

ACELRX PHARMACEUTICALS INC

Form 424B5

July 17, 2013

Table of Contents

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Registration No. 333-183237

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been declared effective by the Securities and Exchange Commission. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting offers to buy these securities, in any state or other jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED JULY 17, 2013

PROSPECTUS SUPPLEMENT

(To Prospectus dated August 31, 2012)

Shares

Common Stock

We are offering _____ shares of our common stock. Our common stock is listed on The NASDAQ Global Market under the symbol **ACRX**. On July 16, 2013, the last reported sale price of our common stock on The NASDAQ Global Market was \$11.98 per share.

Investing in our common stock involves a high degree of risk. Please read Risk Factors beginning on page S-9 of this prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement or the accompanying 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⁾ We have agreed to reimburse the underwriters for certain FINRA related expenses. See Underwriting. Delivery of the shares of common stock is expected to be made on or about July , 2013. We have granted the underwriters an option for a period of 30 days to purchase up to an additional 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

Co-Manager

Piper Jaffray

Guggenheim Securities

Prospectus Supplement dated July , 2013

Table of Contents

TABLE OF CONTENTS

	PAGE
Prospectus Supplement	
<u>About this Prospectus Supplement</u>	S-iii
<u>Prospectus Supplement Summary</u>	S-1
<u>Risk Factors</u>	S-9
<u>Special Note Regarding Forward-Looking Statements</u>	S-32
<u>Use of Proceeds</u>	S-34
<u>Dilution</u>	S-35
<u>Material U.S. Federal Income Tax Consequences to Non-U.S. Holders</u>	S-37
<u>Underwriting</u>	S-40
<u>Legal Matters</u>	S-47
<u>Experts</u>	S-47
<u>Where You Can Find More Information</u>	S-47
<u>Incorporation of Certain Information by Reference</u>	S-48
	PAGE
Prospectus	
<u>About this Prospectus</u>	i
<u>Prospectus Summary</u>	1
<u>Risk Factors</u>	6
<u>Special Note Regarding Forward-Looking Statements</u>	6
<u>Use of Proceeds</u>	8
<u>Selected Financial Data</u>	8
<u>Description of Capital Stock</u>	9
<u>Description of Debt Securities</u>	13
 Table of Contents	 3

<u>Description of Warrants</u>	20
<u>Legal Ownership of Securities</u>	22

Table of Contents

	PAGE
<u>Plan of Distribution</u>	26
<u>Legal Matters</u>	28
<u>Experts</u>	28
<u>Where You Can Find More Information</u>	28
<u>Incorporation of Certain Information by Reference</u>	28

You should rely only on the information contained in or incorporated by reference in this prospectus supplement, the accompanying prospectus and in any free writing prospectus that we have authorized for use in connection with this offering. We have not, and the underwriters have not, authorized anyone to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We and the underwriters take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. 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 supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying 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, regardless of the time of delivery of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying 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 we have referred you to in the sections of this prospectus supplement entitled **Where You Can Find More Information** and **Incorporation of Certain Information by Reference**.

Table of Contents

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of common stock and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus dated August 31, 2012, including the documents incorporated by reference therein, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or in any document incorporated by reference that was filed with the Securities and Exchange Commission, or SEC, before the date of this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement. If any statement in one of these documents is inconsistent with a statement in another document having a later date or example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement.

All references in this prospectus supplement and the accompanying prospectus to AcelRx, AcelRx Pharmaceuticals, the company, we, us, similar references refer to AcelRx Pharmaceuticals, Inc., except where the context otherwise requires or as otherwise indicated.

ACELRX, NANOTAB and ACCELERATE.INNOVATE.ALLEVIATE are registered trademarks of AcelRx Pharmaceuticals, Inc. Other trademarks of AcelRx Pharmaceuticals, Inc., including ZALVISO, appearing in this prospectus are the property of AcelRx Pharmaceuticals, Inc. This report also contains trademarks and trade names that are the property of their respective owners.

Table of Contents

PROSPECTUS SUPPLEMENT SUMMARY

*This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference into this prospectus supplement. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in our common stock. For a more complete understanding of our company and this offering, you should read and consider carefully the more detailed information in this prospectus supplement and the accompanying prospectus, including the information incorporated by reference in this prospectus supplement and the accompanying prospectus, and the information included in any free writing prospectus that we have authorized for use in connection with this offering. If you invest in our common stock, you are assuming a high degree of risk. See *Risk Factors* beginning on page S-9 of this prospectus supplement.*

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, Zalviso, formerly known as the Sufentanil NanoTab PCA System, or ARX-01, is designed to improve the management of moderate-to-severe acute pain in patients in the hospital setting. Although widely used, the current standard of care for patients with moderate-to-severe post-operative pain in the hospital, intravenous patient-controlled analgesia, or IV PCA, has been shown to cause harm and inconvenience to patients following surgery because of the side effects of commonly used IV PCA opioids, the invasive IV needle route of delivery and the inherent potential for programming and delivery errors associated with the complexity of infusion pumps.

Zalviso

Zalviso is an investigational pre-programmed, non-invasive, handheld system that allows hospitalized patients with moderate-to-severe acute pain to self-dose with sublingual sufentanil NanoTabs to manage their pain. Zalviso is designed to address the limitations of IV PCA by offering:

- n **A high therapeutic index opioid:** Zalviso uses the high therapeutic index opioid sufentanil; it offers hospitalized patients with moderate-to-severe acute pain the potential for effective patient-controlled analgesia with a low incidence of drug-related side effects.

- n **A non-invasive route of delivery:** The sublingual route of delivery used by Zalviso provides rapid onset of analgesia, therefore eliminating the risk of IV-related analgesic gaps and IV complications, such as catheter-related infections in IV PCA treated patients. In addition, because patients are not tethered to IV tubing and a pump for pain relief, Zalviso allows for ease of patient mobility.

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

Our Phase 3 clinical program for Zalviso consists of three trials; two placebo-controlled efficacy and safety trials and one open-label active comparator trial, in which Zalviso was compared to IV PCA morphine. Each of the three Phase 3 trials achieved its primary endpoint, and we believe the trial data support the submission of a New Drug Application, or NDA, which we anticipate will occur in the third quarter of 2013. A summary of the Phase 3 trials and results is as follows:

Active comparator trial (IAP 309)

In November 2012, we reported top-line data demonstrating that Zalviso met its primary endpoint of non-inferiority in a Phase 3 open-label active comparator trial designed to compare the efficacy and safety of Zalviso (15 mcg/dose, 20 minute lock-out) to IV PCA with morphine (1mg/dose, 6 minute lock-out) for the treatment of moderate-to-severe acute post-operative pain immediately following major abdominal or orthopedic surgery.

Table of Contents

Top-line primary endpoint results of this Phase 3 clinical trial demonstrate that:

- n Zalviso was non-inferior ($p < 0.001$) to IV PCA morphine for the primary endpoint of Patient Global Assessment of method of pain control, or PGA, comparison over the 48-hour trial period as determined by the combined percentage of patients with PGA ratings of good or excellent (78.5% vs. 65.6%, respectively).
- n A secondary comparison of the primary endpoint, specifically a statistical analysis of superiority, demonstrated that Zalviso was statistically superior to IV PCA morphine for the PGA endpoint ($p = 0.007$). Statistically superior and non-inferior PGA for Zalviso compared to IV PCA morphine was also seen at the 24 hour and 72 hour time points.

The trial also demonstrated that Zalviso produced a significantly faster onset of pain relief and reduction in pain intensity compared to IV PCA morphine that separated at 45 minutes and achieved statistical significance at 1, 2 and 4 hours ($p < 0.01$). Furthermore, there were statistically fewer patients in the Zalviso group that experienced oxygen desaturation to a level less than 95% compared to the IV PCA morphine group ($p = 0.028$).

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

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

In March 2013, we reported top-line data demonstrating that Zalviso met its primary endpoint in a pivotal Phase 3 trial designed to compare the efficacy and safety of Zalviso to placebo in the management of acute post-operative pain after major open abdominal surgery. Adverse events reported in the trial were generally mild or moderate in nature and similar in both placebo and treatment groups. Utilizing a randomized, double-blind, placebo-controlled design, this pivotal Phase 3 trial enrolled 178 adult patients at 13 U.S. sites.

The primary endpoint evaluated pain intensity over the 48-hour trial period compared to baseline, or Summed Pain Intensity Difference (SPID-48), in patients following major open abdominal surgery. SPID-48 is the endpoint requested by FDA to demonstrate effectiveness of a pain control medicine. Patients receiving Zalviso demonstrated a significantly greater SPID-48 (pain reduction) compared to placebo treated patients during the trial period (105.6 and 55.6, respectively; $p = 0.001$). Additionally, secondary endpoint data showed that 24 hours and 72 hours after first dose, SPID was significantly greater in Zalviso-treated patients than in the placebo-treated patients ($p < 0.001$ and $p = 0.004$ respectively).

Eighty, or 70.2%, of the Zalviso-treated patients completed the 48-hour trial period, compared to 30, or 51.7%, of placebo-treated patients. Reasons for drop-out in Zalviso-treated and placebo-treated groups were adverse events (5.3% and 6.9%, respectively), lack of efficacy (16.7% and 31.0%, respectively) and other (7.9% and 10.3%, respectively).

Treatment-emergent adverse events occurred in 64.0% of Zalviso-treated patients and 67.2% of placebo-treated patients. Adverse events with an occurrence greater than 5% in either the Zalviso group or the placebo group were nausea (30.7% and 41.4%, respectively), fever (14.9% and 8.6%, respectively), vomiting (8.8% and 6.9%, respectively), itching (8.8% and 0.0%, respectively), oxygen saturation decrease (6.1% and 1.7%, respectively), and hypertension (2.6% and 5.2%, respectively). Itching, a frequently observed side effect of opioids, was the only adverse event that was significantly different between the groups ($p = 0.017$). All reported cases of itching in the trial were mild in nature.

Only one patient, in the Zalviso group, experienced a serious adverse event, which was determined to be unrelated to the trial drug by the investigator.

Table of Contents*Double-blind, placebo-controlled, orthopedic surgery trial (IAP 311)*

In May 2013, we reported top-line data results demonstrating that Zalviso met its primary endpoint in a pivotal Phase 3 trial designed to compare the efficacy and safety of Zalviso to placebo in the management of acute post-operative pain after major orthopedic surgery. Utilizing a randomized, double-blind, placebo-controlled design, this pivotal Phase 3 trial enrolled 426 adult patients at 34 U.S. sites.

The primary endpoint evaluated pain intensity over the 48-hour trial period compared to baseline, or SPID-48, in patients following major orthopedic surgery. Patients receiving Zalviso demonstrated a significantly greater SPID-48 (pain reduction) compared to placebo -treated patients during the trial period (+76.1 vs -11.5, $p<0.001$). Secondary endpoint data demonstrated that SPID at 24 hours and 72 hours was also significantly greater in the Zalviso-treated patients than in the placebo-treated patients ($p<0.001$ in each case).

Two hundred fifteen, or (68.3%), Zalviso-treated patients completed the 48-hour trial period, compared to 43 (41.3%) placebo-treated patients. Primary reasons for drop-out in the Zalviso- and placebo-treated groups were adverse events (7.0% and 6.7%, respectively) and lack of efficacy (14.3% and 48.1%, respectively).

Treatment-emergent adverse events were generally mild to moderate in nature and similar for the majority of adverse events between Zalviso and placebo treated patients, despite the shorter duration of exposure in the placebo-treated patients caused by early termination due to inadequate analgesia. Adverse events of nausea (occurring in 52.7% of sufentanil-treated patients vs 33.7% of placebo-treated patients), vomiting (12.7% vs 5.8%, respectively), dizziness (6% vs 1%, respectively) and itching (6% vs 0%, respectively) were the only adverse effects that were statistically significantly greater for Zalviso-treated patients as compared to placebo-treated patients. Nausea, vomiting and itching are common in treatment of post-operative patients, and are managed with anti-emetic and anti-histamine treatment. Effective management of these symptoms is demonstrated by the low drop-out rate due to nausea (1.6% of Zalviso-treated patients vs 2.9% of placebo-treated patients), vomiting (0.6% vs 0%, respectively) and itching (0.3% vs 0%, respectively) in this trial. Two patients (one each in the Zalviso group and placebo group) experienced an SAE considered possibly or probably related to the trial drug by the investigator.

ARX-04

We are also developing a Sufentanil Single-Dose NanoTab, or ARX-04, for the treatment of moderate-to-severe acute pain on the battlefield, in the emergency room or in ambulatory care facilities. In April 2013, we reported top-line data showing that the primary endpoint was achieved in a placebo-controlled, dose-finding, Phase 2 clinical trial of ARX-04 for acute pain. This trial randomized 101 patients following bunionectomy surgery in a 2:2:1 ratio to 30 mcg sufentanil, 20 mcg sufentanil or placebo treatment arms. Ninety-one percent of patients entering the trial completed the 12-hour trial period.

Results demonstrated that patients receiving 30 mcg sufentanil NanoTab doses, administered by a healthcare professional, no more frequently than once per hour, had significantly greater pain reduction as measured by Summed Pain Intensity Difference to baseline during the 12-hour trial period (SPID-12) than placebo-treated patients ($p=0.003$). Adverse events reported in the trial were generally mild-to-moderate in nature, with two serious adverse events of post-surgical infection reported, both of which were determined by the investigator to be unrelated to trial drug. Two patients dropped out of the trial due to adverse events, one patient's discontinuation considered unrelated to trial drug, and the other considered probably related to trial drug, both in the 30 mcg-treated group.

