ACELRX PHARMACEUTICALS INC
Form 10-K
March 13, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

FORM 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2014

or

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

Commission File Number: 001-35068

ACELRX PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**41-2193603**
(State or other jurisdiction of incorporation or organization)	**(IRS Employer Identification No.)**
351 Galveston Drive	
Redwood City, CA 94063	
(650) 216-3500	
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)	

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

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

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

None

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

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

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

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

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

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

Large accelerated filer Accelerated filer
Non-accelerated filer (Do not check if a smaller reporting company) Smaller reporting company
Indicate by check mark whether the registrant is a shell company (as defined in Exchange Act Rule 12b-2) Yes No

The aggregate market value of the voting stock held by non-affiliates of the registrant on June 30, 2014 (the last business day of the registrant’s most recently completed second fiscal quarter), based upon the last sale price reported on the NASDAQ Global Market on that date, was approximately $318,700,000. The calculation excludes 12,280,685 shares of the registrant’s common stock held by current executive officers, directors and stockholders that the registrant has concluded are affiliates of the registrant. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the registrant.

As of February 25, 2015, the number of outstanding shares of the registrant’s common stock was 43,714,665.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's notice of annual meeting of stockholders and proxy statement to be filed pursuant to Regulation 14A within 120 days after Registrant's fiscal year end of December 31, 2014, are incorporated by reference into Part III of this report.

1

ACELRX PHARMACEUTICALS, INC.

2014 ANNUAL REPORT ON FORM 10-K

TABLE OF CONTENTS

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

ACELRX and "ACCELERATE.INNOVATE.ALLEVIATE." are registered trademarks of AcelRx Pharmaceuticals, Inc. Other trademarks of AcelRx Pharmaceuticals, Inc., including ZALVISO™, appearing in this annual report on Form

10-K are the property of AcelRx Pharmaceuticals, Inc. This report also contains trademarks and trade names that are the property of their respective owners.

Forward-Looking Statements

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

- our ability to resubmit the Zalviso NDA, including our ability to satisfactorily conduct the additional clinical study requested by the FDA, and any additional studies that may be required by the FDA in order to resubmit the Zalviso NDA, and the time and resources required to do so;
- 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;
- the success, cost and timing of our product development activities and clinical trials, including an additional clinical study for Zalviso;
- 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 including our planned Phase 3 clinical program for ARX-04;
- the potential achievement of collaboration milestones, including the approval of the Marketing Authorization Application for Zalviso in the European Union and the timing thereof;
- our plans to research, develop and commercialize our product candidates;

- our ability to attract additional collaborators with development, regulatory and commercialization expertise;
- the size and growth potential of the markets for our product candidates, and our ability to serve those markets;
- our liquidity and capital resources;
- our ability to successfully commercialize our product candidates;
- the rate and degree of market acceptance of our product candidates;
- our ability to develop sales and marketing capabilities, whether alone or with potential future collaborators;
- regulatory developments in the United States and foreign countries;
- the performance of our third party suppliers and manufacturers;
- the success of competing therapies that are or become available;
- the loss of key scientific or management personnel;
- the accuracy of our estimates regarding expenses, future revenues, capital requirements and needs for additional financing; and
- our ability to obtain and maintain intellectual property protection for our product candidates.

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

PART I

Item 1. Business

Overview

We are a specialty pharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of acute pain. Our lead product candidate is Zalviso™, formerly known as ARX-01. Zalviso is intended for the management of moderate-to-severe acute pain in hospitalized adult patients. Zalviso consists of sufentanil sublingual tablets delivered by the Zalviso System, a needle-free, handheld, patient-administered, pain management system (together, "Zalviso").

