ACELRX PHARMACEUTICALS INC
Form 10-K
March 07, 2019

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, 2018

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 every Interactive Data File required to be submitted 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 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, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer Accelerated filer
Non-accelerated filer Smaller reporting company
Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

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 29, 2018 (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 $177,225,920. The calculation excludes 893,483 shares of the registrant's common stock held by current executive officers and directors 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, 2019, the number of outstanding shares of the registrant's common stock was 78,757,930.

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, 2018, are incorporated by reference into Part III of this report.	

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ACELRX PHARMACEUTICALS, INC.

2018 ANNUAL REPORT ON FORM 10-K

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

Pharmaceuticals, Inc. “DSUVIA” is a trademark, and “ACELRX” and “Zalviso” are registered trademarks, all owned by 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 success in commercializing DSUVIA™ (sufentanil sublingual tablet, 30 mcg) in the United States, including the marketing, sales, and distribution of the product;
- our ability to maintain regulatory approval of DSUVIA in the United States, including effective management of and compliance with the DSUVIA Risk Evaluation and Mitigation Strategies, or REMS, program;
- acceptance of DSUVIA by physicians, patients and the healthcare community, including the acceptance of pricing and placement of DSUVIA on payers' formularies;
- our ability to develop sales and marketing capabilities in a timely fashion, whether alone through recruiting qualified employees, by engaging a contract sales organization, or with potential future collaborators;
- successfully establishing and maintaining commercial manufacturing with third parties;
- our ability to manage effectively, and the impact of any costs associated with, potential governmental investigations, inquiries, regulatory actions or lawsuits that may be brought against us;
- continued demonstration of an acceptable safety profile of DSUVIA;
-

effectively competing with other medications for the treatment of moderate-to-severe acute pain in medically supervised settings, including IV-opioids and any subsequently approved products;

- our ability to maintain regulatory approval of DZUVEO™ in the European Union or EU, and enter into a collaboration agreement with a strategic partner for the commercialization of DZUVEO in Europe;

- our ability to manufacture and supply DZUVEO in Europe to any future strategic partner;

- our ability to successfully execute the pathway towards a resubmission of the Zalviso® (sufentanil sublingual tablet system) New Drug Application, or NDA, and subsequently obtain, without further delays, and maintain regulatory approval of Zalviso in the United States and any related restrictions, limitations, and/or warnings in the label of Zalviso, if approved;

- the outcome of any potential FDA Advisory Committee meeting held for Zalviso;

- our ability to manufacture and supply Zalviso to Grünenthal GmbH, or Grünenthal, in accordance with their forecast and the Manufacture and Supply Agreement with Grünenthal;

- the status of the Collaboration and License Agreement with Grünenthal or any other future potential collaborations, including potential milestones and royalty payments under the Grünenthal agreement and obligations under the Purchase and Sale Agreement with PDL BioPharma, Inc., or PDL;

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

- our ability to successfully retain our key commercial, scientific, engineering, medical or management personnel and hire new personnel as needed;

- the size and growth potential of the markets for DSUVIA, and Zalviso, if approved in the United States, and our ability to serve those markets;

- our ability to successfully commercialize Zalviso, if approved in the United States;

- the rate and degree of market acceptance of Zalviso, if approved in the United States;

- our ability to obtain adequate government or third-party payer reimbursement;

- 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 accuracy of our estimates regarding expenses, future revenues, capital requirements and needs for additional financing;
- our liquidity and capital resources; and
- our ability to obtain and maintain intellectual property protection for DSUVIA/DZUVEO and Zalviso.

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 use in medically supervised settings. DSUVIA™ (known as DZUVEO in Europe) and Zalviso, are both focused on the treatment of acute pain, and each utilize sufentanil, delivered via a non-invasive route of sublingual administration, exclusively for use in medically supervised settings. On November 2, 2018, the U.S. Food and Drug Administration, or FDA, approved our resubmitted NDA for DSUVIA for use in adults in certified medically supervised healthcare settings, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. In June 2018, the European Commission, or EC, granted marketing approval of DZUVEO for the treatment of patients with moderate-to-severe acute pain in medically monitored settings. We are developing a distribution capability and commercial organization to market and sell DSUVIA in the United States. The commercial launch of DSUVIA in the United States occurred in the first quarter of 2019. In geographies where we decide not to commercialize ourselves,

including for DZUVEO in Europe, we may seek to out-license commercialization rights. We currently intend to commercialize and promote DSUVIA/DZUVEO outside the United States with one or more strategic partners, although we have not yet entered into any such arrangement. We are currently evaluating the timing of the resubmission of the NDA for Zalviso. If we are successful in obtaining approval of Zalviso in the United States, we plan to potentially promote Zalviso either by ourselves or with strategic partners. Zalviso is approved in Europe and is currently being commercialized by Grünenthal GmbH, or Grünenthal.

