS

An investment in our common stock is highly risky. You should carefully consider the following risks, as well as the other information contained and incorporated by reference in this prospectus, before you decide whether to buy our common stock. We believe the risks and uncertainties described below are the most significant risks we face. If any of the following events actually occurs, our business, business prospects, financial condition, cash flow and results of operations would likely be materially and adversely affected. In these circumstances, the trading price of our common stock would likely decline, and you could lose all or part of your investment.

We have identified the following risks and uncertainties that may have a material adverse effect on our business, financial condition or results of operations. The risks described below are not the only ones we face. Additional risks not presently known to us or that we currently believe are immaterial may also significantly impair our business operations.

Risks Related to Our Financial Condition and Need for Additional Capital

We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.

We are a development stage company with limited operating history. To date, we have focused primarily on developing our lead product candidate, the Sufentanil NanoTab PCA System, or the NanoTab System or ARX-01. We have three additional product candidates, the Sufentanil NanoTab BTP Management System, or ARX-02, the Sufentanil/Triazolam NanoTab, or ARX-03, and Sufentanil Single-Dose Acute Pain NanoTab, or ARX-04. We have incurred significant net losses in each year since our inception in July 2005 and as of September 30, 2012, we had an accumulated deficit of $111.5 million.

We have devoted most of our financial resources to research and development, including our non-clinical development activities and clinical trials. To date, we have financed our operations primarily through the sale of equity securities and debt. The size of our future net losses will depend, in part, on the rate of future expenditures and our ability to generate revenues. To date, none of our product candidates have been commercialized, and if our product candidates are not successfully developed or commercialized, or if revenues are insufficient following marketing approval, we will not achieve profitability and our business may fail. Even if we successfully obtain regulatory approval to market our product candidates in the United States, our revenues are also dependent upon the size of the markets outside of the United States, as well as our ability to obtain market approval and achieve commercial success.

We expect to continue to incur substantial and increased expenses as we expand our research and development activities and advance our clinical programs. We also expect an increase in our expenses associated with preparing for the potential commercialization of the NanoTab System. As a result of the foregoing, we expect to continue to incur significant and increasing operating losses and negative cash flows for the foreseeable future.

We have never generated any product or commercial revenue and may never be profitable.

Our ability to generate revenue from commercial sales and achieve profitability depends on our ability, alone or with collaborators, to successfully complete the development of, obtain the necessary regulatory approvals for, and commercialize our product candidates. Other than the revenue received from the US Army Medical Research and Materiel Command, or USAMRMC, for research and development reimbursement under the terms of the grant for ARX-04 we received from the USAMRMC, we do not anticipate generating revenues from sales of our product candidates for the foreseeable future, if ever. Our ability to generate future revenues from product sales depends heavily on our success in:

- completing the clinical development of the NanoTab System, initially for the treatment of post-operative pain in the hospital setting;
- obtaining regulatory approval for the NanoTab System, which will require additional funding;
- launching and commercializing the NanoTab System, including building a hospital-directed sales force in the U.S. and collaborating with third parties internationally, which will require additional funding; and

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completing the clinical development of, obtaining regulatory approval for, and launching and commercializing ARX-02, ARX-03 and ARX-04, which will require additional funding or corporate partnership resources.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to predict the timing or amount of increased expenses, or when, or if, we will be able to achieve or maintain profitability. In addition, our expenses could increase beyond expectations if we are required by the United States Food and Drug Administration, or FDA, to perform trials in addition to those that we currently anticipate.

Even if one or more of our product candidates is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Even if we are able to generate revenues from the sale of our products, we may not become profitable and may need to obtain additional funding to continue operations.

We have a limited operating history that may make it difficult to predict our future performance or evaluate our business and prospects.

We were incorporated in 2005. Since inception, our operations have been primarily limited to organizing and staffing our company, developing our technology and undertaking preclinical studies and clinical trials for our product candidates. We have not yet obtained regulatory approval for any of our product candidates. Consequently, any predictions you make about our future success or viability or evaluation of our business and prospects may not be accurate.

We will require substantial additional capital following this offering and may be unable to raise capital, which would force us to delay, reduce or eliminate our product development programs and could cause us to cease operations. We cannot be certain that funds will be available and, if they are not available, we may not be able to continue as a going concern which may result in actions that could adversely impact our stockholders.

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is expensive. We expect our research and development expenses to substantially increase in connection with our ongoing activities, particularly as we advance our clinical programs, including our ongoing Phase 3 NanoTab System clinical trials. As of September 30, 2012, we had working capital of $13.1 million.

We believe that the net proceeds from this offering, together with our current cash, cash equivalents and investment balances, will be sufficient to fund our current operations through the end of the second quarter of 2014. We may be able to extend this time period to the extent that we can access additional capital through equity offerings, including our Sales Agreement with MLV. However, we will need to raise substantial additional funds following this offering to support our future operations, and such funding may not be available to us on acceptable terms, or at all. Additionally, changing circumstances beyond our control may cause us to consume capital more rapidly than we currently anticipate. For example, we believe the net proceeds from this offering, together with our existing cash resources, based on our current estimates of clinical trial expenditures and enrollment pace, are adequate to complete our ongoing NanoTab System Phase 3 clinical trials, to submit our planned New Drug Application, or NDA, to the FDA for the NanoTab System, and to begin preparation for commercialization and manufacturing of the NanoTab System in the United States. However, our clinical trials may encounter technical, enrollment or other difficulties that could increase our development costs more than we expected. Even if we are able to submit an NDA, the FDA could require us to complete further studies, which would require additional capital before we receive our regulatory approval, if at all. In any event, we will require substantial additional capital to obtain regulatory approval for, and to commercialize, our product candidates, including the NanoTab System. Raising funds in the current economic environment, when the capital markets have been affected by the global recession, may present additional challenges. To raise capital, we may seek to sell additional equity or debt securities, obtain a credit facility or enter into product development, license or distribution agreements with third parties or divest one or more of our product candidates. Any product development, licensing, distribution or sale agreements that we enter into may require us to relinquish valuable rights. We may not be able to obtain sufficient additional funding or enter into a strategic transaction in a timely manner.

Securing additional financing may divert our management from our day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future

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financing will be available in sufficient amounts or on terms acceptable to us, if at all. If we are unable to raise additional capital when required or on acceptable terms, we may be required to:

- significantly delay, scale back or discontinue the development or commercialization of our product candidates;
- seek corporate partners for the NanoTab System on terms that might be less favorable than might otherwise be available; or
- relinquish or license on unfavorable terms, our rights to technologies or product candidates that we otherwise would seek to develop or commercialize ourselves.

If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we will not be able to continue our planned level of operations beyond the second quarter of 2014 and will not have sufficient capital to complete the regulatory approval process for the NanoTab System in the United States, which would have a material adverse effect on our business, operating results and prospects. If adequate funds are not available, we would be required to reduce our workforce, delay, reduce the scope of or eliminate one or more of our research and development programs in advance of the date on which we exhaust our cash resources to ensure that we have sufficient capital to meet our obligations and continue on a path designed to preserve stockholder value.

We may sell additional equity or debt securities to fund our operations, which may result in dilution to our stockholders and impose restrictions on our business.

In order to raise additional funds to support our operations, we may sell additional equity or debt securities, including under our Sales Agreement with MLV, which would result in dilution to all of our stockholders or impose restrictive covenants that adversely impact our business. The sale of additional equity or convertible debt securities would result in the issuance of additional shares of our capital stock and dilution to all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and could also result in certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. If we are unable to expand our operations or otherwise capitalize on our business opportunities, our business, financial condition and results of operations could be materially adversely affected and we may not be able to meet our debt service obligations.

We might be unable to service our current debt due to a lack of cash flow and might be subject to default.

In June 2011, we entered into a loan and security agreement with Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc., collectively referred to as Hercules, under which we borrowed $20.0 million in two tranches of $10.0 million each, represented by secured convertible term promissory notes. The interest rate is 8.50%, with the initial 12 months of the facility requiring interest only payments. The notes issued pursuant to the loan and security agreement mature on December 1, 2014. Since entering into the agreement with Hercules, we have been making monthly interest-only payments to Hercules of approximately $140,000 per month until June 30, 2012. According to the terms of the Hercules agreement, beginning on July 1, 2012, we began repaying Hercules principal, with equal monthly payments of $742,000, consisting of both principal and interest payments until the maturity date of the loan. As of September 30, 2012, the outstanding principal owed to Hercules was $18.2 million. We granted Hercules a first priority security interest in substantially all of our assets, with the exception of our intellectual property, where the security interest is limited to proceeds of intellectual property.

If we do not make the required payments when due, either at maturity, or at applicable installment payment dates, or if we breach the agreement or become insolvent, Hercules could elect to declare all amounts outstanding, together with accrued and unpaid interest and penalty, to be immediately due and payable. In order to continue our planned operations and satisfy our debt obligations with Hercules, we will need to raise additional capital in the future. Additional capital may not be available in terms acceptable to us, or at all. Even if we were able to repay the full amount in cash, any such repayment could leave us with little or no working capital for our business. If we are unable to repay those amounts, Hercules will have a first claim on our assets pledged under the loan agreement. If Hercules should attempt to foreclose on the collateral, it is unlikely that there would be any assets remaining after repayment in full of such secured indebtedness. Any default under the loan agreement and resulting foreclosure would have a material adverse effect on our financial condition and our ability to continue our operations.

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Risks Related to Clinical Development and Regulatory Approval

We depend substantially on the success of our NanoTab System, which is still under clinical development, and may not obtain regulatory approval or be successfully commercialized.

We have not marketed, distributed or sold any products. The success of our business depends primarily upon our ability to develop and commercialize the NanoTab System for the treatment of post-operative pain. We recently completed the first of three planned Phase 3 NanoTab System clinical trials, with two Phase 3 NanoTab System clinical trials ongoing.

Contingent upon receipt of successful data from the remaining two Phase 3 clinical trials, we intend to submit an NDA for the NanoTab System to the FDA in the third quarter of 2013. There is no guarantee that the remaining two Phase 3 NanoTab System clinical trials, Human Factors studies, or any of the remaining two pharmacokinetic studies, or PK studies, or non-clinical trial to be included in the planned NDA, will be completed on schedule or if at all, or if completed, will be successful. Even if we are able to submit an NDA, the FDA could require us to complete further studies, which could delay or preclude any approval of the NDA and would require us to obtain significant additional funding.

Any delay in obtaining, or inability to obtain, regulatory approval would prevent us from commercializing the NanoTab System, generating revenues and achieving profitability. If any of these events occur, we may be forced to abandon our development efforts for the NanoTab System, which would have a material adverse effect on our business and could potentially cause us to cease operations.

We depend substantially on the successful completion of Phase 3 clinical trials for our product candidates. The positive clinical results obtained to date for our product candidates may not be repeated in the future.

In November 2012, we announced positive top-line data from our active comparator NanoTab System Phase 3 clinical trial; however, subsequent analyses of the remaining data set may lead to different, including less favorable, interpretations of the results than the analyses conducted to date or may identify important implications of the trial that are not currently known, or be subject to differing interpretations by the regulatory agencies. In addition, we are still awaiting conclusion and results of our two remaining NanoTab System Phase 3 clinical trials, which are expected to be released during the first quarter of 2013. There is no guarantee that the results of these remaining two Phase 3 clinical trials will be positive, and the positive results in first Phase 3 clinical trial are not an indication or guarantee that the other Phase 3 clinical trials results will be positive.

Our product candidates are subject to the risks of failure inherent in pharmaceutical and medical device development. Before obtaining regulatory approval for the commercial sale of any product candidate, we must successfully complete all required Phase 3 clinical trials. Negative or inconclusive results of a Phase 3 clinical trial could cause the FDA to require that we repeat it or conduct additional clinical trials. Even if we believe that the data from required Phase 3 clinical trials is positive, the FDA could analyze our data using alternative imputation strategies and determine that any trial was negative or inconclusive. Furthermore, while we have completed multiple Phase 2 clinical trials for the NanoTab System, ARX-02 and ARX-03 and have obtained positive safety and efficacy results for our sufentanil-based product candidates during our prior clinical trials, we cannot be certain that these results will be duplicated when our product candidates are tested in a larger number of patients in our Phase 3 clinical trials, including in our ongoing Phase 3 clinical trials of the NanoTab System.

Delays in clinical trials are common and have many causes, and any delay could result in increased costs to us and jeopardize or delay our ability to obtain regulatory approval and commence product sales.

We have experienced and may in the future experience delays in clinical trials of our product candidates. We are conducting three Phase 3 clinical trials for the NanoTab System, and recently announced top-line results from the first such Phase 3 clinical trial. The other two remaining Phase 3 clinical trials are currently underway. In November 2012, we initiated a Phase 2 clinical trial for ARX-04. Our current and planned clinical trials may not begin on time, have an effective design, enroll a sufficient number of patients or be completed on schedule, if at all. Our clinical trials for any of our product candidates could be delayed for a variety of reasons, including:

- inability to raise funding necessary to initiate or continue a trial;
- delays in obtaining regulatory approval to commence a trial;

delays in reaching agreement with the FDA on final trial design;

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imposition of a clinical hold following an inspection of our clinical trial operations or trial sites by the FDA or other regulatory authorities;

delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;

delays in obtaining required institutional review board approval at each site;

delays in recruiting suitable patients to participate in a trial;

delays in the testing, validation, manufacturing and delivery of the device components of our product candidates;

delays in having patients complete participation in a trial or return for post-treatment follow-up;

clinical sites dropping out of a trial to the detriment of enrollment;

time required to add new clinical sites; or

delays by our contract manufacturers to produce and deliver sufficient supply of clinical trial materials.

If our clinical trials, including our ongoing Phase 3 clinical trials for the NanoTab System or Phase 2 clinical trial for ARX-04, are delayed for any of the above reasons, our development costs may increase, our approval process could be delayed and our ability to commercialize and commence sales of our product candidates could be materially harmed, which could have a material adverse effect on our business.

Our product candidates may cause adverse effects or have other properties that could delay or prevent their regulatory approval or limit the scope of any approved label or market acceptance.

Adverse events, or AEs, caused by our product candidates could cause us, other reviewing entities, clinical trial sites or regulatory authorities to interrupt, delay or halt clinical trials and could result in the denial of regulatory approval. Phase 2 clinical trials conducted by us with our NanoTab System, ARX-02 and ARX-03 product candidates have generated some AEs, but no serious adverse events, or SAEs, related to the trial drug. For example, in the NanoTab System Phase 2 clinical trials completed to date, 11% of the patients experienced vomiting and 8% experienced itching for 10 mcg and 15 mcg treated groups, as compared to the placebo treated subjects, of which 6% experienced vomiting and none experienced itching. In addition, in our active comparator NanoTab System Phase 3 clinical trial, 7.9% of NanoTab System treated patients dropped out of the trial prematurely due to an adverse event, and we observed two SAEs that were assessed as possibly or probably related to the trial drug, one of which was related to the NanoTab System. Moreover, the analysis of the remaining data set from our active comparator NanoTab System Phase 3 clinical trial or the analysis of the data set from our remaining two Phase 3 NanoTab System trials, when available, could result in identification of additional AEs or SAEs, related to the trial drug. Additional SAEs related to the trial drug observed in any of our clinical trials, including in our ongoing Phase 3 clinical trials, may adversely impact our ability to obtain regulatory approval for our product candidates.

Further, if our products cause serious or unexpected side effects after receiving market approval, a number of potentially significant negative consequences could result, including:

regulatory authorities may withdraw their approval of the product or impose restrictions on its distribution in the form of a modified Risk Evaluation and Mitigation Strategy, or REMS;

regulatory authorities may require the addition of labeling statements, such as warnings or contraindications;

we may be required to change the way the product is administered or conduct additional clinical trials;

we could be sued and held liable for harm caused to patients; or

our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected product candidate and could substantially increase the costs of commercializing our product candidates.

Additional time may be required to obtain regulatory approval for our NanoTab System product candidate because it is a drug/device combination.

The NanoTab System is a drug/device combination product candidate with both drug and device components submitted in the investigational new drug, or IND, application. Based on our discussions with the FDA, we believe that the NanoTab System is viewed as a combination product by the FDA, and both drug and device components will be required for review as part of an NDA submission. There are very few examples of the FDA approval process for drug/device combination products such as the NanoTab System. As a result, we have in the past and may in the

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future experience delays for the NanoTab System due to regulatory uncertainties in the product development and approval process, in particular as it relates to a drug/device combination product approval under an NDA.

After the completion of our clinical trials, we cannot predict whether or when we will obtain regulatory approval to commercialize any of our product candidates, and we cannot, therefore, predict the timing of any future revenue.

We cannot commercialize any of our product candidates, including the NanoTab System, until the appropriate regulatory authorities, such as the FDA or the European Medicines Agency, or EMA, have reviewed and approved the product candidate. The regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval for the NanoTab System. Additional delays may result if the NanoTab System is taken before an FDA Advisory Committee which may recommend restrictions on approval or recommend non-approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process.

The process for obtaining approval of an NDA is time consuming, subject to unanticipated delays and costs, and requires the commitment of substantial resources.

If the FDA determines that the clinical trials submitted for a product candidate in support of an NDA were not conducted in full compliance with the applicable protocols for these trials, as well as with applicable regulations and standards, or if the FDA does not agree with our interpretation of the results of such trials, the FDA may reject the data that resulted from such trials. The rejection of data from clinical trials required to support an NDA could negatively impact our ability to obtain marketing authorization for a product candidate and would have a material adverse effect on our business and financial condition.

In addition, an NDA may not be approved, or approval may be delayed, as a result of changes in FDA policies for drug approval during the review period. For example, although many products have been approved by the FDA in recent years under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, or FDCA, objections have been raised to the FDA s interpretation of Section 505(b)(2). If challenges to the FDA s interpretation of Section 505(b)(2) are successful, the FDA may be required to change its interpretation, which could delay or prevent the approval of such an NDA. Any significant delay in the review or approval of an NDA that we submit would have a material adverse effect on our business and financial condition.

Regulatory authorities may not approve our product candidates even if they meet safety and efficacy endpoints in clinical trials.

The FDA and other foreign regulatory agencies, such as the EMA, can delay, limit or deny marketing approval for many reasons, including:

- a product candidate may not be considered safe or effective;
- the manufacturing processes or facilities we have selected may not meet the applicable requirements; and
- changes in their approval policies or adoption of new regulations may require additional work on our part.

Part of the regulatory approval process includes compliance inspections of manufacturing facilities to ensure adherence to applicable regulations and guidelines. The regulatory agency may delay, limit or deny marketing approval of our product candidates as a result of such inspections.

Any delay in, or failure to receive or maintain, approval for any of our product candidates could prevent us from generating meaningful revenues or achieving profitability.

Our product candidates may not be approved even if they achieve their endpoints in clinical trials. Regulatory agencies, including the FDA, or their advisors may disagree with our trial design and our interpretations of data from preclinical trials and clinical trials. Regulatory agencies may change requirements for approval even after a clinical trial design has been approved. The FDA exercises significant discretion over the regulation of combination products, including the discretion to require separate marketing applications for the drug and device components in a combination product. To date, our product candidates are being regulated as drug products under the NDA process administered by the FDA. The FDA could in the future require additional regulation of our product candidates under the medical device provisions of the FDCA. Our

systems are designed to comply with Quality Systems Regulation, or

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QSR, which sets forth the FDA s current good manufacturing practice, or GMP, requirements for medical devices, and other applicable government regulations and corresponding foreign standards for drug GMPs. If we fail to comply with these regulations, it could have a material adverse effect on our business and financial condition.

Regulatory agencies also may approve a product candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing trials. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates.

Even if we obtain regulatory approval for the NanoTab System and our other product candidates, we will still face extensive regulatory requirements and our products may face future development and regulatory difficulties.

Even if we obtain regulatory approval in the United States, the FDA may still impose significant restrictions on the indicated uses or marketing of our product candidates, or impose ongoing requirements for potentially costly post-approval trials or post-market surveillance. For example, the labeling ultimately approved for the NanoTab System and our other product candidates will likely include restrictions on use due to the opioid nature of sufentanil. The NanoTab System and our other product candidates will also be subject to ongoing FDA requirements governing the labeling, packaging, storage, distribution, safety surveillance, advertising, promotion, record-keeping and reporting of safety and other post-market information. The holder of an approved NDA is obligated to monitor and report AEs and any failure of a product to meet the specifications in the NDA. The holder of an approved NDA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, manufacturers of drug products and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with current good manufacturing practices, or cGMP, and adherence to commitments made in the NDA. If we, or a regulatory agency, discover previously unknown problems with a product, such as AEs of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facility, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of our product candidate, a regulatory agency may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending NDA or supplements to an NDA submitted by us;
- seize product; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our products and generate revenues.

Even if we obtain FDA approval for the NanoTab System or any of our product candidates in the United States, we may never obtain approval for or commercialize our products outside of the United States, which would limit our ability to realize their full market potential.

In order to market any products outside of the United States, we must establish and comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy. In October 2012, we received notice from the EMA that the NanoTab System was eligible for centralized European review. Outside of Europe, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approval could result in difficulties and costs for us and

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require additional non-clinical trials or clinical trials, which could be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our products in those countries. We do not have any product candidates approved for sale in any jurisdiction, including international markets, and we do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of our products will be harmed.

The NanoTab System and our other product candidates will require Risk Evaluation and Mitigation Strategies, or REMS.

The FDA Amendments Act of 2007 implemented safety-related changes to product labeling and require the adoption of REMS. Our product candidates will require REMS. The REMS may include requirements for special labeling or medication guides for patients, special communication plans to health care professionals and restrictions on distribution and use. While we have received information from the FDA regarding certain aspects of the required REMS for the NanoTab System, we cannot predict the specific REMS to be required as part of the FDA s approval of the NanoTab System. Depending on the extent of the REMS requirements, our costs to commercialize the NanoTab System may be substantial. ARX-02, ARX-03 and ARX-04, if approved, will also require REMS programs that may significantly increase our costs to commercialize these product candidates. Furthermore, risks of sufentanil that are not adequately addressed through proposed REMS for our product candidates may also prevent or delay their approval for commercialization.

Risks Related to Our Reliance on Third Parties

We rely on third party manufacturers to produce our preclinical and clinical drug supplies, and we intend to rely on third parties to produce commercial supplies of any approved product candidates.

Reliance on third party manufacturers entails many risks including:

- the inability to meet our product specifications and quality requirements consistently;
- a delay or inability to procure or expand sufficient manufacturing capacity;
- manufacturing and product quality issues related to scale-up of manufacturing;
- costs and validation of new equipment and facilities required for scale-up;
- a failure to comply with cGMP and similar foreign standards;
- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us;
- the reliance on a limited number of sources, and in some cases, single sources for product components, such that if we are unable to secure a sufficient supply of these product components, we will be unable to manufacture and sell our product candidates in a timely fashion, in sufficient quantities or under acceptable terms;

the lack of qualified backup suppliers for those components that are currently purchased from a sole or single source supplier;

operations of our third party manufacturers or suppliers could be disrupted by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier;

carrier disruptions or increased costs that are beyond our control; and

the failure to deliver our products under specified storage conditions and in a timely manner.

Any of these events could lead to clinical trial delays, failure to obtain regulatory approval or impact our ability to successfully commercialize our products. Some of these events could be the basis for FDA action, including injunction, recall, seizure, or total or partial suspension of production.

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We rely on limited sources of supply for the drug component of our product candidates and any disruption in the chain of supply may cause delay in developing and commercializing our product candidates.

Currently, we use two established suppliers of sufentanil citrate for our NanoTabs. For each product candidate, only one of the two suppliers will be qualified as a vendor with the FDA. If supply from the approved vendor is interrupted, there could be a significant disruption in commercial supply. The alternative vendor would need to be qualified through an NDA supplement which could result in further delay. The FDA or other regulatory agencies outside of the United States may also require additional trials if a new sufentanil supplier is relied upon for commercial production. In addition, the Drug Enforcement Administration, or the DEA, may reduce, delay or refuse our quota for sufentanil, which would disrupt our supply of sufentanil citrate and cause delay in the development and commercialization of our product candidates.

Currently, we use one supplier of triazolam for our ARX-03 NanoTabs. Switching triazolam suppliers may involve substantial cost and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of clinical trials, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing them successfully. Furthermore, if our suppliers fail to deliver the required commercial quantities of active pharmaceutical ingredient on a timely basis and at commercially reasonable prices, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical trials may be delayed or we could lose potential revenue.

Manufacture of Sufentanil NanoTabs requires specialized equipment and expertise.

Ethanol, which is used in the manufacturing process for our Sufentanil NanoTabs, is flammable, and sufentanil is a highly potent, Schedule II compound. These factors necessitate the use of specialized equipment and facilities for manufacture of sufentanil NanoTabs. There are a limited number of facilities that can accommodate our manufacturing process and we need to use dedicated equipment throughout development and commercial manufacturing to avoid the possibility of cross-contamination. If our equipment breaks down or needs to be repaired or replaced, it may cause significant disruption in clinical or commercial supply, which could result in delay in the process of obtaining approval for or sale of our products. Furthermore, we are using one manufacturer to produce our sufentanil NanoTabs and have not identified a back-up commercial facility to date. Any problems with our existing facility or equipment may delay or impair our ability to complete our clinical trials or commercialize our product candidates and increase our cost.

Manufacturing issues may arise that could delay or increase costs related to product and regulatory approval and commercialization.

As we scale up manufacturing of our product candidates and conduct required stability testing, product, packaging, equipment and process-related issues may require refinement or resolution in order to proceed with our planned clinical trials and obtain regulatory approval for commercial marketing. In the past we have identified impurities in our product candidates. In the future we may identify significant impurities, which could result in increased scrutiny by the regulatory agencies, delays in clinical program and regulatory approval, increases in our operating expenses, or failure to obtain or maintain approval for our products.

Historically, we have manufactured the majority of our NanoTab supplies at Patheon Inc., or Patheon, in Toronto, Canada. Because the DEA requires that sufentanil be manufactured in the United States if our product candidates are marketed in the United States, we transferred our manufacturing capability in the third quarter of 2011 from Patheon in Toronto, Canada to Patheon s production facility in Cincinnati, Ohio, where we have built out a suite within their existing buildings that will serve as a manufacturing facility for clinical and commercial supplies of NanoTabs. The new facility has been qualified; however, we have not yet produced commercial supplies out of this facility and we may encounter difficulties in production at the new facility, which may adversely affect our clinical and commercial plans. In addition, the FDA or other regulatory agencies may require that a bioequivalence study be conducted, which is designed to ensure that the Phase 3 drug lots made at Patheon, Toronto are equivalent to one of the registration drug lots made at Patheon, Cincinnati. There is risk that this bioequivalence study could fail the FDA s bioequivalence requirements which would adversely affect our clinical and commercial plans.

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Our designs for the PCA device components of our NanoTab System for Phase 3 clinical trials may not be fully functional or commercially viable.