On July 25, 2014, the U.S. Food and Drug Administration, or FDA, issued a Complete Response Letter, or CRL, for our New Drug Application, or NDA, for Zalviso. The CRL contains requests for additional information on the Zalviso System to ensure proper use of the device. The requests include submission of data demonstrating a reduction in the incidence of optical system errors, changes to the Instructions for Use for the device to address inadvertent dosing, among other items, and submission of additional data to support the shelf life of the product. In the third quarter of 2014, we held a Type A meeting with the FDA to discuss the Zalviso CRL received in July. During the meeting we discussed the resubmission of the Zalviso NDA and the steps necessary for the resubmission. In advance of resubmitting our Zalviso NDA, we agreed with the FDA to submit protocols for the bench testing and Human Factors, or HF, studies for their review and comment. In addition, the FDA requested in the minutes of the meeting that we provide a risk assessment that analyzes the risks associated with inadvertent dosing and the rationale that bench testing and HF studies are sufficient to address the specific items included in the CRL. We submitted the protocols and this rationale in the fourth quarter of 2014. In January 2015, we received feedback from the FDA on the protocol and the planned analysis of the results of the bench test. No modifications to the conduct of the bench test were necessary; however, in response to the FDA's request, we refined the planned analysis of the bench test results. In February 2015, we received feedback from the FDA on the HF protocols. In this feedback, the FDA confirmed that the HF studies as proposed were acceptable to evaluate the design changes related to inadvertent dispensing of tablets. In March 2015, we received additional correspondence from the FDA stating that in addition to the bench testing and two Human Factors studies we have performed in response to the issues identified in the CRL, an additional clinical study is needed to assess the risk of inadvertent dispensing and overall risk of dispensing failures. We plan to meet with the FDA to discuss and clarify the need for an additional clinical study, and the potential design and objectives of such a study. As a result of this most recent FDA communication and the need for clarity with the FDA, the Zalviso NDA resubmission is on hold. We will provide an update on the timing of the resubmission of the Zalviso NDA after we obtain more information from the FDA. The FDA has precleared certain aspects of our proposed Risk Evaluation and Mitigation Strategy, or REMS, and indicated that they will continue discussion of our proposed REMS after the Zalviso NDA has been resubmitted.

Zalviso

Zalviso is an investigational, pre-programmed, non-invasive system to allow hospital patients with moderate-to-severe acute pain to self-dose with sufentanil sublingual tablets to manage their pain. Zalviso is designed to help address certain problems associated with post-operative intravenous patient-controlled analgesia, by offering:

- **A high therapeutic index opioid:** Zalviso uses sufentanil, an opioid that has a high therapeutic index. The therapeutic index is the ratio of the effective dose versus the lethal dose. In animal studies, the therapeutic index for sufentanil was approximately 100 times larger than fentanyl and 300 times larger than morphine.

- **A non-invasive route of delivery:** Zalviso utilizes a sufentanil tablet which allows for a sublingual (under the tongue) route of delivery. Sufentanil is highly lipophilic which provides for rapid absorption in the fatty cells (or mucosal tissue) found under the tongue, and for rapid transit across the blood-brain barrier to reach the mu-opioid receptors in the brain. The sublingual delivery used by Zalviso provides rapid onset of analgesia. The sublingual delivery system also eliminates the risk of IV-related analgesic gaps and IV complications, such as catheter-related infections. In addition, because patients do not require direct connection to an IV patient-controlled analgesia, or PCA, infusion pump through IV tubing, Zalviso allows for ease of patient mobility.

- **A simple, pre-programmed PCA solution:** Zalviso allows patients to self-dose sufentanil sublingual tablets via a pre-programmed, secure system designed to eliminate the risk of programming errors.

We submitted an NDA for Zalviso in September 2013 and, as mentioned above, the FDA issued a CRL for Zalviso on July 25, 2014. We have conducted additional Human Factors studies and bench testing to address the related issues within the CRL. As mentioned above, in March 2015 we received correspondence from the FDA stating that in addition to the bench testing and two Human Factors studies we have performed in response to the issues identified in the CRL, an additional clinical study is needed to assess the risk of inadvertent dispensing and overall risk of dispensing failures. We plan to meet with the FDA to discuss the need for an additional clinical study, and the potential design and objectives of such a study.

The 505(b)(2) NDA submission for Zalviso is based on a development program that includes data from seven Phase 1 studies, three Phase 2 clinical trials, and three Phase 3 clinical trials. The Phase 3 trial program included two placebo-controlled efficacy and safety trials and one open-label active comparator trial, in which Zalviso was compared to IV PCA with morphine. To date, the Zalviso safety database includes more than 600 patients. Zalviso successfully achieved the primary efficacy endpoints for each of the Phase 2 and Phase 3 trials. A summary of the Phase 3 trials and results is as follows:

- *Active comparator trial (IAP309)*—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.