Our Portfolio

The following table summarizes our portfolio.

Product	Description	Target Use	Status
DSUVIA (known as DZUVEO in Europe)	Sufentanil sublingual tablet, 30 mcg	Moderate-to-severe acute pain in a medically supervised setting, administered by a healthcare professional	Received FDA approval in November 2018, commercial launch began Q1 2019. Received European Commission (EC) approval in June 2018.
Zalviso	Sufentanil sublingual tablet system, 15 mcg	Moderate-to-severe acute pain in the hospital setting, administered by the patient as needed	Positive results from Phase 3 trial, IAP312, announced in August 2017. Currently evaluating the timing of the resubmission of the NDA. Zalviso is approved in the European Union where it is marketed commercially by Grünenthal.

We have chosen sufentanil as the therapeutic ingredient for DSUVIA and Zalviso. Opioids have been utilized for pain relief for centuries and are the standard-of-care for the treatment of moderate-to-severe acute pain. Sufentanil, a high-therapeutic index opioid, which has no active metabolites, is available as an injectable in several markets around the world and is used by anesthesiologists for induction of sedation or as an epidural; however, the injectable formulation is not suitable for the treatment of acute pain. 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 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 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	250

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 intravenous, or IV, administration.

We have created a proprietary sublingual (under the tongue) formulation of sufentanil intended for the treatment of moderate-to-severe acute pain. We believe our non-invasive, proprietary sublingual sufentanil tablet potentially overcomes many of the limitations of current treatment options available for moderate-to-severe acute pain. The sublingual formulation retains the therapeutic value of sufentanil, and novel delivery devices provide a non-invasive route of administration. Sufentanil is highly lipophilic which provides for rapid absorption in the mucosal tissue, or fatty cells, found under the tongue, and for rapid transit across the blood-brain barrier to reach the mu-opioid receptors in the brain. The sublingual route of delivery used by DSUVIA and Zalviso provides a predictable onset of analgesia. The sublingual delivery system also eliminates the risk of intravenous, or IV, complications, such as catheter-related infections. In addition, because patients do not require direct connection to an IV infusion pump, or IV line, DSUVIA and Zalviso may allow for ease of patient mobility.

DSUVIA™ (sufentanil sublingual tablet, 30 mcg)

DSUVIA, known as DZUVEO in Europe, approved by the FDA in November 2018, is indicated for use in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. DSUVIA was designed to provide rapid analgesia via a non-invasive route and to eliminate dosing errors associated with IV administration. DSUVIA is a single-strength solid dosage form administered sublingually via a single-dose applicator, or SDA, by healthcare professionals. Sufentanil is an opioid analgesic currently marketed for intravenous, or IV, and epidural anesthesia and analgesia. The sufentanil pharmacokinetic profile when delivered sublingually avoids the high peak plasma levels and short duration of action observed with IV administration. The European Commission, or EC, approved DZUVEO for marketing in Europe in June 2018.

DSUVIA was approved with a Risk Evaluation and Mitigation Strategy, or REMS, which restricts distribution to certified medically supervised healthcare settings in order to prevent respiratory depression resulting from accidental exposure. DSUVIA will only be distributed to facilities certified in the DSUVIA REMS program following attestation by an authorized representative to comply with appropriate dispensing and use restrictions of DSUVIA. To become certified, a healthcare setting will need to train their healthcare professionals on the proper use of DSUVIA and have the ability to manage respiratory depression. DSUVIA will not be available in retail pharmacies or for outpatient use. As part of the REMS program, we will monitor distribution and audit wholesalers' data, evaluate proper usage within the healthcare settings and monitor for any diversion and abuse. Additionally, we will de-certify healthcare settings that are non-compliant with the REMS program.

