AcelRx Pharmaceuticals

Corporate Presentation
January 2016
Forward-Looking Statements

This presentation contains forward-looking statements including, but not limited to, statements related to the process and timing of anticipated future development of AcelRx's product candidates, including Zalviso and ARX-04; anticipated results and timing of the completion of the SAP302 and SAP303 studies for ARX-04; AcelRx's plans to seek a pathway forward towards gaining approval of Zalviso in the United States, including the anticipated timing, design and results of the additional clinical trial for Zalviso (IAP312); the timing of anticipated resubmission of the Zalviso NDA to the FDA; statements related to the timing and success of commercial launch of Zalviso in Europe; ability to fund ARX-04 development from the contract with the Department of Defense; the status of the Collaboration and License Agreement with Grunenthal, including potential milestones and royalty payments under the Grunenthal Collaboration and License Agreement; anticipated cash balance at year-end 2015 and cash forecasts. These forward-looking statements are based on AcelRx's current expectations and inherently involve significant risks and uncertainties. AcelRx's actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks related to: any delays or inability to obtain and maintain regulatory approval of its product candidates, including Zalviso and ARX-04; its ability to successfully design and complete the additional clinical study (IAP312) requested by the FDA to support resubmission of the Zalviso NDA; its ability to timely resubmit the Zalviso NDA to the FDA and to receive regulatory approval for Zalviso; the fact that the FDA may dispute or interpret differently positive clinical results obtained to date from the pivotal Phase 3 SAP301 ambulatory surgery study of ARX-04; its ability to complete Phase 3 clinical development of ARX-04; inability to successfully manufacture Zalviso to meet the requirements of Grunenthal and potential delays in the timing of the European launch; the success, cost and timing of all product development activities and clinical trials, including the SAP302 and SAP303 ARX-04 trials and the IAP312 Zalviso trial; and other risks detailed in the "Risk Factors" and elsewhere in AcelRx's U.S. Securities and Exchange Commission filings and reports, including its Quarterly Report on Form 10-Q filed with the SEC on November 3, 2015. AcelRx undertakes no duty or obligation to update any forward-looking statements contained in this release as a result of new information, future events or changes in its expectations.
Sublingual Sufentanil: 
New Approach to Treat Moderate-to-Severe Acute Pain

AcelRx Highlights: 
- Over $100 million in cash
- Two US Phase 3 products

ARX-04
- Emergencies
- Procedures and Short-stay Surgeries

Zalviso
- Inpatient Surgeries
- Approved in EU
Zalviso and ARX-04 Anticipated Timelines
Two US Submissions Planned in 2016

**ARX-04**

<table>
<thead>
<tr>
<th>2H 15</th>
<th>1H 16</th>
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<tbody>
<tr>
<td>SAP 302 Clinical Study</td>
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<td>FDA Pre-NDA Mtg (Dec)</td>
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<td><strong>NDA Submission</strong></td>
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<td><strong>NDA Review</strong></td>
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<td><strong>PDUFA</strong></td>
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**Zalviso**

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<tbody>
<tr>
<td>Type C FDA Mtg (Sep)</td>
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<tr>
<td>IAP312 Clinical Study</td>
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<td><strong>NDA Resubmission</strong></td>
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**EU Timeline**

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<tbody>
<tr>
<td>EC Approval for Zalviso (Sep)</td>
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<tr>
<td>ZALVISO Launch Readiness</td>
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<td><strong>1\textsuperscript{st} Wave Country Launches</strong></td>
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<td><strong>2\textsuperscript{nd} &amp; 3\textsuperscript{rd} Wave Country Launches</strong></td>
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Opioids Remain Important Analgesics

- The Ebers Papyrus (ca. 1500 B.C.) documents many opioid remedies for pain and suffering\(^1\)
- Over 3000 years later, opioids remain an important treatment for moderate-to-severe acute pain\(^2\)
- Following major surgery, non-opioid adjuvants only reduce postoperative opioid use by 0 – 50\%\(^3\)
- Opioid medications remain the mainstay for treatment of severe pain in the ER\(^4\)
- AcelRx products are for short-term use and only to be used in hospitals or administered by trained medical professionals

## Unmet Needs in Treatment of Moderate-to-Severe Acute Pain

<table>
<thead>
<tr>
<th>Route of Delivery</th>
<th>Emergencies</th>
<th>Procedures/ Short-Stay Surgeries</th>
<th>Inpatient Surgeries</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM/IV are invasive • Oral = slow onset</td>
<td>• IV may prolong stay • Oral = slow onset</td>
<td>• IV may limit mobility • PCA pump = potential for programming errors</td>
<td></td>
</tr>
<tr>
<td>Common Opioids</td>
<td>• IV morphine and hydromorphone = slow on/slow off; active metabolites can cause prolonged opioid effects/side effects • IV fentanyl = rapid on/too short-acting requiring frequent redosing</td>
<td></td>
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</tr>
</tbody>
</table>
Commonly used IV opioids have a delayed equilibration time between plasma and brain.