- *Double-blind, placebo-controlled, abdominal surgery trial (IAP310)*—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.

- *Double-blind, placebo-controlled, orthopedic surgery trial (IAP311)*—in May 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 orthopedic surgery. Utilizing a randomized, double-blind, placebo-controlled design, this pivotal Phase 3 trial enrolled 426 adult patients at 34 U.S. sites. 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.

In December 2013, we announced a commercial collaboration with Grünenthal, covering the territory of the European Union, certain other European countries and Australia for Zalviso for use in the management of moderate-to-severe acute pain within a hospital, hospice, nursing home or other medically supervised setting. We retain all rights in remaining countries, including the United States, Asia and Latin America. The collaboration included a Collaboration and License Agreement, or License Agreement, and a Manufacturing and Supply Agreement, or Supply Agreement.

Under the terms of the License Agreement, we received an upfront cash payment of $30.0 million in December 2013, and in the third quarter of 2014, we received a milestone payment of $5.0 million related to the Marketing Authorization Application, or MAA, submission to the European Medicines Agency, or EMA. We are eligible to receive an additional $15.0 million milestone payment upon the approval of the MAA. If approved, we are eligible to receive approximately $200.0 million in additional milestone payments, based upon successful regulatory and product development efforts ($28.5 million) and net sales target achievements ($171.5 million). Grünenthal will also make tiered royalty, supply and trademark fee payments in the mid-teens up to the mid-twenties percent range, on net sales

of Zalviso in the Grünenthal territory.

Grünenthal will be responsible for all commercial activities for Zalviso, including obtaining and maintaining pharmaceutical product regulatory approval in the Grünenthal territory. We will be responsible for obtaining and maintaining device regulatory approval in the Grünenthal territory and manufacturing and supply of Zalviso to Grünenthal for commercial sales.

In July 2014, Grünenthal filed an MAA with the EMA under the centralized procedure in the European Union, or EU, for Zalviso for the management of moderate-to-severe acute pain in adult patients in a medically-supervised environment. In the fourth quarter of 2014, Grünenthal received 120-day questions from the EMA per the EMA's standard regulatory review process. We have been working with Grünenthal towards the submission of the response to the 120-day questions. Grünenthal is currently working to complete the response and submit it to the EMA by the end of March 2015. Assuming the EMA accepts this filing, we anticipate a Committee for Medicinal Products for Human Use, or CHMP, opinion in the summer of 2015 and a final decision by the EMA in the fall of 2015.

In association with potential commercialization of Zalviso in the European Union, we underwent a Conformite Europeenne approval process for the Zalviso device, more commonly known as a CE Mark approval process. In December 2014, we received CE Mark approval, which permits the commercial use of the Zalviso device in the European Union. However, as a drug-device combination product, Zalviso will not be utilized commercially unless and until the EMA approves the Zalviso MAA. In connection with the CE Mark approval, we were also granted International Standards Organization, or ISO, 13485:2003 certification of our quality management system in November 2014. This is an internationally recognized quality standard for medical devices issued by our notified body, the British Standards Institution, or BSI.

ISO 13485:2003 certification recognizes that consistent quality policies and procedures are in place for the development, design and manufacturing of medical devices. The certification indicates that we have successfully implemented a quality system that conforms to ISO 13485 standards for medical devices. Certification to this standard is one of the key regulatory requirements for a CE Mark in the European Union as well as to meet equivalent requirements in other international markets. The certification applies to the Redwood City, California location which designs, manufactures and distributes finished medical devices.

ARX-04

We are also developing a Sufentanil Sublingual Single-Dose Tablet, or ARX-04, for the treatment of moderate-to-severe acute pain to be administered by a healthcare professional to a patient in settings of acute pain, such as in the emergency room, hospital floor, ambulatory care environment, or on the battlefield. In December 2013, we completed an End-of-Phase 2 Meeting with the FDA to identify a Phase 3 program pathway forward for evaluation of ARX-04. We plan to initiate a pivotal Phase 3 trial for ARX-04 in patients with post-operative pain following abdominal surgery by the end of March 2015. Pending completion of enrollment, we anticipate top-line data from this study in the fourth quarter of 2015.