Research and development of ARX-04, including the Phase 2 trial and pre-Phase 3 development, is funded by a \$5.6 million grant from the U.S. Army Medical Research and Materiel Command, or USAMRMC. Future development of ARX-04 is contingent on identification of additional resources.

Table of Contents

ARX-02 and ARX-03

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

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 modestly-sized commercial organizations in the United States. We selectively utilize third party contractors in order to maximize the capital efficiency of our development and planned commercialization efforts. We plan to enter into partnerships to market our product candidates outside the United States.

Our lead product candidate, Zalviso, has been evaluated in three positive Phase 3 clinical trials. We intend to submit an NDA to the FDA in the third quarter of 2013 and, if approved, to commercialize Zalviso ourselves in the United States, and commercialize it outside the United States with a partner. Our strategy for Zalviso is to develop a hospital-directed sales force and/or collaborate with third parties to promote Zalviso to healthcare professionals and third-party payors in the United States. We have completed Phase 2 development of ARX-04, and plan to explore regulatory approaches for Phase 3 development of this candidate, subject to establishment of funding for that program. Further development of ARX-02 or ARX-03 will likely depend on the identification of a partner to support this effort.

Recent Financial Developments

While we have not finalized our full financial results for the quarter ended June 30, 2013, we expect to report that we had \$36.8M million of cash, cash equivalents and investments as of June 30, 2013.

Intellectual Property

We have developed significant know-how regarding our manufacturing process and protect our technology through trade secrets and patents. We seek patent protection in the United States and internationally for our product candidates.

As of July 1, 2013, we were the owner of record of six issued U.S. patents, five of which provide coverage for composition of matter and methods of using NanoTabs for oral transmucosal delivery of sufentanil, and one of which provides coverage of key features of the Zalviso device. Of these six patents, five expire in 2027 and one expires in 2030. We are also the owner of record of three issued European patents. Issued European patents EP 2114383 and EP 1873593, each expire in 2027 and include national validation in ten countries and seven countries, respectively. A third issued European patent EP 2367537 expires in 2029 and includes national validation in ten countries. Further, we own one issued Mexican patent and one issued New Zealand patent, each of which expires in 2029, one issued Chinese patent, which expires in 2028, and one issued Japanese patent, which expires in 2027. We are pursuing 15 U.S. non-provisional patent applications, and 53 foreign national applications, including six European Regional Phase applications directed to our product candidates. 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.

Table of Contents

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 Zalviso, ARX-02, ARX-03 and ARX-04 NanoTabs and formulations, our Zalviso PCA device, the combination of drugs and our Zalviso PCA device, our ARX-02, ARX-03 and ARX-04 single dose applicator, or SDA, as well as to methods of treatment using such drug and device compositions.

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. 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. We have additionally applied for registration of our ZALVISO mark in the United States on an intent-to-use basis and that application has been allowed.

Risks Associated with Our Business

Our business is subject to numerous risks, as more fully described under **Risk Factors** beginning on page S-9 of this prospectus supplement. 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:

- n We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.
- n We have never generated any product or commercial revenue and may never be profitable.
- n 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.
- n We depend substantially on the success of Zalviso, which may not receive regulatory approval or be successfully commercialized.
- n Positive clinical results obtained to date for our product candidates may be disputed in FDA review, do not guarantee regulatory approval and may not be obtained from future clinical trials.
- n 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.
- n The Zalviso PCA device components may not be fully functional or commercially viable.

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- The commercial success of Zalviso 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.

S-5

Table of Contents

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, and is not incorporated into, this prospectus supplement or the accompanying prospectus and should not be considered part of this prospectus supplement or the accompanying prospectus.

S-6

Table of Contents

THE OFFERING

Common stock offered by us shares shares

Common stock to be outstanding immediately after this offering shares

Option to Purchase Additional Shares

We have granted the underwriters an option to purchase up to 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 supplement.

Use of Proceeds

We intend to use the net proceeds from this offering to fund potential regulatory approval of Zalviso both in the United States and Europe, our continuing preparation for the potential commercial launch of Zalviso in the United States, and for working capital and other general corporate purposes. See Use of Proceeds on page S-34 of this prospectus supplement.

NASDAQ Global Market Listing

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

Risk Factors

An investment in our common stock involves a high degree of risk. See Risk Factors beginning on page S-9 of this prospectus supplement.

Outstanding Shares

The number of shares of common stock outstanding immediately after this offering is based on 37,237,319 shares of common stock outstanding as of March 31, 2013. This number excludes:

- n 2,908,036 shares of common stock issuable upon the exercise of warrants outstanding as of March 31, 2013, at a weighted average exercise price of \$3.38 per share;
- n 5,092,513 shares of common stock issuable upon the exercise of options outstanding as of March 31, 2013, at a weighted average exercise price of \$3.89 per share;
- n 65,765 shares of common stock issuable upon the vesting of restricted stock units outstanding as of March 31, 2013;
- n 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 under our outstanding promissory notes issued to Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc., or the Hercules Notes, into shares of our common stock; and
- n 1,012,150 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 March 31, 2013, plus any annual increases in the number of shares of

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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, 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 applicable to us and described under the section of this prospectus entitled "Underwriting" in such amounts as we may determine, subject to certain limitations under applicable securities laws.

S-7

Table of Contents

Except as otherwise indicated, all information included or incorporated by reference in this prospectus supplement 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 option to purchase additional shares.

S-8

Table of Contents

RISK FACTORS

An investment in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risks described below together with the other information in this prospectus supplement, the accompanying prospectus, the information and documents incorporated by reference, and in any free writing prospectus that we have authorized for use in connection with this offering. If any of these risks actually occur, our business, financial condition, results of operations or cash flows could be seriously harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment.

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, Zalviso. 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 March 31, 2013 we had an accumulated deficit of \$134.8 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. We expect to continue to incur substantial expenses as we prepare for the potential commercialization of Zalviso and continue our research and development activities for our product candidates. 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. 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 U.S. 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:

- n obtaining and maintaining regulatory approval for Zalviso;
- n launching and commercializing Zalviso, including building or contracting out, a hospital-directed sales force in the U.S. and collaborating with third parties internationally, which will require additional funding; and
- n 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 delayed in obtaining approval of, or launching, Zalviso, or are required by the United States Food and Drug Administration, or FDA, to perform trials in addition to those that we have completed.

Table of Contents

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.

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is expensive. We expect to incur significant expenditures in connection with our ongoing activities, particularly preparation for the potential commercialization of Zalviso and future advancement of our other product candidates. As of March 31, 2013, we had working capital of \$35.4 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 at least through the end 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 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 that the net proceeds from this offering, together with our existing cash resources, based on our current estimates, are adequate to fund potential regulatory approval of Zalviso both in the United States and Europe, and to continue preparation for the potential commercial launch of Zalviso in the United States. However, our planned regulatory filings and commercialization efforts may encounter technical 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 Zalviso. 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. 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.

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 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:

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

Table of Contents

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 our stockholders or impose restrictive covenants that may 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 existing 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. 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 in December, 2014. As of March 31, 2013, our outstanding debt balance related to the Hercules agreement was \$14.2 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. Additional capital may not be available on 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.

Risks Related to Clinical Development and Regulatory Approval

We depend substantially on the success of Zalviso, which may not receive 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 Zalviso for the management of moderate-to-severe acute pain in patients in the hospital setting. Our Phase 3 program consisted of three Phase 3 clinical trials. We have reported positive top-line data from each of these trials and intend to submit an NDA for Zalviso to the FDA in the third quarter of 2013. There is no guarantee that the NDA will be completed on schedule or at all, or if completed and submitted, will be successfully filed or approved by the FDA. 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.

Our proposed tradename of Zalviso has not received final approval from FDA, which must approve all drug tradenames to avoid medication errors and misbranding. Any brand recognition or goodwill that we establish with the name Zalviso prior to approval may be worthless if the FDA rejects this tradename.

Any delay or change in the current schedule of our planned NDA filing for Zalviso may negatively impact our stock price and harm our business operations. Any delay in obtaining, or inability to obtain, regulatory approval would prevent us from commercializing Zalviso, generating revenues and achieving profitability. If any of these events occur, we may be forced to delay or abandon our development efforts for Zalviso, which would have a material adverse effect on our business and could potentially cause us to cease operations.

Table of Contents

Positive clinical results obtained to date for our product candidates may be disputed in FDA review, do not guarantee regulatory approval and may not be obtained from future clinical trials.

We have reported positive top-line data from each of our three Zalviso Phase 3 clinical trials. However, even if we believe that the data from required Phase 3 clinical trials is positive, the FDA could analyze our data using alternative strategies and determine that the data from our trials was negative or inconclusive. Negative or inconclusive results of a Phase 3 clinical trial could cause the FDA to require us to repeat the trial or conduct additional clinical trials prior to obtaining approval for commercialization, and there is no guarantee that additional trials would achieve positive results. Any such determination by the FDA would delay the timing of our commercialization plan for Zalviso and adversely affect our business operations.

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. While we have completed our planned trials for Zalviso and the Phase 2 clinical trial for ARX-04, and have no additional trials currently planned, potential future 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:

- n inability to raise funding necessary to initiate or continue a trial;
- n delays in obtaining regulatory approval to commence a trial;
- n delays in reaching agreement with the FDA on final trial design;
- n imposition of a clinical hold following an inspection of our clinical trial operations or trial sites by the FDA or other regulatory authorities;
- n delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;
- n delays in obtaining required institutional review board approval at each site;
- n delays in recruiting suitable patients to participate in a trial;
- n delays in the testing, validation, manufacturing and delivery of the device components of our product candidates;
- n delays in having patients complete participation in a trial or return for post-treatment follow-up;
- n clinical sites dropping out of a trial to the detriment of enrollment or being delayed in entering data to allow for clinical trial database closure;

n time required to add new clinical sites; or

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

If any future clinical trials 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. In our Phase 3 active comparator clinical trial (IAP 309), 7.9% of Zalviso treated patients dropped out of the trial prematurely due to an AE, and we observed one serious adverse event, or SAE, that was assessed as possibly or probably related to Zalviso. In our Phase 3, double-blind, placebo-controlled, abdominal surgery trial (IAP 310), adverse events reported in the trial were generally mild or moderate in nature and similar in both placebo and treatment groups. In addition, one patient in the trial, who was in the sufentanil group, experienced an SAE, which was determined to be unrelated to the trial drug. In our Phase 3, double-blind, placebo-controlled, orthopedic surgery trial (IAP 311), treatment-emergent adverse events were generally mild to moderate in nature and similar for the majority of adverse events between sufentanil and placebo treated patients. Two patients (one each in the sufentanil group and placebo group) experienced a serious adverse event considered possibly or probably related to the trial drug by the investigator.

Table of Contents

Phase 2 clinical trials conducted by us with our Zalviso, ARX-02, ARX-03 and ARX-04 product candidates have generated some AEs, but no SAEs, related to the trial drug.

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

- n 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;
- n regulatory authorities may require the addition of labeling statements, such as warnings or contraindications;
- n we may be required to change the way the product is administered or conduct additional clinical trials;
- n we could be sued and held liable for harm caused to patients; or
- n 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 Zalviso because it is a drug/device combination.

Zalviso 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 Zalviso 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 Zalviso. As a result, we have in the past and may in the future experience delays in the development and commercialization of Zalviso 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 Zalviso, 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 Zalviso. Additional delays may result if Zalviso 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, including Zalviso, 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 from such trials. Such rejection would 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.

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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.

S-13

Table of Contents

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:

- n a product candidate may not be considered safe or effective;
- n the manufacturing processes or facilities we have selected may not meet the applicable requirements; and
- n 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 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. For example, we intend to seek approval of Zalviso for the management of moderate-to-severe acute pain in patients in the hospital setting; however, our clinical trial data was generated exclusively from the post-operative segment of this population, and FDA may restrict any approval to post-operative patients only, which would limit our commercial opportunity.

Even if we obtain regulatory approval for Zalviso 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 Zalviso and our other product candidates will likely include restrictions on use due to the opioid nature of sufentanil. Zalviso 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

Table of Contents

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:

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

Zalviso and our other product candidates will require Risk Evaluation and Mitigation Strategies.

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 Zalviso, we cannot predict the specific REMS to be required as part of any FDA approval of Zalviso. Depending on the extent of the REMS requirements, our costs to commercialize Zalviso 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:

- n the inability to meet our product specifications and quality requirements consistently;
- n a delay or inability to procure or expand sufficient manufacturing capacity;

S-15

Table of Contents

- n manufacturing and product quality issues related to scale-up of manufacturing;
- n costs and validation of new equipment and facilities required for scale-up;
- n a failure to comply with cGMP and similar foreign standards;
- n the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- n termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us;
- n 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;
- n the lack of qualified backup suppliers for those components that are currently purchased from a sole or single source supplier;
- n 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;
- n carrier disruptions or increased costs that are beyond our control; and
- n 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.

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.

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 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.