The NanoTab System device we are using in Phase 3 clinical trials and plan to use commercially, or the Phase 3 device, has more features than the device used in Phase 2, including additional software. We have conducted multiple Design Validation, Software Verification and Validation, Reprocessing and Human Factors studies, which have informed the design of the Phase 3 device and we plan to conduct additional Human Factors studies prior to submitting the planned NDA for the NanoTab System. However, we cannot predict if the Phase 3 device will be fully functional or acceptable throughout all Phase 3 clinical trials or for commercial use. If we need to modify the Phase 3 device either during or after the remaining Phase 3 clinical trials, we may incur higher costs and experience delay in regulatory approval and commercialization of the NanoTab System. Furthermore, if the changes to the device are substantial, we may need to conduct further clinical trials in order to have the commercial device approved by the FDA.

We have limited experience manufacturing the NanoTab System Phase 3 device on a clinical scale, no experience on a commercial scale and do not own or operate a manufacturing facility.

We have manufactured the NanoTab System devices and supplies on a small scale, including those needed for our Phase 3 clinical trials. We continue to rely on contract manufacturers, component fabricators and secondary service providers to produce the necessary NanoTab System devices for the remaining Phase 3 clinical trials and the commercial marketplace. We currently outsource manufacturing and packaging of the controller, dispenser and cartridge components of the NanoTab System device to third parties and intend to continue to do so. These purchases of Phase 3 devices and components were made and will continue to be made utilizing short term purchase agreements and we may not be able to enter into long-term agreements for commercial supply of the NanoTab System devices with third party manufacturers, or may be unable to do so on acceptable terms. We may encounter unanticipated problems in the scale-up and automation process that will result in delays in the manufacturing of the NanoTab System cartridge, dispenser or controller.

We may not be able to establish additional sources of supply for device manufacture. Such suppliers are subject to FDA regulations requiring that materials be produced under current Good Manufacturing Practices, or cGMPs, or Quality System Regulations, or QSR, and subject to ongoing inspections by regulatory agencies. Failure by any of our suppliers to comply with applicable regulations may result in delays and interruptions to our product candidate supply while we seek to secure another supplier that meets all regulatory requirements.

Reliance on third party manufacturers entails risks to which we would not be subject if we manufactured the product candidates ourselves, including the possible breach of the manufacturing agreements by the third parties because of factors beyond our control; and the possibility of termination or nonrenewal of the agreements by the third parties because of our breach of the manufacturing agreement or based on their own business priorities.

We rely on third parties to conduct, supervise and monitor our clinical trials, and if those third parties perform in an unsatisfactory manner, it may harm our business.

We have selected and executed agreements with CROs to conduct our three Phase 3 clinical trials for the NanoTab System and for the Phase 2 clinical trial for ARX-04. We will rely on these CROs, as well as clinical trial sites, to ensure the proper and timely conduct of our clinical trials. While we have agreements governing their activities, we have limited influence over their actual performance. We have relied and plan to continue to rely upon CROs to monitor and manage data for our ongoing clinical programs for the NanoTab System and our other product candidates, as well as the execution of nonclinical trials. We control only certain aspects of our CROs activities. Nevertheless, we are responsible for ensuring that each of our trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with the FDA s current good clinical practices, or cGCPs, which are regulations and guidelines enforced by the FDA for all of our product candidates in clinical development. The FDA enforces these cGCPs through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA may require us to perform additional clinical trials before approving our marketing applications. Upon inspection, the FDA may determine that our Phase 3 clinical trials do not comply with cGCPs. In addition, our Phase 3 clinical trials will require a sufficiently large number of test subjects to evaluate the safety and effectiveness of the NanoTab System.

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Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of patients, we may be required to repeat the Phase 3 clinical trials, which would delay the regulatory approval process.

Our CROs are not our employees, and we cannot control whether or not they devote sufficient time and resources to our ongoing clinical and nonclinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials, or other drug development activities which could harm our competitive position. We face the risk of potential unauthorized disclosure or misappropriation of our intellectual property by CROs, which may allow our potential competitors to access our proprietary technology. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize the NanoTab System, or our other product candidates. As a result, our financial results and the commercial prospects for the NanoTab System and any future product candidates that we develop would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

Development of ARX-04 is dependent on funding from our government grant with the USAMRMC.

In May 2011, we received a grant from the USAMRMC, effective June 1, 2011, in which the USAMRMC granted $5.6 million to us in order to support the development of ARX-04. Under the terms of the grant, the USAMRMC will reimburse us for development, manufacturing and clinical costs necessary to prepare for and complete our ongoing Phase 2 dose-finding trial for the treatment of moderate-to-severe pain, and to prepare to enter into planned Phase 3 development. The period of research under the grant ends on May 31, 2013, with a final report due on June 30, 2013. The grant gives the USAMRMC the option to extend the term of the grant and provide additional funding for the research.

Development of ARX-04 is dependent on the continued performance by the USAMRMC of its responsibilities under this agreement, including adequate continued funding of USAMRMC programs. We have no control over the resources and funding that USAMRMC may devote to this or future agreements, which may be subject to annual renewal and which generally may be terminated by USAMRMC at any time.

USAMRMC may fail to perform their responsibilities under the agreement, which may result in the termination of the agreement. In addition, we may fail to perform our responsibilities under the agreement, which may also lead to the termination of this agreement. Our government agreement is subject to audits, which may occur several years after the period to which the audit relates. If an audit identifies significant unallowable costs, we could incur a material charge to our earnings or reduction in our cash position. As a result, we may be unsuccessful in entering, or ineligible to enter, into future government agreements.

There can be no assurances that this agreement will continue or that we will be able to enter into new contracts with USAMRMC or obtain funding from other sources to continue to support development of ARX-04 beyond the Phase 2 clinical trial and preparation for Phase 3 activities. The process of obtaining USAMRMC contracts is lengthy and uncertain and we will have to compete with other companies for each contract. Further, changes in government budgets and agendas may result in a decreased and de-prioritized emphasis on supporting research and development programs, including ARX-04.

Risks Related to Commercialization of Our Product Candidates

The commercial success of the NanoTab System and our other product candidates will depend upon the acceptance of these products by the medical community, including physicians, nurses, patients, and pharmacy and therapeutics committees.

The degree of market acceptance of any of our product candidates will depend on a number of factors, including:

- demonstration of clinical safety and efficacy compared to other products;
- the relative convenience, ease of administration and acceptance by physicians, patients and health care payors;
- the prevalence and severity of any AEs or SAEs;

overcoming the perception of sufentanil as a potentially unsafe drug due to its high potency;

limitations or warnings contained in the FDA-approved label for the NanoTab System;

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availability of alternative treatments;

existing capital investment by hospitals in IV PCA technology;

pricing and cost-effectiveness;

the effectiveness of our or any future collaborators sales and marketing strategies;

our ability to obtain hospital formulary approval;

our ability to obtain and maintain sufficient third party coverage or reimbursement; and

the willingness of patients to pay out-of-pocket in the absence of third party coverage.

If the NanoTab System is approved, but does not achieve an adequate level of acceptance by physicians, nurses, patients and pharmacy and therapeutics committees, or P&T Committees, we may not generate sufficient revenue from the NanoTab System and we may not become or remain profitable.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any revenue.

We currently do not have an organization for the sales, marketing and distribution of pharmaceutical products and the cost of establishing and maintaining such an organization may exceed the cost-effectiveness of doing so. In order to market any products that may be approved, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. We intend to enter into strategic partnerships with third parties to commercialize our product candidates outside of the United States. We will also consider the option to enter into strategic partnerships for our product candidates in the United States.

To date, we have not entered into any strategic partnerships for any of our product candidates. We face significant competition in seeking appropriate strategic partners, and these strategic partnerships can be intricate and time consuming to negotiate and document. We may not be able to negotiate strategic partnerships on acceptable terms, or at all. We are unable to predict when, if ever, we will enter into any strategic partnerships because of the numerous risks and uncertainties associated with establishing strategic partnerships. Our strategy for the NanoTab System is to develop a hospital-directed sales force and/or collaborate with third parties to promote the product to healthcare professionals and third-party payors in the United States. Our future collaboration partners, if any, may not dedicate sufficient resources to the commercialization of our product candidates or may otherwise fail in their commercialization due to factors beyond our control. If we are unable to establish effective collaborations to enable the sale of our product candidates to healthcare professionals and in geographical regions, including the United States, that will not be covered by our own marketing and sales force, or if our potential future collaboration partners do not successfully commercialize our product candidates, our ability to generate revenues from product sales will be adversely affected.

Until we are able to negotiate a strategic partnership or obtain additional financial resources for ARX-02 or ARX-03, we will not progress development or generate any revenue from these product candidates. We are developing ARX-04 under a grant from USAMRMC and if new funding from USAMRMC to cover Phase 3 costs is not obtained, we may be required to curtail all activities associated with ARX-04. In addition, without a partnership or additional grant funding, we would bear all the risk related to the development of ARX-02, ARX-03 and ARX-04. If we elect to increase our expenditures to fund development or commercialization activities ourselves, we will need to obtain additional capital, which may not be available to us on acceptable terms, or at all. If we do not have sufficient funds, we will not be able to bring ARX-02, ARX-03 or ARX-04 to market or generate product revenue.

If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not be able to generate sufficient product revenue and may not become profitable. We will be competing with many companies that currently have extensive and well-funded marketing and sales operations. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

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If we obtain approval to commercialize our products outside of the United States, a variety of risks associated with international operations could materially adversely affect our business.

If our product candidates are approved for commercialization, we intend to enter into agreements with third parties to market the NanoTab System outside the United States. We expect that we will be subject to additional risks related to entering into international business relationships, including:

- different regulatory requirements for drug approvals in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

If we, or potential partners, are unable to compete effectively, our product candidates may not reach their commercial potential.

The market for our product candidates is characterized by intense competition and rapid technological advances. If our product candidates obtain FDA approval, they will compete with a number of existing and future pharmaceuticals and drug delivery devices developed, manufactured and marketed by others. We or potential partners will compete against fully integrated pharmaceutical companies and smaller companies that are collaborating with larger pharmaceutical companies, academic institutions, government agencies and other public and private research organizations.

We believe that the NanoTab System would compete with a number of opioid-based treatment options that are currently available. The market for opioids for post-operative pain is large and competitive. The primary competition for the NanoTab System is the IV PCA pump, which is widely used in the post-operative setting. Leading manufacturers of IV PCA pumps include Hospira Inc., CareFusion Corporation, Baxter International Inc., Curlin Medical, Inc. and Smiths Medical. The most common opioids used to treat post-operative pain are morphine, hydromorphone and fentanyl, all of which are available as generics. Also available on the market is the Avancen Medication on Demand, or MOD, Oral PCA Device developed by Avancen MOD Corporation.

Additional potential competitors for the NanoTab System include products in development, including the fentanyl iontophoretic transdermal system, IONSYS, originally developed by ALZA Corporation and Ortho-McNeil Pharmaceutical, Inc., both Johnson & Johnson subsidiaries, and currently under development by Incline Therapeutics, Inc. Also in development is MoxDuo, an orally administered, fixed ratio combination of morphine and oxycodone being developed by QRx Pharma, an Australian company. This drug is also in development as an IV product.

Our potential competitors for ARX-02 include products approved in the United States for cancer breakthrough pain, including: ACTIQ and FENTORA, currently manufactured by Teva Pharmaceuticals; Onsolis, currently manufactured by BioDelivery Sciences International, Inc.; Abstral, currently manufactured by ProStrakan Group plc; Lazanda, currently manufactured by Archimedes Pharma Limited, as well as products approved in Europe, including: Instanyl, currently manufactured by Nycomed International Management GmbH. The active ingredient in all approved products for cancer breakthrough pain is fentanyl. Additional potential competitors for ARX-02 include products in late stage development for cancer breakthrough pain, such as: Fentanyl TAIFUN, currently manufactured by Akela Pharma, Inc.; and SL Spray, currently manufactured by Insys Therapeutics, Inc.

We are not aware of any approved or development stage non-IV sedative/analgesic products that would present competition to ARX-03. In the future, there may be products developed or approved for this market which could directly compete with ARX-03.

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Competitors for ARX-04 within the military environment include intramuscular morphine injections which are marketed by a variety of generic manufacturers. Within the civilian environment, there are a wide variety of approved injectable and oral opioid products to treat moderate-to-severe acute pain, including IV opioids such as morphine, fentanyl, hydromorphone and meperidine or oral opioids such as oxycodone and hydrocodone.

It is possible that any of these competitors could develop or improve technologies or products that would render our product candidates obsolete or non-competitive, which could adversely affect our revenue potential. Key competitive factors affecting the commercial success of our product candidates are likely to be efficacy, safety profile, reliability, convenience of dosing, price and reimbursement.

Many of our potential competitors have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of drug candidates, obtaining FDA and other regulatory approval of products and the commercialization of those products. Accordingly, our competitors may be more successful than we are in obtaining FDA approval for drugs and achieving widespread market acceptance. Our competitors drugs or drug delivery systems may be more effective, have fewer adverse effects, be less expensive to develop and manufacture, or be more effectively marketed and sold than any product candidate we may commercialize. This may render our product candidates obsolete or non-competitive before we can recover our losses. We anticipate that we will face intense and increasing competition as new drugs enter the market and additional technologies become available. These entities may also establish collaborative or licensing relationships with our competitors, which may adversely affect our competitive position. Finally, the development of different methods for the treatment of post-operative pain or breakthrough pain could render the NanoTab System and ARX-02, respectively, non-competitive or obsolete. These and other risks may materially adversely affect our ability to attain or sustain profitable operations.

Hospital formulary approval and reimbursement may not be available for the NanoTab System and our other product candidates, which could make it difficult for us to sell our products profitably.

Obtaining formulary approval can be an expensive and time-consuming process. We cannot be certain if and when we will obtain formulary approval to allow us to sell our products into our target markets. Failure to obtain timely formulary approval will limit our commercial success.

Furthermore, market acceptance and sales of the NanoTab System, or any of our other product candidates, will depend on reimbursement policies and may be affected by future healthcare reform measures. Government authorities and third party payors, such as private health insurers, hospitals and health maintenance organizations, decide which drugs they will pay for and establish reimbursement levels. We cannot be sure that reimbursement will be available for the NanoTab System, or any of our other product candidates. Also, reimbursement amounts may reduce the demand for, or the price of, our products. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize the NanoTab System, or any of our other product candidates.

There have been a number of legislative and regulatory proposals to change the healthcare system in the United States and in some foreign jurisdictions that could affect our ability to sell our products profitably. These legislative and/or regulatory changes may negatively impact the reimbursement for our products, following approval. The availability of numerous generic pain medications may also substantially reduce the likelihood of reimbursement for the NanoTab System or any of our other product candidates. The application of user fees to generic drug products may expedite the approval of additional pain medication generic drugs. We expect to experience pricing pressures in connection with any sale of the NanoTab System and any of our other product candidates, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. If we fail to successfully secure and maintain reimbursement coverage for our products or are significantly delayed in doing so, we will have difficulty achieving market acceptance of our products and our business will be harmed.

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Risks Related to Our Business Operations and Industry

Failure to comply with the Drug Enforcement Administration regulations, or the cost of compliance with these regulations, may adversely affect our business.

Our sufentanil-based products are subject to extensive regulation by the DEA, due to their status as scheduled drugs. Sufentanil is a Schedule II opioid, considered to present the highest risk of abuse. The manufacture, shipment, storage, sale and use of controlled substances are subject to a high degree of regulation, including security, record-keeping and reporting obligations enforced by the DEA. This high degree of regulation can result in significant costs in order to comply with the required regulations, which may have an adverse effect on the development and commercialization of our product candidates.

The DEA limits the availability and production of all Schedule II substances, including sufentanil, through a quota system. The DEA requires substantial evidence and documentation of expected legitimate medical and scientific needs before assigning quotas to manufacturers. Our contract manufacturers have applied annually for a quota on our behalf. In future years, we may need greater amounts of sufentanil to continue development of our product candidates, and we will need significantly greater amounts of sufentanil to implement our commercialization plans for any of our products that may be approved by the FDA, including the NanoTab System if approved by the FDA. Any delay or refusal by the DEA in establishing the procurement quota or a reduction in our quota for sufentanil or a failure to increase it over time to meet anticipated increases in demand could delay or stop the clinical development or commercial sale of the NanoTab System or any of our other product candidates. This could have a material adverse effect on our business, results of operations, financial condition and prospects.

Drug Enforcement Administration regulations require that sufentanil be manufactured in the United States if sufentanil-based products are to be marketed in the United States, and there is no guarantee that we will secure a commercial supply agreement with a manufacturer based in the United States.

A substantial portion of our clinical trial manufacturing to date has been completed at Patheon in Toronto, Canada. Because the DEA requires that sufentanil be manufactured in the United States if our product candidates are marketed in the United States, we transferred our manufacturing capability in the third quarter of 2011 from Patheon in Toronto, Canada to Patheon s production facility in Cincinnati, Ohio, where we have built out a suite within their existing buildings that will serve as a manufacturing facility for clinical and commercial supplies of NanoTabs. The new facility has been qualified; however, we have not yet produced commercial supplies out of this facility and we may encounter difficulties in production at the new facility, or otherwise, which may adversely affect our clinical and commercial plans.

We do not yet have a commercial supply contract in place with Patheon or any other manufacturer. If we cannot establish a supply contract on commercially reasonable terms, or if equipment manufacture or modifications do not meet expected deadlines, the timing for our planned NDA submission for the NanoTab System may be delayed.

Switching or adding commercial manufacturing capability can involve substantial cost and require extensive management time and focus, as well as additional regulatory filings. In addition, there is a natural transition period when a new manufacturing facility commences work. As a result, delays may occur, which can materially impact our ability to meet our desired commercial timelines, thereby increasing our costs and reducing our ability to generate revenue.

The facilities of any of our future manufacturers of sufentanil-containing NanoTabs must be approved by the FDA after we submit our planned NDA and before approval of the NanoTab System and our other product candidates. We do not control the manufacturing process of sufentanil NanoTabs and are completely dependent on these third party manufacturing partners for compliance with the FDA s requirements for manufacture. In addition, although our third party manufacturers are well established commercial manufacturers, we are dependent on their continued adherence to cGMP manufacturing and acceptable changes to their process. If our manufacturers do not meet the FDA s strict regulatory requirements, they will not be able to secure FDA approval for their manufacturing facilities. If the FDA does not approve these facilities for the commercial manufacture of sufentanil NanoTabs, we will need to find alternative suppliers, which would result in significant delays in obtaining FDA approval for the NanoTab System. These challenges may have a material adverse impact on our business, results of operations, financial condition and prospects.

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Business interruptions could delay us in the process of developing our products and could disrupt our sales.

Our headquarters is located in the San Francisco Bay Area, near known earthquake fault zones and is vulnerable to significant damage from earthquakes. We are also vulnerable to other types of natural disasters and other events that could disrupt our operations. We do not carry insurance for earthquakes or other natural disasters and we may not carry sufficient business interruption insurance to compensate us for losses that may occur. Any losses or damages we incur could have a material adverse effect on our business operations.

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on principal members of our executive team, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into offer letters with each of our executive officers, any of them could leave our employment at any time, as all of our employees are at will employees. Recruiting and retaining other qualified employees for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical companies for individuals with similar skill sets. In addition, failure to succeed in clinical trials may make it more challenging to recruit and retain qualified personnel. The inability to recruit or loss of the services of any executive or key employee might impede the progress of our research, development and commercialization objectives.

We will need to expand our organization, and we may experience difficulties in managing this growth, which could disrupt our operations.

As of November 1, 2012, we only had 24 full-time employees. As our company matures, we expect to expand our employee base to increase our managerial, scientific and engineering, operational, sales, marketing, financial and other resources and to hire more consultants and contractors. Future growth would impose significant additional responsibilities on our management, including the need to identify, recruit, maintain, motivate and integrate additional employees, consultants and contractors. Also, our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize the NanoTab System and our other product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability.

The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, health care providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation;
- withdrawal of clinical trial participants;
- costs due to related litigation;
- distraction of management s attention from our primary business;

substantial monetary awards to patients or other claimants;

the inability to commercialize our product candidates; and

decreased demand for our product candidates, if approved for commercial sale.

Our current product liability insurance coverage may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive and in the future we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for our product candidates, we intend to expand our insurance

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coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Risks Related to Our Intellectual Property

If we cannot defend our issued patents from third party claims or if our pending patent applications fail to issue, our business could be adversely affected.

To protect our proprietary technology, we rely on patents as well as other intellectual property protections including trade secrets, nondisclosure agreements, and confidentiality provisions. As of October 1, 2012, we are the owner of record of one issued European patent, including national validation in ten countries, which expires in 2027, one Mexican patent which expires in 2029, four issued U.S. patents which provide coverage through at least 2027, and one issued U.S. patent which provides coverage through at least 2030. In addition, we are pursuing 15 U.S. non-provisional patent applications, one pending international Patent Cooperation Treaty application and 59 foreign national applications, including seven European Regional Phase applications directed to our product candidates. We have not yet obtained any issued patents that provide protection for key features of our ARX-01 PCA device or our ARX-02, ARX-03 and ARX-04 SDAs independent of the drug composition used in them. The patent applications that we have filed and have not yet been granted may fail to result in issued patents in the United States or in foreign countries. Even if the patents do successfully issue, third parties may challenge the patents.

Our commercial success will depend in part on successfully defending our current sufentanil formulation patents against third party challenges and expanding our existing formulation patent portfolio to provide additional layers of patent protection, as well as extending patent protection to our proprietary delivery devices. There can be no assurance that we will be successful in defending our existing and future patents against third party challenges, or that our pending patent applications will result in issued patents. The patent positions of pharmaceutical companies, including us, can be highly uncertain and involve complex and evolving legal and factual questions. No consistent policy regarding the breadth of claims allowed in pharmaceutical patents has emerged to date in the United States. Legal developments may preclude or limit the scope of available patent protection.

The patent positions of pharmaceutical companies, including us, can be highly uncertain and involve complex and evolving legal and factual questions. No consistent policy regarding the breadth of claims allowed in pharmaceutical patents has emerged to date in the United States. Legal developments may preclude or limit the scope of available patent protection.

There is also no assurance that any patents issued to us will not become the subject of a re-examination or other post-grant review, will provide us with competitive advantages, will not be challenged by any third parties, or that the patents of others will not prevent the commercialization of products incorporating our technology. Furthermore, there can be no guarantee that others will not independently develop similar products, duplicate any of our products, or design around our patents.

Litigation involving patents, patent applications and other proprietary rights is expensive and time consuming. If we are involved in such litigation, it could cause delays in bringing our product candidates to market and interfere with our business.

Our commercial success depends in part on not infringing patents and proprietary rights of third parties. Although we are not currently aware of litigation or other proceedings or third party claims of intellectual property infringement related to our product candidates, the pharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights.

As we enter our target markets, it is possible that competitors or other third parties will claim that our products and/or processes infringe their intellectual property rights. These third parties may have obtained and may in the future obtain patents covering products or processes that are similar to, or may include compositions or methods that encompass our technology, allowing them to claim that the use of our technologies infringes these patents.

In a patent infringement claim against us, we may assert, as a defense, that we do not infringe the relevant patent claims, that the patent is invalid or both. The strength of our defenses will depend on the patents asserted, the

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interpretation of these patents, and our ability to invalidate the asserted patents. However, we could be unsuccessful in advancing non-infringement and/or invalidity arguments in our defense. In the United States, issued patents enjoy a presumption of validity, and the party challenging the validity of a patent claim must present clear and convincing evidence of invalidity, which is a high burden of proof. Conversely, the patent owner need only prove infringement by a preponderance of the evidence, which is a lower burden of proof.

If we were found by a court to have infringed a valid patent claim, we could be prevented from using the patented technology or be required to pay the owner of the patent for the right to license the patented technology. If we decide to pursue a license to one or more of these patents, we may not be able to obtain a license on commercially reasonable terms, if at all, or the license we obtain may require us to pay substantial royalties or grant cross licenses to our patent rights. For example, if the relevant patent is owned by a competitor, that competitor may choose not to license patent rights to us. If we decide to develop alternative technology, we may not be able to do so in a timely or cost-effective manner, if at all.

In addition, because patent applications can take years to issue and are often afforded confidentiality for some period of time there may currently be pending applications, unknown to us, that later result in issued patents that could cover one or more of our products.

It is possible that we may in the future receive, particularly as a public company, communications from competitors and other companies alleging that we may be infringing their patents, trade secrets or other intellectual property rights, offering licenses to such intellectual property or threatening litigation. In addition to patent infringement claims, third parties may assert copyright, trademark or other proprietary rights against us. We may need to expend considerable resources to counter such claims and may not be able to successful in our defense. Our business may suffer if a finding of infringement is established.

It is difficult and costly to protect our proprietary rights, and we may not be able to ensure their protection.

The patent positions of pharmaceutical companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in pharmaceutical patents has emerged to date in the United States. The pharmaceutical patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. Many of the substantive changes to patent law associated with the Leahy-Smith Act will not become effective until March 16, 2013. Accordingly, it is not yet clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in the patents that may be issued from the applications we currently or may in the future own or license from third parties. Further, if any patents license we obtain is deemed invalid and/or unenforceable, it could impact our ability to commercialize or partner our technology.

Competitors or third parties may infringe our patents. We may be required to file patent infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is not valid or is unenforceable, or that the third party s technology does not in fact infringe upon our patents. An adverse determination of any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our related pending patent applications at risk of not issuing. Litigation may fail and, even if successful, may result in substantial costs and be a distraction to our management. We may not be able to prevent misappropriation of our proprietary rights, particularly in countries outside the United States where patent rights may be more difficult to enforce. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential or sensitive information could be compromised by disclosure in the event of litigation. In addition, during the course of

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litigation there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

The degree of future protection for our proprietary rights is uncertain, and we cannot ensure that:

- we were the first to make the inventions covered by each of our pending patent applications;
- we were the first to file patent applications for these inventions;
- others will not independently develop similar or alternative technologies or duplicate any of our technologies;
- any patents issued to us or our collaborators will provide a basis for commercially viable products, will provide us with any competitive advantages or will not be challenged by third parties; or
- the patents of others will not have an adverse effect on our business.

If we do not adequately protect our proprietary rights, competitors may be able to use our technologies and erode or negate any competitive advantage we may have, which could materially harm our business, negatively affect our position in the marketplace, limit our ability to commercialize our product candidates and delay or render impossible our achievement of profitability.

We may be unable to adequately prevent disclosure of trade secrets and other proprietary information.

We rely on trade secrets to protect our proprietary know-how and technological advances, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. We rely in part on confidentiality agreements with our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to protect our trade secrets and other proprietary information. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, others may independently discover our trade secrets and proprietary information. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights. Failure to obtain or maintain trade secret protection could enable competitors to use our proprietary information to develop products that compete with our products or cause additional, material adverse effects upon our competitive business position.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to be paid to the United States Patent and Trademark Office and various foreign governmental patent agencies in several stages over the lifetime of the patents and/or applications.

We have systems in place, including use of third party vendors, to manage payment of periodic maintenance fees, renewal fees, annuity fees and various other patent and application fees. The United States Patent and Trademark Office, or the USPTO, and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. There are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. If this occurs, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may not be able to enforce our intellectual property rights throughout the world.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to life sciences. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a

patent owner must grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit.

Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate. In addition, changes in the law and legal decisions by courts in the United States and foreign countries may affect our ability to obtain adequate protection for our technology and the enforcement of intellectual property.

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We have not yet registered our trademarks in all of our potential markets, and failure to secure those registrations could adversely affect our business.

We have registered our ACELRX mark in the United States, Canada, the European Union and India. We have also registered our NANOTAB mark in the United States, Hong Kong and Singapore, and our ACCELERATE. INNOVATE. ALLEVIATE. tagline in the United States. Although we are not currently aware of any oppositions to or cancellations of our registered trademarks or pending applications, it is possible that one or more of the applications could be subject to opposition or cancellation after the marks are registered. The registrations will be subject to use and maintenance requirements. It is also possible that we have not yet registered all of our trademarks in all of our potential markets, and that there are names or symbols other than ACELRX that may be protectable marks for which we have not sought registration, and failure to secure those registrations could adversely affect our business. Opposition or cancellation proceedings may be filed against our trademarks and our trademarks may not survive such proceedings.

Risks Related to this Offering and Ownership of Our Common Stock

The market price of our common stock may be highly volatile and you may not be able to resell your shares at or above the public offering price.

Prior to our initial public offering, or IPO, in February 2011, there was no public market for our common stock. An active public trading market for our common stock has not developed and may never develop or, if developed, may not be sustained. Moreover, the trading price of our common stock is likely to be volatile. As a result of this volatility, investors may not be able to sell their common stock at or above the public offering price. Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following:

- adverse results or delays in clinical trials;
- inability to obtain additional funding, 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;
- any delay in submitting an NDA for any of our product candidates and any adverse development or perceived adverse development with respect to the FDA s filing or review of that NDA;
- failure to successfully develop and commercialize our product candidates;
- changes in laws or regulations applicable to our products;
- inability to obtain adequate product supply for our product candidates, or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services or technologies by our competitors;
- failure to meet or exceed financial projections we provide to the public;

failure to meet or exceed the estimates and projections of the investment community;

the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;

announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;

disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;

additions or departures of key scientific or management personnel;

significant lawsuits, including patent or stockholder litigation;

changes in the market valuations of similar companies;

sales of our common stock by us or our stockholders in the future; and

trading volume of our common stock.

In addition, the stock market in general, and The NASDAQ Global Market in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of

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these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

Our common stock is thinly traded and in the future, may continue to be thinly traded, and investors may be unable to sell at or near asking prices, the public offering price or at all if they need to sell their shares to raise money or otherwise desire to liquidate such shares.

To date, we have a low volume of daily trades in our common stock on The NASDAQ Global Market. For example, the average daily trading volume in our common stock on The NASDAQ Global Market during the third quarter of 2012 was approximately 37,000 shares per day. Investors purchasing our common stock in this offering may be unable to sell their common stock at or near their asking prices, the public offering price or at all, which may result in substantial losses to our investors.

The market for our common stock may be characterized by significant price volatility when compared to seasoned issuers, and we expect that our share price will be more volatile than a seasoned issuer for the indefinite future. As noted above, our common stock may be sporadically and/or thinly traded. As a consequence of this lack of liquidity, the trading of relatively small quantities of shares by our stockholders may disproportionately influence the price of those shares in either direction. The price for our shares could, for example, decline significantly in the event that a large number of our common stock are sold on the market without commensurate demand, as compared to a seasoned issuer that could better absorb those sales without adverse impact on its share price.

Our principal stockholders and management own a significant percentage of our stock and are able to exert significant control over matters subject to stockholder approval.

Our executive officers and directors, together with the stockholders with whom our executive officers and directors are affiliated or associated, beneficially owned approximately 72% of our outstanding voting stock as of November 1, 2012. Upon completion of this offering, our executive officers, directors and their affiliates will continue to beneficially own in excess of a majority of our voting stock. Therefore, these stockholders have the ability to influence us through this ownership position. These stockholders are able to determine all matters requiring stockholder approval. For example, these stockholders, acting together, are able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

We incur significant increased costs as a result of operating as a public company, and our management is required to devote substantial time to new compliance initiatives.

As a public company, we incur significant legal, accounting and other expenses. In addition, the Sarbanes-Oxley Act of 2002, as amended, or the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC and The NASDAQ Stock Market have imposed various requirements on public companies. Our management and other personnel need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly. For example, these rules and regulations make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain our current levels of such coverage.

As a public company, we are subject to the requirements of Section 404 of the Sarbanes-Oxley Act. If we are unable to comply with Section 404 in a timely manner, it may affect the reliability of our internal control over financial reporting. Assessing our staffing and training procedures to improve our internal control over financial reporting is an ongoing process.

We plan to continue to assess our internal controls and procedures and intend to take further action as necessary or appropriate to address any other matters we identify. However, our independent registered public accounting firm is not currently required to deliver an attestation report on the effectiveness of our internal control over financial reporting as we qualify for an exemption as a non-accelerated filer under the applicable SEC rules and regulations.

We have been and will continue to be involved in a substantial effort to implement appropriate processes, document the system of internal control over key processes, assess their design, remediate any deficiencies identified and test their operation. We cannot be certain at this time whether our measures to improve internal controls will be

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successful, that we will be able to successfully complete the procedures, certification and attestation requirements of Section 404 or that we or our independent registered public accounting firm will not identify material weaknesses in our internal control over financial reporting. If we fail to comply with the requirements of Section 404, it may affect the reliability of our internal control over financial reporting and negatively impact the quality of disclosure to our stockholders. If we or our independent registered public accounting firm identify and report a material weakness, it could adversely affect our stock price.

Sales of a substantial number of shares of our common stock in the public market by our existing stockholders could cause our stock price to fall.

Sales of a substantial number of shares of our common stock in the public market or the perception that these sales might occur, could depress the market price of our common stock and could impair our ability to raise capital through the sale of additional equity securities. We are unable to predict the effect that sales may have on the prevailing market price of our common stock. As of September 30, 2012, we had 22,646,773 shares of common stock outstanding, all of which is eligible for sale in the public market, subject in some cases to the volume limitations and manner of sale requirements of Rule 144 under the Securities Act. Sales of stock by our stockholders could have a material adverse effect on the trading price of our common stock.

Our executive officers and directors and their affiliated funds have agreed that, subject to certain exceptions, during the period ending 90 days after the date of this prospectus, they will not offer, pledge, sell or otherwise transfer or dispose of shares of our common stock or any securities convertible into or exchangeable for our common stock, without the prior written consent of Jefferies & Company, Inc., who may release any of the securities subject to these lock-up agreements at any time without notice. Exceptions to the lock-up restrictions are described in more detail in this prospectus under the caption Underwriting.

In June 2012, we filed a shelf registration statement pursuant to which certain of our stockholders may freely resell up to 5,552,440 shares of our common stock, including 2,630,103 shares issuable upon the exercise of outstanding warrants, subject to the 90-day lock-up arrangement described above with respect to our executive officers and directors and their affiliated funds. In addition, certain holders of our securities are entitled to additional rights with respect to the registration of their shares of common stock under the Securities Act, subject to the 90-day lock-up arrangement described above with respect to executive officers and directors and their affiliated funds. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

If you purchase our common stock in this offering, you will incur immediate and substantial dilution in your investment.

Since the price per share of our common stock being offered is substantially higher than the net tangible book value (deficit) per share of our common stock, you will suffer substantial dilution with respect to the net tangible book value of the common stock you purchase in this offering. Assuming that we sell 10,000,000 shares of our common stock in this offering at an assumed public offering price of $4.16 per share (which was the last reported sale price of our common stock as reported on The NASDAQ Global Market on December 3, 2012), and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us, you will experience immediate dilution of $2.99 per share, representing the difference between our as adjusted net tangible book value per share as of September 30, 2012 after giving effect to this offering and the assumed public offering price. See the section entitled Dilution below for a more detailed illustration of the dilution you would incur if you purchase common stock in this offering.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We expect that in addition to this offering significant additional capital will be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, including pursuant to our Sales Agreement with MLV, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one

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transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

Pursuant to our 2011 Equity Incentive Plan, or the 2011 Incentive Plan, our management is authorized to grant stock options and other equity-based awards to our employees, directors and consultants. The number of shares available for future grant under our 2011 Incentive Plan will automatically increase each year by 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our board of directors to take action to reduce the size of the increase in any given year. Currently, we plan to register the increased number of shares available for issuance under our 2011 Incentive Plan each year. If our board of directors elects to increase the number of shares available for future grant by the maximum amount each year, our stockholders may experience additional dilution, which could cause our stock price to fall.

Our management will have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering and our stockholders will not have the opportunity as part of their investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. The failure by our management to apply these funds effectively could harm our business. Pending their use, we may invest the net proceeds from this offering in high quality, short-term, interest-bearing securities. These investments may not yield a favorable return to our stockholders.

We are at risk of securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management s attention and resources, which could harm our business.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an ownership change, generally defined as a greater than 50% change (by value) in its equity ownership over a three year period, the corporation s ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes (such as research tax credits) to offset its post-change income may be limited. The completion of this offering, together with our initial public offering, private placements and other transactions that have occurred, may trigger such an ownership change. In addition, since we will need to raise substantial additional funding to finance our operations, we may undergo further ownership changes in the future. As a result, if we earn net taxable income, our ability to use our pre-change net operating loss carryforwards to offset United States federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividends on our capital stock, and we are prohibited from doing so under the terms of our loan and security agreement with Hercules. Regardless of the restrictions in our loan and security agreement with Hercules or the terms of any potential future indebtedness, we anticipate that we will retain all available funds and any future earnings to support our operations and finance the growth and development of our business and, therefore, we do not expect to pay cash dividends in the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors and will depend on then-existing conditions, including our financial condition, operating results, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

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Provisions in our amended and restated certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.

Some provisions of our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders and may prevent attempts by our stockholders to replace or remove our current management. These provisions include:

- authorizing the issuance of blank check preferred stock, the terms of which may be established and shares of which may be issued without stockholder approval;
- limiting the removal of directors by the stockholders;
- creating a staggered board of directors;
- prohibiting stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders;
- eliminating the ability of stockholders to call a special meeting of stockholders; and
- establishing advance notice requirements for nominations for election to our board of directors or for proposing matters that can be acted upon at stockholder meetings.

These provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management. In addition, we are subject to Section 203 of the Delaware General Corporation Law, which generally prohibits a Delaware corporation from engaging in any of a broad range of business combinations with an interested stockholder for a period of three years following the date on which the stockholder became an interested stockholder, unless such transactions are approved by our board of directors. This provision could have the effect of delaying or preventing a change of control, whether or not it is desired by or beneficial to our stockholders. Further, other provisions of Delaware law may also discourage, delay or prevent someone from acquiring us or merging with us.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, including the information that we incorporate by reference, contains various forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These statements relate to future events or our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to differ materially from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as anticipates, believes, continue estimates, expects, intends, may, plan predicts, should, will, or the negative of these terms or other comparable terminology. These forward-looking statements may also use different phrases. 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 prospectus, including the information that we incorporate by reference, 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;

our use of the proceeds from this offering;

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 the Risk Factors section of this prospectus for a discussion of other important factors, risks and uncertainties that may cause our actual results to differ materially from those expressed or implied by these forward-looking statements. Given these other important factors, risks and uncertainties, you should not place undue reliance on these forward-looking statements. Also, these forward-looking statements represent our estimates and assumptions only as of the date such forward-looking statements are made. You should carefully read this prospectus, together with the information incorporated herein by reference as described under the section entitled Incorporation of Certain Information by Reference, completely and with the understanding that our actual future results may be materially different from what we expect. We can give no assurances that any of the events anticipated by the forward-looking statements will occur or, if any of them do, what impact they will have on our business, results of operations and financial condition. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements.

Except as required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. You should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements.

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USE OF PROCEEDS

We estimate that the net proceeds from the sale of the 10,000,000 shares of common stock that we are offering will be approximately $38.6 million, or approximately $44.4 million if the underwriters exercise in full their option to purchase up to 1,500,000 additional shares of common stock, based on the assumed public offering price of $4.16 per share (which was the last reported sale price of our common stock as reported on The NASDAQ Global Market on December 3, 2012) and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. Each $0.50 increase (decrease) in the assumed public offering price of $4.16 per share would increase (decrease) the net proceeds to us from this offering by approximately $4.7 million, assuming the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same. We may also increase or decrease the number of shares we are offering. Each increase (decrease) of 1,500,000 shares in the number of shares offered by us would increase (decrease) the net proceeds to us from this offering by approximately $5.9 million, assuming that the assumed public offering price remains the same, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The principal purpose of this offering is to obtain additional capital to support our operations, including the costs of preparing and submitting a planned NDA to the FDA for our lead product candidate, the NanoTab System, and preparation for the planned commercialization and manufacturing of the NanoTab System in the United States. Proceeds will also be used for working capital and other general corporate purposes, including general and administrative costs and our research and development activities for our other current product candidates and any future product candidates that we may develop or acquire. The costs and timing of drug development and marketing approval, particularly conducting clinical trials, are highly uncertain, are subject to substantial risks and can often change. We therefore cannot estimate the amount of net proceeds to be used for all of the purposes described above. Accordingly, we may change the allocation of use of these proceeds as a result of contingencies such as the progress and results of our clinical trials and other development activities, the establishment of collaborations, our manufacturing requirements and regulatory or competitive developments. We may find it necessary or advisable to use the net proceeds for other purposes, and we will have broad discretion in the application of net proceeds.

Pending their use as described above, we intend to invest the net proceeds in high quality, short-term, interest-bearing securities.

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PRICE RANGE OF COMMON STOCK

Our common stock has been trading on The NASDAQ Global Market under the symbol ACRX since our IPO on February 11, 2011. Prior to this date, there was no public market for our common stock. The following table sets forth the high and low intraday sales prices of our common stock for the periods indicated as reported by The NASDAQ Global Market:

	Price	
	High	**Low**
Year ended 2012		
First Quarter	$ 3.76	$ 1.89
Second Quarter	$ 4.00	$ 2.77
Third Quarter	$ 3.88	$ 2.54
Fourth Quarter (through December 4, 2012)	$ 5.25	$ 2.27
Year ended 2011		
First Quarter (beginning February 11, 2011)	$ 5.09	$ 2.97
Second Quarter	$ 5.00	$ 2.90
Third Quarter	$ 4.70	$ 2.90
Fourth Quarter	$ 3.32	$ 1.76

The reported last sale price of our common stock on The NASDAQ Global Market on December 3, 2012 was $4.16 per share. As of November 1, 2012, there were 36 holders of record of our common stock.

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DIVIDEND POLICY

We have never declared or paid any cash dividends on our capital stock, and we are prohibited from doing so under the terms of our loan and security agreement with Hercules. Regardless of the restrictions in our loan and security agreement with Hercules or the terms of any potential future indebtedness, we anticipate that we will retain all available funds and any future earnings to support our operations and finance the growth and development of our business and, therefore, we do not expect to pay cash dividends in the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors and will depend on then-existing conditions, including our financial condition, operating results, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

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CAPITALIZATION

The following table sets forth our cash, cash equivalents and short-term investments and our capitalization as of September 30, 2012:

- on an actual basis;
- on an as adjusted basis to give effect to the sale of the 10,000,000 shares of our common stock that we are offering at an assumed public offering price of $4.16 per share (the last reported sale price of our common stock as reported on The NASDAQ Global Market on December 3, 2012), after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this table with our financial statements and related notes and Management s Discussion and Analysis of Financial Condition and Results of Operations incorporated by reference in this prospectus.

	As of September 30, 2012	
	Actual	As Adjusted [1]
	(in thousands, except share and per share data) (Unaudited)	
Cash, cash equivalents and short-term investments	$ 23,375	$ 61,929
Long-term debt, including current portion	17,682	17,682
Stockholders equity (deficit):		
Common stock, $0.001 par value: 100,000,000 shares authorized; 22,646,773 shares issued and outstanding, actual; 32,646,773 shares issued and outstanding, as adjusted	23	33
Additional paid-in capital	111,154	149,698
Deficit accumulated during the development stage	(111,505)	(111,505)
Accumulated other comprehensive income	1	1
Total stockholders equity (deficit)	(327)	38,227
Total capitalization	$ 17,355	$ 55,909

[1] Each $0.50 increase (decrease) in the assumed public offering price of $4.16 per share would increase (decrease) each of cash, cash equivalents and short-term investments, additional paid-in capital, total stockholders equity (deficit) and total capitalization by approximately $4.7 million, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. We may also increase or decrease the number of shares we are offering. Each increase (decrease) of 1,500,000 shares in the number of shares offered by us would increase (decrease) each of cash, cash equivalents and short-term investments, additional paid-in capital, total stockholders equity (deficit) and total capitalization by approximately $5.9 million, assuming that the assumed public offering price remains the same, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. The as adjusted information discussed above is illustrative only and will be adjusted based on the actual public offering price and other terms of this offering determined at pricing.

The number of shares of common stock shown above is based on 22,646,773 shares of common stock outstanding as of September 30, 2012. This number excludes:

3,136,300 shares of common stock issuable upon the exercise of warrants outstanding as of September 30, 2012, at a weighted average exercise price of $3.42 per share;

3,321,038 shares of common stock issuable upon the exercise of options outstanding as of September 30, 2012, at a weighted average exercise price of $3.18 per share;

161,096 shares of common stock issuable upon the vesting of restricted stock units outstanding as of September 30, 2012;

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up to 539,267 shares of common stock that we may, subject to certain conditions and limitations, issue upon our election to convert up to $3.0 million of principal amount into shares of our common stock under outstanding promissory notes that we issued to Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc.; and

1,392,284 additional shares of common stock reserved for future issuance under our 2011 Equity Incentive Plan, or 2011 Plan, and our 2011 Employee Stock Purchase Plan, or Purchase Plan, as of September 30, 2012, plus any annual increases in the number of shares of common stock reserved for future issuance under the 2011 Plan and the Purchase Plan pursuant to evergreen provisions and any other shares that may become issuable under the 2011 Plan or the Purchase Plan pursuant to their terms.

In addition, the number of shares outstanding immediately after this offering does not include the shares of common stock that we may sell pursuant to the Sales Agreement with MLV.

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DILUTION

If you invest in our common stock, you will experience immediate and substantial dilution to the extent of the difference between the public offering price of our common stock in this offering and the as adjusted net tangible book value per share of our common stock immediately after the offering.

Our historical net tangible book value (deficit) per share is determined by dividing our total tangible assets, less total liabilities, by the actual number of outstanding shares of our common stock. The historical net tangible book value (deficit) of our common stock as of September 30, 2012 was $(0.3) million, or $(0.01) per share.

Assuming that we sell 10,000,000 shares of our common stock in this offering at an assumed public offering price of $4.16 per share (the last reported sale price of our common stock on The NASDAQ Global Market on December 3, 2012), after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us, our net tangible book value as of September 30, 2012 would have been approximately $38.2 million, or $1.17 per share of common stock. This represents an immediate increase in net tangible book value of $1.18 per share to existing stockholders and an immediate dilution of $2.99 per share to new investors purchasing shares of common stock in this offering at the assumed public offering price. The following table illustrates this dilution on a per share basis:

Assumed public offering price per share		$ 4.16
Net tangible book value (deficit) per share as of September 30, 2012	$ (0.01)	
Increase per share attributable to investors purchasing our common stock in this offering	1.18	
As adjusted net tangible book value per share after this offering		1.17
Dilution per share to investors purchasing our common stock in this offering		$ 2.99

Each $0.50 increase (decrease) in the assumed public offering price of $4.16 per share would increase (decrease) our as adjusted net tangible book value after this offering by approximately $4.7 million, or approximately $0.14 per share, and the dilution per share to new investors by approximately $0.36 per share, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. We may also increase or decrease the number of shares we are offering. An increase of 1,500,000 shares in the number of shares offered by us would increase our as adjusted net tangible book value after this offering by approximately $5.9 million, or $0.12 per share, and the dilution per share to new investors would be $2.87 per share, assuming that the assumed public offering price remains the same, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. Similarly, a decrease of 1,500,000 shares in the number of shares offered by us would decrease our as adjusted net tangible book value after this offering by approximately $5.9 million, or $0.13 per share, and the dilution per share to new investors would be $3.12 per share, assuming that the assumed public offering price remains the same, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. The information discussed above is illustrative only and will adjust based on the actual public offering price and other terms of this offering determined at pricing.

If the underwriters exercise in full their option to purchase up to 1,500,000 additional shares of common stock at the assumed public offering price of $4.16 per share and assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same, the as adjusted net tangible book value after this offering would be $1.29 per share, representing an increase in net tangible book value of $1.30 per share to existing stockholders and immediate dilution in net tangible book value of $2.87 per share to investors purchasing our common stock in this offering at the assumed public offering price.

The above discussion and table are based on 22,646,773 shares of common stock outstanding as of September 30, 2012 and exclude:

- 3,136,300 shares of common stock issuable upon the exercise of warrants outstanding as of September 30, 2012, at a weighted average exercise price of $3.42 per share;

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- 3,321,038 shares of common stock issuable upon the exercise of options outstanding as of September 30, 2012, at a weighted average exercise price of $3.18 per share;

- 161,096 shares of common stock issuable upon the vesting of restricted stock units outstanding as of September 30, 2012;

- up to 539,267 shares of common stock that we may, subject to certain conditions and limitations, issue upon our election to convert up to $3.0 million of principal amount into shares of our common stock under outstanding promissory notes that we issued to Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc.; and

- 1,392,284 additional shares of common stock reserved for future issuance under our 2011 Equity Incentive Plan, or 2011 Plan, and our 2011 Employee Stock Purchase Plan, or Purchase Plan, as of September 30, 2012, plus any annual increases in the number of shares of common stock reserved for future issuance under the 2011 Plan and the Purchase Plan pursuant to evergreen provisions and any other shares that may become issuable under the 2011 Plan or the Purchase Plan pursuant to their terms.

In addition, the number of shares outstanding immediately after this offering does not include the shares of common stock that we may sell pursuant to the Sales Agreement with MLV.

To the extent that options or warrants outstanding as of September 30, 2012 have been or are exercised, or other shares are issued, including pursuant to the Sales Agreement with MLV or upon conversion of the promissory notes we issued to Hercules, investors purchasing shares in this offering could experience further dilution. In addition, we may choose to raise capital in addition to the amounts remaining available to be sold under our Sales Agreement with MLV due to market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

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PRESENTATION OF COMPREHENSIVE LOSS

The following table presents the retrospective application of the Financial Accounting Standards Board s Accounting Standards Update (ASU) No. 2011-05, Comprehensive Income (Topic 220): Presentation of Comprehensive Income, as amended by ASU 2011-12, Comprehensive Income (Topic 220): Deferral of the Effective Date for Amendments to the Presentation of Reclassifications of Items Out of Accumulated Other Comprehensive Income in Accounting Standards Update No. 2011-05. These updates, which were adopted by us effective January 1, 2012, revise the manner in which entities present comprehensive income (loss) in their financial statements. The following financial information revises historical information to illustrate the new presentation required by this pronouncement.

STATEMENTS OF COMPREHENSIVE LOSS

(Unaudited, in thousands)

	December 31, 2009	December 31, 2010	December 31, 2011	Period from July 13, 2005 (Inception) Through December 31, 2011
Net (loss)	$ (20,119)	$ (14,344)	$ (20,101)	$ (88,664)
Unrealized gain (loss) on available-for-sale securities	(41)	2		
Comprehensive (loss)	$ (20,160)	$ (14,342)	$ (20,101)	$ (88,664)

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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 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 morphine, 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 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 moderate-to-severe 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.

In November 2012, we reported top-line data showing that the primary end point of non-inferiority was met in an open-label active-comparator Phase 3 clinical trial for our lead product candidate, the NanoTab System. We are also conducting two placebo-controlled efficacy and safety Phase 3 clinical trials for the NanoTab System, the first trial in patients with post-operative pain following open-abdominal surgery and the second trial in patients with post-operative pain following hip and knee replacement surgeries. We expect top-line data from both placebo-controlled efficacy and safety Phase 3 clinical trials in the first quarter of 2013.

In addition to our NanoTab System, our product pipeline consists of three 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 upon additional funding or corporate partnership resources. 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 (Sufentanil NanoTab) for the treatment of moderate-to-severe acute pain. In November 2012, we initiated the Phase 2 clinical trial for ARX-04 pursuant to the USAMRMC grant.

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 relatively safe solution for the treatment of acute and breakthrough pain. The following table illustrates the difference between the therapeutic index of different opioids.

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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.

Sublingual Delivery of Sufentanil: Summary of Phase 1 Clinical Trials Results

We have completed four Phase 1 pharmacokinetic, or PK, trials with our proprietary sublingual sufentanil NanoTabs to support our four product candidates under development. These trials 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.

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 trials.

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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 below, 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.

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.

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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 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 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 post-operative pain following open-abdominal surgery. We expect top-line data for this trial in the first quarter of 2013.
			In August 2012, we initiated a double-blind placebo-controlled efficacy and safety Phase 3 clinical trial in patients with post-operative pain following major orthopedic surgeries. We expect top-line data for this trial in the first 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 additional funding or 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.

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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 Decision 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 Decision Resources Report projects that in 2013, 20.7 million in-patient procedures performed in the United States and Europe 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 in which patients experience moderate-to-severe pain in other moderate-to-high per capita healthcare expenditure nations on an annual basis.

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

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

Our novel handheld PCA device has the following safety features:

- a wireless system access key for the healthcare professional;

a wireless, electronic, adhesive thumb tag that acts as a single-patient identification key;

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pre-programmed 20-minute lock-out to avoid overdosing;

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 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.

The NanoTab System Phase 3 device is an upgraded version of the Phase 2 device, with enhanced features, including a color graphical user interface screen, security features to allow only the patient to use the device and prevent unauthorized access to the drug, and improved industrial design for hospital use.

In the active comparator Phase 3 clinical trial comparing the NanoTab System to the standard of care, IV PCA with morphine, both nurses and patients reported a significantly greater level of Overall Satisfaction with the NanoTab System as compared to IV PCA with morphine. Additionally, during our Phase 2 clinical trial evaluating device functionality, 100% of patients reported that they could handle the NanoTab System easily and that user instructions were clear.

NanoTab System Clinical Program

Summary

Our Phase 3 program for the NanoTab System consists of three Phase 3 clinical trials. Two of these Phase 3 clinical trials are ongoing, and are expected to report top-line data in the first quarter of 2013. The third Phase 3 clinical trial, an open-label active comparator trial designed to compare the efficacy and safety of the NanoTab System to IV PCA with morphine for the treatment of post-operative pain was recently completed and we reported that the primary endpoint for the trial was met. 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

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 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.

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 their method of

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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. 66.1%, 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 +3.2% to +21.6% 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 ($p=0.009$). 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 70.6% 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 +2.0% to +19.6% 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 ($p=0.017$). 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 8.3% of patients treated with IV PCA morphine. Additionally, 7.9% of the patients treated with the NanoTab System dropped out of the trial due to an adverse event compared to 11.1% of the IV PCA morphine patients. We observed eleven serious adverse events, or SAEs, in the trial, of which two were assessed as possibly or probably related to the trial drug, one of which was related to the NanoTab System and one of which was 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.

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.