We have also been notified by the Department of Defense, or DoD, that they are preparing a contract to provide partial funding to support further development of ARX-04. We are currently engaged in the contracting process with the DoD to determine the nature, scope, amount and timing of the contract.

Phase 3 Program

- In June 2014, we completed a pharmacokinetic study in support of the ARX-04 development program. In this study of healthy volunteers, it was shown that two sublingual administrations of a Zalviso 15mcg sufentanil sublingual tablet dosed 20 minutes apart were comparable, in terms of area under the plasma concentration time curve, or AUC, exposure and peak plasma concentration, to one sublingual administration of an ARX-04 30mcg sufentanil sublingual tablet. We have proposed the inclusion of approximately 300 patients from the Zalviso clinical program in the ARX-04 safety database to the FDA and we have designed the two Phase 3 ARX-04 trials accordingly. The ARX-04 safety database required by the FDA is 500 patients. We have confirmation from FDA that some of the Zalviso patients can be included in the overall ARX-04 safety database; however, further discussion is needed to determine the exact number of such patients that can be used towards achieving the 500 patient minimum total safety exposure number required for ARX-04. Based on an ongoing pharmacokinetic analysis, we may need to increase enrollment in our planned Phase 3 clinical trial program to meet the FDA's requested exposure requirements to ARX-04.

- We plan to initiate a Phase 3 clinical trial, a double-blind, placebo-controlled efficacy and safety study of patients with post-operative pain following abdominal surgery by the end of March 2015. We expect top-line data from this trial in the fourth quarter of 2015. Approximately 160 patients are planned to be enrolled in this study.

- In the first half of 2015, contingent on DoD funding, we plan to initiate our second planned Phase 3 clinical trial, an open-label safety study of patients who present to the emergency room with moderate-to-severe pain due to trauma or injury. We expect top-line data from this trial in the second half of 2015. Approximately 40 patients are planned to be enrolled in this study. Timing of this trial is currently pending finalization of the DoD contract. Should we experience delays in such contract negotiations, we may elect to delay this Phase 3 trial beyond the first half of 2015.

Phase 2 Clinical Study Results

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 sublingual tablet, 20 mcg sufentanil sublingual tablet, 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 sublingual tablet 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, or AEs, reported in the trial were generally mild-to-moderate in nature, with two serious adverse events, or SAEs, of post-surgical infection reported, both of which were determined by the investigator to be unrelated to trial drug.

Research and development of ARX-04, including the Phase 2 trial and pre-Phase 3 development, was funded by a $5.6 million grant from the U.S. Army Medical Research and Materiel Command, or USAMRMC. As of December 31, 2013, we had recognized the full amount of the grant of $5.6 million.

ARX-02 and ARX-03

In addition to ARX-04, our product candidate pipeline consists of two other sufentanil-based sublingual product candidates. The Sufentanil Sublingual Tablet Breakthrough Pain, or BTP, Management System, or ARX-02, is a pain management system for the treatment of cancer patients who suffer from BTP. The Sufentanil/Triazolam Sublingual Tablet, or ARX-03, is a single, fixed-dose, combination drug 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 funding from a corporate partnership or other external funding source.

Sufentanil Sublingual Tablets

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

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

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

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

Our portfolio of product candidates leverages the above mentioned advantages of sufentanil delivered via the sublingual route. We believe our non-invasive, proprietary sufentanil tablet sublingual dosage form potentially overcomes many of the limitations of current treatment options available for acute pain.

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

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

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

- relatively high bioavailability via the oral mucosa and very low gastrointestinal, or GI, bioavailability;
- prolonged plasma levels relative to IV delivery;
- PK parameters proportional to dose across a wide range of doses (2.5 mcg to 80 mcg);
- lower peak plasma concentration, or Cmax, than IV delivery;
- time to maximum plasma concentrations, or Tmax, range from 20 to 120 minutes;
- while clearance increased in younger patients and heavier patients, clearance was not affected by race, sex, renal or hepatic parameters or concomitant CYP3A4 substrates;
- slightly increased Cmax and prolonged half-life with concomitant administration of the CYP3A4 inhibitor ketoconazole;
- lack of drug accumulation with repeat-dosing and achievement of steady-state plasma concentrations after the 13th dose (with 20 minutes between dosings);
- relatively low patient to patient variability in Tmax and Cmax; and
- repeat dosing PK that supports a 20-minute minimum re-dosing interval.