S-16

Table of Contents

Historically, we have manufactured the majority of our NanoTab supplies 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, which may adversely affect our clinical and commercial plans. In addition, regulatory agencies may require that a bioequivalence trial 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 trial could fail the FDA's bioequivalence requirements which would adversely affect our clinical and commercial plans. Any such additional trials or other FDA requirements would delay the timing of our commercialization plans for Zalviso and adversely affect our business operations.

The Zalviso PCA device components may not be fully functional or commercially viable.

The Zalviso device we have used in our Phase 3 clinical trials and plan to use commercially 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 Zalviso device and we plan to conduct additional Human Factors studies prior to submitting the planned NDA for Zalviso. However, we cannot predict if the Phase 3 device will be fully functional or ready for commercial use. If we need to modify the Phase 3 device, we may incur higher costs and experience delay in regulatory approval and commercialization of Zalviso. 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 Zalviso device on a clinical scale, no experience on a commercial scale and do not own or operate a manufacturing facility.

We have manufactured Zalviso devices and supplies on a small scale, including those needed for our Phase 3 clinical trials. We will continue to rely on contract manufacturers, component fabricators and third party service providers to produce the necessary Zalviso devices for the commercial marketplace. We currently outsource manufacturing and packaging of the controller, dispenser and cartridge components of the Zalviso device to third parties and intend to continue to do so. These purchases 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 Zalviso 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 Zalviso 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 utilized CROs for the conduct of our Phase 3 clinical trials of Zalviso and for the Phase 2 clinical trial of ARX-04. We rely on 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 clinical programs for Zalviso 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.

Table of Contents

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. Accordingly, if our CROs or clinical trial sites fail to comply with these regulations, 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 Zalviso, or our other product candidates. As a result, our financial results and the commercial prospects for Zalviso and any future product candidates that we develop would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

Pre-Phase 3 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 the Phase 2 dose-finding trial for the treatment of moderate-to-severe acute pain as well as Phase 3 readiness activities. The grant gives the USAMRMC the option to extend the term of the grant and provide additional funding for the research.

Pre-Phase 3 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 Zalviso 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:

- n demonstration of clinical safety and efficacy compared to other products;
- n the relative convenience, ease of administration and acceptance by physicians, patients and health care payors;

Table of Contents

- n the prevalence and severity of any AEs or SAEs;
- n overcoming the perception of sufentanil as a potentially unsafe drug due to its high potency;
- n limitations or warnings contained in the FDA-approved label for Zalviso;
- n availability of alternative treatments;
- n existing capital investment by hospitals in IV PCA technology;
- n pricing and cost-effectiveness;
- n the effectiveness of our or any future collaborators' sales and marketing strategies;
- n our ability to obtain hospital formulary approval;
- n our ability to obtain and maintain sufficient third party coverage or reimbursement; and
- n the willingness of patients to pay out-of-pocket in the absence of third party coverage.

If Zalviso 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 Zalviso 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 Zalviso 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.

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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.

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

- n different regulatory requirements for drug approvals in foreign countries;
- n reduced protection for intellectual property rights;
- n unexpected changes in tariffs, trade barriers and regulatory requirements;

S-19

Table of Contents

- n economic weakness, including inflation, or political instability in particular foreign economies and markets;
- n compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- n foreign taxes, including withholding of payroll taxes;
- n foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- n workforce uncertainty in countries where labor unrest is more common than in the United States;
- n production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- n 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 our 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 Zalviso would compete with a number of opioid-based treatment options that are currently available. The hospital market for opioids for moderate-to-severe acute pain is large and competitive. The primary competition for Zalviso is the IV PCA pump, which is widely used in the moderate-to-severe acute pain in the hospital 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 moderate-to-severe acute 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 Zalviso 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., which was acquired by The Medicines Company. 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.

S-20

Table of Contents

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 mild-to-moderate acute pain or breakthrough pain could render Zalviso 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 Zalviso 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 Zalviso, 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 Zalviso, 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 Zalviso, 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 Zalviso 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 Zalviso 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.

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.

Table of Contents

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 Zalviso 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 Zalviso or any of our other product candidates. This could have a material adverse effect on our business, results of operations, financial condition and prospects.

We have not yet produced commercial supplies and we may encounter difficulties in production, which may adversely affect our clinical and commercial plans.

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 at this facility and we may encounter difficulties in production at the new facility, which may adversely affect our clinical and commercial plans.

In January 2013, we entered into a Manufacturing Services Agreement, or the Services Agreement, with Patheon under which Patheon has agreed to manufacture, supply, and provide certain validation and stability services with respect to Zalviso for potential sales in the United States, Canada, Mexico and other countries, subject to agreement by the parties to any additional fees for such other countries. There is no guarantee that Patheon's services will be satisfactory or that they will continue to meet the strict regulatory guidelines of the FDA or other regulatory agencies. In addition, in January 2013, we entered into a Capital Expenditure and Equipment Agreement, or the Capital Agreement, with Patheon, relating to the manufacture of Sufentanil NanoTabs. Under the terms of the Capital Agreement, we have planned certain future modifications to Patheon's Cincinnati facility. If equipment manufacture or modifications do not meet expected deadlines, the timing for our planned NDA submission for Zalviso may be delayed.

If Patheon cannot provide us with an adequate supply of NanoTabs, we may be required to pursue alternative sources of manufacturing capacity. 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 Zalviso and our other product candidates for commercial distribution. We do not fully 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 Zalviso. These challenges may have a material adverse impact on our business, results of operations, financial condition and prospects.

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

Table of Contents

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 March 31, 2013, we had 25 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, particularly in preparation for the commercial launch of Zalviso if our NDA submission is approved by the FDA. 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 Zalviso 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:

- n impairment of our business reputation;
- n withdrawal of clinical trial participants;
- n costs due to related litigation;
- n distraction of management's attention from our primary business;
- n substantial monetary awards to patients or other claimants;

n the inability to commercialize our product candidates; and

n 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

S-23

Table of Contents

liability. If and when we obtain marketing approval for our product candidates, we intend to expand our insurance 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 July 1, 2013, we were the owner of record of one issued European patent (EP 2114383), including national validation in ten countries, which expires in 2027, one issued European patent (EP 2367537), including national validation in ten countries, which expires in 2029, one issued European patent (EP 1873593), including national validation in seven countries, which expires in 2027, one Mexican patent, which expires in 2029, one Japanese patent, which expires in 2027, one New Zealand patent, which expires in 2029, one Chinese patent, which expires in 2028, five issued U.S. patents which expire in 2027, and one issued U.S. patent which expires in 2030. In addition, we are pursuing 15 U.S. non-provisional patent applications, and 53 foreign national applications, including six European Regional Phase applications directed to our product candidates. One of our issued U.S. patents, Patent Number 8,357,114, covers key features of our Zalviso (ARX-01) PCA device, but we have not yet obtained any issued patents that provide protection for key features of our ARX-02, ARX-03 and ARX-04 SDAs independent of the drug composition used in them. We have received a Notice of Allowance for two of our pending U.S. applications that include claims covering key features of our ARX-02, ARX-03 and ARX-04 SDA device. 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.

There is also no assurance that any patents issued to us will not become the subject of adversarial proceedings such as opposition, inter partes review, post-grant review, reissue, re-examination or other post-issuance proceedings, 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

Table of Contents

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 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. For example, 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. The United States Patent Office has developed new and untested regulations and procedures to govern the full implementation of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, that became effective March 16, 2013. It is too early to tell 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

Table of Contents

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 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:

- n we were the first to make the inventions covered by each of our pending patent applications;
- n we were the first to file patent applications for these inventions;
- n others will not independently develop similar or alternative technologies or duplicate any of our technologies;
- n 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
- n 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 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.

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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

S-26

Table of Contents

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.

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. We have additionally applied for registration of our ZALVISO mark in the United States on an intent-to-use basis and that application has been allowed. 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.

Since our initial public offering, or IPO, in February 2011, the trading price of our common stock has experienced significant volatility and is likely to be volatile in the future. 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:

- n any delay in submitting an NDA for Zalviso or any of our other product candidates and any adverse development or perceived adverse development with respect to the FDA's filing or review of that NDA;
- n adverse results or delays in future clinical trials;
- n inability to obtain additional funding, including funding necessary for the planned commercialization and manufacturing of Zalviso in the United States and advancement of clinical trials for other product candidates;
- n failure to successfully develop and commercialize our product candidates;
- n changes in laws or regulations applicable to our products;
- n inability to obtain adequate product supply for our product candidates, or the inability to do so at acceptable prices;
- n adverse regulatory decisions;

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- n introduction of new products, services or technologies by our competitors;
- n failure to meet or exceed financial projections we provide to the public;
- n failure to meet or exceed the estimates and projections of the investment community;
- n the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- n announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;
- n disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- n additions or departures of key scientific or management personnel;
- n significant lawsuits, including patent or stockholder litigation;

S-27

Table of Contents

- n changes in the market valuations of similar companies;

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

- n trading volume of our common stock.

In addition, the stock market in general, and The NASDAQ Global Market, or NASDAQ, in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

Until recently our common stock has thinly traded and in the future, may continue to be thinly traded, and our 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.

Until recently, we had a low volume of daily trades in our common stock on NASDAQ. For example, the average daily trading volume in our common stock on NASDAQ during the first quarter of 2013 was approximately 275,000 shares per day. A more active market for our stock has only recently developed and may not be sustained. 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 52% of our outstanding voting stock as of March 31, 2013. Upon completion of this offering, our executive officers, directors and their affiliates will continue to beneficially own in a significant percentage 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 NASDAQ, 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 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

Table of Contents

their operation. We cannot be certain at this time whether our measures to improve internal controls will be 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 March 31, 2013, we had 37,237,319 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 60 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 LLC, 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 supplement under the caption Underwriting.

In addition, certain holders of our securities are entitled to certain rights with respect to the registration of their shares of common stock under the Securities Act, subject to the 60 day lock up 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 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. After giving effect to the sale of shares of our common stock in this offering at the public offering price of \$ per share, and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, you will experience immediate dilution of \$ per share, representing the difference between our as adjusted net tangible book value per share as of March 31, 2013 after giving effect to this offering and the public offering price. See the section entitled Dilution below for a more detailed illustration of the dilution you will 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 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 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

Table of Contents

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 public offering in December 2012, 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.

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:

- n 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;

- n limiting the removal of directors by the stockholders;

S-30

Table of Contents

- n creating a staggered board of directors;

- n prohibiting stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders;

- n eliminating the ability of stockholders to call a special meeting of stockholders; and

- n 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.

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus, the documents we have filed with the SEC that are incorporated herein by reference and any free writing prospectus that we have authorized for use in connection with this offering contain 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, plans, potential, 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 supplement and the accompanying prospectus, including the information incorporated 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:

- n the success, cost and timing of our product development activities;
- n our ability to obtain and maintain regulatory approval of Zalviso and other product candidates, and any related restrictions, limitations, and/or warnings in the label of an approved product candidate;
- n our ability to obtain funding for our operations, including funding necessary for the planned commercialization and manufacturing of Zalviso in the United States and advancement of clinical trials for other product candidates;
- n our plans to research, develop and commercialize our product candidates;
- n our ability to attract collaborators with development, regulatory and commercialization expertise;
- n the size and growth potential of the markets for our product candidates, and our ability to serve those markets;
- n our ability to successfully commercialize our product candidates;
- n the rate and degree of market acceptance of our product candidates;
- n our ability to develop sales and marketing capabilities, whether alone or with potential future collaborators;
- n regulatory developments in the United States and foreign countries;
- n the performance of our third party suppliers and manufacturers;

- n the success of competing therapies that are or become available;

- n the loss of key scientific or management personnel;

- n our use of the proceeds from this offering;

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

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

We discuss these and other important factors, risks and uncertainties that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements in greater detail under **Risk Factors** beginning on page S-9 of this prospectus supplement. Given these risks, uncertainties and other important factors, 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 supplement, the accompanying prospectus, together with the information incorporated herein by reference as described under the heading **Incorporation of Certain Information by Reference** in this prospectus supplement, and any free writing prospectus that we have authorized for use in connection with this offering, completely and with the understanding that our actual future results may be materially different from what

Table of Contents

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.

S-33

Table of Contents

USE OF PROCEEDS

We estimate that the net proceeds from the sale of the shares of common stock that we are offering will be approximately \$ million, or approximately \$ million if the underwriters exercise in full their option to purchase additional shares of common stock, based on the public offering price of \$ per share and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this offering to fund potential regulatory approval of Zalviso both in the United States and Europe, our continuing preparation for the potential commercial launch of Zalviso in the United States and for working capital and general corporate purposes. We may also use a portion of the net proceeds from this offering to acquire or invest in complementary businesses, technologies, product candidates or other intellectual property, although we have no present commitments or agreements to do so.

The costs and timing of drug development and marketing approval 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 our ability to timely obtain regulatory approvals necessary for potential commercialization of Zalviso, the establishment of collaborations, our manufacturing requirements 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, interest-bearing securities or accounts.

Table of Contents**DILUTION**

Our net tangible book value as of March 31, 2013 was approximately \$21.9 million, or \$0.59 per share. Net tangible book value per share is determined by dividing our total tangible assets, less total liabilities, by the number of shares of our common stock outstanding as of March 31, 2013. Dilution in net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the net tangible book value per share of our common stock immediately after this offering.