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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. 3.83, respectively, out of a 0 to 5 scale, with a p-value equal to 0.003).

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 (3.93 vs. 3.32, 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 (4.26 vs. 3.82, respectively, out of a 0 to 5 scale, with a p-value equal to 0.018).

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	0.93	1.27	0.066

Bothersome	0.54	1.09	0.006

Double-blind, placebo-controlled trials

In March 2012, we initiated a Phase 3 clinical trial with the NanoTab System in a double-blind, placebo-controlled trial for a minimum of 48 hours and up to 72 hours in adult patients undergoing open abdominal surgery. The objective is to compare the efficacy and safety of the NanoTab System to placebo in the management of acute post-operative pain after open abdominal surgery. Up to 180 patients will be randomly assigned to treatment with sufentanil or placebo. The primary endpoint will be the summed pain intensity difference over the first 48 hours of the trial period, or SPID-48. We expect to receive top-line data from this trial in the first quarter of 2013. Key secondary endpoints include an assessment of different imputation strategies for the use of rescue opioids, pain intensity and relief scores and patient and healthcare professional Global Assessments and Ease of Care questionnaires.

In August 2012, we initiated a Phase 3 clinical trial with the NanoTab System in a double-blind, placebo-controlled trial for a minimum of 48 hours and up to 72 hours in patients who are undergoing a total hip or knee replacement. The objective is to compare the efficacy and safety of the Sufentanil NanoTab PCA System to placebo in the management of acute post-operative pain after major orthopedic surgery. Up to 440 patients will be randomly assigned to treatment with sufentanil or placebo. The primary endpoint will be SPID-48. We expect to receive top-line data from this trial in the first quarter of 2013. Key secondary endpoints include an assessment of different imputation strategies for the use of rescue opioids, pain intensity and relief scores and patient and healthcare professional Global Assessments and Ease of Care questionnaires.

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Phase 2 Clinical Results for ARX-01

We completed three Phase 2 clinical trials in support of sufentanil NanoTabs. Across all trials, the average time interval between doses was approximately 80 minutes. This compares favorably to typical redosing intervals for IV PCA with average period between dosing of 20 to 40 minutes. No SAEs were reported that were considered to be related to the trial drug. Adverse events, or AEs, that were reported were similar to those reported for placebo-treated patients. These results demonstrate that sufentanil NanoTabs are effective and well tolerated by patients undergoing both major orthopedic and abdominal surgical procedures.

Phase 2 Clinical Results in Unilateral Knee Replacement (ARX-C-001)

In the first Phase 2 clinical trial, we conducted a randomized, double-blind, placebo-controlled, multicenter Phase 2 clinical trial to evaluate the efficacy, safety and tolerability of sublingual sufentanil NanoTabs in patients undergoing elective unilateral knee replacement. The trial enrolled 101 male and female patients 45 to 80 years of age who were undergoing elective knee replacement surgery. This procedure was chosen as it represents one of the most painful procedures patients undergo in the hospital setting. Patients were randomly assigned to treatment with sufentanil NanoTab 5 mcg, 10 mcg, 15 mcg, or placebo. Sufentanil NanoTabs were administered by trial staff at the request of the patient with at least 20 minutes between doses. The primary endpoint was the sum of the pain intensity difference at each evaluation time point compared to baseline over the 12-hour trial duration, or SPID-12.

The trial results demonstrated that sufentanil NanoTab 15 mcg was effective, safe and well-tolerated for the treatment of acute post-operative pain in patients who had undergone unilateral knee replacement. The sufentanil NanoTab 15 mcg SPID-12 was higher than placebo ($p=0.018$) using the last observation carried forward, or LOCF, imputation method. The sufentanil NanoTab 5 mcg or 10 mcg dosage strengths did not achieve a statistically significant separation from placebo overall. However, the 10 mcg dose was statistically significant as compared with placebo for women ($p<0.05$). Throughout the trial there were statistically significant differences in SPID-12 scores between the sufentanil NanoTab 15 mcg dose group and the placebo group, even at the earliest time point of 15 minutes ($p=0.038$). There were no clinically significant changes in laboratory variables, vital signs or oxygen saturation during the trial. The five SAEs reported were all considered unrelated to trial drug and occurred after the end of trial drug dosing.

The following figure shows the Summed Pain Intensity Difference over the 12-Hour Trial Period for the placebo, 5 mcg, 10 mcg and 15 mcg groups.

* Intent-to-Treat Population: The intent-to-treat, or ITT, population includes all randomized patients regardless of whether they received or adhered to the allocated treatment group. ITT analysis provides unbiased comparisons among the treatment groups and is the primary statistical analysis used by the FDA.

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Phase 2 Clinical Results in Open-Abdominal Surgery (ARX-C-005)

Our second Phase 2 clinical trial tested sufentanil NanoTabs 10 mcg, 15 mcg or placebo in patients undergoing open- abdominal surgery. In all other respects this trial was similar in design to our first trial. Both dosage strengths were significantly more effective than placebo for SPID-12 ($p<0.001$) as well as for all measures of pain intensity and pain relief. Significant differences between the sufentanil NanoTab treatment groups and the placebo group were observed within 2 hours after the first dose of trial drug and continued until the end of the 12-hour treatment period. There were no clinically significant changes in laboratory variables, vital signs or oxygen saturation during the trial. There were no SAEs reported during the trial drug treatment period. The following figure shows the SPID-12 for the placebo, 10 mcg and 15 mcg groups.

Phase 2 Clinical Results in Open-Label Device Functionality Trial in Unilateral Knee Replacement (ARX-C-004)

We conducted an open-label functionality, safety and efficacy trial of the ARX-01 NanoTab delivery System in patients undergoing elective unilateral knee replacement surgery. The trial was a prospective, open-label, multicenter trial in 30 male and female patients 45 to 80 years of age with an average age of 66. All patients were treated with sufentanil NanoTab 15 mcg dosage strength. The primary endpoint was the percent of patients who completed the trial without any Sufentanil NanoTab PCA System failures. The trial also collected patient feedback on the design characteristics of the PCA System.

Patients self-administered sufentanil NanoTabs repeatedly over the 12-hour trial using the NanoTab System without any system failures or dosing errors for all 30 patients. Over 80% of the patients reported the two highest scores on the 5-point Likert scale of overall patient s satisfaction with the Sufentanil NanoTab PCA System 15 mcg. All 30 enrolled patients indicated that they could handle the Sufentanil NanoTab PCA System easily, that the user instructions were clear, that the dosing tone was loud enough and that the time required for dosing was just right. Ninety percent of the patients indicated that the size and the shape of the dosing tip were also just right. The majority of patients indicated that the other system features (weight, size, shape, dose button function) were acceptable.

The mean pain intensity scores decreased from 5.5 at baseline to the lowest score of 3.0 at 2 hours. Dropout due to inadequate analgesia was 6.7%. There were no clinically significant changes in laboratory variables or vital signs and no SAEs reported during the trial drug treatment period.

Summary of Phase 2 Adverse Events

Overall the AE profile for the three Phase 2 clinical trials suggests that ARX-01 is well-tolerated compared to typical AE rates seen with post-operative opioids. Published data indicates a much higher rate of somnolence (approximately 50%) and oxygen desaturation (approximately 10%) during standard IV PCA use compared to results

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obtained in our Phase 2 trials. The high therapeutic index of sufentanil (26,716) in animal trials suggests that opioid-induced sedation and oxygen desaturation does not occur with sufentanil until doses much higher than required for analgesia are administered. We believe our Phase 2 AE data confirm the high safety index of sufentanil in these trials. The table below summarizes the investigator s rating of probably or possibly related AEs based on sufentanil NanoTab dosage strength.

Adverse Events	Placebo N=54	Sufentanil NanoTab (5 mcg) N=24	Sufentanil NanoTab (10 mcg) N=55	Sufentanil NanoTab (15 mcg) N=79
Nausea	17(31%)	7(29%)	22(40%)	23(29%)
Vomiting	3(6%)	2(8%)	6(11%)	9(11%)
Itching	0(0%)	1(4%)	4(8%)	6(8%)
Somnolence	1(2%)	1(4%)	0(0%)	2(3%)
Oxygen desaturation	0(0%)	0(0%)	1(2%)	1(1%)
Respiratory depression	1(2%)	0(0%)	2(4%)	0(0%)

ARX-02 Sufentanil NanoTab BTP Management System

The Market Opportunity for ARX-02

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.

According to the American Cancer Society, there were more than 1.5 million new cancer cases in the United States in 2010. It is estimated that over 625,000 of these cases result in patients who experience breakthrough pain. We estimate the prescription volume for oral transmucosal products for the management of cancer breakthrough pain to be 220,000 prescriptions per year. This suggests that less than 10% of cancer patients with cancer breakthrough pain are treated with approved transmucosal breakthrough pain medications. In addition, many physicians use immediate release oral opioids to treat cancer breakthrough pain. We believe that this market is significantly larger than the transmucosal product market.

Market research among physicians managing cancer patients indicates that ARX-02 could capture approximately a quarter of the cancer breakthrough pain prescriptions. In this research, ARX-02 was predicted to take share equally from both the immediate release oral products and the transmucosal products. Given the positive reaction to the product profile and the potential benefits of ARX-02 compared to currently available products, we believe that ARX-02 represents a significant commercial opportunity.

How ARX-02 Addresses the Unmet Medical Need in Cancer Breakthrough Pain

All products approved for the treatment of cancer breakthrough pain available today are fentanyl-based and have a number of limitations, including:

elimination half-lives of 6 to 14 hours to treat a cancer breakthrough pain event that typically lasts 15 to 60 minutes;

inconsistent T_{max} that ranges from 20 to 240 minutes, and can result in erratic onset of action and the potential for dose-stacking;

local adverse events, such as dental caries and oral mucosal irritation; and

drug packaging that lacks effective deterrence against abuse and misuse.

We designed ARX-02 to address these problems by:

providing sufentanil, a shorter duration of action opioid with an elimination half-life ranging from 2 to 4 hours, which more closely matches the duration of a cancer breakthrough pain event;

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utilizing sufentanil, which provides for a consistent T_{max} with a narrow range of 30 to 90 minutes, thereby reducing the risk of dose-stacking;

avoiding irritation of the oral mucosa, as demonstrated in our clinical trials; and

packaging technology that enhances patient safety by reducing the possibility of misuse or abuse, while providing healthcare professionals with usage data.

In addition, continual use of any given opioid by a patient creates a risk of tolerance specific to that molecule, reducing the effectiveness of the drug. We believe the availability of ARX-02, as a non-fentanyl based product, will allow physicians to rotate opioids prescribed for cancer breakthrough pain, thereby maintaining the effectiveness of treatment.

ARX-02 Description

ARX-02 is a product candidate for the treatment of cancer patients who suffer from breakthrough pain. ARX-02 consists of a magazine containing 30 single dose applicators, or SDAs, loaded into a multiple SDA dispenser, or MSD. Each SDA includes a sufentanil NanoTab that a patient can self-administer to his or her sublingual space for oral transmucosal absorption. The MSD:

protects and dispenses SDAs, one at a time;

displays a recent dose indicator that is designed to mitigate overdosing;

has child-resistant, elderly-friendly features; and

provides electronic date and time stamping of each SDA removal event.

The date and time event log is designed to be retrieved from the MSD by a healthcare professional during an office visit to assist the prescriber in understanding the usage profile of the medication, including diversion or abuse. Overall, our goal is to improve the treatment of cancer breakthrough pain while adding a substantially heightened level of detection and deterrence around prescription opioid use, misuse and abuse. While the initial dispenser for outpatient use is designed for dispensing sufentanil NanoTabs for cancer breakthrough pain events, we believe this concept could be adapted into developing dispensers for other scheduled drugs in the future.

Sufentanil NanoTab BTP Management System ARX-02 Clinical Program

Summary

We held an End of Phase 2 meeting with the FDA in July 2010. The FDA stated that the demonstration of efficacy versus placebo in a single Phase 3 clinical trial with a total safety database of 300 to 500 patients exposed to active drug, with at least 100 patients treated for a minimum of three months, may support an indication for the treatment of cancer breakthrough pain with underlying chronic pain.

Planned Phase 3 Clinical Trials for ARX-02

Future development of ARX-02 is contingent upon additional funding or corporate partnership resources. Should such funds or resources become available, we could proceed with the planned trials and future development described below.

We would plan to conduct one Phase 3 efficacy and safety trial for ARX-02 for the management of cancer breakthrough pain in adult patients who are already taking opioids for their underlying persistent cancer pain. In addition, we would plan to conduct two open-label trials to demonstrate long term safety, which will include the use of the MSD.

The first planned Phase 3 clinical trial for ARX-02 is a multi-center, randomized, double-blind, placebo-controlled crossover trial for the evaluation of the safety and efficacy of the Sufentanil NanoTab BTP Management System in the treatment of cancer breakthrough pain. We plan to screen 170 patients in order to titrate approximately 140 patients, of whom 110 will be randomized, such that at least 100 patients will generate primary efficacy data for analysis. The planned trial consists of a screening visit, an open-label titration phase of up to three weeks to establish a dose of sufentanil (20, 30, 40, 60, 80 or 100 mcg) at home or in a hospice setting that provides adequate relief of cancer breakthrough pain with tolerable side effects. This will be followed by a randomized, double-blind treatment phase of up to three weeks. Patients will be randomized to one of six sequences, each including nine doses of which six are active and three are placebo. Patients will use an electronic diary to record primary and secondary efficacy outcomes

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including pain intensity, pain relief, and global evaluation of treatment. The primary endpoint is the time-weighted summed pain intensity difference over 30 minutes, or SPID-30, following treatment.

Patients who complete our Phase 3 efficacy trial will be allowed to participate in an open-label extension trial to continue evaluating the safety of ARX-02 for up to one year. During each month while participating in the trial, patients will present to the clinical site for visits to assess their medical status and proper use of trial medication. The primary objective is to determine the long-term safety of sufentanil NanoTabs in patients with cancer breakthrough pain.

The dispensing device that was used in the Phase 2 clinical trial for ARX-02 was a simple, mechanical single dose applicator, or SDA, designed for a single use. The design for Phase 3 device contains both mechanical and electronic components and is intended to be a multiple use device with a magazine containing smaller SDAs than those used in Phase 2. The magazine is loaded into a multiple SDA dispenser, or MSD, which will include software to electronically track removal of each SDA from the MSD. Several industrial models have been developed that depict the size and form factor of the smaller SDA and the MSD.

We also plan to conduct an additional open-label trial to ensure there is adequate data for analysis of drug safety and device functionality. We plan to screen approximately 470 patients in order to titrate approximately 370 patients, such that at least 300 patients will enroll in this trial. Patients will use the MSD that will contain a magazine holding 30 SDAs. Each SDA will contain a single sufentanil NanoTab. The MSD will electronically track removal of each SDA from the MSD in order to record dosing history in the outpatient setting. This trial will be up to three months in duration and will utilize the same titration scheme as in the Phase 3 efficacy trial. After patients reach an efficacious and tolerable dose, they will use the MSDs to dispense the SDAs throughout the three-month trial.

Phase 2 Clinical Results for ARX-02

We have completed a Phase 2 clinical trial of the analgesic efficacy of the sufentanil NanoTab in adult cancer patients who are opioid tolerant and suffering from breakthrough pain events. This trial was a prospective, multicenter, randomized, placebo-controlled multicenter, crossover trial for the evaluation of the safety, efficacy and tolerability of the Sufentanil NanoTab BTP Management System in the treatment of cancer breakthrough pain.

Patients were screened and, if qualified for the trial, titrated to an effective dose of sufentanil that provided adequate relief of cancer breakthrough pain without producing intolerable side effects. Patients self-administered a single sufentanil NanoTab using a single-dose applicator, starting with a 20 mcg dose, followed by titration with 30, 40, 60 and 80 mcg sufentanil NanoTabs. The primary objective during the titration phase was to assess the safety and efficacy of ARX-02. The primary endpoint during the randomized, double-blind phase was to assess the efficacy of ARX-02 compared to placebo in the management of cancer breakthrough pain as determined by SPID-30.

Once a dosage strength that alleviated pain without producing intolerable side effects was identified, the patient was randomized to that dosage strength in the double-blind phase of the trial. Patients were randomized to receive 10 doses, of which seven were active and three were placebo. Efficacy was assessed by patient data recorded and scored in an electronic diary, including pain intensity, pain relief and global medication performance assessment just prior to and after taking each of the ten doses of trial drug in the double-blind phase of the trial. Forty-two patients were enrolled and received titration trial medication. Eighty-four percent of patients with a mean age of 53.5 years (range 25 to 73 years) were randomized to the double-blind treatment period. Thirty-three patients completed the trial.

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The primary endpoint of time-weighted SPID-30 for sufentanil NanoTab-treated episodes was greater than placebo-treated episodes (p<0.001) as shown in the figure below.

* Modified Intent-to-Treat Population: The modified intent-to-treat population is a subset of the ITT population and included all randomized patients who took at least one active dose and one placebo dose, and had pre-treatment and at least one post-treatment pain intensity score for each of these episodes.

Pain intensity and pain relief were included as secondary endpoints. Lower scores for pain intensity were reported at each evaluation time point for sufentanil-treated episodes compared to placebo-treated episodes (p=0.027 at 15 minutes and p<0.001 at all other time points). Time reported time-weighted total pain relief, or TOTPAR, was greater at all time points for sufentanil-treated episodes compared to placebo-treated episodes (p=0.049 and p=0.009 for the 10 and 15 minute time points, respectively, and p=<0.001 for the remaining time points).

Patient Global Medication Performance Assessment, or GMPA, at 60 minutes after each dose of trial medication showed 59 (27.4%) and 37 (17.2%) of the sufentanil-treated episodes were rated as very good or excellent on the GMPA, respectively, compared with seven (7.5%) and nine (9.7%), respectively, in the placebo-treated episodes. There was a statistically significant difference for GMPA measurements between the sufentanil-treated episodes and the placebo-treated episodes (p<0.001).

Three patients reported an SAE; however, all SAEs were considered unrelated to trial drug. The most common AEs during the titration period were nervous system disorders, general disorders, and gastrointestinal disorders. The most common nervous system disorder was dysgeusia, or altered sense of taste (four patients, 9.5%). The most common gastrointestinal disorder was dry mouth (three patients, 7.1%). The most common AEs during the double-blind period were nervous system disorders, general disorders, and gastrointestinal disorders. The most common nervous system disorder was headache (two patients, 5.9%). The most common gastrointestinal disorder was nausea (three patients, 8.8%). There was no statistical difference between sufentanil and placebo treatments for any AE.

There were a few statistically significant mean changes and no clinically significant changes from baseline in laboratory hematology and chemistry variables. During the safety monitoring period at the site, there were no statistically significant changes in vital signs from baseline in heart rate or respiratory rate, and no clinically significant changes in oxygen saturation.

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ARX-03 Sufentanil/Triazolam NanoTab

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 ARX-03

Each year in the United States, more than 100 million procedures take place in a physician s office that are known to be anxiety-inducing and painful, according to commissioned market research data that was completed in 2010. These include diagnostic procedures such as breast and prostate biopsies, cosmetic procedures such as liposuction and dermal abrasions, interventional radiology procedures, and therapeutic procedures such as vasectomies and endometrial ablation procedures. IV sedative medications are typically not offered to these patients because of the high cost of the specialized personnel and monitoring equipment. Despite the high potential for pain and anxiety, most patients currently undergo these procedures with only a local anesthetic, resulting in unnecessary procedure discomfort. We believe there is significant opportunity for a fast-acting, effective and safe product that can provide mild levels of sedation, anxiety reduction and analgesia for painful procedures conducted in a physician s office without the need for specialized personnel to monitor the patient.

How ARX-03 Addresses the Unmet Medical Need for Painful Procedures in a Physician s Office

The Joint Commission on the Accreditation of Healthcare Organizations, or JCAHO, mandates that IV sedation requires specialized monitoring, resuscitative equipment and appropriately trained staff. As a result, many practitioners do not provide any IV sedation to their patients prior to or during painful procedures that take place in a physician s office, and instead rely only on the analgesic benefit of local anesthetics.

The anxiety and pain that an individual experiences during painful procedures in a physician s office without sedation has been studied and reported in peer-reviewed journals. Ninety-six percent of men report moderate pain immediately after prostate biopsy, with only 4% of patients reporting no pain during the biopsy. Similarly, women undergoing breast biopsies have pre-procedural scores averaging 60 to 70 out of 100 for visual analog scale measurements of nervousness, tension and fearfulness. This data highlights the need for a mild sedative with analgesic and anxiety-reducing properties in addition to a local anesthetic for painful procedures in a physician s office.

We believe that ARX-03 can provide physicians with a non-invasive, rapid-acting product for mild sedation, anxiety reduction and pain relief during painful diagnostic and therapeutic procedures in a physician s office. We believe the availability of ARX-03 may increase the number of diagnostic and therapeutic procedures performed in a physician s office, resulting in cost savings because specialized personnel and equipment would not be necessary.

ARX-03 Description

ARX-03 Sufentanil/Triazolam NanoTab is a single, fixed-dose sublingual product candidate designed to be administered by a healthcare professional prior to a painful procedure in a physician s office. An important advantage of sufentanil and triazolam over other drugs in their classes is their rapid uptake from the sublingual mucosa. Our Phase 2 clinical data showed that administering ARX-03 via sublingual route prior to a procedure results in a rapid onset of mild sedation and reduction in anxiety in 15 to 30 minutes. Sufentanil and triazolam have short half-lives compared to many other agents in the same class of compounds, enabling patients treated with ARX-03 to be discharged immediately following completion of the procedure. The sublingual route of administration avoids the high plasma concentrations associated with IV delivery, thereby obviating the need for specialized personnel and extensive monitoring.

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Sufentanil/Triazolam NanoTab ARX-03 Clinical Program

Summary

We have completed a successful Phase 2 clinical trial of ARX-03 demonstrating rapid onset of mild sedation and anxiety reduction, with a low adverse event profile during an abdominal liposuction procedure. We participated in an End of Phase 2 meeting with the FDA in May 2010 to discuss the Phase 3 clinical program and requirements for an NDA submission. Based on these discussions, two four-arm factorial Phase 3 clinical trials will be required with a minimum of 700 patients exposed to active drug.

Planned Phase 3 Clinical Trials for ARX-03

Future development of ARX-03 is contingent upon additional funding or corporate partnership resources. Should such funds or resources become available, we could proceed with the planned trials and future development described below.

We would plan to conduct two Phase 3 efficacy and safety trials in a range of painful procedures, such as prostate biopsy, breast biopsy, vasectomy and low-volume abdominal liposuction. In each trial, approximately 720 patients will be randomized to treatment with one of the following: sufentanil/triazolam 15 mcg/200 mcg NanoTab, sufentanil 15 mcg NanoTab, triazolam 200 mcg NanoTab, or placebo NanoTab. We intend to evaluate the time-weighted summed Richmond Agitation-Sedation Scale, or RASS, score over the 4-hour trial period, or SRS-4, compared to placebo as the primary efficacy endpoint. RASS is a ten-point scale to evaluate agitated behavior where unarousable is graded as -5 and combative is graded as a +4 and a score of 0 is alert and calm. Secondary endpoints are intended to include comparisons of SRS-4 among active comparator arms, patient report of procedural anxiety and pain intensity using an 11-point Numerical Rating Scale, or NRS, patient and physician global assessments of satisfaction with trial drug and time to a modified Aldrete score of 8 (readiness for discharge measurement).

The design for a Phase 3 device for ARX-03 consists of a simple mechanical dispenser or SDA. We have produced several working prototypes.

Phase 1 and Phase 2 Clinical Results for ARX-03

We completed an initial dose finding trial for three different strengths of sublingual Sufentanil/Triazolam NanoTabs (10 mcg/100 mcg, 10 mcg/200 mcg and 15 mcg/200 mcg) in 24 subjects. The onset of sedation was approximately 40% faster with the sufentanil 15 mcg/triazolam 200 mcg NanoTab treatment compared to the sufentanil 10 mcg/triazolam 200 mcg NanoTab treatment in younger subjects. There were minimal differences between treatments for time to maximum sedation and for total duration of sedation, leading us to select the sufentanil 15 mcg/triazolam 200 mcg NanoTab dosage strength to trial further in a Phase 2 trial.

We completed a Phase 2 clinical trial of analgesic and anxiety reducing efficacy of the sufentanil/triazolam NanoTab in patients undergoing an elective abdominal liposuction procedure. The trial was a prospective, randomized, double-blind, placebo-controlled single center trial in adult patients. Patients were randomly assigned to treatment with the sufentanil 15 mcg/triazolam 200 mcg NanoTab or placebo. Forty-one patients were randomized and 40 patients received trial drug and underwent the procedure and completed the 4-hour trial period. The mean age for all randomized patients was 36.7 years (range 19 to 55 years). The primary endpoint was the SRS-4 and the sufentanil/triazolam NanoTab demonstrated superiority over placebo ($p<0.001$). The sufentanil/triazolam NanoTab was more effective than placebo in reducing anxiety as measured by the secondary endpoint, the NRS anxiety scale. A significant difference ($p<0.05$) in anxiety score between the sufentanil/triazolam NanoTab and placebo was seen at 15 minutes, the first time point measured after trial drug dosing.

The sufentanil/triazolam NanoTab did not show a statistical difference from placebo in providing analgesia as measured by the NRS pain intensity scale ($p=0.311$). The summed pain intensity score was lower for the sufentanil/triazolam NanoTab compared to placebo for all time points; however, the difference was not significant with the small number of patients.

There was a statistically significant difference between the sufentanil/triazolam NanoTab treatment group and placebo ($p<0.001$) in the proportion of patients for which the physician rated the treatment very good or excellent on the global assessment of effectiveness and tolerability. There was also a statistically significant difference between the sufentanil/triazolam NanoTab treatment group and placebo ($p=0.028$) for the proportion of patients who rated

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the treatment very good or excellent on the global assessment of effectiveness and tolerability. All patients in both the sufentanil/triazolam NanoTab treatment group and the placebo group were ready for discharge immediately following the procedure.

There were no SAEs reported during treatment or 12 hours after dosing. The most frequent AE was nervous system disorders, which were observed in two patients (9.5%) in the sufentanil/triazolam NanoTab treatment group and in two patients (10.5%) in the placebo group. Dizziness was also reported by two patients (9.5%) in the sufentanil/triazolam NanoTab treatment group and one patient (5.3%) in the placebo group. There were no significant differences between the treatment groups for any AEs. All events were mild or moderate in severity. There were no clinically significant changes in vital signs or oxygen saturation during the trial.

There was no dispensing device used in the ARX-03 Phase 2 clinical trials. Tablets were placed in the patients sublingual space through the use of forceps.

ARX-04 Sufentanil Single-Dose NanoTab

The Market Opportunity for ARX-04

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.

We believe that ARX-04 could be useful in a variety of medically supervised settings, including for battlefield casualty treatment, by paramedics during patient transport, in the emergency room, or for post-operative patients, following either short-stay or ambulatory surgery, who do not require more long-term patient-controlled analgesia. According to the Centers for Disease Control and Prevention, or CDC, there were more than 136 million emergency room visits in 2009, of which it is estimated that more than 45 million were injury-related emergency room visits, and analgesics were provided or prescribed during more than 94 million of these visits. In addition, based on CDC data, there were more than 43 million ambulatory surgery procedures conducted in the U.S. in 2006.