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

In summary, we have demonstrated that sublingual delivery of sufentanil avoids the high peak plasma levels and short duration of action of IV administration, potentially enabling broader use of sufentanil. Our proprietary sufentanil sublingual tablet dosage form is a very small disc-shaped tablet with a bioadhesive excipient, or inactive ingredient, which enables the tablet to adhere to mucosal tissues. When placed under the tongue, the sufentanil sublingual tablet imbibes saliva, adhering it to the sublingual tissues and forming a hydrogel patch. Sufentanil, from the sublingual tablet, rapidly deposits into the fatty tissues under the tongue. The drug then absorbs into the plasma over several hours at roughly the same rate as it is being redistributed and/or cleared from the plasma resulting in a plateau plasma concentration from approximately 20 to 120 minutes. The sufentanil sublingual tablet fully disintegrates within 5-10 minutes. The small size of the sufentanil sublingual tablet, pictured above, is designed to minimize the saliva response and amount of sufentanil swallowed, resulting in high oral transmucosal uptake, whereby a majority of the drug is absorbed via the oral tissues ultimately into the bloodstream, and thereby provides consistent pharmacokinetics.

Our Product Candidates

The following table summarizes key information about our existing product candidates.

Product Candidate	Description	Target Indication	Status
Zalviso	Sufentanil Sublingual Tablet System	Moderate-to-severe acute pain in the hospital setting	NDA submitted to the FDA in September 2013, CRL received July 25, 2014. In March 2015, we received correspondence from the FDA stating that an additional clinical study is needed. We intend to meet with the FDA to discuss and clarify the need for an additional clinical study, and the potential design and objectives of such a study. Timing of the NDA resubmission is to be clarified after the FDA meeting.
			MAA submitted to EMA in July 2014. Assuming the EMA accepts this filing, we anticipate a CHMP opinion in the summer of 2015 and a final decision by the EMA in the fall of 2015.
ARX-04	Sufentanil Sublingual Single-Dose Tablet	Moderate-to-severe acute pain	In April 2013, we reported that a Phase 2 trial of ARX-04 in patients after bunionectomy surgery achieved its primary endpoint. The FDA agreed that this was a well-controlled study and could be used as a pivotal study.
			We plan to initiate a Phase 3 clinical trial that will evaluate the efficacy and safety of ARX-04 vs. placebo for the treatment of moderate-to-severe acute pain following ambulatory abdominal surgery by the end of March 2015, with top-line data anticipated in the fourth quarter of 2015, pending completion of enrollment. This trial was designed as the second of two well-controlled studies required for potential NDA filing for ARX-04, the first was the bunionectomy Phase 2 study.

			We plan to initiate our second planned Phase 3 clinical trial, an open-label safety study of patients who present to the emergency room with moderate-to-severe pain due to trauma or injury in the first half of 2015, with top-line data anticipated in the second half of 2015, contingent on DoD funding. This study is not required to satisfy the regulatory requirements for ARX-04. Timing of this trial is currently pending finalization of the DoD contract. Should we have delays in such contract negotiations we may elect to delay this Phase 3 trial beyond the first half of 2015.
ARX-02	Sufentanil Sublingual Tablet Breakthrough Pain, or BTP, Management System	Cancer breakthrough pain	Phase 2 clinical trial and End of Phase 2 meeting completed. Future development contingent upon identification of corporate partnership resources.
ARX-03	Sufentanil/Triazolam Sublingual Tablet	Mild sedation and pain relief during painful procedures in a physician’s office	Phase 2 clinical trial and End of Phase 2 meeting completed. Future development contingent upon identification of corporate partnership resources.