After giving effect to the sale of shares of our common stock in this offering at the public offering price of \$ _____ per share and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2013 would have been approximately \$ _____ million, or \$ _____ per share. This represents an immediate increase in net tangible book value of \$ _____ per share to existing stockholders and immediate dilution in net tangible book value of \$ _____ per share to investors purchasing our common stock in this offering at the public offering price. The following table illustrates this dilution on a per share basis:

Public offering price per share	\$
Net tangible book value per share as of March 31, 2013	\$ (0.59)
Increase per share attributable to investors purchasing our common stock in this offering	

As adjusted net tangible book value per share after this offering

Dilution per share to investors purchasing our common stock in this offering	\$
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If the underwriters exercise in full their option to purchase _____ additional shares of common stock at the public offering price of \$ _____ per share, the as adjusted net tangible book value after this offering would be \$ _____ per share, representing an increase in net tangible book value of \$ _____ per share to existing stockholders and immediate dilution of \$ _____ per share to investors purchasing our common stock in this offering at the public offering price.

The above discussion and table are based on 37,237,319 shares of common stock outstanding as of March 31, 2013 and exclude:

- n 2,908,036 shares of common stock issuable upon the exercise of warrants outstanding as of March 31, 2013, at a weighted average exercise price of \$3.38 per share;
- n 5,092,513 shares of common stock issuable upon the exercise of options outstanding as of March 31, 2013, at a weighted average exercise price of \$3.89 per share;
- n 65,765 shares of common stock issuable upon the vesting of restricted stock units outstanding as of March 31, 2013;
- n 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 under the Hercules Notes into shares of our common stock; and

- n 1,012,150 additional shares of common stock reserved for future issuance under the 2011 Plan and the Purchase Plan, as of March 31, 2013, 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 above discussion and table exclude shares of common stock that we may sell pursuant to the Sales Agreement with MLV. 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.

S-35

Table of Contents

To the extent that options or warrants outstanding as of March 31, 2013 have been or are exercised, or other shares are issued, including pursuant to the Sales Agreement with MLV, investors purchasing shares of common stock 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.

S-36

Table of Contents

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

The following is a discussion of the material federal income tax considerations to non-U.S. Holders (as defined below) with respect to their ownership and disposition of our common stock issued pursuant to this offering.

This discussion is based on current provisions of the Internal Revenue Code of 1986, as amended, or the Code, U.S. Treasury Regulations promulgated under the Code, judicial opinions, published positions of the Internal Revenue Service, or IRS, and all other applicable authorities, all of which are subject to change, possibly with retroactive effect. No ruling has been or will be sought from the IRS with respect to the matters discussed below, and there can be no assurance that the IRS will not take a contrary position or that any such contrary position would not be sustained by a court. This discussion assumes that the non-U.S. Holder will hold our common stock as a capital asset (generally, property held for investment).

This discussion does not address all aspects of U.S. federal income taxation (including alternative minimum and Medicare contribution taxation) or any aspects of estate, state, local, or non-U.S. taxation. It also does not consider any specific facts or circumstances that may apply to particular non-U.S. Holders, and does not address special treatment under the U.S. federal income tax laws that may apply to non-U.S. Holders, including, but not limited to:

- n U.S. expatriates and certain former citizens or long-term residents of the United States;
- n persons subject to the alternative minimum tax or medicare contribution tax;
- n persons holding our common stock as part of a hedge, straddle or other risk reduction strategy or as part of a conversion transaction or other integrated investment;
- n banks, insurance companies and other financial institutions;
- n brokers, dealers or traders in securities;
- n controlled foreign corporations, passive foreign investment companies and corporations that accumulate earnings to avoid U.S. federal income tax;
- n partnerships or other entities or arrangements treated as partnerships for U.S. federal income tax purposes;
- n entities that are treated as disregarded entities for U.S. federal income tax purposes;
- n tax-exempt organizations or governmental organizations;
- n persons deemed to sell our common stock under the constructive sale provisions of the Internal Revenue Code;
- n persons who hold or receive our common stock pursuant to the exercise of any employee stock option or otherwise as compensation; and

n tax qualified retirement plans.

For purposes of this discussion, the term "non-U.S. Holder" means a beneficial owner of our shares that is not a partnership (or entity or arrangement treated as a partnership for U.S. federal income tax purposes) and is not:

n an individual who is a citizen or resident of the United States;

n a corporation created or organized in the United States or under the laws of the United States or of any state thereof or the District of Columbia;

n an estate, the income of which is subject to U.S. federal income tax regardless of its source; or

n a trust if (1) a U.S. court can exercise primary supervision over the trust's administration and one or more U.S. persons have the authority to control all of the trust's substantial decisions or (2) the trust has a valid election in effect under applicable U.S. Treasury Regulations to be treated as a U.S. person.

If a partnership or any other entity or arrangement taxed as a partnership for U.S. federal income tax purposes is a beneficial owner of our common stock, the treatment of a partner in the partnership will generally depend upon the status of the equity owner of such partnership and the activities of the partnership. Accordingly, partnerships (and entities and arrangements taxed as partnerships) that hold our common stock and owners in such partnerships (or other entities or arrangements taxed as partnerships) are urged to consult their tax advisors regarding the specific U.S. federal income tax consequences to them of acquiring, owning or disposing of our common stock.

Table of Contents

PROSPECTIVE INVESTORS ARE URGED TO CONSULT THEIR TAX ADVISORS REGARDING THE PARTICULAR U.S. FEDERAL INCOME TAX CONSEQUENCES TO THEM OF ACQUIRING, OWNING AND DISPOSING OF SHARES OF OUR COMMON STOCK, AS WELL AS THE U.S. FEDERAL, STATE, LOCAL AND NON-U.S. INCOME AND OTHER TAX CONSIDERATIONS OF ACQUIRING, OWNING AND DISPOSING OF SHARES OF COMMON STOCK.

Distributions

We do not anticipate declaring or paying any cash distributions on our common stock in the foreseeable future. However, if we do make distributions on our common stock, those payments will constitute dividends for U.S. tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. To the extent those distributions exceed our current and accumulated earnings and profits, they will constitute a return of capital and will first reduce the recipient's adjusted tax basis in our common stock, but not below zero, and then will be treated as gain from the sale of stock as described below under the heading **Gain on Sale or Other Disposition of Common Stock**.

Dividends paid to a non-U.S. Holder will be subject to U.S. federal withholding tax at a rate equal to 30 percent of the gross amount of the dividend, or a lower rate prescribed by an applicable income tax treaty, unless the dividends are effectively connected with a trade or business carried on by the non-U.S. Holder within the United States (and, if required by an applicable income tax treaty, are attributable to a U.S. permanent establishment maintained by the non-U.S. Holder). Under applicable Treasury Regulations, a non-U.S. Holder will be required to satisfy certain certification requirements, generally on IRS Form W-8BEN (or applicable successor form), directly or through an intermediary, in order to claim a reduced rate of withholding under an applicable income tax treaty. If tax is withheld in an amount in excess of the amount prescribed by an applicable income tax treaty, a refund of the excess amount may be obtained by the non-U.S. Holder by timely filing an appropriate claim for refund with the IRS.

Dividends that are effectively connected with such a U.S. trade or business (and, if required by an applicable income tax treaty, are attributable to a U.S. permanent establishment maintained by the recipient) will not be subject to U.S. withholding tax if the non-U.S. Holder files the required forms, generally an IRS Form W-8ECI (or applicable successor form), with the payor of the dividend, but instead will be subject to U.S. federal income tax on a net income basis in the same manner as if the non-U.S. Holder were a resident of the United States. A foreign corporation that receives dividends constituting effectively connected income may, under certain circumstances, be subject to an additional branch profits tax at a rate of 30 percent, or a lower rate prescribed by an applicable income tax treaty, with respect to such effectively connected income.

Gain on Sale or Other Disposition of Common Stock

Except as described under **Foreign Accounts**, below, a non-U.S. Holder will not be subject to U.S. federal income tax or withholding on any gain realized upon the sale or other taxable disposition of the non-U.S. Holder's shares of common stock unless:

- n the gain is effectively connected with a trade or business carried on by the non-U.S. Holder within the United States (and, if required by an applicable tax treaty, is attributable to a U.S. permanent establishment or a fixed base maintained by the non-U.S. Holder), in which case the non-U.S. Holder generally will be required to pay tax on the net gain derived from the sale under regular graduated U.S. federal income tax rates and, if the non-U.S. Holder is a corporation, the branch profits tax may apply at a 30 percent rate or such lower rate as may be specified by an applicable income tax treaty;
- n the non-U.S. Holder is a nonresident alien individual who is present in the United States for 183 days or more in the taxable year of disposition (and is not otherwise treated as a U.S. resident alien for U.S. federal income tax purposes) and certain other conditions are met, in which case the non-U.S. Holder will be required to pay a flat 30 percent tax (or such lower rate as may be specified by an applicable income tax treaty between the United States and such non-U.S. Holder's country of residence) on the net gain derived from the disposition, which net gain may be offset by U.S. source capital losses, if any, provided that the non-U.S. Holder has timely filed U.S. federal income tax returns with respect to such losses; or
- n our common stock constitutes a U.S. real property interest by reason of our status as a United States real property holding corporation, or USRPHC, for U.S. federal income tax purposes at any time within the shorter of the five-year period preceding the disposition or the non-U.S. Holder's holding period for our common stock.

Table of Contents

We believe that we are not currently and will not become a USRPHC. However, because the determination of whether we are a USRPHC depends on the fair market value of our U.S. real property relative to the fair market value of our other business assets, there can be no assurance that we will not become a USRPHC in the future. Even if we become a USRPHC, however, as long as our common stock is regularly traded on an established securities market, such common stock will be treated as U.S. real property interests only if the non-U.S. Holder actually or constructively held more than five percent of our common stock at any time during the shorter of the five-year period preceding the disposition or the non-U.S. Holder's holding period for our common stock.

Information Reporting and Backup Withholding

We must report annually to the IRS and to each non-U.S. Holder the amount of dividends on our common stock, the name and address of the recipient and the amount, if any, of tax withheld with respect to such dividends. These information reporting requirements apply even if withholding was not required because the dividends were effectively connected dividends or withholding was reduced by an applicable income tax treaty. Under tax treaties or other agreements, the IRS may make its reports available to tax authorities in the country in which the non-U.S. Holder resides or is established.

Dividend payments made to a non-U.S. Holder that is not an exempt recipient generally will be subject to backup withholding at the then applicable rate (currently 28 percent) unless the non-U.S. Holder certifies as to its foreign status, which certification may be made by providing the Company with an IRS Form W-8BEN or IRS Form W-8ECI, as applicable, and certain other requirements are met. Notwithstanding the foregoing, backup withholding may apply if either we or our paying agent has actual knowledge, or reason to know, that the holder is a U.S. person that is not an exempt recipient.

Proceeds from the sale or other disposition of common stock by a non-U.S. Holder effected by or through a U.S. office of a broker will generally be subject to information reporting and backup withholding, currently at a rate of 28 percent unless the non-U.S. Holder certifies to the payor under penalties of perjury as to, among other things, its name, address and status as a non-U.S. Holder or otherwise establishes an exemption. Payment of disposition proceeds effected outside the United States by or through a non-U.S. office of a non-U.S. broker generally will not be subject to information reporting or backup withholding if the payment is not received in the United States. Information reporting, but generally not backup withholding, will apply to such a payment if the broker has certain connections with the United States unless the broker has documentary evidence in its records that the beneficial owner thereof is a non-U.S. Holder and specified conditions are met or an exemption is otherwise established.

Backup withholding is not an additional tax. Rather, the amount of tax withheld is applied to the U.S. federal income tax liability of persons subject to backup withholding. If backup withholding results in an overpayment of U.S. federal income taxes, a refund may be obtained, provided the required documents are timely filed with the IRS.

Foreign Accounts

The Code generally will impose a U.S. federal withholding tax of 30 percent on dividends and the gross proceeds of a disposition of our common stock paid to a foreign financial institution (as specifically defined for this purpose) unless such institution enters into an agreement with the U.S. government to, among other things, 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 and debt holders of such institution, as well as certain account holders that are foreign entities with U.S. owners), or otherwise establishes an exemption. A U.S. federal withholding tax of 30 percent also applies to dividends and the gross proceeds of a disposition of our common stock paid to a non-financial foreign entity unless such entity provides the withholding agent with a certification that it does not have any substantial direct or indirect U.S. owners, provides information regarding direct and indirect U.S. owners of the entity or otherwise establishes an exemption. The withholding provisions described above will generally apply to dividends on our common stock paid on or after January 1, 2014 and with respect to gross proceeds of a sale or other disposition of our common stock on or after January 1, 2017. Under certain circumstances, a non-U.S. Holder might be eligible for refunds or credits of such taxes.

Table of Contents

UNDERWRITING

Subject to the terms and conditions set forth in the underwriting agreement, dated July , 2013, between us and Jefferies LLC and Piper Jaffray & Co., as the representatives of the underwriters named below and the joint book-running managers of this offering, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the respective number of shares of common stock shown opposite its name below:

UNDERWRITERS	NUMBER OF SHARES
Jefferies LLC	
Piper Jaffray & Co.	
Guggenheim Securities, LLC	

Total

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 of common stock if any of them are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the nondefaulting 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, following the completion of this offering, they currently intend to make a market in the common stock as permitted by applicable laws and regulations. However, the underwriters are not obligated to do so, and the underwriters may discontinue any market-making activities at any time without notice in their sole discretion. Accordingly, no assurance can be given as to the liquidity of the trading market for the common stock, that you will be able to sell any of the common stock held by you at a particular time or that the prices that you receive when you sell will be favorable.