How ARX-04 Addresses the Unmet Medical Need for Moderate-to-Severe Acute Pain

ARX-04 is a non-invasive, fast-onset sufentanil product candidate for treatment of patients with moderate-to-severe acute pain, either on the battlefield or in civilian settings of trauma or injury. On the battlefield, in the emergency room and in ambulatory care environments, patients often do not have immediate IV access available. Intramuscular injections are a current standard of care on the battlefield, but they are invasive, painful and present an increased risk of infection to both patient and healthcare professional. In addition, in cases of severe trauma where the patient is often in hypovolemic shock and muscles are not well perfused, pain medication given by intramuscular injection may not readily reach the bloodstream to provide pain relief, rendering this route of delivery suboptimal. Oral pills and liquids generally have slow and erratic onset of analgesia. Even patients with IV access may have undesirable side effects with the commonly used IV opioids morphine and hydromorphone, such as sedation or oxygen desaturation. Moreover, IV dosing results in high peak plasma levels, thereby limiting the opioid dose and requiring frequent redosing intervals to titrate to satisfactory analgesia. Additional treatment options are needed that can safely and rapidly treat acute trauma pain, in both civilian and military settings. ARX-04 features sufentanil, a high therapeutic index opioid, in our proprietary NanoTab technology that enables rapid sublingual absorption when the NanoTab is placed under the tongue. As a result, sufentanil NanoTabs can provide rapid onset of analgesia and display a consistent pharmacokinetic profile due to a high percentage of drug being absorbed sublingually instead of through the gastrointestinal tract.

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ARX-04 Description

ARX-04 is a non-invasive, fast-onset sufentanil product candidate for treatment of patients with moderate-to-severe acute pain, either on the battlefield or in civilian settings of trauma or injury. ARX-04 features sufentanil, a high therapeutic index opioid, in our proprietary NanoTab technology that enables rapid sublingual absorption when the NanoTab is placed under the tongue. As a result, sufentanil NanoTabs can provide rapid onset of analgesia and display a consistent pharmacokinetic profile due to a high percentage of drug being absorbed sublingually instead of through the gastrointestinal tract. In addition to battlefield casualty treatment, if approved, we anticipate that ARX-04 could be useful in a variety of medically supervised settings, including by paramedics during patient transport, in the emergency room, for non-surgical patients experiencing pain in the hospital, or for post-operative patients, following either short-stay or ambulatory surgery, who do not require more long-term patient-controlled analgesia.

Sufentanil Single-Dose NanoTab ARX-04 Clinical Program

Summary

In May 2011, we received a grant from the US Army Medical Research and Materiel Command, or USAMRMC, to conduct a Phase 2 dose finding trial, and to prepare to enter Phase 3. In the Phase 2 clinical trial of ARX-04, two different doses of sufentanil are being evaluated in patients suffering from moderate-to-severe acute pain, with the goal of determining an appropriate dose to take into Phase 3.

Phase 2 Clinical Trial for ARX-04

In November 2012, we initiated our ARX-04 Phase 2 dose-finding trial, a prospective, randomized, double-blind multicenter trial in patients 18 to 80 years of age that are undergoing primary, unilateral first metatarsal bunionectomy surgery alone or with ipsilateral hammertoe repair. Patients who meet all inclusion and exclusion criteria following surgery will be randomly assigned (2:2:1) to treatment with Sufentanil NanoTab 20 mcg, Sufentanil NanoTab 30 mcg, or placebo. Randomization will be stratified within each site by two age groups: 18 64 years and 65 80. At least 100 patients (40 patients in Sufentanil NanoTab 20 mcg group, 40 patients in Sufentanil NanoTab 30 mcg group and 20 patients in placebo treatment group) will receive trial drug and provide primary efficacy data for analysis. Efficacy will be assessed as follows: 1) patient reports of pain intensity on an NRS, 2) pain relief on a 5-point pain relief scale, 3) percentage of patients requiring rescue analgesics due to inadequate analgesia, and 4) patient global assessment of effectiveness and tolerability. Also, a double stop-watch technique will be used to assess onset of perceived and meaningful analgesia after the first dose of trial drug.

The primary endpoint is the SPID-12. Secondary endpoints include: TOTPAR over the 12-hour trial period, proportion of patients requiring rescue analgesics due to inadequate analgesia over the 12-hour trial period, proportion of patients who responded in each category of the Patient Global Assessment, time to onset of perceived and meaningful analgesia and time to first use of rescue analgesics and total number of doses of rescue analgesic used.

Other Potential Applications for Our NanoTab Technology

We believe that as a platform technology, the NanoTab, either as a standalone dosage form or in conjunction with various forms of dispensing mechanisms, has the potential to enable other product candidates utilizing a number of additional compounds to be delivered sublingually to the oral mucosa. There are numerous compounds used for the treatment of pain as well as other therapeutic indications which are dosed in microgram quantities and possess characteristics that we believe make them potential candidates for sublingual delivery via the NanoTab.

Our Strategy

Our strategy is to develop and commercialize a portfolio of sufentanil NanoTab-based products in specialty markets. We have designed and are developing product candidates that have clearly defined clinical development programs, target large commercial market opportunities, and require modest commercial organizations in the United States. We selectively utilize third party contractors in order to maximize the capital efficiency of our development and commercialization efforts. In addition, we plan to enter into partnerships to market our product candidates outside the United States.

Our lead product candidate, the NanoTab System, is currently in Phase 3 development. We have advanced the NanoTab System into three Phase 3 clinical trials, one of which has been completed and for which we reported positive top-line results in November 2012. Contingent upon receipt of successful data from the remaining two NanoTab System Phase 3 clinical trials, which is expected in the first quarter of 2013, we intend to submit an NDA to the FDA in the third quarter of 2013. If our planned NDA is submitted and approved, we plan to commercialize

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the NanoTab System ourselves in the United States, and commercialize it outside the United States with a partner. Our second program, ARX-02, is focused on the management of cancer breakthrough pain and has completed Phase 2 development. Based on the availability of financial resources, we plan to advance ARX-02 into Phase 3 clinical trials, submit an NDA and, if approved, commercialize ARX-02 ourselves or with a partner in the United States. Further development of ARX-03 will likely depend on the identification of a partner to support this effort. Development of ARX-04 beyond the current grant-supported activities is contingent upon the successful completion of our Phase 2 clinical trial.

Our specific strategy with respect to the NanoTab System is to:

- complete the remaining two Phase 3 efficacy trials and seek regulatory approval in the United States and other countries;
- strengthen our commercial relationships for the manufacturing of the components and assembly of the NanoTab System;
- build a targeted hospital-directed sales force in the United States; and
- partner with third parties for commercialization outside of the United States.

Sales and Marketing

We anticipate developing a distribution capability and commercial organization in the United States to market and sell our product candidates alone or with partners, while out-licensing commercialization rights outside of the United States. In executing our strategy, our goal is to have significant control over the development process and commercial execution for our product candidates, while retaining meaningful economics.

We plan to progressively build commercial capability to support introduction of the NanoTab System to the United States market as we move toward potential NDA submission and approval. We foresee two stages of commercial execution to support successful introduction of the NanoTab System in the United States:

In parallel with our remaining Phase 3 clinical studies and the planned submission of an NDA for the NanoTab System, we plan to:

- highlight the clinical and health economic data identifying the limitations of IV PCA in use today;
- increase awareness of the clinical profile of the NanoTab System through publication of our clinical data;
- create and deploy a focused scientific support team to gather a detailed understanding of individual hospital needs in order to be prepared to present the NanoTab System effectively at the time of commercial launch;
- establish advisory boards with anesthesiologists, surgeons, nurses and P&T committees to provide us with input on appropriate commercial positioning for the NanoTab System for each of these key audiences;
- build a marketing organization that can define appropriate segmentation and positioning strategies and tactics for the NanoTab System; and

design a post-approval clinical development program.

Assuming FDA approval, we plan to:

establish the NanoTab System on hospital formularies through deployment of an experienced team to explain and promote the clinical and pharmacoeconomic benefits of the NanoTab System in comparison to IV PCA;

create and progressively deploy a high-quality, customer focused and experienced sales organization dedicated to bringing innovative, highly-valued healthcare solutions to patients, payors and healthcare providers, including progressively building a targeted hospital-directed sales force of up to 60 people in the United States;

conduct a post-approval clinical program for the NanoTab System;

establish the NanoTab System as the product of choice for traditional post-operative PCA; and

expand the market through deployment of the NanoTab System for 24 hour stay patients, and other in hospital acute pain conditions.

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Intellectual Property

We seek patent protection in the United States and internationally for our product candidates. Our policy is to pursue, maintain and defend patent rights developed internally and to protect the technology, inventions and improvements that are commercially important to the development of our business. We cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents granted to us in the future will be commercially useful in protecting our technology. We also rely on trade secrets to protect our product candidates. Our commercial success also depends in part on our non-infringement of the patents or proprietary rights of third parties. For a more comprehensive discussion of the risks related to our intellectual property, please see Risk Factors Risks Related to Our Intellectual Property appearing elsewhere in this prospectus.

Our success will depend significantly on our ability to:

- obtain and maintain patent and other proprietary protection for our product candidates;
- defend our patents;
- preserve the confidentiality of our trade secrets; and
- operate our business without infringing the patents and proprietary rights of third parties.

We have established and continue to build proprietary positions for our product candidates and related technology in the United States and abroad.

As of October 1, 2012, we are the owner of record of one issued European patent, including national validation in ten countries, which expires in 2027, one Mexican patent which expires in 2029, four issued U.S. patents which provide coverage through at least 2027, and one issued U.S. patent which provides coverage through at least 2030, and we are pursuing 15 U.S. non-provisional patent applications, one pending international Patent Cooperation Treaty applications and 59 foreign national applications, including seven European Regional Phase applications directed to our product candidates. We have not yet obtained any issued patents that provide protection for key features of our ARX-01 PCA device or our ARX-02, ARX-03 and ARX-04 SDAs independent of the drug composition used in them. The patent applications that we have filed and have not yet been granted may fail to result in issued patents in the United States or in foreign countries. Even if the patents do successfully issue, third parties may challenge the patents.

We continue to seek and expand our patent protection for both compositions of matter and delivery devices, as well as methods of treatment related to our product candidates. In particular, we are pursuing additional patent protection for our ARX-01, ARX-02, ARX-03 and ARX-04 NanoTabs and formulations, our ARX-01 PCA device, the combination of drugs and our ARX-01 PCA device, our ARX-02, ARX-03 and ARX-04 SDA, as well as to methods of treatment using such drug and device compositions.

Issued European Patent No. EP2114383, including national validation in ten countries, includes composition of matter claims directed to ARX-01, ARX-02, ARX-03 and ARX-04 NanoTabs for oral transmucosal delivery of sufentanil, alone and in combination with key features of the ARX-01 PCA device, the ARX-02, ARX-03 and ARX-04 SDAs, respectively, and use of the claimed compositions in the treatment of pain.

All issued U.S. Patents provide coverage for all of our development candidates, including ARX-01, ARX-02, ARX-03 and ARX-04, and provide protection for both composition of matter and methods of using NanoTabs for oral transmucosal delivery of sufentanil.

Issued U.S. Patent Number 8,202,535 entitled Small-Volume Oral Transmucosal Dosage Forms describes a method of treating pain by administering a small-volume solid tablet containing sufentanil by adhering to the oral mucosa.

Issued U.S. Patent Number 8,226,978 is a composition of matter patent, which covers our proprietary NanoTab technology for delivering sufentanil with claims to a bioadhesive dosage form for oral transmucosal administration to a subject.

Issued U.S. Patent Number 8,231,900 covers the composition of sufentanil NanoTabs with claims to a single dose of sufentanil provided as a substantially homogeneous, bioadhesive solid tablet for oral transmucosal administration

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to a subject, comprising from about 0.25 micrograms to 200 micrograms of sufentanil, a volume of less than 30 microliters, with complete erosion of the tablet evident after about 5, 10 or 15 minutes.

Issued U.S. Patent Number 8,252,328 is a composition of matter patent which provides protection in the United States for each of our four development programs. The 328 patent covers our proprietary NanoTab technology for delivering sufentanil with claims to a substantially homogenous bioadhesive tablet, comprising from about 2.5 to about 100 micrograms of sufentanil and a volume of from about 3 to about 15 microliters, which adheres throughout the period of drug delivery, generates a minimal saliva response and delivers a majority of the drug through the oral mucosa.

Issued U.S. Patent Number 8,252,329 also covers the composition of sufentanil NanoTabs with claims to a bioadhesive tablet for sublingual administration to a subject, comprising from about 2.5 micrograms to about 100 micrograms of sufentanil, a volume of about 0.1 microliters to about 50 microliters, wherein the bioadhesive material is present at between 2% and 30% by weight, and the tablet generates a minimal saliva response and minimal swallowed drug and delivers at least 55% of the sufentanil through the oral transmucosal route. U.S. Patent No. 8,252,329 also includes claims to this composition of sufentanil NanoTabs in combination with key features of the ARX-01 PCA device and the ARX-02, ARX-03 and ARX-04 SDAs.

We have filed for additional patent coverage in the United States, Europe as well as many other foreign jurisdictions including, Japan, China, India, Canada and Korea. If issued, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, we expect that these patents will expire between 2027 and 2030, excluding any additional term for patent term adjustments or patent term extensions in the United States. We note that the patent laws of foreign countries differ from those in United States, and the degree of protection afforded by foreign patents may be different from the protection offered by U.S. patents.

Further, we seek trademark protection in the United States and internationally where available and when appropriate. We have registered our ACELRX mark in Class 5, Pharmaceutical preparations for treating pain; pharmaceutical preparations for treating anxiety, and Class 10, Drug delivery systems; medical device, namely, a mechanical and electronic device used to administer medications, perform timed medication delivery, and to provide secure access to and delivery of medications, in the United States.

Our ACELRX mark is also registered in the European Community, Canada, and India. We have also registered our NANOTAB mark in the United States, Hong Kong, and Singapore and our ACCELERATE. INNOVATE. ALLEVIATE. tagline in the United States.

Competition

Our industry is highly competitive and subject to rapid and significant technological change. Our potential competitors include large pharmaceutical and biotechnology companies, specialty pharmaceutical and generic drug companies, and medical technology companies. We believe the key competitive factors that will affect the development and commercial success of our product candidates are the safety, efficacy and tolerability profile, the patient and healthcare professional satisfaction with using our product candidates in relation to available alternatives and the reliability, convenience of dosing, price and reimbursement of our product candidates.

Many of our potential competitors, including many of the organizations named below, have substantially greater financial, technical and human resources than we do and significantly greater experience in the development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in obtaining FDA approval for drugs and achieving widespread market acceptance. Our competitors drugs may be more effective, or may be more effectively marketed and sold, than any drug we may commercialize, which may render our product candidates obsolete or non-competitive before we can recover our losses. We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available.

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Potential Competition for the NanoTab System

We are developing the NanoTab System for the management of moderate-to-severe post-operative pain in adult patients during hospitalization. We believe that the NanoTab System would compete with a number of opioid-based treatment options that are currently available. The market for opioids for post-operative pain is large and competitive. The primary competition for the NanoTab System is the IV PCA pump, which is widely used in the post-operative setting. Leading manufacturers of IV PCA pumps include Hospira Inc., CareFusion Corporation, Baxter International Inc., Curlin Medical, Inc. and Smiths Medical. The most common opioids used to treat post-operative pain are morphine, hydromorphone and fentanyl, all of which are available as generics. Also available on the market is the Avancen Medication on Demand, or MOD, Oral PCA Device developed by Avancen MOD Corporation. Additional potential competitors for the NanoTab System include products in development, including the fentanyl iontophoretic transdermal system, IONSYS, originally developed by ALZA Corporation and Ortho-McNeil Pharmaceutical, Inc., both Johnson & Johnson subsidiaries, and currently under development by Incline Therapeutics, Inc. Also in development is MoxDuo, an orally administered, fixed ratio combination of morphine and oxycodone being developed by QRx Pharma, an Australian company. This drug is also in development in an IV product.

Potential Competition for ARX-02

We are developing ARX-02, the Sufentanil NanoTab BTP Management System, for the treatment of breakthrough pain in opioid tolerant patients, with an initial indication in cancer patients. The market for opioids for treatment of cancer breakthrough pain is large and competitive; however, currently there are no sufentanil products approved by the FDA for this indication. Our potential competitors for ARX-02 include products approved in the United States for cancer breakthrough pain, including: ACTIQ and FENTORA, currently manufactured by Teva Pharmaceuticals; Onsolis, currently manufactured by BioDelivery Sciences International, Inc.; Abstral, currently manufactured by ProStrakan Group plc; Lazanda, currently manufactured by Archimedes Pharma Limited, as well as products approved in Europe, including Instanyl, currently manufactured by Nycomed International Management GmbH. The active ingredient in all approved products for cancer breakthrough pain is fentanyl. Additional potential competitors for ARX-02 include products in late stage development for cancer breakthrough pain, such as: Fentanyl TAIFUN, currently manufactured by Akela Pharma, Inc.; and SL Spray, currently manufactured by Insys Therapeutics, Inc.

Potential Competition for ARX-03

We are developing ARX-03, the Sufentanil/Triazolam NanoTab, for use in diagnostic or therapeutic painful procedures of short duration in a physician s office. For these procedures, many practitioners rely primarily on local anesthetics injected to the procedural area to reduce the pain of the procedure, and do not use IV sedatives to manage the anxiety of patients because of the cost of having additional trained staff to monitor the patients. Currently, we are not aware of any products on the market which combine an opioid with a benzodiazepine in a single dosage form to manage the anxiety and pain of procedures in a physician s office. We are not aware of any approved or development stage non-IV sedative/analgesic products that would present competition to ARX-03. In the future, there may be products developed or approved for this market which could directly compete with ARX-03.

Potential Competition for ARX-04

Competitors for ARX-04 within the military environment include intramuscular morphine injections which are marketed by a variety of generic manufacturers. Within the civilian environment, there are a wide variety of approved injectable and oral opioid products to treat moderate-to-severe acute pain, including IV opioids such as morphine, fentanyl, hydromorphone and meperidine or oral opioids such as oxycodone and hydrocodone.

Pharmaceutical Manufacturing and Supply

We currently rely on contract manufacturers to produce sufentanil and sufentanil/triazolam NanoTabs for our clinical trials under current Good Manufacturing Practices, or cGMP, with oversight by our internal managers. Equipment specific to the pharmaceutical manufacturing process was purchased and customized by us and is currently owned by us. We plan to continue to rely on contract manufacturers and, potentially, collaboration partners to manufacture commercial quantities of our product candidates if and when approved for marketing by the FDA. We currently rely on a single manufacturer for the preclinical and clinical supplies of our drug product for each of our product candidates and do not currently have agreements in place for redundant supply or a second source for any of our product candidates. We have identified other drug product manufacturers that could satisfy our clinical trial requirements but this would require a significant delay in setting up the facility and moving equipment. Additionally,

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should a supplier or a manufacturer on whom we rely to produce a product candidate provide us with a faulty product or such product is later recalled, we would likely experience significant delays and material additional costs.

Device Manufacturing and Supply

The NanoTab System handheld PCA device is manufactured by contract manufacturers, component fabricators and secondary service providers. Suppliers of components, subassemblies and other materials are located in Korea, Japan, Germany, China, Taiwan, Canada and the United States. All contract manufacturers and component suppliers have been selected for their specific competencies in the manufacturing processes and materials that make up the NanoTab System. FDA regulations require that materials be produced under cGMPs or Quality System Regulation, or QSR. We outsource injection molding of all the plastic parts for the cartridge and device and product sub-assemblies; NanoTab cartridge filling and packaging; and assembly, packaging and labeling of the dispenser and controller.

ARX-02 is manufactured by contract manufacturers, component fabricators and secondary service providers. Suppliers of components, subassemblies and other materials are located in Korea, Japan, China, Taiwan, Canada and the United States. All contract manufacturers and component suppliers have been selected for their specific competencies in the manufacturing processes and materials that make up the ARX-02. FDA regulations require that materials be produced under cGMPs or QSR, as required for the respective unit operation within the manufacturing process. We outsource injection molding of all the plastic parts for the SDA and MSD and product sub-assemblies; and filling, packaging and labeling of SDAs.

ARX-03 and ARX-04 both utilize SDAs in the delivery of the NanoTab. FDA regulations require that materials be produced under cGMPs or QSR, as required for the respective unit operation within the manufacturing process. We outsource injection molding of all the plastic parts for the SDA, and product sub-assemblies; and filling, packaging and labeling of SDAs.

Government Regulation

Government authorities in the United States at the federal, state and local level, and in other countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, marketing, export and import of products such as those we are developing. Our product candidates must be approved by the FDA through the NDA process before they may legally be marketed in the United States.

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and regulations. The process of obtaining regulatory approvals and complying with applicable laws and regulations requires the expenditure of substantial time and financial resources. Failure to comply at any time during the product development and approval process, or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include the FDA s refusal to approve pending applications, withdrawal of an approval, a clinical hold, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties. The process required by the FDA before a drug product may be marketed in the United States generally involves the following:

- completion of non-clinical laboratory tests, animal trials and formulation studies according to Good Laboratory Practices regulations;
- submission to the FDA of an investigational new drug, or IND, application which must become effective before human clinical trials may begin;
- performance of adequate and well-controlled human clinical trials according to Good Clinical Practices, or GCP, to establish the clinical safety and efficacy of the proposed drug product for its intended use;
- submission to the FDA of an NDA for a new drug product;

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug product and the drug substance(s) are produced to assess compliance with cGMP;

payment of user and facility fees; and

FDA review and approval of the NDA.

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The testing and approval process requires substantial time, effort and financial resources and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

Human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

Phase 1. The product is initially introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

Phase 2. Involves trials in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted conditions and to determine dosage tolerance and optimal dosage and schedule.

Phase 3. Clinical trials are undertaken to further evaluate dosage, clinical safety and efficacy in an expanded patient population at geographically dispersed clinical trial sites. These trials are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for product labeling.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse events. The FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an institutional review board, or IRB, can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB s requirements or if the drug or biological product has been associated with unexpected serious harm to patients.

Concurrent with clinical trials, companies usually complete additional animal trials and must also develop additional information about the chemistry and physical characteristics of the product and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP and QSR for medical devices requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

Our product candidates, the NanoTab System, ARX-02, ARX-03 and ARX-04, are regulated under IND applications for clinical development and in the case of the NanoTab System, all device related information is filed under the Chemistry, Manufacturing and Controls Section, or CMC, of an IND.

The results of product development, preclinical trials and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on our drug products, proposed labeling and other relevant information, will be submitted to the FDA as part of an NDA for a new drug product, requesting approval to market the product in the United States. The submission of an NDA is subject to the payment of a substantial user fee; a waiver of such fee may be obtained under certain limited circumstances.

In addition, under the Pediatric Research Equity Act, an NDA or supplement to an NDA must contain data to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers.

The approval process is lengthy and difficult and the FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical data or other data and information. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

If one or more of our product candidates receive regulatory approval, the approval may be limited to specific conditions and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Our product candidates, if approved, will

also require Risk Evaluations and Mitigation

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Strategies, or REMS, that can include a medication guide, patient package insert, a communication plan, elements to assure safe use and implementation system, and must include a timetable for assessment of the REMS. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. In addition, the FDA may require post-approval testing which involves clinical trials designed to further assess a drug product s safety and effectiveness after the NDA.

Post-Approval Requirements

Any drug products for which we receive FDA approvals are subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse experiences with the product, providing the FDA with updated clinical safety and efficacy information, product sampling and distribution requirements, complying with certain electronic records and signature requirements and complying with FDA promotion and advertising requirements. The FDA strictly regulates labeling, advertising, promotion and other types of information on products that are placed on the market. Drug products may be promoted only for the approved indications and in accordance with the provisions of the approved label. Further, manufacturers of drug products must continue to comply with cGMP requirements, which are extensive and require considerable time, resources and ongoing investment to ensure compliance. In addition, changes to the manufacturing process generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

Drug product manufacturers and other entities involved in the manufacturing and distribution of approved drug products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. The cGMP requirements apply to all stages of the manufacturing process, including the production, processing, packaging, labeling, storage and shipment of the drug product. Manufacturers must establish validated systems to ensure that products meet specifications and regulatory standards, and test each product batch or lot prior to its release. In the case of the NanoTab System, the device component must comply with 21 CFR 820.

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products. Future FDA and state inspections may identify compliance issues at the facilities of our contract manufacturers that may disrupt production or distribution or may require substantial resources to correct.

The FDA may withdraw a product approval if compliance with regulatory standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product may result in restrictions on the product or even complete withdrawal of the product from the market. Further, the failure to maintain compliance with regulatory requirements may result in administrative or judicial actions, such as fines, warning letters, holds on clinical trials, product recalls or seizures, product detention or refusal to permit the import or export of products, refusal to approve pending applications or supplements, restrictions on marketing or manufacturing, injunctions or civil or criminal penalties.

Foreign Regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products to the extent we choose to sell any products outside of the United States. In October 2012, we received notice from the EMA that the NanoTab System was eligible for centralized European review for up to 31 countries in Europe. Outside of Europe, the requirements and approval process vary from country to country and the time may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country.

Controlled Substances Regulations

Sufentanil, a Schedule II controlled substance, is the active pharmaceutical ingredient in the NanoTab System, ARX-02, ARX-03 and ARX-04. Triazolam, a Schedule IV controlled substance, is also an active pharmaceutical ingredient in ARX-03. Controlled substances are governed by the Drug Enforcement Administration, or DEA, of the U.S. Department of Justice. The handling of controlled substances and/or drug product by us, our contract

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manufacturers, analytical laboratories, packagers and distributors, are regulated by the Controlled Substances Act and Title 21 CFR, Part 1300-1399. Our current supply chain is also subject to the regulations of Health Canada s Drug Strategy and Controlled Substances Programmed, and specifically, the Office of Controlled Substances.

Unforeseen delays to the drug substance and drug product manufacture and supply chain may occur due to delays, errors or other unforeseen problems with the permitting process. Also, any one of our suppliers, contract manufacturers, laboratories, packagers and/or distributors could be the subject of DEA violations and enforcement could lead to delays or even loss of DEA license by the contractors.

Health Law Compliance

In addition to FDA laws and regulations, we must comply with a variety of federal and state laws governing, among other things, the privacy of healthcare information, our relationships with healthcare providers and the reimbursement of prescription drug products. Although the federal health care program anti-kickback statute has a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Federal false claims laws prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to get a false claim paid. The majority of states also have statutes or regulations similar to the federal anti-kickback law and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer. Sanctions under these federal and state laws may include civil monetary penalties, exclusion of a manufacturer s products from reimbursement under government programs, criminal fines, and imprisonment. Because of the breadth of these laws and the narrowness of the safe harbors, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Such a challenge could have a material adverse effect on our business, financial condition and results of operations.