Zalviso— Sufentanil Sublingual Tablet System

The Market Opportunity for Zalviso

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

According to the 2014 Decision Resources Acute Pain Report, or 2014 DR Report, the acute pain market (represented by treatments for post-operative pain, acute musculoskeletal pain and cancer breakthrough pain) in the United States, Europe and Japan realized 2013 revenues of $12.7 billion, and is expected to reach approximately $13.3 billion by 2023. Opioid analgesic use dominates the management of acute pain, representing 44% of the 2013 market, and is projected to grow to 46% of the 2023 market. Post-operative acute pain treatment in the United States is projected to grow significantly in the 2013 to 2023 period, from management of 13.8 million procedures in 2011 to 16.0 million procedures in 2023, a 1.5% CAGR. Despite its size, this market remains underserved. Studies report that up to 75% of patients experience inadequate pain relief after surgery. Inadequate pain relief can lead to decreased mobility, which increases the risks of other medical complications, including deep vein thrombosis and partial lung collapse, and can result in extended hospital stays. Additionally, based on an analysis of data published in 2008 from the World Health Organization, we estimate that there are approximately 27 million surgical procedures annually in other moderate-to-high per capita healthcare expenditure nations in which patients experience moderate-to-severe pain.

In the United States, we estimate that approximately one third of all procedures conducted are orthopedic in nature, one third are gastrointestinal, obstetric or gynecologic, and the remaining third are a mix of spinal, cardiothoracic and other procedures. Commissioned market research targeting surgeons and anesthesiologists has identified a consistent positive response to the attributes of Zalviso and indicates an interest in using Zalviso in at least 75% of their eligible patients. Additional market research indicated that physicians expressed interest in using Zalviso for patients who stay in the hospital for less than 24 hours and are not traditionally treated with IV PCA. Regardless of size or affiliation of hospitals, the majority of Pharmacy and Therapeutics, or P&T, committees we surveyed were likely to review and approve Zalviso, subject to demonstration of satisfactory pharmacoeconomic value.

How Zalviso Addresses the Unmet Medical Need in Moderate-To-Severe Acute Pain Management in a Hospital Setting

Hospitalized patients in moderate-to-severe acute pain could significantly benefit from the following items:

- more rapid onset of analgesia;

- fewer medication errors, especially relating to the use of opioids;
- fewer side effects, including infection and bleeding risks due to invasive routes of delivery;
- enhanced ability for patients to ambulate after surgery and avoid falls; and
- patient control over their pain medication which has been shown to increase patient satisfaction.

For example, epidural catheters delivering local anesthetic are invasive and have a significant risk of lower extremity weakness and tethering the patient to a pump attached to an IV pole, creating multiple mobility impediments and fall risks; nerve blocks of the lower extremities (e.g., femoral nerve blocks) are also invasive and create weakness and fall risks; oral multimodal analgesia is not patient-controlled, is nurse-intensive and suffers from slow onset of action. While IV PCA does allow patient control over their pain medication, it suffers from the following:

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

In our clinical studies, Zalviso has demonstrated the following attributes:

- a rapid onset of effect in comparison to intravenous delivery of morphine, and an ability to control pain as a monotherapy after moderate to severely painful surgeries such as knee replacement or colectomies;
- an ability for young and old patients alike to use Zalviso;
- a low rate of severe adverse event experiences;
- a rate of adverse events that is similar to a placebo-treated patient population, with the exception of opioid induced itching;
- a high level of Patient Satisfaction as a result of Zalviso usage under patient control to manage pain after surgery over 48 to 72 hours; and
- a high Nurse Ease of Care rating for ease of set-up and use of Zalviso by the health care professional.

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

Zalviso has the potential to address many of the key disadvantages of IV PCA, including:

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

We believe that Zalviso provides a favorable safety, efficacy and tolerability profile, potentially enabling Zalviso to become a new standard of care for moderate to severe acute pain control via patient-controlled analgesia.

Zalviso Description

The benefits of Zalviso are the result of combining the following three elements:

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

Zalviso allows patients to self-administer sufentanil sublingual tablets as needed to manage their moderate-to-severe acute pain in the hospital setting, and provides the record-keeping attributes of a conventional IV PCA pump while avoiding some of the key issues, such as programming errors, associated with conventional IV PCA use.

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

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

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

from the sale of any of our product candidates.