The underwriters are offering the shares of common stock subject to their acceptance of the shares of common stock 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.

Commission and Expenses

The underwriters have advised us that they propose to offer the shares of common stock to the public at the public offering price set forth on the cover page of this prospectus supplement and to certain dealers, which may include the underwriters, at that price less a concession not in excess of \$ per share of common stock. The underwriters may allow, and certain dealers may reallow, a discount from the concession not in excess of \$ per share of common stock 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 supplement.

Table of Contents

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.

	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 reimburse up to \$20,000 of the legal fees and expenses incurred by the underwriters in connection with determining their compliance with the rules and regulations of FINRA in connection with this offering.

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately \$.

Listing

Our common stock is 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 supplement, to purchase, from time to time, in whole or in part, up to an aggregate of additional shares of common stock from us at the public offering price set forth on the cover page of this prospectus supplement, 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 of common stock proportionate to that underwriter's initial purchase commitment as indicated in the table above.

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 in our case, and 60 days in the case of officers, directors and their affiliated funds, 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.

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Each lock-up period described in the preceding paragraph will be extended if (i) during the last 17 days of the 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 lock-up period, we announce that we will release earnings results during the 16-day period beginning on the last day of the lock-up 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

S-41

Table of Contents

occurrence of the material news or material event, unless such extension is waived, in writing, by Jefferies LLC 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 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. Finally, the lock-up agreement for us does not prohibit us from keeping in effect the Sales Agreement with MLV, provided that no sales of our common stock under the Sales Agreement may be made during the 90-day lock-up period.

Jefferies LLC may, in its sole discretion and at any time or from time to time before the termination of the lock-up 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 will execute a lock-up agreement, providing consent to the sale of shares prior to the expiration of the 60-day 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 our 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 of common stock 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 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 common stock 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 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 underwriters' purchases to cover the syndicate short

Table of Contents

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.

Neither we, nor any of the underwriters make 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

This prospectus supplement and the accompanying 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 our 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 this prospectus supplement and the accompanying 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 supplement or the accompanying prospectus, has not been approved and/or endorsed by us or the underwriters and should not be relied upon by investors.

Other Activities and Relationships

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 commercial and investment banking and financial advisory services for us and our affiliates, 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 issued by us and our affiliates. If the underwriters or their respective affiliates have a lending relationship with us, they routinely hedge their credit exposure to us consistent with their customary risk management policies. The underwriters and their respective affiliates may hedge such exposure by entering into transactions which consist of either the purchase of credit default swaps or the creation of short positions in our securities or the securities of our affiliates, including potentially the common stock offered hereby. Any such short positions could adversely affect future trading prices of the common stock offered hereby. The underwriters and certain of their respective affiliates may also communicate independent investment recommendations, market color or trading ideas 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.

Table of Contents

Notice to Investors

Australia

This prospectus supplement 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 supplement in Australia:

A. You confirm and warrant that you are either:

n a sophisticated investor under section 708(8)(a) or (b) of the Corporations Act;

n 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

n 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 supplement is void and incapable of acceptance.

B. You warrant and agree that you will not offer any of the shares issued to you pursuant to this prospectus supplement 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, a Relevant Member State, with effect from and including the date on which the Prospectus Directive is implemented in that Relevant Member State, which is referred to as the Relevant Implementation Date, no offer of any securities which are the subject of the offering contemplated by this prospectus supplement 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:

a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;

b) 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

c) to any other circumstances falling within Article 3(2) of the Prospectus Directive,

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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.

S-44

Table of Contents

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 supplement has not been registered with the Registrar of Companies in Hong Kong. Accordingly, this prospectus supplement 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 supplement 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 underwriters 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 supplement has not been and will not be lodged or registered with the Monetary Authority of Singapore. Accordingly, this prospectus supplement 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) 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
- b) 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 such securities under Section 275 of the SFA except:
 - i) 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, whether such amount is to be paid for in cash or by exchange of

Table of Contents

securities or other assets, and further for corporations, in accordance with the conditions, specified in Section 275 of the SFA;

ii) where no consideration is given for the transfer; or

iii) 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 supplement 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 supplement 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 supplement 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 supplement will not be filed with, and the offer of securities will not be supervised by, the Swiss Financial Market Supervisory Authority, 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 supplement 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, which is referred to 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 being referred to as a relevant person.

This prospectus supplement 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.

Table of Contents

LEGAL MATTERS

The validity of the shares of common stock offered by this prospectus supplement and the accompanying prospectus will be passed upon for us by Cooley LLP, Palo Alto, California. Morgan, Lewis & Bockius LLP, New York, New York, is counsel to the underwriters in connection with this offering.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2012, as set forth in their report, which is incorporated by reference in this prospectus supplement and elsewhere in the registration statement of which this prospectus supplement and the accompanying prospectus form a part. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus supplement and the accompanying prospectus are part of the registration statement on Form S-3 we filed with the SEC under the Securities Act on August 10, 2012, and do not contain all the information set forth in the registration statement. Whenever a reference is made in this prospectus supplement or the accompanying prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference in this prospectus supplement and the accompanying prospectus for a copy of such contract, agreement or other document. Because we are subject to the information and reporting requirements of the Exchange Act, we file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at <http://www.sec.gov>. You may also read and copy any document we file 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.

Table of Contents

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference information from other documents that we file with them, 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 supplement and the accompanying prospectus. Information contained in this prospectus supplement and the accompanying prospectus and information that we file with the SEC in the future and incorporate by reference in this prospectus supplement and the accompanying prospectus will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings (other than Current Reports on Form 8-K furnished under Item 2.02 or Item 7.01 and exhibits filed on such form that are related to such items) we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, after the date of the prospectus supplement and before the sale of all the securities covered by this prospectus supplement (Commission File No. 001-35068):

- n our Annual Report on Form 10-K for the year ended December 31, 2012, filed with the SEC on March 12, 2013;
- n our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2013, filed with the SEC on May 8, 2013;
- n our Current Reports on Form 8-K filed with the SEC on January 25, 2013, February 11, 2013, February 12, 2013, March 6, 2013 and May 10, 2013; and
- n the description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on February 1, 2011, including any amendments or reports filed for the purpose of updating such description.

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

Table of Contents

Prospectus

\$50,000,000

Common Stock

Preferred Stock

Debt Securities

Warrants

From time to time, we may offer and sell any combination of the securities described in this prospectus, either individually or in combination, for total gross proceeds of up to \$50,000,000. We may also offer common stock or preferred stock upon conversion of debt securities, common stock upon conversion of preferred stock, or common stock, preferred stock or debt securities upon the exercise of warrants.

We will provide the specific terms of these offerings and securities in one or more supplements to this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. You should carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectus, as well as any documents incorporated by reference, before buying any of the securities being offered.

Our common stock is listed on The NASDAQ Global Market under the trading symbol ACRX. On August 9, 2012, the last reported sale price of our common stock was \$3.07 per share. The applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on The NASDAQ Global Market or other securities exchange of the securities covered by the prospectus supplement.

As of July 12, 2012, the aggregate market value of our outstanding common stock held by non-affiliates was approximately \$23,662,644, based on 22,625,000 shares of outstanding common stock, of which approximately 6,898,730 shares were held by non-affiliates, and a price of \$3.43 per share, which was the last reported sale price of our common stock on The NASDAQ Global Market on July 12, 2012. As of the date of this prospectus, we have not offered any securities pursuant to General Instruction I.B.6. of Form S-3 during the prior 12 calendar month period that ends on, and includes, the date of this prospectus.

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading Risk Factors contained in the applicable prospectus supplement and in any free writing prospectuses we have authorized for use in connection with a specific offering, and under similar headings in the other documents that are incorporated by reference into this prospectus.

This prospectus may not be used to consummate a sale of securities unless accompanied by a prospectus supplement.

The securities may be sold directly by us to investors, through agents designated from time to time or to or through underwriters or dealers, on a continuous or delayed basis. The supplements to this prospectus will provide the specific terms of the plan of distribution. If any agents or

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underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such agents or underwriters and any applicable fees, commissions, discounts and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds that we expect to receive from such sale will also be set forth in a prospectus supplement.

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.

The date of this prospectus is August 31, 2012.

Table of Contents**TABLE OF CONTENTS**

<u>ABOUT THIS PROSPECTUS</u>	i
<u>PROSPECTUS SUMMARY</u>	1
<u>RISK FACTORS</u>	6
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	6
<u>USE OF PROCEEDS</u>	8
<u>SELECTED FINANCIAL DATA</u>	8
<u>DESCRIPTION OF CAPITAL STOCK</u>	9
<u>DESCRIPTION OF DEBT SECURITIES</u>	13
<u>DESCRIPTION OF WARRANTS</u>	20
<u>LEGAL OWNERSHIP OF SECURITIES</u>	22
<u>PLAN OF DISTRIBUTION</u>	26
<u>LEGAL MATTERS</u>	28
<u>EXPERTS</u>	28
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	28
<u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u>	28

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or SEC, utilizing a shelf registration process. Under this shelf registration process, we may offer and sell, either individually or in combination, in one or more offerings, any combination of the securities described in this prospectus, for total gross proceeds of up to \$50,000,000. This prospectus provides you with a general description of the securities we may offer.

Each time we offer securities under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change any of the information contained in this prospectus or in the documents that we have incorporated by reference into this prospectus. We urge you to read carefully this prospectus, any applicable prospectus supplement and any free writing prospectuses we have authorized for use in connection with a specific offering, together with the information incorporated herein by reference as described under the heading "Incorporation of Certain Information by Reference," before buying any of the securities being offered.

This prospectus may not be used to consummate a sale of securities unless it is accompanied by a prospectus supplement.

You should rely only on the information contained in, or incorporated by reference into, this prospectus and any applicable prospectus supplement, along with the information contained in any free writing prospectuses we have authorized for use in connection with a specific offering. We have not authorized anyone to provide you with different or additional information. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so.

Table of Contents

The information appearing in this prospectus, any applicable prospectus supplement or any related free writing prospectus is accurate only as of the date on the front of the document and that any information we have incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus, any applicable prospectus supplement or any related free writing prospectus, or any sale of a security. Our business, financial condition, results of operations and prospects may have changed since those dates.

This prospectus contains summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described below under the section entitled **Where You Can Find More Information**.

This prospectus contains and incorporates by reference, and any prospectus supplement or free writing prospectus may contain and incorporate by reference, market data and industry statistics and forecasts that are based on independent industry publications and other publicly available information. Although we believe these sources are reliable, we do not guarantee the accuracy or completeness of this information and we have not independently verified this information. Although we are not aware of any misstatements regarding the market and industry data presented in this prospectus and the documents incorporated herein by reference, these estimates involve risks and uncertainties and are subject to change based on various factors, including those discussed under the heading **Risk Factors** contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. Accordingly, investors should not place undue reliance on this information.

This prospectus and the information incorporated herein by reference include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus, any applicable prospectus supplement or any related free writing prospectus are the property of their respective owners.

Table of Contents

PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus or incorporated by reference in this prospectus, and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus, the applicable prospectus supplement and any related free writing prospectus, including the risks of investing in our securities discussed under the heading Risk Factors contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. You should also carefully read the information incorporated by reference into this prospectus, including our financial statements, and the exhibits to the registration statement of which this prospectus is a part.

References in this prospectus to AcelRx, the Company, we, us and our refer to AcelRx Pharmaceuticals, Inc., a Delaware corporation, and its consolidated subsidiaries, if any, unless otherwise specified.

AcelRx Pharmaceuticals, Inc.

About AcelRx Pharmaceuticals

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. We were founded to solve the problems associated with post-operative intravenous patient-controlled analgesia, or IV PCA. Although widely used, IV PCA has been shown to cause harm to patients following surgery because of the side effects of morphine, the invasive IV route of delivery and the inherent potential for programming and delivery errors associated with the complexity of infusion pumps. In March 2012, we initiated the first of three Phase 3 clinical trials for our lead product candidate, the Sufentanil NanoTab PCA System, or ARX-01 System, or ARX-01. In April 2012, we initiated the second Phase 3 trial, an open-label active-comparator study. The final planned Phase 3 efficacy and safety study, a double-blind, placebo-controlled trial is expected to begin in the third quarter of 2012. We expect top-line data from the first and second Phase 3 trials in the fourth quarter of 2012 and top-line data from the final planned Phase 3 trial in the first quarter of 2013.

The ARX-01 System is designed to address the problems associated with IV PCA by utilizing:

Sufentanil, a high therapeutic index opioid;

NanoTabs, our proprietary, non-invasive sublingual dosage form; and

our novel handheld PCA device that enables simple patient-controlled delivery of NanoTabs in the hospital setting and eliminates the risk of programming errors.

We have completed Phase 2 clinical development for two additional product candidates, the Sufentanil NanoTab BTP Management System, or ARX-02, for the treatment of cancer breakthrough pain, or BTP, and the Sufentanil/Triazolam NanoTab, or ARX-03, designed to provide mild sedation, anxiety reduction and pain relief for patients undergoing painful procedures in a physician's office. In May 2011, we announced that the US Army Medical Research and Materiel Command, or USAMRMC, awarded us a \$5.6 million grant to support the development of a new product candidate, ARX-04, a Sufentanil NanoTab for the treatment of moderate-to-severe acute pain. Under the terms of the grant, the USAMRMC will reimburse us for development, manufacturing and clinical expenses necessary to prepare for and complete the planned Phase 2 dose-finding trial in a study of moderate-to-severe acute pain, and to prepare to enter Phase 3 development.