In March 2010, the Patient Protection and Affordable Health Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the PPACA, was enacted, which includes measures to significantly change the way health care is financed by both governmental and private insurers. Many of the details regarding the implementation of the PPACA are yet to be determined, and at this time, it remains unclear the full effect that the PPACA would have on our business.

Research and Development

Conducting research and development is central to our business model. We have invested and expect to continue to invest significant time and capital in our research and development operations. Our research and development expenses were $17.1 million for the nine months ended September 30, 2012 and were $13.6 million, $8.2 million and $15.5 million during the years ended December 31, 2011, 2010 and 2009, respectively. We plan to increase our research and development expenses for the foreseeable future as we seek to continue development of the NanoTab System and ARX-04, and subsequently advance the development of ARX-02 and ARX-03 contingent upon additional funding or identification of corporate partnership resources.

Employees

As of October 31, 2012, we employed 24 full-time employees, all of whom are located at our headquarters in Redwood City, California. None of our employees are subject to a collective bargaining agreement. We consider our relationship with our employees to be good.

Facilities

We lease approximately 13,787 square feet of space in Redwood City, California, under a lease agreement which expires in May 2016. We believe that our facilities are adequate to meet our current needs.

Legal Proceedings

From time to time we may be involved in legal proceedings arising in the ordinary course of business. We believe there is no litigation currently pending that could have, individually or in the aggregate, a material adverse effect on our results of operations or financial condition.

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PRINCIPAL STOCKHOLDERS

The following table sets forth information known to us about the beneficial ownership of our common stock at November 1, 2012 (except as noted) by:

- our Chief Executive Officer, our Chief Financial Officer and each of our three other most highly compensated executive officers as of December 31, 2011, which officers are referred to in this prospectus as our named executive officers ;
- each of our directors;
- each person known to us to be the beneficial owner of more than 5% of our common stock; and
- all of our executive officers and directors as a group.

Unless otherwise noted below, the address of each beneficial owner listed on the table is c/o AcelRx Pharmaceuticals, Inc., 351 Galveston Drive, Redwood City, CA 94063. We have determined beneficial ownership in accordance with the rules of the SEC. Except as indicated by the footnotes below, we believe, based on the information furnished to us, that the persons and entities named in the table below have sole voting and investment power with respect to all shares of common stock that they beneficially own, subject to applicable community property laws. The table is based upon information supplied by officers, directors and principal shareholders and Schedules 13G or 13D filed with the Securities and Exchange Commission, or the SEC.

In computing the number of shares of common stock beneficially owned by a person and the percentage ownership of that person, we deemed outstanding shares of common stock subject to options or warrants held by that person that are currently exercisable or exercisable within 60 days of November 1, 2012. We did not deem these shares outstanding, however, for the purpose of computing the percentage ownership of any other person.

The percentages in the table below are based on 22,649,273 shares of our common stock outstanding as of November 1, 2012.

Name and Address of Beneficial Owner	Number of Shares Beneficially Owned	Percentage of Common Stock Beneficially Owned
5% Stockholders:		
Funds affiliated with Three Arch Partners (1)	8,206,351	35.83%
Fund affiliated with Skyline Venture Partners (2)	4,428,161	19.33%
Fund affiliated with Alta Partners (3)	2,794,907	12.34%
Entities affiliated with Deerfield (4)	2,671,380	11.27%
LSP Life Sciences Fund, N.V. (5)	1,788,234	7.61%
Named Executive Officers and Directors:		
Richard King (6)	439,442	1.91%
Jim Welch (7)	101,249	0.45%
Pamela Palmer (8)	694,694	3.01%
Anil Dasu (9)	125,510	0.55%
Thomas Schreck (10)	673,109	2.93%
Lawrence G. Hamel (11)	160,182	0.70%
Mark Wan (12)	8,208,955	35.83%

Stephen J. Hoffman [13]	4,430,765	19.34%
Guy P. Nohra [14]	2,797,511	12.35%
Howard B. Rosen [15]	43,551	0.19%
Mark G. Edwards [16]	58,854	0.26%
All executive officers and directors as a group (11 persons) [17]	17,733,823	71.95%

(1) Includes 199,174 shares held by Three Arch Associates III, L.P., 87,408 shares held by Three Arch Associates IV, L.P., 3,704,712 shares held by Three Arch Partners III, L.P. and 3,958,829 shares held by Three Arch Partners IV, L.P. In addition, the number of

shares beneficially owned includes 3,268 shares of common stock issuable upon the exercise of warrants held by Three Arch Associates III, L.P., 4,151 shares of common stock issuable upon the exercise of warrants held by Three Arch Associates IV, L.P., 60,789 shares of common stock issuable upon the exercise of warrants held by Three Arch Partners III, L.P. and 188,020 shares of common stock issuable upon the exercise of warrants held by Three Arch Partners IV, L.P. The voting and dispositive decisions with respect to the shares held by Three Arch Associates III, L.P. and Three Arch Partners III, L.P., are made by the following Managing Members of their general partner, Three Arch Management III, L.L.C.: Mark Wan and Wilfred Jaeger, each of whom disclaims beneficial ownership of such shares. The voting and dispositive decisions with respect to the shares held by Three Arch Partners IV, L.P. and Three Arch Associates IV, L.P. are made by the following Managing Members of their general partner, Three Arch Management IV, L.L.C.: Mark Wan and Wilfred Jaeger, each of whom disclaims beneficial ownership of such shares. The address for the funds affiliated with Three Arch Partners is 3200 Alpine Road, Portola Valley, CA 94028.

(2) Includes 4,171,933 shares held by Skyline Venture Partners Qualified Purchaser Fund IV, L.P. In addition, the number of shares beneficially owned includes 256,228 shares of common stock issuable upon the exercise of warrants held by Skyline Venture Partners Qualified Purchaser Fund IV, L.P. John G. Freund and Yasunori Kaneko are the Managing Members of Skyline Venture Management IV, LLC, which is the general partner of Skyline Venture Partners Qualified Purchaser Fund IV, L.P., and as such Drs. Freund and Kaneko may be deemed to share voting and dispositive power with respect to all shares of common stock held by Skyline Venture Partners Qualified Purchaser Fund IV, L.P. In addition, Dr. Hoffman, one of our directors, is a Managing Director of Skyline Ventures and as such may be deemed to share voting and dispositive power with respect to all shares of common stock held by Skyline Venture Partners Qualified Purchaser Fund IV, L.P. Each of Drs. Freund, Kaneko and Hoffman disclaims beneficial ownership of such shares. The address for the funds affiliated with Skyline Venture Partners is 525 University Avenue, Ste. 520, Palo Alto, CA 94301.

(3) The 2,794,907 shares are held by ACP IV, L.P., or ACPIV. ACMP IV, LLC, or ACMPIV, is the general partner of ACPIV. Dan Janney, David Mack and Guy Nohra are directors of ACMPIV and they exercise shared voting and investment power with respect to the securities held by ACPIV. Each of Messrs. Janney, Mack and Nohra disclaims beneficial ownership of such securities. The address for funds affiliated with Alta Partners is One Embarcadero Center 37th Floor, San Francisco, CA 94111.

(4) Includes 940,121 shares held by Deerfield Special Situations Fund International, Limited and 672,435 shares held by Deerfield Special Situations Fund, L.P. In addition, the number of shares beneficially owned includes 617,295 shares of common stock issuable upon the exercise of warrants held by Deerfield Special Situations Fund International, Limited and 441,529 shares of common stock issuable upon the exercise of warrants held by Deerfield Special Situations Fund, L.P. James E. Flynn may be deemed to beneficially own the shares of common stock held by all of the foregoing entities; Deerfield Capital, L.P. may be deemed to beneficially own the shares of common stock held by Deerfield Special Situations Fund, L.P.; and Deerfield Management Company, L.P. may be deemed to beneficially own the shares of common stock held by Deerfield Special Situations Fund International Limited. The principal business office of Deerfield Capital, L.P., Deerfield Special Situations Fund, L.P., Deerfield Management Company, L.P. and James E. Flynn is 780 Third Avenue, 37th Floor, New York, New York 10017. The principal business office of Deerfield Special Situations Fund International Limited is c/o Citi Hedge Fund Services (B.V.I.), Bison Court, P.O. Box 3460, Road Town, Tortola, British Virgin Islands. The foregoing information is based solely on a Schedule 13G filed with the SEC on June 7, 2012, which provides information as of June 1, 2012. This information may have changed between that date and November 1, 2012.

(5) Includes 847,058 shares of common stock issuable upon the exercise of warrants held by LSP Life Sciences Fund, N.V. M. Wegter and J.P.P. Muijrers, managing directors of LSP Advisory B.V., managing director of LSP Life Sciences Fund N.V., share voting and investment power over the shares listed above. Beneficial ownership is reported based on the information provided to us as of May 29, 2012. This information may have changed between that date and November 1, 2012.

(6) Includes 364,322 shares issuable pursuant to stock options exercisable within 60 days of November 1, 2012.

(7) Includes 81,249 shares issuable pursuant to stock options exercisable within 60 days of November 1, 2012.

(8) Includes 393,749 shares issuable pursuant to stock options exercisable within 60 days of November 1, 2012.

(9) Includes 115,468 shares issuable pursuant to stock options exercisable within 60 days of November 1, 2012.

(10) Includes 327,604 shares issuable pursuant to stock options exercisable within 60 days of November 1, 2012, and 16,482 shares held in trust for Mr. Schreck s children. Mr. Schreck disclaims beneficial ownership of the shares held in trust for Mr. Schreck s children.

(11) Includes 144,812 shares issuable pursuant to stock options exercisable within 60 days of November 1, 2012.

(12) Includes 2,604 shares issuable pursuant to stock options exercisable within 60 days of November 1, 2012 and the shares referenced in footnote 1 above. Mr. Wan is a managing partner of Three Arch Management III, L.L.C. and Three Arch Management IV, L.L.C., and in such capacities he may be deemed to beneficially own the shares beneficially owned by the funds affiliated with Three Arch Partners. Mr. Wan disclaims beneficial ownership of these shares. The address of Mr. Wan is c/o Three Arch Partners, 3200 Alpine Road, Portola Valley, CA 94028.

(13) Includes 2,604 shares issuable pursuant to stock options exercisable within 60 days of November 1, 2012 and the shares referenced in footnote 2 above. Dr. Hoffman, is a Managing Director of Skyline Ventures and as such may be deemed to share voting and dispositive power with respect to all shares of common stock beneficially owned by Skyline Venture Partners Qualified Purchaser Fund IV, L.P. Dr. Hoffman disclaims beneficial ownership of such shares. The address for Dr. Hoffman is c/o Skyline Ventures, 525 University Avenue, Suite 520, Palo Alto, CA 94301.

(14) Includes 2,604 shares issuable pursuant to stock options exercisable within 60 days of November 1, 2012 and the shares referenced in footnote 3 above. Mr. Nohra is a director of ACMPIV, and in such capacity he may be deemed to beneficially own the shares beneficially owned by ACPIV. Mr. Nohra disclaims beneficial ownership of these shares. The address for Mr. Nohra is c/o Alta Partners, One Embarcadero Center 37th Floor, San Francisco, CA 94111.

(15) Includes 41,354 shares issuable pursuant to stock options exercisable within 60 days of November 1, 2012.

(16) Includes 8,854 shares issuable pursuant to stock options exercisable within 60 days of November 1, 2012.

(17) Includes 1,477,412 shares issuable pursuant to stock options exercisable within 60 days of November 1, 2012.

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DESCRIPTION OF CAPITAL STOCK

As of the date of this prospectus, our authorized capital stock consists of 100,000,000 shares of common stock, par value $0.001 per share, and 10,000,000 shares of preferred stock, par value $0.001 per share. As of November 1, 2012, 22,649,273 shares of our common stock were outstanding and no shares of our preferred stock were outstanding.

The following summary description of our capital stock is based on the provisions of our amended and restated certificate of incorporation and amended and restated bylaws and the applicable provisions of the Delaware General Corporation Law. This information may not be complete in all respects and is qualified entirely by reference to the provisions of our amended and restated certificate of incorporation, amended and restated bylaws and the Delaware General Corporation Law. For information on how to obtain copies of our amended and restated certificate of incorporation and amended and restated bylaws, which are exhibits to the registration statement of which this prospectus is a part, see Where You Can Find Additional Information.

Common stock

Voting Rights. Each holder of our common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors; provided, however, holders of our common stock may not, unless otherwise required by law, vote on any amendment to our amended and restated certificate of incorporation that relates solely to the terms of one or more series of preferred stock that we may issue if the holders of such preferred stock are entitled to vote on such amendment. Directors shall be elected by a plurality of the votes of the shares present in person, by remote communication, or represented by proxy at a meeting of the stockholders and entitled to vote generally on the election of directors. Our stockholders do not have cumulative voting rights in the election of directors. Accordingly, holders of a majority of the voting shares are able to elect all of the directors to be elected at any particular time.

Dividends. Subject to preferences that may be applicable to any then outstanding preferred stock, holders of our common stock are entitled to receive dividends, if any, as may be declared from time to time by our board of directors out of legally available funds.

Liquidation. In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any then outstanding shares of preferred stock.

Rights and Preferences. Holders of our common stock have no preemptive, conversion, subscription or other rights, and there are no redemption provisions applicable to our common stock. The rights, preferences and privileges of the holders of our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of our preferred stock that we may designate in the future.

Fully Paid and Nonassessable. All of our outstanding shares of common stock are, and the shares of common stock to be issued in this offering will be, fully paid and nonassessable.

Preferred stock

Our board of directors is authorized, subject to limitations prescribed by Delaware law, to issue up to 10,000,000 shares of preferred stock in one or more series, to establish from time to time the number of shares to be included in each series and to fix the designation, powers, preferences and rights of the shares of each series and any of its qualifications, limitations or restrictions. Our board of directors can also increase or decrease the number of shares of any series, but not below the number of shares of that series then outstanding, without any further vote or action by our stockholders. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of the common stock. The issuance of preferred stock, while providing flexibility in connection with financings, possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring, discouraging or preventing a change in

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control of our company, may adversely affect the market price of our common stock and the voting and other rights of the holders of common stock, and may reduce the likelihood that common stockholders will receive dividend payments and payments upon liquidation.

Registration Rights

Pursuant to our second amended and restated investors rights agreement, or the investors rights agreement, certain holders of our previously outstanding preferred stock and previously outstanding warrants to purchase our preferred stock, which shares we refer to as registrable securities, have the right to demand that we file a registration statement or request that their shares be covered by a registration statement that we are otherwise filing pursuant to an investors rights agreement we entered into with certain of our stockholders. In the event that we propose to register any of our securities under the Securities Act, either for our own account or for the account of other security holders, these holders are entitled to notice of our registration and are entitled to certain piggyback registration rights allowing the holders to include their registrable securities in such registration, subject to certain marketing and other limitations. Pursuant to the investors rights agreement, the holders of registrable securities have the right to require us to file a registration statement under the Securities Act in order to register the resale of their shares of registrable securities, provided that the registration meets certain thresholds. We may, in certain circumstances, defer such registrations. In an underwritten offering, the managing underwriter has the right, subject to specified conditions, to limit the number of registrable securities such holders may include. The holders of registrable securities have waived their rights to include any of their shares in this offering.

Pursuant to a purchase agreement entered in connection with a private placement of our common stock and warrants in May 2012, we agreed to register the resale of the shares of our common stock we issued and any common stock issuable upon the exercise of the warrants that we issued in that private placement. Pursuant to our obligations under the purchase agreement, we filed a registration statement with the SEC registering the resale of these shares on June 21, 2012 and it was declared effective by the SEC on July 2, 2012. We agreed to use our commercially reasonable best efforts to keep the registration statement we filed registering the resale of these shares continuously effective until the earlier of (i) such time as all of the such shares have been sold under the registration statement or Rule 144 under the Securities Act or (ii) such time as all of the shares may be sold pursuant to Rule 144 without compliance with Rule 144(c)(1).

Anti-takeover effects of provisions of our certificate of incorporation and bylaws and Delaware law

Certificate of incorporation and bylaws. Our amended and restated certificate of incorporation and amended and restated bylaws include a number of provisions that may deter or impede hostile takeovers or changes of control or management. These provisions include:

Issuance of undesignated preferred stock. Under our amended and restated certificate of incorporation, our board of directors has the authority, without further action by the stockholders, to issue up to 10,000,000 shares of undesignated preferred stock with rights and preferences, including voting rights, designated from time to time by the board of directors. The existence of authorized but unissued shares of preferred stock enables our board of directors to make it more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise.

Classified board. Our amended and restated certificate of incorporation provides for a classified board of directors consisting of three classes of directors, with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. This provision may have the effect of delaying a change in control of the board.

Board of directors vacancies. Our amended and restated certificate of incorporation and amended and restated bylaws authorize only our board of directors to fill vacant directorships, unless our board of directors determines by resolution that the stockholders shall fill such vacant directorships. In addition, the number of directors constituting our board of directors may be set only by resolution adopted by a majority vote of our entire board of directors. These provisions prevent a stockholder from increasing the size of our board of directors and gaining control of our board of directors by filling the resulting vacancies with its own nominees.

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Stockholder action; special meetings of stockholders. Our amended and restated certificate of incorporation provides that our stockholders may not take action by written consent, but may only take action at annual or special meetings of our stockholders. Stockholders will not be permitted to cumulate their votes for the election of directors. Our amended and restated bylaws further provide that special meetings of our stockholders may be called only by a majority of our board of directors, the chairman of our board of directors, or our chief executive officer. These provisions may prevent stockholders from corporate actions as stockholders at times when they otherwise would like to do so.

Advance notice requirements for stockholder proposals and director nominations. Our amended and restated bylaws provide advance notice procedures for stockholders seeking to bring business before our annual meeting of stockholders, or to nominate candidates for election as directors at our annual meeting of stockholders. Our bylaws also specify certain requirements as to the form and content of a stockholder s notice. These provisions may make it more difficult for our stockholders to bring matters before our annual meeting of stockholders or to nominate directors at our annual meeting of stockholders.

These provisions are intended to enhance the likelihood of continued stability in the composition of our board of directors and its policies and to discourage certain types of transactions that may involve an actual or threatened acquisition of us. These provisions are designed to reduce our vulnerability to an unsolicited acquisition proposal. The provisions also are intended to discourage certain tactics that may be used in proxy fights. However, these provisions could have the effect of discouraging others from making tender offers for our shares and, as a consequence, they may also reduce fluctuations in the market price of our shares that could result from actual or rumored takeover attempts.

Section 203 of the Delaware General Corporation Law

We are subject to Section 203 of the Delaware General Corporation Law. Section 203 generally prohibits certain Delaware corporations from engaging, under certain circumstances, in a business combination with any interested stockholder for a period of three years following the time that such stockholder became an interested stockholder, unless:

- prior to such time the board of directors approved either the business combination or transaction which resulted in the stockholder becoming an interested stockholder;
- upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding (a) shares owned by persons who are directors and also officers and (b) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- at or subsequent to such time the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66-2/3% of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, lease, exchange, mortgage, pledge, transfer or other disposition (in one transaction or a series of transactions) involving the interested stockholder of 10% or more of the assets of the corporation (or its majority-owned subsidiary);
- subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

subject to exceptions, any transaction involving the corporation that has the effect, directly or indirectly, of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; and

the receipt by the interested stockholder of the benefit, directly or indirectly (except proportionately as a stockholder of such corporation), of any loans, advances, guarantees, pledges or other financial benefits, other than certain benefits set forth in Section 203, provided by or through the corporation.

In general, Section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person that is an affiliate or associate of such entity or person.

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A Delaware corporation may opt out of these provisions with an express provision in its original certificate of incorporation or an express provision in its certificate or incorporation or bylaws resulting from a stockholders amendment approved by a majority of the outstanding voting shares. We have not opted out of these provisions and do not plan to do so. The statute could prohibit or delay mergers or other takeover or change in control attempts and, accordingly, may discourage attempts to acquire us.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A. Its address is 250 Royall Street, Canton, MA 02021.

Listing on The NASDAQ Global Market

Our common stock is listed on The NASDAQ Global Market under the symbol ACRX .

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CERTAIN RELATIONSHIPS AND RELATED PARTY TRANSACTIONS

Certain Transactions With or Involving Related Persons

The following is a summary of transactions since January 1, 2009 to which we have been a party in which the amount involved exceeded the lesser of $120,000 or one percent of the average of our total assets at fiscal years ended 2010 and 2011, and in which any of our executive officers, directors or holders of more than 5% of our capital stock, or any member of the immediate family of any of the foregoing persons, had or will have a direct or indirect material interest, other than compensation arrangements previously reported in our Annual Report on Form 10-K for the year ended December 31, 2011, which is incorporated by reference in this prospectus.

Private Placement Financings

Preferred Stock Financing

The following table summarizes purchases of our Series C convertible preferred stock by holders of more than 5% of our capital stock and their affiliated entities.

Name	Series C Preferred Stock[1]	Aggregate Purchase Price of Series C Preferred Stock
Funds affiliated with Three Arch Partners [2]	1,752,337	$ 6,909,117
Fund affiliated with Skyline Venture Partners [3]	915,798	$ 3,610,810
Fund affiliated with Alta Partners [4]	810,129	$ 3,194,178
Approximate price per share	$ 3.94	
Date of purchase	11/23/09	

[1] The shares of Series C preferred stock were automatically converted into common stock in connection with our IPO.

[2] Includes 44,702 shares of Series C convertible preferred stock purchased by Three Arch Associates III, L.P., 18,928 shares of Series C convertible preferred stock purchased by Three Arch Associates IV, L.P., 831,466 shares of Series C convertible preferred stock purchased by Three Arch Partners III, L.P. and 857,241 shares of Series C convertible preferred stock purchased by Three Arch Partners IV, L.P. Mark A. Wan, one of our directors, is managing partner of Three Arch Management III, L.L.C. and Three Arch Management IV, L.L.C., and in such capacities he may be deemed to beneficially own the shares owned by the funds affiliated with Three Arch Partners.

[3] These shares were purchased by Skyline Venture Partners Qualified Purchaser Fund IV, L.P. Stephen Hoffman, one of our directors, is a Managing Director of Skyline Ventures and as such may be deemed to share voting and dispositive power with respect to all shares of stock held by Skyline Venture Partners Qualified Purchaser Fund IV, L.P.

[4] These shares were purchased by ACP IV, L.P. Guy Nohra is one of our directors and is a director of ACMP IV, LLC, the general partner of ACP IV, L.P., and shares voting and investment power with respect to such shares. Mr. Nohra disclaims beneficial ownership of these shares.

2010 Bridge Loan Financing

On September 14, 2010, we sold convertible promissory notes, or the 2010 notes, and warrants, or the 2010 warrants, to purchase shares of our equity securities to certain of our existing investors for an aggregate purchase price of $8.0 million. Upon the election of the holders of a majority of the aggregate principal amount payable under the 2010 notes outstanding, we were to sell an additional $4.0 million of 2010 notes and corresponding 2010 warrants. However, this $4.0 million call option expired upon the closing of our IPO.

The 2010 notes bore interest at a rate of 4.0% per annum. No payment of principal or interest was paid on the 2010 notes and the aggregate amount of principal outstanding on 2010 notes was $8.0 million as of February 16, 2011, the closing of our IPO. In connection with our IPO, the outstanding principal and accrued interest under the 2010 notes automatically converted into common stock at a conversion price equal to $4.00.

The 2010 warrants became exercisable by their terms for an aggregate of 507,249 shares of Series C preferred stock at an exercise price of approximately $3.94 immediately prior to the closing of our IPO. Each 2010 warrant contained a customary net issuance feature, which allowed the warrant holder to pay the exercise price of the warrant by forfeiting a portion of the exercised warrant shares with a value equal to the aggregate exercise price. All of the holders of the 2010 warrants elected to exercise the 2010 warrants on a net issuance basis contingent upon and effective immediately prior to the completion of our IPO.

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2010 Bridge Loan Financing Participation

The following table summarizes the participation in the 2010 bridge financing by holders of more than 5% of our capital stock and their affiliated entities:

Name	Aggregate Loan Amount	Aggregate Shares of Series C Preferred Stock Issued Upon Exercise of 2010 Warrants [1]
Funds affiliated with Three Arch Partners [2]	$ 3,793,273	50,854
Fund affiliated with Skyline Venture Partners [3]	$ 1,977,503	26,511
Fund affiliated with Alta Partners [4]	$ 1,742,044	23,355

[1] The above table and footnotes give effect to the exercise, on a net issuance basis, of the 2010 warrants, which were exercised upon and effective immediately prior to the completion of our IPO. The shares of Series C preferred stock issued upon the exercise of the 2010 warrants were automatically converted into common stock in connection with our IPO.

[2] Includes a note purchased by Three Arch Associates III, L.P. with a principal amount of $96,767, a note purchased by Three Arch Associates IV, L.P. with a principal amount of $40,973, a note purchased by Three Arch Partners III, L.P. with a principal amount of $1,799,869 and a note purchased by Three Arch Partners IV, L.P. with a principal amount of $1,855,663. Includes a warrant purchased by Three Arch Associates III, L.P., exercised, on a net issuance basis, for 1,297 shares of Series C preferred stock, a warrant purchased by Three Arch Associates IV, L.P., exercised, on a net issuance basis, for 549 shares of Series C preferred stock, a warrant purchased by Three Arch Partners III, L.P., exercised, on a net issuance basis, for 24,130 shares of Series C preferred stock and a warrant purchased by Three Arch Partners IV, L.P., exercised, on a net issuance basis, for 24,878 shares of Series C preferred stock. Mark A. Wan, one of our directors, is managing partner of Three Arch Management II, L.L.C. and Three Arch Management IV, L.L.C., and in such capacities he may be deemed to beneficially own the securities owned by the funds affiliated with Three Arch Partners.

[3] This note and warrant were purchased by Skyline Venture Partners Qualified Purchaser Fund IV, L.P. Stephen Hoffman, one of our directors, is a Managing Director of Skyline Ventures and as such may be deemed to share voting and dispositive power with respect to all securities held by Skyline Venture Partners Qualified Purchaser Fund IV, L.P.

[4] This note and warrant were purchased by ACP IV, L.P. Guy Nohra is one of our directors and is a director of ACMP IV, LLC, the general partner of ACP IV, L.P., and shares voting and investment power with respect to such securities. Mr. Nohra disclaims beneficial ownership of these securities. In February 2011, ACP IV, L.P. agreed to transfer a portion of the note and the associated portion of the warrant held by ACP IV, L.P. as described under Bridge Note and Warrant Transfer below.