Drugs are classified or scheduled by the Drug Enforcement Agency, or DEA, according to their potential for abuse and addiction. Sufentanil is scheduled as a class II opioid. Scheduled drugs, when they are under patient control in a hospital setting, must be secured and have adequate dose access control and tracking mechanisms. Our novel handheld PCA device has the following safety features:

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

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

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

To use Zalviso, the patient would:

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

Zalviso—Development Status

We submitted an NDA for Zalviso in September 2013 and, as mentioned above, the FDA issued a CRL for Zalviso on July 25, 2014. In March 2015, we received correspondence from the FDA stating that in addition to the bench testing and two Human Factors studies we have performed in response to the issues identified in the CRL, an additional clinical study is needed to assess the risk of inadvertent dispensing and overall risk of dispensing failures. We plan to meet with the FDA to discuss and clarify the need for an additional clinical study, and the potential design and objectives of such a study.

The 505(b)(2) NDA submission for Zalviso is based on a development program that includes data from seven Phase 1 studies, three Phase 2 clinical trials, and three Phase 3 clinical trials. The Phase 3 trial program included two placebo-controlled efficacy and safety trials and one open-label active comparator trial, in which Zalviso was compared to IV PCA with morphine. To date, the Zalviso safety database includes more than 600 patients. Zalviso successfully achieved the primary efficacy endpoints for each of the Phase 2 and Phase 3 trials.

Zalviso—Clinical Program

Summary

Our Phase 3 program for Zalviso consisted of three Phase 3 clinical trials. We have reported positive top-line results from each of the three clinical trials. Prior to our Phase 3 program, we completed three successful Phase 2 clinical trials of sufentanil sublingual tablets in the post-operative setting. These Phase 2 clinical trials demonstrated analgesic efficacy over a 12-hour study period, a low adverse event profile and excellent device functionality. During our End of Phase 2 meeting with the FDA, the FDA stated that the demonstration of efficacy versus placebo in two Phase 3 clinical trials with a total safety database of at least 600 patients exposed to the active drug should suffice to support an NDA. We designed our Phase 3 clinical trials based on the feedback from the FDA.

Phase 3 Clinical Trials for Zalviso

Active comparator trial (IAP309)

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

Regarding disposition and safety assessments, 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, one was related to Zalviso and two were related to IV PCA morphine. Overall the adverse events were similar between the two groups, however, continuous oxygen saturation monitoring demonstrated a lower percentage of patients with desaturations below 95% in the Zalviso group compared to IV PCA morphine ($p = 0.028$).

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

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

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

A number of secondary endpoints were also evaluated, including pain intensity difference, or PID, and pain relief at each evaluation time point, comparison of individual PGA ratings, a Healthcare Professional Global Assessment, or HPGA, of method of pain control, dropouts from the trial due to inadequate analgesia and adverse events, and Patient and Nurse Ease of Care Questionnaires using a validated questionnaire methodology specifically to evaluate PCA systems.

Zalviso had a significantly more rapid onset of action based on both PID and pain relief scores from 1 to 4 hours after initiation of dosing compared to IV PCA morphine (PID: $p \leq 0.001$ for 1 and 2 hours and $p = 0.002$ at 4 hours; pain relief: $p = 0.003$ at 1 hour and $p < 0.001$ at 2 and 4 hours). Zalviso achieved a PGA rating of "excellent" in 42.9% of treated patients, compared to 30.6% for IV PCA with morphine, with a p-value of 0.016.

The Healthcare Professional Global Assessment, or HPGA, was measured at 24, 48 and 72 hours, and produced similar results to the Patient Global Assessment. HPGA ratings of "good" or "excellent" at 48 hours were 81.4% for Zalviso compared to 70.0% for IV PCA morphine. An assessment of non-inferiority was conducted and demonstrated that Zalviso was non-inferior to IV PCA morphine ($p < 0.001$) in the trial. Because the 95% CI was +2.6% to +20.2% for the 48 hour HPGA and therefore didn't cross the zero difference line, a statistical analysis for superiority could be performed, which demonstrated that for this trial, Zalviso was statistically superior to IV PCA morphine for the HPGA endpoint at 48 hours ($p=0.012$). Statistically superior HPGA was also seen at the 24 hour and 72 hour time points.