Development of therapeutic products is costly and is subject to a lengthy and uncertain regulatory process by the United States Food and Drug Administration, or FDA. Adverse events in both our own clinical program and other programs may have a negative impact on regulatory approval, the willingness of potential commercial partners to enter into agreements and the perception of the public.

Table of Contents

Product Development

ARX-01

We continue to make progress in the development of our lead product candidate, ARX-01, including the following activities:

In March 2012, we initiated the first of three Phase 3 clinical trials, a double-blind, placebo-controlled efficacy and safety trial of patients with post-operative pain following open-abdominal surgery. We expect top-line data for this trial in the fourth quarter of 2012;

In April 2012, we initiated our second planned Phase 3 clinical trial, an open-label active-comparator study 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. We expect top-line data for this trial in the fourth quarter of 2012; and

In the third quarter of 2012, we plan to initiate our third planned Phase 3 clinical trial, a double-blind, placebo-controlled efficacy and safety study of patients with post-operative pain following hip and knee replacement surgeries. We expect top-line data for this trial in the first quarter of 2013.

ARX-04

We continue to make progress towards the initiation of our planned ARX-04 Phase 2 dose-finding clinical trial. In October 2011, we filed an Investigational New Drug application for ARX-04, our product candidate for management of moderate-to-severe acute pain, with the FDA, and we plan to initiate the Phase 2 study contingent on approval of the proposed clinical protocol for the study from the USAMRMC.

ARX-02 and ARX-03

Future development of ARX-02 and ARX-03 is contingent upon additional funding or establishing corporate partnerships.

Company Information

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

Our corporate address is 351 Galveston Drive, Redwood City, California 94063, and our telephone number is (650) 216-3500. Our website address is www.acerlx.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this prospectus, and you should not consider it part of this prospectus or part of any prospectus supplement. Our website address is included in this document as an inactive textual reference only.

The Securities We May Offer

We may offer shares of our common stock and preferred stock, various series of debt securities and/or warrants to purchase any of such securities, either individually or in combination, up to an aggregate dollar amount of \$50,000,000, from time to time under this prospectus, together with the applicable prospectus supplement and any related free writing prospectus, at prices and on terms to be determined by market conditions at the time of any offering. We may also offer common stock, preferred stock and/or debt securities upon the exercise of warrants. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities, including, to the extent applicable:

designation or classification;

aggregate principal amount or aggregate offering price;

Table of Contents

maturity date, if applicable;

original issue discount, if any;

rates and times of payment of interest or dividends, if any;

redemption, conversion, exercise, exchange or sinking fund terms, if any;

conversion or exchange prices or rates, if any, and, if applicable, any provisions for changes to or adjustments in the conversion or exchange prices or rates and in the securities or other property receivable upon conversion or exchange;

ranking;

restrictive covenants, if any;

voting or other rights, if any; and

material or special U.S. federal income tax considerations, if any.

The applicable prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change any of the information contained in this prospectus or in the documents we have incorporated by reference. However, no prospectus supplement or free writing prospectus will offer a security that is not registered and described in this prospectus at the time of the effectiveness of the registration statement of which this prospectus is a part.

We may sell the securities directly to investors or to or through agents, underwriters or dealers. We, and our agents or underwriters, reserve the right to accept or reject all or part of any proposed purchase of securities. If we do offer securities to or through agents or underwriters, we will include in the applicable prospectus supplement:

the names of those agents or underwriters;

applicable fees, discounts and commissions to be paid to them;

details regarding over-allotment options, if any; and

the net proceeds to us.

THIS PROSPECTUS MAY NOT BE USED TO CONSUMMATE A SALE OF SECURITIES UNLESS IT IS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.

Common Stock. We may issue shares of our common stock from time to time. The holders of our common stock are entitled to one vote for each share held of record on all matters submitted to a vote of stockholders. Subject to preferences that may be applicable to any outstanding shares of

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preferred stock, the holders of common stock are entitled to receive ratably such dividends as may be declared by our board of directors out of legally available funds. Upon our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preferences of any outstanding shares of preferred stock. Holders of common stock have no preemptive rights and no right to convert their common stock into any other securities. There are no redemption provisions applicable to our common stock. In this prospectus, we have summarized certain general features of the common stock under Description of Capital Stock Common stock. We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to any common stock being offered.

Table of Contents

Preferred Stock. We may issue shares of our preferred stock from time to time, in one or more series. Our board of directors will determine the designations, voting powers, preferences and rights of the preferred stock, as well as the qualifications, limitations or restrictions thereof, including dividend rights, conversion rights, preemptive rights, terms of redemption or repurchase, liquidation preferences and the number of shares constituting any series or the designation of any series. Convertible preferred stock will be convertible into our common stock or exchangeable for other securities. Conversion may be mandatory or at your option and would be at prescribed conversion rates.

If we sell any series of preferred stock under this prospectus, we will fix the designations, voting powers, preferences and rights of the preferred stock of each series we issue under this prospectus, as well as the qualifications, limitations or restrictions thereof, in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that contains the terms of the series of preferred stock we are offering. In this prospectus, we have summarized certain general features of the preferred stock under *Description of Capital Stock Preferred stock*. We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to the series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

Debt Securities. We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. The senior debt securities will rank equally with any other unsecured and unsubordinated debt. The subordinated debt securities will be subordinate and junior in right of payment, to the extent and in the manner described in the instrument governing the debt, to all of our senior indebtedness. Convertible debt securities will be convertible into or exchangeable for our common stock or other securities. Conversion may be mandatory or at your option and would be at prescribed conversion rates.

Any debt securities issued under this prospectus will be issued under one or more documents called indentures, which are contracts between us and a national banking association or other eligible party, as trustee. In this prospectus, we have summarized certain general features of the debt securities under *Description of Debt Securities*. We urge you, however, to read the applicable prospectus supplement (and any free writing prospectus that we may authorize to be provided to you) related to the series of debt securities being offered, as well as the complete indentures that contain the terms of the debt securities. We have filed the form of indenture as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

Warrants. We may issue warrants for the purchase of common stock, preferred stock and/or debt securities in one or more series. We may issue warrants independently or in combination with common stock, preferred stock and/or debt securities. In this prospectus, we have summarized certain general features of the warrants under *Description of Warrants*. We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to the particular series of warrants being offered, as well as any warrant agreements and warrant certificates that contain the terms of the warrants. We have filed forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants that may be offered as exhibits to the registration statement of which this prospectus is a part. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of warrant and/or the warrant agreement and warrant certificate, as applicable, that contain the terms of the particular series of warrants we are offering, and any supplemental agreements, before the issuance of such warrants.

Table of Contents

Any warrants issued under this prospectus may be evidenced by warrant certificates. Warrants also may be issued under an applicable warrant agreement that we enter into with a warrant agent. We will indicate the name and address of the warrant agent, if applicable, in the prospectus supplement relating to the particular series of warrants being offered.

Use of Proceeds

Except as described in any applicable prospectus supplement or in any free writing prospectuses we have authorized for use in connection with a specific offering, we currently intend to use the net proceeds from the sale of the securities offered by us hereunder, if any, for working capital and general corporate purposes, including research and development expenses and capital expenditures. See **Use of Proceeds** in this prospectus.

NASDAQ Global Market Listing

Our common stock is listed on the NASDAQ Global Market under the symbol **ACRX**. The applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on the NASDAQ Global Market or other securities exchange of the securities covered by the applicable prospectus supplement.

Table of Contents

RISK FACTORS

Investing in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should consider carefully the risks and uncertainties described under the heading "Risk Factors" contained in the applicable prospectus supplement and any related free writing prospectus, and discussed under the section entitled "Risk Factors" contained in our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus in their entirety, together with other information in this prospectus, the documents incorporated by reference and any free writing prospectus that we may authorize for use in connection with this offering. The risks described in these documents are not the only ones we face, but those that we consider to be material. There may be other unknown or unpredictable economic, business, competitive, regulatory or other factors that could have material adverse effects on our future results. Past financial performance may not be a reliable indicator of future performance, and historical trends should not be used to anticipate results or trends in future periods. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be seriously harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment. Please also read carefully the section below entitled "Special Note Regarding Forward-Looking Statements."

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 to our future operating or 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," "plans," "potential," "predicts," "should," "will," or the negative of these terms or other comparable terminology. These forward-looking statements may also use different phrases. Discussions containing these forward-looking statements may be found, among other places, in "Business," "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" incorporated by reference from our most recent annual report on Form 10-K and in our most recent quarterly report on Form 10-Q subsequent to the filing of our most recent annual report on Form 10-K with the SEC, as well as any amendments thereto reflected in subsequent filings with the SEC. 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 to complete the ARX-01 NDA preparation process and file the NDA with the FDA;

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

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

Table of Contents

- 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 any particular 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 in the applicable prospectus supplement, or in any free writing prospectuses we may authorize for use in connection with a specific offering, 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.

You should rely only on information contained or incorporated by reference in this prospectus, the registration statement of which this prospectus is a part, including the exhibits that we have filed with the registration statement, and the applicable prospectus supplement or in any free writing prospectuses we may authorize for use in connection with a specific offering. You should understand that our actual future results may be materially different from what we expect. 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. Before deciding to purchase our securities, you should carefully consider the risk factors discussed and incorporated by reference in this prospectus and any prospectus supplement and, if required, any post-effective amendment to the registration statement of which this prospectus is a part.

Table of Contents**USE OF PROCEEDS**

Except as described in any applicable prospectus supplement or in any free writing prospectuses we have authorized for use in connection with a specific offering, we currently intend to use the net proceeds from the sale of the securities offered by us hereunder, if any, for working capital and general corporate purposes, including research and development expenses and capital expenditures.

The amounts and timing of our use of the net proceeds from this offering will depend on a number of factors, such as the timing and progress of our research and development efforts, the timing and progress of any partnering and commercialization efforts, technological advances and the competitive environment for our products. As of the date of this prospectus, we cannot specify with certainty all of the particular uses for the net proceeds to us from the sale of the securities offered by us hereunder. Accordingly, our management will have broad discretion in the timing and application of these proceeds. Pending application of the net proceeds as described above, we intend to temporarily invest the proceeds in short-term, interest-bearing instruments.

SELECTED FINANCIAL DATA

The following table sets forth historical selected financial information. Effective January 1, 2012, we adopted the Financial Accounting Standards Board's (FASB) 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 revise the manner in which entities present comprehensive income in their financial statements. The following selected financial information revises historical information to illustrate the new presentation required by this pronouncement for the periods presented.

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)

Table of Contents

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of 100,000,000 shares of common stock, \$0.001 par value, and 10,000,000 shares of preferred stock, \$0.001 par value. A description of material terms and provisions of our certificate of incorporation and bylaws affecting the rights of holders of our capital stock is set forth below. The description is intended as a summary, and is qualified in its entirety by reference to our certificate of incorporation and the bylaws.

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. In all matters other than the election of directors, the affirmative vote of the majority of shares present in person, by remote communication, or represented by proxy at a meeting of the stockholders and entitled to vote generally on the subject matter shall be the act of the stockholders. 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 pursuant to any offering we may make pursuant to this prospectus and any related prospectus supplement will be, fully paid and nonassessable.

Preferred stock

Our board of directors is authorized, subject to limitations prescribed by Delaware law, to issue 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 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.

Table of Contents

We will fix the designations, voting powers, preferences and rights of the preferred stock of each series we issue under this prospectus, as well as the qualifications, limitations or restrictions thereof, in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that contains the terms of the series of preferred stock we are offering. We will describe in the applicable prospectus supplement the terms of the series of preferred stock being offered, including, to the extent applicable:

the title and stated value;

the number of shares we are offering;

the liquidation preference per share;

the purchase price;

the dividend rate, period and payment date and method of calculation for dividends;

whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;

the procedures for any auction and remarketing, if applicable;

the provisions for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;

any listing of the preferred stock on any securities exchange or market;

whether the preferred stock will be convertible into our common stock, and, if applicable, the conversion price, or how it will be calculated, and the conversion period;

whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange price, or how it will be calculated, and the exchange period;

voting rights of the preferred stock;

preemptive rights, if any;

restrictions on transfer, sale or other assignment;

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whether interests in the preferred stock will be represented by depositary shares;

a discussion of material United States federal income tax considerations applicable to the preferred stock;

the relative ranking and preferences of the preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs;

any limitations on the issuance of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs; and

any other specific terms, preferences, rights or limitations of, or restrictions on, the preferred stock.

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.

Table of Contents

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. 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.

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 the provisions of Section 203 of the Delaware General Corporation Law regulating corporate takeovers. This section prevents some Delaware corporations from engaging, under some circumstances, in a business combination, which includes a merger or sale of at least 10% of the corporation's assets with any interested stockholder, meaning a stockholder who, together with affiliates and associates, owns or, within three years prior to the determination of interested stockholder status, did own 15% or more of the corporation's outstanding voting stock, unless:

the transaction is approved by the board of directors prior to the time that the interested stockholder became an interested stockholder;

upon consummation of the transaction which resulted in the stockholder's 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; or

Table of Contents

at or subsequent to such time that the stockholder became an interested stockholder the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders by at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

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 of 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, Inc.: 1-800-736-3001.