Examples of potential patient populations and settings in which DSUVIA could be used include: emergency room patients; patients who are recovering from short-stay or ambulatory surgery and do not require more long-term analgesia; post-operative patients who are transitioning from the operating room to the recovery floor; certain types of office-based or hospital-based procedures; patients being treated and transported by paramedics; and for battlefield casualties. In the emergency room and in ambulatory care environments, patients often do not have immediate IV access available, or maintaining IV access may provide an impediment to rapid discharge. Moreover, IV dosing results in high peak plasma levels, thereby limiting the opioid dose and requiring frequent redosing intervals to titrate to satisfactory analgesia. Oral pills and liquids generally have slow and erratic onset of analgesia. Based on internal market research conducted to date, we believe that additional treatment options are needed that can safely and effectively treat acute trauma pain, in both civilian and military settings, and that can provide an alternative to currently marketed oral pills and liquids, as well as IV-administered opioids, for moderate-to-severe acute pain.

Zalviso® (sufentanil sublingual tablet system, 15 mcg)

Zalviso is intended for the management of moderate-to-severe acute pain in hospitalized adult patients. Zalviso consists of a pre-filled cartridge of 40 sufentanil sublingual tablets, 15 mcg, delivered by the Zalviso System, a

needle-free, handheld, patient-administered, pain management system. While still under development in the U.S., as discussed further below, Zalviso is approved and marketed in the EU.

Zalviso is a pre-programmed non-invasive system to allow hospital patients with moderate-to-severe acute pain to self-dose with sufentanil sublingual tablets, 15 mcg, to manage their pain. Zalviso is designed to help address certain problems associated with post-operative IV patient-controlled analgesia, or PCA. Zalviso allows patients to self-administer sufentanil sublingual tablets via a pre-programmed, secure system designed in part to eliminate the risk of healthcare provider programming errors.

The potential 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.

The Zalviso System consists of the following components: a disposable dispenser tip, a disposable dispenser cap, an adhesive thumb tag, a cartridge of 40 sufentanil sublingual 15 mcg tablets (approximately a two-day supply) in a disposable radio frequency identification and bar-coded cartridge, a reusable, rechargeable handheld controller, a tether, and an authorized access card.

Drugs are classified or scheduled by the Drug Enforcement Agency, or DEA, according to their potential for abuse and addiction. Sufentanil is classified as a Schedule II controlled substance. 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.

On December 16, 2013, AcelRx and Grünenthal GmbH, or Grünenthal, entered into a Collaboration and License Agreement, or the License Agreement, and related Manufacture and Supply Agreement, or the MSA, and together with the License Agreement, the Agreements, as amended July 17, 2015 and September 20, 2016, or the Amended Agreements. The License Agreement grants Grünenthal rights to commercialize Zalviso, our novel sublingual PCA system, or the Product, in the countries of the EU, Switzerland, Liechtenstein, Iceland, Norway and Australia, or the Territory, for human use in pain treatment within, or dispensed by, hospitals, hospices, nursing homes and other medically supervised settings, or the Field. We retain rights with respect to the Product in countries outside the Territory, including the United States, Asia and Latin America. Under the MSA, we will exclusively manufacture and supply the Product to Grünenthal for the Field in the Territory. Grünenthal shall purchase from us, during the first five years after the effective date of the MSA, 100% and thereafter 80% of Grünenthal's and its sublicensees' and distributors' requirements of Product for use in the Field for the Territory. For additional information on the Amended Agreements, see Note 7 "Collaboration Agreement" in the accompanying notes to the Consolidated Financial Statements.

Zalviso was approved for commercial sale by the EC in September 2015 and Grünenthal began its commercial launch of Zalviso in the European Union in April 2016. On September 18, 2015, we sold a majority of the expected royalty stream and commercial milestones from the sales of Zalviso in Europe by Grünenthal to PDL, which we refer to in this report as the Royalty Monetization. For additional information on the Royalty Monetization with PDL, see Note 9 "Liability Related to Sale of Future Royalties" in the accompanying notes to the Consolidated Financial Statements. Royalty revenues and non-cash royalty revenues from the commercial sales of Zalviso in the EU are expected to be minimal for 2019.

We submitted an NDA for Zalviso in September 2013, or Zalviso NDA, and on July 25, 2014, the Division of Anesthesia, Analgesia, and Addiction Products of the FDA issued a Complete Response Letter, or CRL, for the Zalviso NDA. The CRL contained 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 device errors, changes to address inadvertent dosing, among other items, and submission of additional data to support the shelf life of the product. In March 2015, we received correspondence from the FDA stating that, in addition to the work we had performed to address the items in the CRL, a clinical study would be required to test the modifications to the Zalviso device and mitigations put in place to reduce the risk of inadvertent dosing/misplaced tablets.