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

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

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

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

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

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

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

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

Patient Ease of Care

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

Nurse Ease of Care

Subscale (0-5 scale)	**Zalviso**	**IV PCA morphine**	**p Value**
Time consuming	0.92	1.24	0.076
Bothersome	0.54	1.09	0.006

Double-blind, placebo-controlled, abdominal surgery trial (IAP310)

In March 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 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 for the treatment of acute post-operative pain immediately following major abdominal surgery. Patients were treated for post-operative pain for a minimum of 48 hours, and up to 72 hours. Patients were randomized 2:1, with 119 patients randomized to sufentanil sublingual tablet treatment and 59 to placebo treatment. Both treatments were delivered by the patient, as needed, using Zalviso with a 20-minute lock-out period. Patients in both groups could receive up to 2 mg morphine intravenously per hour as a rescue medication, the primary purpose of this rescue medication being to provide placebo-treated patients access to pain medication to enable them to stay in the trial as long as possible. Pre-rescue pain scores were imputed to minimize the impact of this rescue opioid on efficacy evaluations.

The primary endpoint evaluated pain intensity over the 48-hour study period compared to baseline, or Summed Pain Intensity Difference (SPID-48), in patients following major open abdominal surgery. Patients receiving sufentanil sublingual tablets demonstrated a significantly greater SPID-48 compared to placebo-treated patients during the study period (105.6 and 55.6, respectively; p=0.001).

A number of secondary endpoints were also evaluated, including SPID at 24 hours and 72 hours, PID and pain relief values for each evaluation time point, drop outs from the trial due to inadequate analgesia and adverse events, and Patient Ease of Care Questionnaires using a validated questionnaire methodology specifically to evaluate patient-controlled analgesia systems. A summary of the results for the secondary endpoints is as follows:

- 24 hours and 72 hours after first dose, SPID was significantly greater in the sufentanil sublingual tablet-treated patients than in the placebo-treated patients (p<0.001 and p=0.004, respectively).

- PID and pain relief values separated statistically from placebo as early as 45 minutes (p=0.027 for both).

- A summed pain relief measure over the 48-hour study period, commonly referred to as TOTPAR, was significantly greater for sufentanil sublingual tablet-treated patients than placebo-treated patients (p=0.002)

- Eighty, or 70.2%, of the sufentanil sublingual tablet-treated patients completed the 48-hour study period, compared to 30, or 51.7%, of placebo-treated patients. Reasons for drop-out in the sufentanil sublingual tablet-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).

- Only one patient, in the sufentanil sublingual tablet-treated group, experienced a serious adverse event, which was determined to be unrelated to the study drug by the investigator.

- Patients in the trial who were treated with sufentanil sublingual tablets reported an average Overall Ease of Care of 4.39 out of a 0 to 5 scale. In addition, patients in the placebo arm of the trial also reported favorable Overall Ease of Care scores, with an average score of 4.36. These results are comparable to the results from the active comparator trial, which is summarized above.

The chart below illustrates the SPID-48 results from the pivotal Phase 3, double-blind, placebo-controlled, abdominal surgery trial (IAP310).

Double-blind, placebo-controlled, orthopedic surgery trial (IAP311)

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

The primary endpoint evaluated pain intensity over the 48-hour study period compared to baseline, or Summed Pain Intensity Difference (SPID-48), in patients following major orthopedic surgery. Patients receiving Zalviso demonstrated a significantly greater SPID-48 compared to placebo-treated patients during the study period (+76.1 and -11.5, respectively; $p < 0.001$). Two hundred fifteen (68.3%) sufentanil sublingual tablet-treated patients completed the 48-hour study period, compared to 43 (41.3%) placebo-treated patients. Primary reasons for drop-out in the sufentanil sublingual tablet- and placebo-treated groups were adverse events (7.0% and 6.7%, respectively) and lack of efficacy (14.3% and 48.1%, respectively).

Secondary endpoint data included PID and pain relief values for each evaluation time point and demonstrated that PID separated from placebo at 1 hour ($p = 0.03$) and pain relief separated at 45 minutes ($p < 0.01$). SPID at 24 and 72 hours was also assessed and was highly significant as illustrated below.

Group	SPID-24	SPID-48	SPID-72
Sufentanil Sublingual Tablet	33.8	76.1	166.2
Placebo	-8.8	-11.5	-2.6
Statistical Comparison	p<0.001	p<0.001	p<0.001

A secondary endpoint focused on Total Pain Relief measured