Listing on the NASDAQ Global Market

Our common stock is listed on the NASDAQ Global Market under the symbol *ACRX*. The applicable prospectus supplement will contain information, where applicable, as to any other listing, if any, on the NASDAQ Global Market or any securities market or other exchange of the preferred stock covered by such prospectus supplement.

Table of Contents

DESCRIPTION OF DEBT SECURITIES

We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. While the terms we have summarized below will apply generally to any debt securities that we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. The terms of any debt securities offered under a prospectus supplement may differ from the terms described below. Unless the context requires otherwise, whenever we refer to the indenture, we also are referring to any supplemental indentures that specify the terms of a particular series of debt securities.

We will issue the debt securities under the indenture that we will enter into with trustee named in the indenture. The indenture will be qualified under the Trust Indenture Act of 1939, as amended, or the Trust Indenture Act. We have filed the form of indenture as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

The following summary of material provisions of the debt securities and the indenture is subject to, and qualified in its entirety by reference to, all of the provisions of the indenture applicable to a particular series of debt securities. We urge you to read the applicable prospectus supplements and any related free writing prospectuses related to the debt securities that we may offer under this prospectus, as well as the complete indenture that contains the terms of the debt securities.

General

The indenture does not limit the amount of debt securities that we may issue. It provides that we may issue debt securities up to the principal amount that we may authorize and may be in any currency or currency unit that we may designate. Except for the limitations on consolidation, merger and sale of all or substantially all of our assets contained in the indenture, the terms of the indenture do not contain any covenants or other provisions designed to give holders of any debt securities protection against changes in our operations, financial condition or transactions involving us.

We may issue the debt securities issued under the indenture as discount securities, which means they may be sold at a discount below their stated principal amount. These debt securities, as well as other debt securities that are not issued at a discount, may be issued with original issue discount, or OID, for U.S. federal income tax purposes because of interest payment and other characteristics or terms of the debt securities. Material U.S. federal income tax considerations applicable to debt securities issued with OID will be described in more detail in any applicable prospectus supplement.

We will describe in the applicable prospectus supplement the terms of the series of debt securities being offered, including:

the title of the series of debt securities;

any limit upon the aggregate principal amount that may be issued;

the maturity date or dates;

the form of the debt securities of the series;

the applicability of any guarantees;

whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;

Table of Contents

whether the debt securities rank as senior debt, senior subordinated debt, subordinated debt or any combination thereof, and the terms of any subordination;

if the price (expressed as a percentage of the aggregate principal amount thereof) at which such debt securities will be issued is a price other than the principal amount thereof, the portion of the principal amount thereof payable upon declaration of acceleration of the maturity thereof, or if applicable, the portion of the principal amount of such debt securities that is convertible into another security or the method by which any such portion shall be determined;

the interest rate or rates, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the dates interest will be payable and the regular record dates for interest payment dates or the method for determining such dates;

our right, if any, to defer payment of interest and the maximum length of any such deferral period;

if applicable, the date or dates after which, or the period or periods during which, and the price or prices at which, we may, at our option, redeem the series of debt securities pursuant to any optional or provisional redemption provisions and the terms of those redemption provisions;

the date or dates, if any, on which, and the price or prices at which we are obligated, pursuant to any mandatory sinking fund or analogous fund provisions or otherwise, to redeem, or at the holder's option to purchase, the series of debt securities and the currency or currency unit in which the debt securities are payable;

the denominations in which we will issue the series of debt securities, if other than denominations of \$1,000 and any integral multiple thereof;

any and all terms, if applicable, relating to any auction or remarketing of the debt securities of that series and any security for our obligations with respect to such debt securities and any other terms which may be advisable in connection with the marketing of debt securities of that series;

whether the debt securities of the series shall be issued in whole or in part in the form of a global security or securities; the terms and conditions, if any, upon which such global security or securities may be exchanged in whole or in part for other individual securities; and the depositary for such global security or securities;

if applicable, the provisions relating to conversion or exchange of any debt securities of the series and the terms and conditions upon which such debt securities will be so convertible or exchangeable, including the conversion or exchange price, as applicable, or how it will be calculated and may be adjusted, any mandatory or optional (at our option or the holders' option) conversion or exchange features, the applicable conversion or exchange period and the manner of settlement for any conversion or exchange;

if other than the full principal amount thereof, the portion of the principal amount of debt securities of the series which shall be payable upon declaration of acceleration of the maturity thereof;

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additions to or changes in the covenants applicable to the particular debt securities being issued, including, among others, the consolidation, merger or sale covenant;

additions to or changes in the events of default with respect to the securities and any change in the right of the trustee or the holders to declare the principal, premium, if any, and interest, if any, with respect to such securities to be due and payable;

additions to or changes in or deletions of the provisions relating to covenant defeasance and legal defeasance;

additions to or changes in the provisions relating to satisfaction and discharge of the indenture;

Table of Contents

additions to or changes in the provisions relating to the modification of the indenture both with and without the consent of holders of debt securities issued under the indenture;

the currency of payment of debt securities if other than U.S. dollars and the manner of determining the equivalent amount in U.S. dollars;

whether interest will be payable in cash or additional debt securities at our or the holders' option and the terms and conditions upon which the election may be made;

the terms and conditions, if any, upon which we will pay amounts in addition to the stated interest, premium, if any and principal amounts of the debt securities of the series to any holder that is not a United States person for federal tax purposes;

any restrictions on transfer, sale or assignment of the debt securities of the series; and

any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities, any other additions or changes in the provisions of the indenture, and any terms that may be required by us or advisable under applicable laws or regulations.

Conversion or Exchange Rights

We will set forth in the prospectus supplement the terms on which a series of debt securities may be convertible into or exchangeable for our common stock or our other securities or other property or assets. We will include provisions as to settlement upon conversion or exchange and whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or our other securities or units of other property or assets that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the indenture will not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of all or substantially all of our assets. However, any successor to or acquirer of such assets must assume all of our obligations under the indenture or the debt securities, as appropriate.

Events of Default Under the Indenture

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the following are events of default under the indenture with respect to any series of debt securities that we may issue:

if we fail to pay any installment of interest on any series of debt securities, as and when the same shall become due and payable, and such default continues for a period of 90 days; provided, however, that a valid extension of an interest payment period by us in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of interest for this purpose;

if we fail to pay the principal of, or premium, if any, on any series of debt securities as and when the same shall become due and payable whether at maturity, upon redemption, by declaration or otherwise, or in any payment required by any sinking or analogous fund established with respect to such series; provided, however, that a valid extension of the maturity of such debt securities in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of principal or premium, if any;

Table of Contents

if we fail to observe or perform any other covenant or agreement contained in the debt securities or the indenture, other than a covenant specifically relating to another series of debt securities, and our failure continues for 90 days after we receive written notice of such failure, requiring the same to be remedied and stating that such is a notice of default thereunder, from the trustee or holders of at least 25% in aggregate principal amount of the outstanding debt securities of the applicable series; and

if specified events of bankruptcy, insolvency or reorganization occur.

If an event of default with respect to debt securities of any series occurs and is continuing, other than an event of default specified in the last bullet point above, the trustee or the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series, by notice to us in writing, and to the trustee if notice is given by such holders, may declare the unpaid principal of, premium, if any, and accrued interest, if any, due and payable immediately. If an event of default specified in the last bullet point above occurs with respect to us, the principal amount of and accrued interest, if any, of each issue of debt securities then outstanding shall be due and payable without any notice or other action on the part of the trustee or any holder.

The holders of a majority in principal amount of the outstanding debt securities of an affected series may waive any default or event of default with respect to the series and its consequences, except defaults or events of default regarding payment of principal, premium, if any, or interest, unless we have cured the default or event of default in accordance with the indenture. Any waiver shall cure the default or event of default.

Subject to the terms of the indenture, if an event of default under an indenture shall occur and be continuing, the trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, or exercising any trust or power conferred on the trustee, with respect to the debt securities of that series, provided that:

the direction so given by the holder is not in conflict with any law or the applicable indenture; and

subject to its duties under the Trust Indenture Act, the trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

A holder of the debt securities of any series will have the right to institute a proceeding under the indenture or to appoint a receiver or trustee, or to seek other remedies only if:

the holder has given written notice to the trustee of a continuing event of default with respect to that series;

the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made written request, and such holders have offered reasonable indemnity to the trustee to institute the proceeding as trustee; and

the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series other conflicting directions within 90 days after the notice, request and offer.

These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.

We will periodically file statements with the trustee regarding our compliance with specified covenants in the indenture.

Table of Contents

Modification of Indenture; Waiver

We and the trustee may change an indenture without the consent of any holders with respect to specific matters:

to cure any ambiguity, defect or inconsistency in the indenture or in the debt securities of any series;

to comply with the provisions described above under **Description of Debt Securities Consolidation, Merger or Sale**;

to provide for uncertificated debt securities in addition to or in place of certificated debt securities;

to add to our covenants, restrictions, conditions or provisions such new covenants, restrictions, conditions or provisions for the benefit of the holders of all or any series of debt securities, to make the occurrence, or the occurrence and the continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default or to surrender any right or power conferred upon us in the indenture;

to add to, delete from or revise the conditions, limitations, and restrictions on the authorized amount, terms, or purposes of issue, authentication and delivery of debt securities, as set forth in the indenture;

to make any change that does not adversely affect the interests of any holder of debt securities of any series in any material respect;

to provide for the issuance of and establish the form and terms and conditions of the debt securities of any series as provided above under **Description of Debt Securities General** to establish the form of any certifications required to be furnished pursuant to the terms of the indenture or any series of debt securities, or to add to the rights of the holders of any series of debt securities;

to evidence and provide for the acceptance of appointment under any indenture by a successor trustee; or

to comply with any requirements of the SEC in connection with the qualification of any indenture under the Trust Indenture Act. In addition, under the indenture, the rights of holders of a series of debt securities may be changed by us and the trustee with the written consent of the holders of a majority in aggregate principal amount of the outstanding debt securities of each series that is affected. However, unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, we and the trustee may make the following changes only with the consent of each holder of any outstanding debt securities affected:

extending the fixed maturity of any debt securities of any series;

reducing the principal amount, reducing the rate of or extending the time of payment of interest, or reducing any premium payable upon the redemption of any series of any debt securities; or

reducing the percentage of debt securities, the holders of which are required to consent to any amendment, supplement, modification or waiver.

Table of Contents

Discharge

Each indenture provides that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for specified obligations, including obligations to:

provide for payment;

register the transfer or exchange of debt securities of the series;

replace stolen, lost or mutilated debt securities of the series;

pay principal of and premium and interest on any debt securities of the series;

maintain paying agencies;

hold monies for payment in trust;

recover excess money held by the trustee;

compensate and indemnify the trustee; and

appoint any successor trustee.

In order to exercise our rights to be discharged, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, any premium, if any, and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we provide otherwise in the applicable prospectus supplement, in denominations of \$1,000 and any integral multiple thereof. The indenture provides that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company, or DTC, or another depository named by us and identified in a prospectus supplement with respect to that series. To the extent the debt securities of a series are issued in global form and as book-entry, a description of terms relating will be set forth in the applicable prospectus supplement.

At the option of the holder, subject to the terms of the indenture and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indenture and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange, we will impose no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental

charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

Table of Contents

If we elect to redeem the debt securities of any series, we will not be required to:

issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or

register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Trustee

The trustee, other than during the occurrence and continuance of an event of default under an indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the trustee must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the trustee is under no obligation to exercise any of the powers given it by the indenture at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, we will make interest payments by check that we will mail to the holder or by wire transfer to certain holders. Unless we otherwise indicate in the applicable prospectus supplement, we will designate the corporate trust office of the trustee as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the trustee for the payment of the principal of or any premium or interest on any debt securities that remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the debt security thereafter may look only to us for payment thereof.

Governing Law

The indenture and the debt securities will be governed by and construed in accordance with the laws of the State of New York, except to the extent that the Trust Indenture Act of 1939 is applicable.

Table of Contents

DESCRIPTION OF WARRANTS

The following description, together with the additional information that we include in any applicable prospectus supplement and in any related free writing prospectus that we may authorize to be distributed to you, summarizes the material terms and provisions of the warrants that we may offer under this prospectus, which may be issued in one or more series. Warrants may be offered independently or in combination with other securities offered by any prospectus supplement. While the terms we have summarized below will apply generally to any warrants that we may offer under this prospectus, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement. The following description of warrants will apply to the warrants offered by this prospectus unless we provide otherwise in the applicable prospectus supplement. The applicable prospectus supplement for a particular series of warrants may specify different or additional terms.

We have filed forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants that may be offered as exhibits to the registration statement of which this prospectus is a part. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of warrant and/or the warrant agreement and warrant certificate, as applicable, that contain the terms of the particular series of warrants we are offering, and any supplemental agreements, before the issuance of such warrants. The following summaries of material terms and provisions of the warrants are subject to, and qualified in their entirety by reference to, all the provisions of the form of warrant and/or the warrant agreement and warrant certificate, as applicable, and any supplemental agreements applicable to a particular series of warrants that we may offer under this prospectus. We urge you to read the applicable prospectus supplement related to the particular series of warrants that we may offer under this prospectus, as well as any related free writing prospectuses, and the complete form of warrant and/or the warrant agreement and warrant certificate, as applicable, and any supplemental agreements, that contain the terms of the warrants.