Bridge Note and Warrant Transfer

In February 2011, ACP IV, L.P., a participant in our 2010 bridge loan and warrant financing, agreed to transfer a 37% interest in its note and the associated portion of its warrant for nominal consideration to funds affiliated with Three Arch Partners, Skyline Venture Partners and Kaiser Foundation Hospitals pro rata among them based on each entity s affiliated funds then-current beneficial ownership of our outstanding capital stock, with such transfer effective immediately prior to the closing of our IPO. As a result of the foregoing transfer, effective immediately prior to the closing of our IPO:

funds affiliated with Three Arch Partners acquired warrants which were subsequently exercised, on a net issuance basis, for an aggregate of 5,236 shares of Series C preferred stock (which shares were converted into the same number of shares of common stock in connection with our IPO) and notes in an aggregate principal amount of $390,704;

funds affiliated with Skyline Venture Partners acquired a warrant which was subsequently exercised, on a net issuance basis, for 2,730 shares of Series C preferred stock (which shares were converted into the same number of shares of common stock in connection with our IPO) and a note in a principal amount of $203,676;

funds affiliated with Kaiser Foundation Hospitals acquired warrants which were subsequently exercised, on a net issuance basis, for an aggregate of 672 shares of Series C preferred stock (which shares were converted into the same number of shares of common stock in connection with our IPO) and notes in an aggregate principal amount of $50,176; and

funds affiliated with ACP IV, L.P. continued to hold a warrant which was subsequently exercised, on a net issuance basis, for 14,713 shares of Series C preferred stock (which shares were converted into the same number of shares of common stock in connection with our IPO) and a note in a principal amount of $1,097,487.

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Participation in Our Initial Public Offering

Entities affiliated with Three Arch Partners, Skyline Venture Partners and Alta Partners, each of which was a holder of more than 5% of our capital stock, purchased an aggregate of 4,495,552 shares of our common stock in our IPO, as follows:

Name	Common Stock Purchased in Initial Public Offering	Aggregate Purchase Price
Funds affiliated with Three Arch Partners [1]	2,579,579	$ 12,897,895
Fund affiliated with Skyline Venture Partners [2]	1,235,943	$ 6,179,715
Fund affiliated with Alta Partners [3]	680,000	$ 3,400,000
Price per share	$ 5.00	
Date of Purchase	2/11/11	

[1] Includes 65,806 shares of common stock purchased by Three Arch Associates III, L.P., 27,863 shares of common stock purchased by Three Arch Associates IV, L.P., 1,223,983 shares of common stock purchased by Three Arch Partners III, L.P. and 1,261,927 shares of common stock purchased by Three Arch Partners IV, L.P. Mark Wan, one of our directors, is managing partner of Three Arch Management III, L.L.C. and Three Arch Management IV, L.L.C., and in such capacities he may be deemed to beneficially own the shares owned by the funds affiliated with Three Arch Partners. Mr. Wan disclaims beneficial ownership of these shares.

[2] These shares were purchased by Skyline Venture Partners Qualified Purchaser Fund IV, L.P. Stephen Hoffman, one of our directors, is a Managing Director of Skyline Ventures and as such may be deemed to share voting and dispositive power with respect to all shares of stock purchased by Skyline Venture Partners Qualified Purchaser Fund IV, L.P. Dr. Hoffman disclaims beneficial ownership of these shares.

[3] These shares were purchased by ACP IV, L.P. Guy Nohra is one of our directors and is a director of ACMP IV, LLC, the general partner of ACP IV, L.P., and shares voting and investment power with respect to such shares. Mr. Nohra disclaims beneficial ownership of these shares.

2012 Private Placement

On May 29, 2012, we entered into a securities purchase agreement, or the Purchase Agreement, with certain accredited investors, including entities affiliated with certain members of our board of directors, providing for a private placement, or the Private Placement, of up to $10.0 million of our securities. At the closing of the Private Placement on June 1, 2012, and pursuant to the Purchase Agreement, we sold shares of common stock and warrants to purchase common stock in immediately separable units, with each unit consisting of (i) one share of common stock and (ii) a warrant to purchase 0.9 of a share of common stock. The per share exercise price of the warrants was $3.40. The offering price per unit was $3.40 for non-affiliated investors, and $3.5125 for affiliated investors, which equals the sum of (i) $3.40, the closing consolidated bid price of our common stock on May 29, 2012, plus (ii) $0.1125 (which is equal to $0.125 per warrant share, multiplied by 0.9), for an aggregate amount of $10.0 million. The warrants issued in the Private Placement become exercisable six months after the issuance date, and expire on the five year anniversary of the initial exercisability date. Entities affiliated with Three Arch Partners and Skyline Venture Partners purchased an aggregate of 569,396 shares of our common stock and 512,456 warrants in the Private Placement, as follows:

Name	Common Stock Purchased in Private Placement	Warrants Purchased in Private Placement	Aggregate Purchase Price
Funds affiliated with Three Arch Partners [1]	284,698	256,228	$ 1,000,001.73
Fund affiliated with Skyline Venture Partners [2]	284,698	256,228	$ 1,000,001.73

(1) Includes 3,631 shares of common stock and 3,268 shares of common stock underlying warrants purchased by Three Arch Associates III, L.P., 4,613 shares of common stock and 4,151 shares of common stock underlying warrants purchased by Three Arch Associates IV, L.P., 67,543 shares of common stock and 60,789 shares of common stock underlying warrants purchased by Three Arch Partners III, L.P. and 208,911 shares of common stock and 188,020 shares of common stock underlying warrants purchased by Three Arch Partners IV, L.P. Mark A. Wan, one of our directors, is managing partner of Three Arch Management III, L.L.C. and Three Arch Management IV, L.L.C., and in such capacities he may be deemed to beneficially own the shares owned by the funds affiliated with Three Arch Partners. Mr. Wan disclaims beneficial ownership of these shares.

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(2) These shares and warrants were purchased by Skyline Venture Partners Qualified Purchaser Fund IV, L.P. Stephen Hoffman, one of our directors, is a Managing Director of Skyline Ventures and as such may be deemed to share voting and dispositive power with respect to all shares of stock purchased by Skyline Venture Partners Qualified Purchaser Fund IV, L.P. Dr. Hoffman disclaims beneficial ownership of these shares.

Pursuant to the Purchase Agreement, we agreed to register the resale of the shares of our common stock we issued and any common stock issuable upon the exercise of the warrants that we issued in the Private Placement, including the shares and warrants held by the entities affiliated with Three Arch Partners and Skyline Venture Partners. Pursuant to our obligation under the Purchase Agreement, we filed a registration statement with the SEC registering the resale of these shares on June 21, 2012 and it was declared effective by the SEC on July 2, 2012. We agreed to use our commercially reasonable best efforts to keep the registrations statement we filed registering the resale of these shares continuously effective until the earlier of (i) such time as all of the such shares have been sold under the registration statement or Rule 144 or (ii) such time as all of the shares may be sold pursuant to Rule 144 without compliance with Rule 144(c)(1).

Investors Rights Agreement

We entered into an investors rights agreement with certain holders of our previously outstanding preferred stock and previously outstanding warrants to purchase our preferred stock, including our principal stockholders with which certain of our directors are affiliated. Pursuant to the investors rights agreement, these holders will have the right to demand that we file a registration statement or request that the common stock issued upon conversion of our previously outstanding preferred stock and the common stock issuable upon the exercise of outstanding warrants to purchase common stock (which, in connection with our IPO, were converted from previously outstanding warrants to purchase our preferred stock), collectively, the registrable securities, be covered by a registration statement that we are otherwise filing. In the event that we propose to register any of our securities under the Securities Act, either for our own account or for the account of other security holders, these holders are entitled to notice of our registration and are entitled to certain piggyback registration rights allowing the holders to include their registrable securities in such registration, subject to certain marketing and other limitations. Pursuant to the investors rights agreement, the holders of registrable securities have the right to require us to file a registration statement under the Securities Act in order to register the resale of their shares of registrable securities, provided that the registration meets certain thresholds. We may, in certain circumstances, defer such registrations. In an underwritten offering, the managing underwriter has the right, subject to specified conditions, to limit the number of registrable securities such holders may include. The holders of registrable securities have waived their rights to include any of their shares in this offering.

Indemnification Agreements

We have entered into indemnification agreements with each of our current directors and officers. These agreements provide for the indemnification of such persons for all reasonable expenses and liabilities incurred in connection with any action or proceeding brought against them by reason of the fact that they are or were serving in such capacity. We believe that these bylaw provisions and indemnification agreements are necessary to attract and retain qualified persons as directors and officers. Furthermore, we have obtained director and officer liability insurance to cover liabilities our directors and officers may incur in connection with their services to us and have increased the level upon the completion of the our IPO.

Policies and Procedures for Related Party Transactions

In January 2011, prior to our IPO, our board of directors adopted an audit committee charter that provides that the audit committee will review and approve all related party transactions. Accordingly, following our IPO, all related party transactions are reviewed and approved by our audit committee, including the 2012 Private Placement described above. This review covers any material transaction, arrangement or relationship, or any series of similar transactions, arrangements or relationships, in which we were or are to be a participant, and a related party had or will have a direct or indirect material interest, including, purchases of goods or services by or from the related party or entities in which the related party has a material interest, indebtedness, guarantees of indebtedness and employment by us of a related party. All of the transactions described above that were transacted prior to our IPO were entered into prior to the adoption of this audit committee charter and were approved by our board of directors.

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MATERIAL U.S. FEDERAL INCOME AND ESTATE TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following summary describes the material U.S. federal income and estate tax consequences of the acquisition, ownership and disposition of our common stock acquired in this offering by Non-U.S. Holders (as defined below). This discussion does not address all aspects of U.S. federal income and estate taxes and does not deal with foreign, state and local consequences that may be relevant to Non-U.S. Holders in light of their particular circumstances, nor does it address U.S. federal tax consequences other than income and estate taxes. Special rules different from those described below may apply to certain Non-U.S. Holders that are subject to special treatment under the Code, such as financial institutions, insurance companies, tax-exempt organizations, broker-dealers and traders in securities, U.S. expatriates, controlled foreign corporations, passive foreign investment companies, corporations that accumulate earnings to avoid U.S. federal income tax, persons that hold our common stock as part of a straddle, hedge, conversion transaction, synthetic security or integrated investment or other risk reduction strategy, partnership and other pass-through entities, and investors in such pass-through entities. Such Non-U.S. Holders are urged to consult their own tax advisors to determine the U.S. federal, state, local and other tax consequences that may be relevant to them. Furthermore, the discussion below is based upon the provisions of the Code, and Treasury regulations, rulings and judicial decisions thereunder as of the date hereof, and such authorities may be repealed, revoked or modified, perhaps retroactively, so as to result in U.S. federal income and estate tax consequences different from those discussed below. We have not requested a ruling from the U.S. Internal Revenue Service, or IRS, with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will agree with such statements and conclusions. This discussion assumes that the Non-U.S. Holder holds our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, property held for investment).

The following discussion is for general information only and is not tax advice. Persons considering the purchase of our common stock pursuant to this offering should consult their own tax advisors concerning the U.S. federal income and estate tax consequences of acquiring, owning and disposing of our common stock in light of their particular situations as well as any consequences arising under the laws of any other taxing jurisdiction, including any state, local or foreign tax consequences.

For the purposes of this discussion, a Non-U.S. Holder is, for U.S. federal income tax purposes, a beneficial owner of common stock that is neither a U.S. Holder, a partnership (or other entity treated as a partnership for U.S. federal income tax purposes regardless of its place of organization or formation), nor an entity that is treated as a disregarded entity for U.S. federal income tax purposes (regardless of its place of organization or formation). A U.S. Holder means a beneficial owner of our common stock that is for U.S. federal income tax purposes (a) an individual who is a citizen or resident of the United States, (b) a corporation or other entity treated as a corporation created or organized in or under the laws of the United States, any state thereof or the District of Columbia, (c) an estate the income of which is subject to U.S. federal income taxation regardless of its source or (d) a trust if it (1) is subject to the primary supervision of a court within the United States and one or more U.S. persons have the authority to control all substantial decisions of the trust or (2) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person.

Distributions

Subject to the discussion below, distributions, if any, made on our common stock to a Non-U.S. Holder of our common stock to the extent made out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles) generally will constitute dividends for U.S. tax purposes and will be subject to withholding tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. To obtain a reduced rate of withholding under a treaty, a Non-U.S. Holder generally will be required to provide us with a properly executed IRS Form W-8BEN, or other appropriate form, certifying the Non-U.S. Holder s entitlement to benefits under that treaty. In the case of a Non-U.S. Holder that is an entity, Treasury Regulations and the relevant tax treaty provide rules to determine whether, for purposes of determining the applicability of a tax treaty, dividends will be treated as paid to the entity or to those holding an interest in that entity. If a Non-U.S. Holder holds stock through a financial institution or other agent acting on the holder s behalf, the holder will be required to provide appropriate documentation to such agent. The holder s agent will then be required to provide certification to us or our paying

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agent, either directly or through other intermediaries. If you are eligible for a reduced rate of U.S. federal withholding tax under an income tax treaty, you may be able to obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for a refund with the IRS.

We generally are not required to withhold tax on dividends paid to a Non-U.S. Holder that are effectively connected with the Non-U.S. Holder s conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, are attributable to a permanent establishment that such holder maintains in the United States) if a properly executed IRS Form W-8ECI, stating that the dividends are so connected, is furnished to us (or, if stock is held through a financial institution or other agent, to such agent). In general, such effectively connected dividends will be subject to U.S. federal income tax, on a net income basis at the regular graduated rates, unless a specific treaty exemption applies. A corporate Non-U.S. Holder receiving effectively connected dividends may also be subject to an additional branch profits tax, which is imposed, under certain circumstances, at a rate of 30% (or such lower rate as may be specified by an applicable treaty) on the corporate Non-U.S. Holder s effectively connected earnings and profits, subject to certain adjustments.

To the extent distributions on our common stock, if any, exceed our current and accumulated earnings and profits, they will first reduce your adjusted basis in our common stock, but not below zero, and then will be treated as gain to the extent of any excess, and taxed in the same manner as gain realized from a sale or other disposition of common stock as described in the next section.

Gain on Disposition of Our Common Stock

Subject to the discussion below regarding backup withholding and foreign accounts, a Non-U.S. Holder generally will not be subject to U.S. federal income tax with respect to gain realized on a sale or other disposition of our common stock unless (a) the gain is effectively connected with a trade or business of such holder in the United States (and, if required by an applicable income tax treaty, is attributable to a permanent establishment that such holder maintains in the United States), (b) the Non-U.S. Holder is a nonresident alien individual and is present in the United States for 183 or more days in the taxable year of the disposition and certain other conditions are met, or (c) we are or have been a United States real property holding corporation within the meaning of Code Section 897(c)(2) at any time within the shorter of the five-year period preceding such disposition or such holder s holding period. In general, we would be a United States real property holding corporation if interests in U.S. real estate comprised (by fair market value) at least half of our business assets. We believe that we are not, and do not anticipate becoming, a United States real property holding corporation. Even if we are treated as a United States real property holding corporation, gain realized by a Non-U.S. Holder on a disposition of our common stock will not be subject to U.S. federal income tax so long as (1) the Non-U.S. Holder owned, directly, indirectly and constructively, no more than five percent of our common stock at all times within the shorter of (i) the five-year period preceding the disposition or (ii) the holder s holding period and (2) our common stock is regularly traded on an established securities market. There can be no assurance that our common stock will continue to qualify as regularly traded on an established securities market.

If you are a Non-U.S. Holder described in (a) above, you will be required to pay tax on the net gain derived from the sale at regular graduated U.S. federal income tax rates, unless a specific treaty exemption applies, and corporate Non-U.S. Holders described in (a) above may be subject to the additional branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. If you are an individual Non-U.S. Holder described in (b) above, you will be required to pay a flat 30% tax on the gain derived from the sale, which gain may be offset by U.S. source capital losses (even though you are not considered a resident of the United States).

Information Reporting Requirements and Backup Withholding

Generally, we must report information to the IRS with respect to any dividends we pay on our common stock including the amount of any such dividends, the name and address of the recipient, and the amount, if any, of tax withheld. A similar report is sent to the holder to whom any such dividends are paid. Pursuant to tax treaties or certain other agreements, the IRS may make its reports available to tax authorities in the recipient s country of residence.

Dividends paid by us (or our paying agents) to a Non-U.S. Holder may also be subject to U.S. backup withholding. U.S. backup withholding generally will not apply to a Non-U.S. Holder who provides a properly executed IRS Form W-8BEN or otherwise establishes an exemption.

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Under current U.S. federal income tax law, U.S. information reporting and backup withholding requirements generally will apply to the proceeds of a disposition of our common stock effected by or through a U.S. office of any broker, U.S. or foreign, except that information reporting and such requirements may be avoided if the holder provides a properly executed IRS Form W-8BEN or otherwise meets documentary evidence requirements for establishing Non-U.S. Holder status or otherwise establishes an exemption. Generally, U.S. information reporting and backup withholding requirements will not apply to a payment of disposition proceeds to a Non-U.S. Holder where the transaction is effected outside the United States through a non-U.S. office of a non-U.S. broker. Information reporting and backup withholding requirements may, however, apply to a payment of disposition proceeds if the broker has actual knowledge, or reason to know, that the holder is, in fact, a U.S. person. For information reporting purposes, certain brokers with substantial U.S. ownership or operations will generally be treated in a manner similar to U.S. brokers.

Any amounts of tax withheld under the backup withholding rules may be credits against the tax liability of persons subject to backup withholding, provided that the required information is timely furnished to the IRS.

Foreign Accounts

A U.S. federal withholding tax of 30% may apply on dividends and the gross proceeds of a disposition of our common stock paid to a foreign financial institution (as specifically defined by applicable rules) unless such institution enters into an agreement with the U.S. government to withhold on certain payments and to collect and provide to the U.S. tax authorities substantial information regarding U.S. account holders of such institution (which includes certain equity holders of such institution, as well as certain account holders that are foreign entities with U.S. owners). This U.S. federal withholding tax of 30% will also apply on dividends and the gross proceeds of a disposition of our common stock to a non-financial foreign entity unless such entity provides the withholding agent with either a certification that it does not have any substantial direct or indirect U.S. owners or provides information regarding direct and indirect U.S. owners of the entity. The withholding tax described above will not apply if the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from the rules. Under certain circumstances, a Non-U.S. Holder might be eligible for refunds or credits of such taxes. Holders are encouraged to consult with their own tax advisors regarding the possible implications of the legislation on their investment in our common stock.

Although these rules currently apply to applicable payments made after December 31, 2012, the IRS has issued guidance providing that the withholding provisions described above will generally apply to payments of dividends made on or after January 1, 2014 and to payments of gross proceeds from a sale or other disposition of common stock on or after January 1, 2017.

Federal Estate Tax

An individual Non-U.S. Holder who is treated as the owner of, or has made certain lifetime transfers of, an interest in our common stock will be required to include the value thereof in his or her gross estate for U.S. federal estate tax purposes, and may be subject to U.S. federal estate tax unless an applicable estate tax treaty provides otherwise, even though such individual was not a citizen or resident of the United States at the time of his or her death.

THE PRECEDING DISCUSSION OF U.S. FEDERAL INCOME AND ESTATE TAX CONSIDERATIONS IS FOR GENERAL INFORMATION ONLY. IT IS NOT TAX ADVICE. EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS OWN TAX ADVISOR REGARDING THE TAX CONSEQUENCES OF PURCHASING, HOLDING AND DISPOSING OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES OF ANY PROPOSED CHANGE IN APPLICABLE LAW.

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UNDERWRITING

Subject to the terms and conditions set forth in the underwriting agreement to be dated on or about , 2012, between us and the underwriters named in the table below, we have agreed to sell to the underwriters and the underwriters have severally agreed to purchase from us, the number of shares of our common stock indicated in the table below:

UNDERWRITERS	NUMBER OF SHARES OF COMMON STOCK
Jefferies & Company, Inc.	
Cowen and Company, LLC	
Canaccord Genuity Inc.	
Total	10,000,000

Jefferies & Company, Inc. and Cowen and Company, LLC are acting as joint book- running managers of this offering and as representatives of the underwriters named above.

The underwriting agreement provides that the obligations of the several underwriters are subject to certain conditions precedent such as the receipt by the underwriters of officers certificates and legal opinions and approval of certain legal matters by their counsel. The underwriting agreement provides that the underwriters will purchase all of the shares if any of them are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the non-defaulting underwriters may be increased or the underwriting agreement may be terminated. We have agreed to indemnify the underwriters and certain of their controlling persons against certain liabilities, including liabilities under the Securities Act, and to contribute to payments that the underwriters may be required to make in respect of those liabilities.

The underwriters have advised us that they currently intend to make a market in the common stock. However, the underwriters are not obligated to do so and may discontinue any market- making activities at any time without notice. No assurance can be given as to the liquidity of the trading market for our common stock.

The underwriters are offering shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part. In addition, the underwriters have advised us that they do not intend to confirm sales to any account over which they exercise discretionary authority.

Commission and Expenses

The underwriters have advised us that they propose to offer shares of our common stock to the public at the public offering price set forth on the cover page of this prospectus and to certain dealers at that price less a concession not in excess of $ per share. The underwriters may allow, and certain dealers may reallow, a discount from the concession not in excess of $ per share to certain brokers and dealers. After the offering, the public offering price, concession and reallowance to dealers may be reduced by the representatives. No such reduction will change the amount of proceeds to be received by us as set forth on the cover page of this prospectus.

The following table shows the public offering price, the underwriting discounts and commissions that we are to pay the underwriters and the proceeds, before expenses, to us in connection with this offering. Such amounts are shown assuming both no exercise and full exercise of the underwriters option to purchase additional shares.

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	Per Share		Total	
	Without Option to Purchase Additional Shares	With Option to Purchase Additional Shares	Without Option to Purchase Additional Shares	With Option to Purchase Additional Shares
Public offering price	$	$	$	$
Underwriting discounts and commissions paid by us	$	$	$	$
Proceeds to us, before expenses	$	$	$	$

We have agreed to pay the following expenses of the underwriters relating to the offering: (a) all filing fees and reasonable fees and disbursements incurred in connection with the qualification of the shares in the offering under the securities or blue sky laws of the states and other foreign jurisdictions designated by the representatives and (b) the filing fees and fees and disbursements of underwriters counsel relating to the review and approval by Financial Industry Regulatory Authority, or FINRA, of the terms of the offering up to an aggregate of $20,000. We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately $550,000.

Listing

Our shares of common stock are listed on The NASDAQ Global Market under the trading symbol ACRX.

Option to Purchase Additional Shares

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase up to an aggregate of additional shares of common stock at the public offering price set forth on the cover page of this prospectus, less underwriting discounts and commissions. If the underwriters exercise this option, each underwriter will be obligated, subject to specified conditions, to purchase a number of additional shares proportionate to that underwriter s initial purchase commitment as indicated in the table above. This option may be exercised only if the underwriters sell more shares than the total number set forth on the cover page of this prospectus.

No Sales of Similar Securities

We, along with our executive officers, directors and their affiliated funds have agreed with the underwriters that, subject to certain exceptions, for a period of 90 days following the date of the underwriting agreement, we or they will not offer, pledge, announce the intention to sell, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, make any short sale or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock or any securities convertible into, exercisable or exchangeable for or that represent the right to receive our common stock (including without limitation, common stock which may be deemed to be beneficially owned by such director, executive officer or security holder in accordance with rules and regulations of the SEC and securities that may be issued upon exercise of a stock option or warrant) whether owned or later acquired, or enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of our common stock or such other securities, or make any demand for, or exercise any right with respect to, the registration of any shares of our common stock or any security convertible into or exercisable or exchangeable for our common stock.

The 90-day lock-up period described in the preceding paragraph will be extended if (i) during the last 17 days of the 90-day lock-up period we issue an earnings release or material news or a material event relating to us occurs, or (ii) prior to the expiration of the 90-day lock-up period, we announce that we will release earnings results during the 16-day period beginning on the last day of the 90-day period, in which case the restrictions described in the preceding paragraph will continue to apply until the expiration of the 18-day period beginning on the issuance of the release or the occurrence of the material news or material event, unless such extension is waived, in writing, by Jefferies & Company, Inc. on behalf of the underwriters; *provided*, *however*, that such extension will not apply if (i) our securities are actively traded securities (as defined in Regulation M of the Exchange Act, (ii) we meet the applicable requirements of paragraph (a)(1) of Rule 139 under the Securities Act, in the

manner contemplated by NASD Conduct Rule 2711(f)(4), and (iii) the provisions of NASD Conduct Rule 2711(f)(4) are not applicable to any

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research reports relating to us published or distributed by any of the underwriters during the 15 days before or after the last day of the lock-up period (before giving effect to such extension).

Among other exceptions and subject to certain conditions, the foregoing restrictions will not apply to (i) the sale of the shares of common stock to the underwriters as contemplated by the underwriting agreement, (ii) our ability to issue up to 5% of our outstanding common stock, as measured immediately following this offering, to one or more counterparties in connection with certain strategic transactions, including partnering or collaboration arrangements, that we may enter into in the future, (iii) certain transfers by gift, or by will or intestate succession, (iv) distributions by the locked up party to its partners, members or stockholders, (v) the exercise or settlement of any equity awards pursuant to our equity incentive plans or the exercise of warrants issued by us, provided that the underlying securities shall continue to be subject to the restrictions set forth in the lock- up agreement, (vi) the establishment of a trading plan pursuant to Rule 10b5- 1 under the Exchange Act for the sale of our securities, provided that such plan does not provide for any sales during the lock- up period, and (vii) transfers of our common stock, or any securities convertible into, exercisable or exchangeable for our common stock, pursuant to a sale or an offer to purchase 100% of our outstanding common stock, whether pursuant to a merger, tender offer or otherwise, to a third party or group of third parties.

Jefferies & Company, Inc. may, in its sole discretion and at any time or from time to time before the termination of the 90- day period, without public notice, release all or any portion of the securities subject to lock- up agreements. There are no existing agreements between the underwriters and any of our stockholders who have executed a lock- up agreement, providing consent to the sale of shares prior to the expiration of the lock- up period.

Stabilization

The underwriters have advised us that, pursuant to Regulation M under the Securities Exchange Act of 1934, as amended, certain persons participating in the offering may engage in short sale transactions, stabilizing transactions, syndicate covering transactions or the imposition of penalty bids in connection with this offering. These activities may have the effect of stabilizing or maintaining the market price of the common stock at a level above that which might otherwise prevail in the open market. Establishing short sales positions may involve either covered short sales or naked short sales.

Covered short sales are sales made in an amount not greater than the underwriters option to purchase additional shares of our common stock in this offering. The underwriters may close out any covered short position by either exercising their option to purchase additional shares of our common stock or purchasing shares of our common stock in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option to purchase additional shares.

Naked short sales are sales in excess of the option to purchase additional shares of our common stock. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the shares of our common stocks in the open market after pricing that could adversely affect investors who purchase in this offering.

A stabilizing bid is a bid for the purchase of shares of common stock on behalf of the underwriters for the purpose of fixing or maintaining the price of the common stock. A syndicate covering transaction is the bid for or the purchase of common stock on behalf of the underwriters to reduce a short position incurred by the underwriters in connection with the offering. Similar to other purchase transactions, the underwriter s purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. A penalty bid is an arrangement permitting the underwriters to reclaim the selling concession otherwise accruing to a syndicate member in connection with the offering if the common stock originally sold by such syndicate member are purchased in a syndicate covering transaction and therefore have not been effectively placed by such syndicate member.

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Neither we, nor any of the underwriters makes any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. The underwriters are not obligated to engage in these activities and, if commenced, any of the activities may be discontinued at any time.

The underwriters may also engage in passive market making transactions in our common stock on The NASDAQ Global Market in accordance with Rule 103 of Regulation M during a period before the commencement of offers or sales of shares of our common stock in this offering and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker s bid, that bid must then be lowered when specified purchase limits are exceeded.