Our IAP312 study was designed to evaluate the effectiveness of changes made to the functionality and usability of the Zalviso device and to take into account comments from the FDA on the study protocol. In the IAP312 study, 320 hospitalized, post-operative patients used Zalviso to self-administer 15 mcg sublingual sufentanil tablets as often as once every 20 minutes for 24-to-72 hours to manage their moderate-to-severe acute pain. Throughout the study, for which top-line results were announced in August 2017, 2.2% of patients experienced a Zalviso device error, which was statistically less than the 5% limit specified in the study objectives. None of these device errors resulted in an over-dosing event. This 2.2% rate was lower ($p < 0.001$) than the 7.9% rate of device errors during patient use previously reported for the earlier version of the Zalviso device in the Phase 3 IAP311 study. In addition, results of this study supported earlier clinical findings, with favorable tolerability and a significant majority of “good” or “excellent” ratings provided by both patients and healthcare providers when assessing the method of pain control. We intend to submit these results, together with our earlier Phase 3 studies (IAP309, IAP310 and IAP311), all of which met safety and efficacy endpoints, as part of our resubmission of the NDA for Zalviso.

Clinical Trials

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.

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 Phase 3 trial enrolled 178 adult patients at 13 U.S. sites. 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, or 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).

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 ITT population. Patients were treated for a minimum of 48 hours, and up to 72 hours. Patients were randomized 3:1, with 323 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 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).

Two patients (one each in the sufentanil sublingual tablet group and placebo group) experienced a serious adverse event considered possibly or probably related to the study drug by the investigator.

Combined related adverse events for the two placebo-controlled pivotal studies (IAP310 and IAP311) compared to placebo are shown below. Only pruritus (itching) was statistically different for Zalviso compared to placebo ($p = 0.002$).

Adverse Reactions Occurring in ≥ 2% in Either Group

Possibly or Probably Related Adverse Reactions	Zalviso n=429	Placebo n=162
At least 2% in either group	Two Placebo-Controlled Phase 3 Studies	
Nausea	29.4%	22.2 %
Vomiting	8.9 %	4.9 %
Oxygen Saturation Decreased	6.1 %	2.5 %
Pruritus	4.7 %	0
Dizziness	4.4 %	1.2 %
Constipation	3.7 %	0.6 %
Headache	3.3 %	3.7 %
Insomnia	3.3 %	1.9 %
Hypotension	3.0 %	1.2 %
Confusional state	2.1 %	0.6 %

3 patients (0.7%) in the Zalviso group had treatment-emergent respiratory events that required naloxone reversal.

Multi-center, single-arm, open-label study (IAP312)

IAP312 was a Phase 3 study designed to evaluate the overall performance of the Zalviso System, in response to the CRL received from the FDA for Zalviso. Throughout the study in 320 enrolled patients, 2.2% of patients experienced a Zalviso device error, which was statistically less than the 5% limit specified in the study objectives. Importantly, none of these device errors resulted in an over-dosing event. This 2.2% rate was lower ($p < 0.001$) than the 7.9% rate of device errors during patient use previously reported for the earlier version of the Zalviso device in the Phase 3 IAP311 study.

In addition, as requested by FDA, the IAP312 study prospectively evaluated the number of inadvertently misplaced tablets which occurred during patient dosing. A small number of inadvertently misplaced tablets (less than 0.1% of total dispensed tablets) was observed in the original Phase 3 studies. However, the presence of inadvertently misplaced tablets had not been routinely assessed as part of the previous protocols. Throughout the IAP312 study, patients self-administered a total of 7,293 sufentanil tablets. Per the updated Zalviso training instructions electronically displayed on the hand-held device, 6 patients called the nurse when they failed to properly self-administer a single tablet to allow for proper retrieval and disposal of the tablet. Also, during inspection by the nurse, which occurred every two hours per protocol, a total of 7 misplaced tablets (<0.1% of total dispensed tablets) were discovered with 6 additional patients. No patient had a repeat incidence of an inadvertently misplaced tablet following re-training on the device. This combination of patient training and nurse inspection, along with the tracking

features of the Zalviso device, could potentially address the FDA's concerns regarding drug accountability.

Finally, in this study, 86%, 89% and 100% of patients at the 24, 48 and 72-hour time points, respectively, recorded "good" or "excellent" ratings on the patient global assessment, or PGA, of the method of pain c