General

We will describe in the applicable prospectus supplement the terms of the series of warrants being offered, including:

the offering price and aggregate number of warrants offered;

the currency for which the warrants may be purchased;

if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;

in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one warrant and the price at, and currency in which, this principal amount of debt securities may be purchased upon such exercise;

in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable upon the exercise of one warrant and the price at which these shares may be purchased upon such exercise;

the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreements and the warrants;

the terms of any rights to redeem or call the warrants;

any provisions for changes to or adjustments in the exercise price or number of securities issuable upon exercise of the warrants;

the dates on which the right to exercise the warrants will commence and expire;

Table of Contents

the manner in which the warrant agreements and warrants may be modified;

a discussion of any material or special U.S. federal income tax considerations of holding or exercising the warrants;

the terms of the securities issuable upon exercise of the warrants; and

any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable upon such exercise, including:

in the case of warrants to purchase debt securities, the right to receive payments of principal of, or premium, if any, or interest on, the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture; or

in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or, payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any.

Exercise of Warrants

Each warrant will entitle the holder to purchase the securities that we specify in the applicable prospectus supplement at the exercise price that we describe in the applicable prospectus supplement. The warrants may be exercised as set forth in the prospectus supplement relating to the warrants offered. Unless we otherwise specify in the applicable prospectus supplement, warrants may be exercised at any time up to the close of business on the expiration date set forth in the prospectus supplement relating to the warrants offered thereby. After the close of business on the expiration date, unexercised warrants will become void.

Upon receipt of payment and the warrant or warrant certificate, as applicable, properly completed and duly executed at the corporate trust office of the warrant agent, if any, or any other office, including ours, indicated in the prospectus supplement, we will, as soon as practicable, issue and deliver the securities purchasable upon such exercise. If less than all of the warrants (or the warrants represented by such warrant certificate) are exercised, a new warrant or a new warrant certificate, as applicable, will be issued for the remaining warrants.

Governing Law

Unless we otherwise specify in the applicable prospectus supplement, the warrants and any warrant agreements will be governed by and construed in accordance with the laws of the State of New York.

Enforceability of Rights by Holders of Warrants

Each warrant agent, if any, will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder of any warrant. A single bank or trust company may act as warrant agent for more than one issue of warrants. A warrant agent will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to exercise, and receive the securities purchasable upon exercise of, its warrants.

Table of Contents

LEGAL OWNERSHIP OF SECURITIES

We can issue securities in registered form or in the form of one or more global securities. We describe global securities in greater detail below. We refer to those persons who have securities registered in their own names on the books that we or any applicable trustee, depository or warrant agent maintain for this purpose as the **holders** of those securities. These persons are the legal holders of the securities. We refer to those persons who, indirectly through others, own beneficial interests in securities that are not registered in their own names, as **indirect holders** of those securities. As we discuss below, indirect holders are not legal holders, and investors in securities issued in book-entry form or in street name will be indirect holders.

Book-Entry Holders

We may issue securities in book-entry form only, as we will specify in the applicable prospectus supplement. This means securities may be represented by one or more global securities registered in the name of a financial institution that holds them as depository on behalf of other financial institutions that participate in the depository's book-entry system. These participating institutions, which are referred to as participants, in turn, hold beneficial interests in the securities on behalf of themselves or their customers.

Only the person in whose name a security is registered is recognized as the holder of that security. Securities issued in global form will be registered in the name of the depository or its participants. Consequently, for securities issued in global form, we will recognize only the depository as the holder of the securities, and we will make all payments on the securities to the depository. The depository passes along the payments it receives to its participants, which in turn pass the payments along to their customers who are the beneficial owners. The depository and its participants do so under agreements they have made with one another or with their customers; they are not obligated to do so under the terms of the securities.

As a result, investors in a book-entry security will not own securities directly. Instead, they will own beneficial interests in a global security, through a bank, broker or other financial institution that participates in the depository's book-entry system or holds an interest through a participant. As long as the securities are issued in global form, investors will be indirect holders, and not holders, of the securities.

Street Name Holders

We may terminate a global security or issue securities in non-global form. In these cases, investors may choose to hold their securities in their own names or in **street name**. Securities held by an investor in street name would be registered in the name of a bank, broker or other financial institution that the investor chooses, and the investor would hold only a beneficial interest in those securities through an account he or she maintains at that institution.

For securities held in street name, we will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those securities, and we will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners, but only because they agree to do so in their customer agreements or because they are legally required to do so. Investors who hold securities in street name will be indirect holders, not holders, of those securities.

Legal Holders

Our obligations, as well as the obligations of any applicable trustee and of any third parties employed by us or a trustee, run only to the legal holders of the securities. We do not have obligations to investors who hold beneficial interests in global securities, in street name or by any other indirect means. This will be the case whether an investor chooses to be an indirect holder of a security or has no choice because we are issuing the securities only in global form.

Table of Contents

For example, once we make a payment or give a notice to the holder, we have no further responsibility for the payment or notice even if that holder is required, under agreements with depositary participants or customers or by law, to pass it along to the indirect holders but does not do so. Similarly, we may want to obtain the approval of the holders to amend an indenture, to relieve us of the consequences of a default or of our obligation to comply with a particular provision of the indenture or for other purposes. In such an event, we would seek approval only from the holders, and not the indirect holders, of the securities. Whether and how the holders contact the indirect holders is up to the holders.

Special Considerations For Indirect Holders

If you hold securities through a bank, broker or other financial institution, either in book-entry form or in street name, you should check with your own institution to find out:

the performance of third party service providers;

how it handles securities payments and notices;

whether it imposes fees or charges;

how it would handle a request for the holders' consent, if ever required;

whether and how you can instruct it to send you securities registered in your own name so you can be a holder, if that is permitted in the future;

how it would exercise rights under the securities if there were a default or other event triggering the need for holders to act to protect their interests; and

if the securities are in book-entry form, how the depositary's rules and procedures will affect these matters.

Global Securities

A global security is a security that represents one or any other number of individual securities held by a depositary. Generally, all securities represented by the same global securities will have the same terms.

Each security issued in book-entry form will be represented by a global security that we deposit with and register in the name of a financial institution or its nominee that we select. The financial institution that we select for this purpose is called the depositary. Unless we specify otherwise in the applicable prospectus supplement, DTC will be the depositary for all securities issued in book-entry form.

A global security may not be transferred to or registered in the name of anyone other than the depositary, its nominee or a successor depositary, unless special termination situations arise. We describe those situations below under the section entitled "Special Situations When a Global Security Will Be Terminated" in this prospectus. As a result of these arrangements, the depositary, or its nominee, will be the sole registered owner and holder of all securities represented by a global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depositary or with another institution that does. Thus, an investor whose security is represented by a global security will not be a holder of the security, but only an indirect holder of a beneficial interest in the global security.

If the prospectus supplement for a particular security indicates that the security will be issued in global form only, then the security will be represented by a global security at all times unless and until the global security is terminated. If termination occurs, we may issue the securities through another book-entry clearing system or decide that the securities may no longer be held through any book-entry clearing system.

Table of Contents

Special Considerations For Global Securities

The rights of an indirect holder relating to a global security will be governed by the account rules of the investor's financial institution and of the depositary, as well as general laws relating to securities transfers. We do not recognize an indirect holder as a holder of securities and instead deal only with the depositary that holds the global security.

If securities are issued only in the form of a global security, an investor should be aware of the following:

an investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;

an investor will be an indirect holder and must look to his or her own bank or broker for payments on the securities and protection of his or her legal rights relating to the securities, as we describe above;

an investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;

an investor may not be able to pledge his or her interest in a global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;

the depositary's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in a global security;

we and any applicable trustee have no responsibility for any aspect of the depositary's actions or for its records of ownership interests in a global security, nor do we or any applicable trustee supervise the depositary in any way;

the depositary may, and we understand that DTC will, require that those who purchase and sell interests in a global security within its book-entry system use immediately available funds, and your broker or bank may require you to do so as well; and

financial institutions that participate in the depositary's book-entry system, and through which an investor holds its interest in a global security, may also have their own policies affecting payments, notices and other matters relating to the securities.

There may be more than one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries.

Special Situations When a Global Security Will Be Terminated

In a few special situations described below, the global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks or brokers to find out how to have their interests in securities transferred to their own name, so that they will be direct holders. We have described the rights of holders and street name investors above.

Unless we provide otherwise in the applicable prospectus supplement, the global security will terminate when the following special situations occur:

if the depositary notifies us that it is unwilling, unable or no longer qualified to continue as depositary for that global security and we do not appoint another institution to act as depositary within 90 days;

if we notify any applicable trustee that we wish to terminate that global security; or

if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived.

Table of Contents

The applicable prospectus supplement may also list additional situations for terminating a global security that would apply only to the particular series of securities covered by the applicable prospectus supplement. When a global security terminates, the depository, and not we or any applicable trustee, is responsible for deciding the names of the institutions that will be the initial direct holders.

Table of Contents

PLAN OF DISTRIBUTION

We may sell the securities from time to time pursuant to underwritten public offerings, direct sales to the public, negotiated transactions, block trades or a combination of these methods. We may sell the securities to or through underwriters or dealers, through agents, or directly to one or more purchasers. We may distribute securities from time to time in one or more transactions:

at a fixed price or prices, which may be changed;

at market prices prevailing at the time of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

A prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you) will describe the terms of the offering of the securities, including, to the extent applicable:

the name or names of the underwriters, if any;

the purchase price of the securities or other consideration therefor, and the proceeds, if any, we will receive from the sale;

any over-allotment options under which underwriters may purchase additional securities from us;

any agency fees or underwriting discounts and other items constituting agents' or underwriters' compensation;

any public offering price;

any discounts or concessions allowed or reallocated or paid to dealers; and

any securities exchange or market on which the securities may be listed.

Only underwriters named in the prospectus supplement will be underwriters of the securities offered by the prospectus supplement.

If underwriters are used in the sale, they will acquire the securities for their own account and may resell the securities from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the securities will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the securities to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all of the securities offered by the prospectus supplement, other than securities covered by any over-allotment option. Any public offering price and any discounts or concessions allowed or reallocated or paid to dealers may change from time to time. We may use underwriters with whom we have a material relationship. We will describe in the prospectus supplement, naming the underwriter, the nature of any such relationship.

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We may sell securities directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of securities and we will describe any commissions we will pay the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, our agent will act on a best-efforts basis for the period of its appointment.

We may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.

Table of Contents

We may provide agents and underwriters with indemnification against civil liabilities, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to these liabilities. Agents and underwriters may engage in transactions with, or perform services for, us in the ordinary course of business.

All securities we may offer, other than common stock, will be new issues of securities with no established trading market. Any underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We cannot guarantee the liquidity of the trading markets for any securities.

Any underwriter may engage in over-allotment, stabilizing transactions, short-covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum price. Syndicate-covering or other short-covering transactions involve purchases of the securities, either through exercise of the over-allotment option or in the open market after the distribution is completed, to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a stabilizing or covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Any underwriters or agents that are qualified market makers on the NASDAQ Global Market may engage in passive market making transactions in the common stock on the NASDAQ Global Market in accordance with Regulation M under the Exchange Act, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded. Passive market making may stabilize the market price of the securities at a level above that which might otherwise prevail in the open market and, if commenced, may be discontinued at any time.

In compliance with guidelines of the Financial Industry Regulatory Authority, or FINRA, the maximum consideration or discount to be received by any FINRA member or independent broker dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus and any applicable prospectus supplement.

Table of Contents

LEGAL MATTERS

Unless otherwise indicated in the applicable prospectus supplement, the validity of the securities offered by this prospectus, and any supplement thereto, will be passed upon for us by Cooley LLP, Palo Alto, California.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2011, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement of which this prospectus forms a part. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of the registration statement on Form S-3 we filed with the SEC under the Securities Act and does not contain all the information set forth in the registration statement. Whenever a reference is made in this prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference into this prospectus for a copy of such contract, agreement or other document. Because we are subject to the information and reporting requirements of the Exchange Act, we file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at <http://www.sec.gov>. You may also read and copy any document we file 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.

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, while information that we file later with the SEC will automatically update and supersede the information in 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, and June 30, 2012, filed with the SEC on May 9, 2012, and August 10, 2012, respectively;

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, and August 3, 2012; and

the description of our common stock, which is registered under Section 12 of the Exchange Act, in our registration statement on Form 8-A, filed with the SEC on February 1, 2011, including any amendments or reports filed for the purpose of updating such description.

Table of Contents

We also incorporate by reference any future filings (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items unless such Form 8-K expressly provides to the contrary) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, including those made after the date of the initial filing of the registration statement of which this prospectus is a part and prior to effectiveness of such registration statement, until we file a post-effective amendment that indicates the termination of the offering of the securities made by this prospectus and will become a part of this prospectus from the date that such documents are filed with the SEC. Information in such future filings updates and supplements the information provided in this prospectus. Any statements in any such future filings will automatically be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

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.

Table of Contents

Shares

Common Stock

PROSPECTUS SUPPLEMENT

Joint Book-Running Managers

Jefferies

Piper Jaffray

Co-Manager

Guggenheim Securities

July , 2013