Electronic Distribution

A prospectus in electronic format may be made available by e- mail or on the web sites or through online services maintained by one or more of the underwriters or their affiliates. In those cases, prospective investors may view offering terms online and may be allowed to place orders online. The underwriters may agree with us to allocate a specific number of shares of common stock for sale to online brokerage account holders. Any such allocation for online distributions will be made by the underwriters on the same basis as other allocations. Other than the prospectus in electronic format, the information on the underwriters web sites and any information contained in any other web site maintained by any of the underwriters is not part of this prospectus, has not been approved and/or endorsed by us or the underwriters and should not be relied upon by investors.

Affiliations and Conflict of Interest

The underwriters and certain of their affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. The underwriters and certain of their affiliates have, from time to time, performed, and may in the future perform, various financial advisory and investment banking services for the issuer, for which they received or will receive customary fees and expenses.

In the ordinary course of their various business activities, the underwriters and certain of their affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers, and such investment and securities activities may involve securities and/or instruments of the issuer. The underwriters and certain of their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

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NOTICE TO INVESTORS

Australia

This prospectus is not a disclosure document for the purposes of Australia s Corporations Act 2001 (Cth) of Australia, or Corporations Act, has not been lodged with the Australian Securities & Investments Commission and is only directed to the categories of exempt persons set out below. Accordingly, if you receive this prospectus in Australia:

You confirm and warrant that you are either:

- a sophisticated investor under section 708(8)(a) or (b) of the Corporations Act;
- a sophisticated investor under section 708(8)(c) or (d) of the Corporations Act and that you have provided an accountant s certificate to the company which complies with the requirements of section 708(8)(c)(i) or (ii) of the Corporations Act and related regulations before the offer has been made; or
- a professional investor within the meaning of section 708(11)(a) or (b) of the Corporations Act.

To the extent that you are unable to confirm or warrant that you are an exempt sophisticated investor or professional investor under the Corporations Act any offer made to you under this prospectus is void and incapable of acceptance.

You warrant and agree that you will not offer any of the shares issued to you pursuant to this prospectus for resale in Australia within 12 months of those shares being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

European Economic Area

In relation to each member state of the European Economic Area which has implemented the Prospectus Directive, each referred to herein as a Relevant Member State, with effect from and including the date on which the Prospectus Directive is implemented in that Relevant Member State, referred to herein as the Relevant Implementation Date, no offer of any securities which are the subject of the offering contemplated by this prospectus has been or will be made to the public in that Relevant Member State other than any offer where a prospectus has been or will be published in relation to such securities that has been approved by the competent authority in that Relevant Member State or, where appropriate, approved in another Relevant Member State and notified to the relevant competent authority in that Relevant Member State in accordance with the Prospectus Directive, except that with effect from and including the Relevant Implementation Date, an offer of such securities may be made to the public in that Relevant Member State:

- to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives of the underwriters for any such offer; or
- in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of securities shall require the Company or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

For the purposes of this provision, the expression an offer to the public in relation to any securities in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the securities to be offered so as to enable an investor to decide to purchase or subscribe the securities, as the same may be varied in that Relevant Member State by any measure implementing the Prospectus Directive in that Relevant Member State and the expression Prospectus Directive means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State), and includes any relevant implementing measure in the Relevant Member State and the expression 2010 PD Amending Directive means Directive 2010/73/EU.

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Hong Kong

No securities have been offered or sold, and no securities may be offered or sold, in Hong Kong, by means of any document, other than to persons whose ordinary business is to buy or sell shares or debentures, whether as principal or agent; or to professional investors as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong and any rules made under that Ordinance; or in other circumstances which do not result in the document being a prospectus as defined in the Companies Ordinance (Cap. 32) of Hong Kong or which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap.32) of Hong Kong. No document, invitation or advertisement relating to the securities has been issued or may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted under the securities laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only to professional investors as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong and any rules made under that Ordinance.

This prospectus has not been registered with the Registrar of Companies in Hong Kong. Accordingly, this prospectus may not be issued, circulated or distributed in Hong Kong, and the securities may not be offered for subscription to members of the public in Hong Kong. Each person acquiring the securities will be required, and is deemed by the acquisition of the securities, to confirm that he is aware of the restriction on offers of the securities described in this prospectus and the relevant offering documents and that he is not acquiring, and has not been offered any securities in circumstances that contravene any such restrictions.

Japan

The offering has not been and will not be registered under the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948 of Japan, as amended), or FIEL, and the Initial Purchaser will not offer or sell any securities, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means, unless otherwise provided herein, any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re- offering or resale, directly or indirectly, in Japan or to a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the FIEL and any other applicable laws, regulations and ministerial guidelines of Japan.

Singapore

This prospectus has not been and will not be lodged or registered with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or the invitation for subscription or purchase of the securities may not be issued, circulated or distributed, nor may the securities be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to the public or any member of the public in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, (ii) to a relevant person as defined under Section 275(2), or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions, specified in Section 275 of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of any other applicable provision of the SFA.

Where the securities are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

a corporation (which is not an accredited investor as defined under Section 4A of the SFA) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or

a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries rights and interest in that trust shall not be transferable for six months after that corporation or that trust has acquired the Offer Shares under Section 275 of the SFA except:

to an institutional investor under Section 274 of the SFA or to a relevant person defined in Section 275(2) of the SFA, or to any person pursuant to an offer that is made on terms that such shares, debentures and units of shares and debentures of that corporation or such rights and interest in that trust are acquired at a consideration of not less than $200,000 (or its equivalent in a foreign

currency) for each transaction,

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whether such amount is to be paid for in cash or by exchange of securities or other assets, and further for corporations, in accordance with the conditions, specified in Section 275 of the SFA;

where no consideration is given for the transfer; or

where the transfer is by operation of law.

Switzerland

The securities may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This prospectus has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this prospectus nor any other offering or marketing material relating to the securities or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this prospectus nor any other offering or marketing material relating to the offering, the Company or the securities have been or will be filed with or approved by any Swiss regulatory authority. In particular, this prospectus will not be filed with, and the offer of securities will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA, or FINMA, and the offer of securities has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of securities.

United Kingdom

This prospectus is only being distributed to, and is only directed at, persons in the United Kingdom that are qualified investors within the meaning of Article 2(1)(e) of the Prospectus Directive that are also (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended, referred to herein as the Order, and/or (ii) high net worth entities falling within Article 49(2)(a) to (d) of the Order and other persons to whom it may lawfully be communicated. Each such person is referred to herein as a Relevant Person.

This prospectus and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other persons in the United Kingdom. Any person in the United Kingdom that is not a Relevant Person should not act or rely on this document or any of its contents.

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LEGAL MATTERS

The validity of our common stock offered by this prospectus will be passed upon for us by Cooley LLP, Palo Alto, California. Cooley LLP and certain attorneys and investment funds affiliated with the firm collectively own an aggregate of 19,022 shares of our common stock. Morgan, Lewis & Bockius LLP, New York, New York, is counsel to the underwriters in connection with this offering.

EXPERTS

The financial statements of AcelRx Pharmaceuticals, Inc. appearing in AcelRx Pharmaceuticals, Inc. s Annual Report (Form 10-K) for the year ended December 31, 2011 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated herein by reference. Such financial statements are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

Any person to whom this prospectus is delivered may request copies of this prospectus and any related amendments or supplements, without charge, by written or telephonic request directed to James H. Welch, Chief Financial Officer, AcelRx Pharmaceuticals, Inc., 351 Galveston Drive, Redwood City, CA 94063; telephone: (650) 216-3500.

We have filed with the SEC a registration statement on Form S-1 under the Securities Act with respect to the shares of our common stock offered under this prospectus. This prospectus does not contain all of the information set forth in the registration statement and the accompanying exhibits. Some items included in the registration statement are omitted from this prospectus in accordance with the rules and regulations of the SEC. For further information with respect to us and the common stock offered in this prospectus, we refer you to the registration statement and the accompanying exhibits. Statements contained or incorporated by reference in this prospectus as to the contents of any contract, agreement or any other document are summaries of the material terms of these contract, agreement or other document. With respect to each of these contracts, agreements or other documents filed as an exhibit to the registration statement, reference is made to such exhibit for a more complete description of the matter involved. A copy of the registration statement, and the accompanying exhibits, may be inspected without charge and copied at the SEC s Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room. The SEC maintains a web site that contains reports, proxy and information statements and other information regarding registrants that file electronically with the SEC. The address of the SEC s website is http://www.sec.gov.

We are subject to the information and reporting requirements of the Exchange Act and, as a result, are required to file periodic reports, proxy statements and other information with the SEC. These periodic reports, proxy statements and other information will be available for inspection and copying at the SEC s Public Reference Room and the SEC s website noted above. We also maintain a website at http://www.acelrx.com. Our website, and the information contained on the website, are not incorporated into and are not part of this prospectus. You may access our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act with the SEC free of charge at our website as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC.

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INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus. Information in this prospectus supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus. We incorporate by reference into this prospectus and the registration statement of which this prospectus is a part the information or documents listed below that we have filed with the SEC (Commission File No. 001-35068):

- our annual report on Form 10-K for the year ended December 31, 2011, filed with the SEC on March 23, 2012;
- our quarterly reports on Form 10-Q for the quarters ended March 31, 2012, June 30, 2012 and September 30, 2012 filed with the SEC on May 9, 2012, August 10, 2012 and November 6, 2012, respectively; and
- our current reports on Form 8-K filed with the SEC on January 25, 2012, February 13, 2012, April 12, 2012, May 30, 2012, June 4, 2012, July 27, 2012, August 3, 2012, August 31, 2012 and November 15, 2012.

We will furnish without charge to you, on written or oral request, a copy of any or all of the documents incorporated by reference, including exhibits to these documents. You should direct any requests for documents to James H. Welch, Chief Financial Officer, AcelRx Pharmaceuticals, Inc., 351 Galveston Drive, Redwood City, CA 94063; telephone: (650) 216-3500.

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus will be deemed modified, superseded or replaced for purposes of this prospectus to the extent that a statement contained in this prospectus modifies, supersedes or replaces such statement.

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These product candidates have 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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10,000,000 Shares

Common Stock

PRELIMINARY PROSPECTUS

Joint Book-Running Managers

Jefferies

Cowen and Company

Co-Lead Manager

Canaccord Genuity

, 2012

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PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

Item 13. Other Expenses of Issuance and Distribution

The following table sets forth the fees and expenses, other than estimated underwriting discounts and commissions, payable in connection with the registration of the common stock hereunder. All amounts are estimates except the SEC registration fee and the FINRA filing fee.

SEC registration fee	$ 6,820
FINRA filing fee	8,000
Printing expenses	25,000
Legal fees and expenses	350,000
Accounting fees and expenses	150,000
Transfer agent and registrar fees	5,000
Miscellaneous expenses	5,180
Total	550,000

Item 14. Indemnification of Directors and Officers

Section 145 of the Delaware General Corporation Law permits a corporation to include in its charter documents, and in agreements between the corporation and its directors and officers, provisions expanding the scope of indemnification beyond that specifically provided by the current law.

The Registrant s amended and restated certificate of incorporation provides for the indemnification of directors to the fullest extent permissible under Delaware law.

The Registrant s amended and restated bylaws provide for the indemnification of officers, directors and third parties acting on the Registrant s behalf if such persons act in good faith and in a manner reasonably believed to be in and not opposed to the Registrant s best interest, and, with respect to any criminal action or proceeding, such indemnified party had no reason to believe his or her conduct was unlawful.

The Registrant has entered into indemnification agreements with each of its directors and executive officers, in addition to the indemnification provisions provided for in its charter documents, and the Registrant intends to enter into indemnification agreements with any new directors and executive officers in the future.

The underwriting agreement (to be filed as Exhibit 1.1 hereto) will provide for indemnification by the underwriters of the Registrant, the Registrant s executive officers and directors, and indemnification of the underwriters by the Registrant for certain liabilities, including liabilities arising under the Securities Act of 1933, as amended, or the Securities Act, in connection with matters specifically provided in writing by the underwriters for inclusion in the registration statement.

The Registrant maintains insurance on behalf of any person who is or was a director or officer against any loss arising from any claim asserted against him or her and incurred by him or her in that capacity, subject to certain exclusions and limits of the amount of coverage.

Item 15. Recent Sales of Unregistered Securities

Since November 1, 2009, the Registrant has issued and sold the following unregistered securities (share amounts and per share amounts have been retroactively adjusted to give effect to a 1-for-4 reverse stock split that became effective on January 28, 2011):

(a) Issuances of Capital Stock

1. In November 2009, the Registrant issued 3,757,253 shares of the Registrant s Series C convertible preferred stock to eight (8) purchasers at approximately $3.94 per share, for approximately $14.8 million. Upon completion of the Registrant s initial public offering, or the IPO, these shares of Series C convertible preferred stock converted into 3,757,253 shares of the Registrant s common stock.

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2. In January 2010, the Registrant issued 19,275 shares of the Registrant s Series C convertible preferred stock to two (2) purchasers at approximately $3.94 per share, for approximately $76,000. Upon completion of the IPO, these shares of Series C convertible preferred stock converted into 19,275 shares of the Registrant s common stock.

3. In June 2012, the Registrant issued 2,922,337 shares of common stock and warrants to purchase 2,630,103 shares of common stock to six (6) purchasers in immediately separable units, with each unit consisting of (i) one share of common stock and (ii) a warrant to purchase 0.9 of a share of common stock. The per share exercise price of the warrants was $3.40. The offering price per unit was $3.40 for non-affiliated investors, and $3.5125 for affiliated investors for an aggregate amount of $10.0 million.

4. Between November 1, 2009 and February 11, 2011, the date of the IPO, the Registrant issued and sold an aggregate of 10,955 shares of its common stock to the Registrant s employees, consultants and directors at prices ranging from $1.20 to $5.52 per share pursuant to exercises of options granted under the Registrant s 2006 Stock Plan.

5. Upon completion of the IPO, the convertible promissory notes held by the eight (8) purchasers described in paragraph 9 below converted into an aggregate of 2,034,438 shares of the Registrant s common stock at a conversion price equal to $4.00 per share, which conversion price was equal to eighty percent (80%) of the price per share of the Registrant s common stock sold by the Registrant in the IPO.

(b) Stock Option Grants and Warrant Issuances

6. Between November 1, 2009 and February 11, 2011, the Registrant granted stock options to purchase an aggregate of 1,441,609 shares of the Registrant s common stock at exercise prices ranging from $1.20 to $5.32 per share to a total of 22 employees, consultants and directors of the Registrant under the Registrant s 2006 Stock Plan. On December 27, 2010, the Registrant amended options to purchase an aggregate of 1,233,485 shares of the Registrant s common stock originally granted to 15 employees on June 15, 2010 to increase the exercise price of these options from $1.20 per share to $2.56 per share.

7. In September 2010, in connection with a bridge loan financing, the Registrant granted warrants to purchase an aggregate of $2.0 million of its preferred stock to eight (8) purchasers. In connection with the IPO, these warrants became warrants to purchase 507,245 shares of the Registrant s Series C convertible preferred stock (convertible into 507,245 shares of the Registrant s common stock) at an exercise price of approximately $3.94 per share.

8. In June 2011, in connection with the Loan Agreement defined below, the Registrant issued a warrant to two (2) lenders which together are exercisable for an aggregate of 274,508 shares of common stock with an exercise price of $3.06.

(c) Issuances of Convertible Promissory Notes

9. In September 2010, in connection with a bridge loan financing, the Registrant issued convertible promissory notes to eight (8) purchasers for an aggregate principal amount of $8.0 million. Upon completion of the IPO, these convertible promissory notes converted into 2,034,438 shares of the Registrant s common stock at a conversion price equal to $4.00 per share, which conversion price was equal to eighty percent (80%) of the price per share of the Registrant s common stock sold by the Registrant in the IPO.

10. In June 2011, the Registrant entered into a loan and security agreement, or the Loan Agreement, with two (2) lenders under which the Registrant has borrowed up to $20.0 million in two tranches of $10.0 million each, represented by secured convertible term promissory notes, or the Notes. Subject to certain conditions and limitations set forth in the Loan Agreement, the Registrant has

the right to convert up to $3.0 million of scheduled principal installments under the Notes into freely tradable shares of the Registrant s common stock, equal to the number determined by dividing (x) the product of (A) the principal amount to be paid in shares of common stock and (B) 103%, by (y) $5.73 (subject to certain proportional adjustments as provided for in the Loan Agreement).

The issuances of securities described above in paragraphs 1 through 3, 5, and 7 through 10 were exempt from registration under the Securities Act of 1933, as amended, or the Securities Act, in reliance on Section 4(2) of the Securities Act, and Regulation D promulgated thereunder, as transactions by an issuer not involving any public offering. The purchasers of the securities in these transactions represented that they were accredited investors and that they were

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acquiring the securities for investment only and not with a view toward the public sale or distribution thereof. Such purchasers received written disclosures that the securities had not been registered under the Securities Act, and that any resale must be made pursuant to a registration statement or an available exemption from registration. All purchasers either received adequate financial statement or non-financial statement information about the Registrant or had adequate access, through their relationship with the Registrant, to financial statement or non-financial statement information about the Registrant. The sale of these securities was made without general solicitation or advertising.

The issuance of securities described above in paragraphs 4 and 6 were exempt from registration under the Securities Act, in reliance on Rule 701 of the Securities Act, pursuant to compensatory benefit plans or agreements approved by the Registrant s board of directors.

Item 16. Exhibits and Financial Statement Schedules

(a) Exhibits

Exhibit Number	Description of the Document
1.1	Form of Underwriting Agreement.
3.1	Amended and Restated Certificate of Incorporation of the Registrant, currently in effect.(1)
3.2	Amended and Restated Bylaws of the Registrant, currently in effect.(2)
4.1	Reference is made to Exhibits 3.1 through 3.2.
4.2	Specimen Common Stock Certificate of the Registrant.(3)
4.3	Second Amended and Restated Investors Rights Agreement, among the Registrant and certain of its security holders, dated as of November 23, 2009.(4)
4.4	Warrant to Purchase Stock of the Registrant, issued to Wells Fargo Bank, N.A., dated March 15, 2007.(5)
4.5	Warrant to Purchase Preferred Stock of the Registrant, issued to Pinnacle Ventures II Equity Holdings, L.L.C., dated September 16, 2008.(6)
4.6	Warrant to Purchase Common Stock of the Registrant, issued to Hercules Technology II, L.P., dated as of June 29, 2011.(7)
4.7	Warrant to Purchase Common Stock of the Registrant, issued to Hercules Technology Growth Capital, dated as of June 29, 2011.(8)
4.8	Form of Warrant issued to certain purchasers pursuant to the Securities Purchase Agreement dated May 29, 2012, between the Registrant and the purchasers identified therein.(9)
5.1	Opinion of Cooley LLP.
10.1+	Form of Indemnification Agreement between the Registrant and each of its directors and executive officers.(10)
10.2+	2006 Stock Plan, as amended.(11)
10.3+	Forms of Notice of Grant of Stock Option, Stock Option Agreement and Stock Option Exercise Notice under 2006 Stock Plan.(12)
10.4+	2011 Equity Incentive Plan.(13)
10.5+	Forms of Stock Option Grant Notice, Notice of Exercise and Option Agreement under 2011 Equity Incentive Plan.(14)
10.6+	Forms of Restricted Stock Unit Grant Notice and Restricted Stock Unit Agreement under 2011 Equity Incentive Plan.(15)
10.7+	2011 Employee Stock Purchase Plan.(16)

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Exhibit Number	Description of the Document
10.8	Lease Agreement, between Metropolitan Life Insurance Company and Registrant, dated January 2, 2007.(17)
10.9	Lease between Metropolitan Life Insurance Company and the Registrant, dated December 15, 2011.(18)
10.10	Loan and Security Agreement between Registrant and Pinnacle Ventures, L.L.C., as agent for the Lenders (as defined therein) and the Lenders, dated September 16, 2008.(19)
10.11	Note and Warrant Purchase Agreement between Registrant and the Purchasers defined therein, dated September 14, 2010, as amended.(20)
10.12	Loan and Security Agreement among the Registrant, Hercules Technology II, L.P. and Hercules Technology Growth Capital, dated as of June 29, 2011.(21)
10.13	Award/Contract with the U.S. Army Medical Research and Materiel Command, dated May 26, 2011.(22)
10.15+	Amended and Restated Offer Letter between the Registrant and Larry Hamel, dated December 31, 2010.(23)
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(7) Incorporated herein by reference to Exhibit 4.4 to the Registrant s current report on Form 8-K (File No. 001-35068), as filed with the SEC on June 30, 2011.

(8) Incorporated herein by reference to Exhibit 4.5 to the Registrant s current report on Form 8-K (File No. 001-35068), as filed with the SEC on June 30, 2011.

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(23) Incorporated herein by reference to Exhibit 10.14 to the Registrant s registration statement on Form S-1, as amended (File No. 333-170594), as filed with the SEC on January 7, 2011.

(24) Incorporated herein by reference to Exhibit 10.15 to the Registrant s registration statement on Form S-1, as amended (File No. 333-170594), as filed with the SEC on January 7, 2011.

(25) Incorporated herein by reference to Exhibit 10.16 to the Registrant s registration statement on Form S-1, as amended (File No. 333-170594), as filed with the SEC on January 7, 2011.

(26) Incorporated herein by reference to Exhibit 10.17 to the Registrant s registration statement on Form S-1, as amended (File No. 333-170594), as filed with the SEC on January 7, 2011.

(27) Incorporated herein by reference to Exhibit 10.18 to the Registrant s registration statement on Form S-1, as amended (File No. 333-170594), as filed with the SEC on January 7, 2011.

(28) Incorporated by reference to the information under Item 11. Executive Compensation Director Compensation Non-Employee Director Compensation of the Registrant s annual report on Form 10-K (File No. 001-35068), as filed with the SEC on March 23, 2012.

(29) Incorporated herein by reference to Exhibit 10.1 to the Registrant s current report on Form 8-K (File No. 001-35068), as filed with the SEC on May 16, 2011.

(30) Incorporated herein by reference to Exhibit 10.23 to the Registrant s current report on Form 8-K (File No. 001-35068), as filed with the SEC on May 30, 2012.

(31) Incorporated herein by reference to Exhibit 10.1 to the Registrant s current report on Form 8-K (File No. 001-35068), as filed with the SEC on August 31, 2012.

(32) Incorporated by reference to the information under Item 5.02 of the Registrant s current report on Form 8-K (File No. 001- 35068), as filed with the SEC on February 13, 2012.

(b) Financial Statement Schedules

No financial statement schedules are provided because the information called for is not required or is shown either in the financial statements or the notes related thereto incorporated by reference from the Registrant s annual report on Form 10-K for the year ended December 31, 2011.

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Item 17. Undertakings

Insofar as indemnification for liabilities arising under the Securities Act of 1933, as amended, may be permitted to directors, officers and controlling persons of the Registrant pursuant to the foregoing provisions, or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act of 1933, as amended, and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act of 1933, as amended, and will be governed by the final adjudication of such issue.

The Registrant hereby undertakes that:

(a) For purposes of determining any liability under the Securities Act of 1933, as amended, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the Registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act of 1933, as amended, shall be deemed to be part of this registration statement as of the time it was declared effective.

(b) For the purpose of determining any liability under the Securities Act of 1933, as amended, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

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SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant has duly caused this Amendment No 1 to Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Redwood City, State of California, on the 4th day of December 2012.

ACELRX PHARMACEUTICALS, INC.

By: /s/ Richard A. King
Richard A. King
President and Chief Executive Officer

Pursuant to the requirements of the Securities Act of 1933, as amended, this Amendment No 1 to Registration Statement has been signed by the following persons in the capacities indicated.

Signature	Title	Date
/s/ Richard A. King **Richard A. King**	Chief Executive Officer and Director *(Principal Executive Officer)*	December 4, 2012
/s/ James H. Welch **James H. Welch**	Chief Financial Officer *(Principal Financial and Accounting Officer)*	December 4, 2012
* **Mark G. Edwards**	Director	December 4, 2012
* **Stephen J. Hoffman, Ph.D., M.D.**	Director	December 4, 2012
* **Guy P. Nohra**	Director	December 4, 2012
* **Pamela P. Palmer, M.D., Ph.D.**	Director	December 4, 2012
* **Howard B. Rosen**	Director	December 4, 2012
* **Thomas A. Schreck**	Director	December 4, 2012
* **Mark Wan**	Director	December 4, 2012

*By: /s/ Richard A. King
Richard A. King

Attorney-in-fact

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EXHIBIT INDEX

Exhibit Number	Description of the Document
1.1	Form of Underwriting Agreement.
3.1	Amended and Restated Certificate of Incorporation of the Registrant, currently in effect.(1)
3.2	Amended and Restated Bylaws of the Registrant, currently in effect.(2)
4.1	Reference is made to Exhibits 3.1 through 3.2.
4.2	Specimen Common Stock Certificate of the Registrant.(3)
4.3	Second Amended and Restated Investors Rights Agreement, among the Registrant and certain of its security holders, dated as of November 23, 2009.(4)
4.4	Warrant to Purchase Stock of the Registrant, issued to Wells Fargo Bank, N.A., dated March 15, 2007.(5)
4.5	Warrant to Purchase Preferred Stock of the Registrant, issued to Pinnacle Ventures II Equity Holdings, L.L.C., dated September 16, 2008.(6)
4.6	Warrant to Purchase Common Stock of the Registrant, issued to Hercules Technology II, L.P., dated as of June 29, 2011.(7)
4.7	Warrant to Purchase Common Stock of the Registrant, issued to Hercules Technology Growth Capital, dated as of June 29, 2011.(8)
4.8	Form of Warrant issued to certain purchasers pursuant to the Securities Purchase Agreement dated May 29, 2012, between the Registrant and the purchasers identified therein.(9)
5.1	Opinion of Cooley LLP.
10.1+	Form of Indemnification Agreement between the Registrant and each of its directors and executive officers.(10)
10.2+	2006 Stock Plan, as amended.(11)
10.3+	Forms of Notice of Grant of Stock Option, Stock Option Agreement and Stock Option Exercise Notice under 2006 Stock Plan.(12)
10.4+	2011 Equity Incentive Plan.(13)
10.5+	Forms of Stock Option Grant Notice, Notice of Exercise and Option Agreement under 2011 Equity Incentive Plan.(14)
10.6+	Forms of Restricted Stock Unit Grant Notice and Restricted Stock Unit Agreement under 2011 Equity Incentive Plan.(15)
10.7+	2011 Employee Stock Purchase Plan.(16)
10.8	Lease Agreement, between Metropolitan Life Insurance Company and Registrant, dated January 2, 2007.(17)
10.9	Lease between Metropolitan Life Insurance Company and the Registrant, dated December 15, 2011.(18)
10.10	Loan and Security Agreement between Registrant and Pinnacle Ventures, L.L.C., as agent for the Lenders (as defined therein) and the Lenders, dated September 16, 2008.(19)
10.11	Note and Warrant Purchase Agreement between Registrant and the Purchasers defined therein, dated September 14, 2010, as amended.(20)
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