1. Lotsch et al., Anesthesiol 95:1329-38, 2001

Sufentanil: Sublingual Route = Rapid Brain Penetration
Sublingual Sufentanil
Potential for Real-Time Tracking Between Dosing & Effect

**Sublingual Sufentanil dosing closely matched with effect**

**Sublingual Sufentanil Plasma vs. Brain Concentrations**

**Brain levels delayed with IV morphine dosing**

**IV Morphine Plasma vs. Brain Concentrations**

- Plasma
- Effect Site

**Morphine/M6G in plasma***

**Morphine/M6G in brain***

* Assumes equipotency of morphine and M6G; other potency ratios achieved similar results

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1 Sublingual sufentanil and IV PCA dosing frequency based on IAP309 study; Plasma and brain concentrations modelled from published plasma and CNS equilibration values by Dr. Fisher – consultant to AcelRx
Proprietary Sublingual Sufentanil Tablets Have Unique Properties

**Sufentanil**
- **Lipophilic** so absorbed sublingually
- **Potent** so small tablet possible
- **Wide therapeutic index** to maximize analgesia while minimizing side effects
- **Low GI bioavailability** minimizes delayed effect of swallowed drug

**Tablet**
- **Small size** dissolves in minutes
- **Minimizes saliva production** to limit swallowed drug and avoid delayed drug uptake from GI
- **Bioadhesive** to keep in place under tongue
- **Discrete dosing unit** reduces errors of continuous dosing
In Medically Supervised Settings, ~90M Pts Treated Annually in the US for Moderate-to-Severe Acute Pain$^{1,2,3}$

$1.7$ Billion Combined Market Potential

ER Departments
Ambulatory Surgery Centers
Short-stay Surgeries
Interventional Procedures

Inpatient Postoperative

$1.3B^{1,2}$

445.5M$^3$

ARX-04  Zalviso

Patient Satisfaction with Pain Management a Focus for Medical Facilities and Healthcare Professionals

Patients now shopping for hospitals and comparing based on HCAHPS scores

The HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems) Survey is the first national, standardized, publicly reported survey of patients' perspectives of hospital care.

<table>
<thead>
<tr>
<th>4) How often was patients’ pain well controlled?</th>
<th>During this hospital stay...</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ How often was your pain well controlled?</td>
<td>♦ How often did the hospital staff do everything they could to help you with your pain?</td>
</tr>
</tbody>
</table>

Medicare & Medicaid reimbursement tied directly to HCAHPS scores

December 2015: Centers for Medicare & Medicaid Services (CMS) refreshed the HCAHPS results on the Hospital Compare Web site, www.medicare.gov/hospitalcompare
ARX-04

Development Status

- SAP302 ongoing in the emergency room
- SAP303 to be initiated in postoperative patients with moderate-to-severe acute pain
- NDA submission anticipated in 2H 2016

- ER Departments
- Ambulatory Surgery Centers
- Short-Stay Surgeries
- Interventional Procedures
Department of Defense Provides Support for Treating Pain Associated with Trauma

**Battlefield**

- IM morphine standard of care\(^1\)
- IM dosing often ineffective due to shock and lack of circulation to muscles; death can occur due to oxygen desaturation upon reperfusion\(^2\)
- IV lines time-consuming and challenging to start
- DoD Needs: Rapid onset with predictable offset and minimal cognitive effects

**Civilian Equivalent = ER**

- Guidelines support opioids for moderate-to-severe acute pain\(^3\)
- IV lines challenging to start in ambulances\(^4\)
- Can take 30 minutes or more to have an IV line inserted in ER\(^5\)

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ARX-04 Sublingual Sufentanilil (30 mcg)

*Intended for Treating Moderate-to-Severe Acute Pain in Medically Supervised Settings*

- Single dosage strength - 30 mcg
- Tablet pre-loaded in a single-dose applicator
- Administered, per patient’s request, by healthcare professional every 60 minutes
- Packaged in a foil pouch making it suitable for field/trauma use
Survey of Emergency Departments Underscores Need for Improvements in Pain Management

- Surveyed physicians expect fewer than 20% of their ER patients to wait 15 min or less for their first dose of IV opioids
- 65% of physicians stated that they would use a product like ARX-04 in their institution

### Areas for Improvement

<table>
<thead>
<tr>
<th>Area</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field Trauma</td>
<td>2.4%</td>
</tr>
<tr>
<td>Pre-Hospital</td>
<td>9.5%</td>
</tr>
<tr>
<td>ED, waiting</td>
<td>52.1%</td>
</tr>
<tr>
<td>ED following eval or during a procedure</td>
<td>23.2%</td>
</tr>
<tr>
<td>ED, awaiting admission</td>
<td>4.7%</td>
</tr>
<tr>
<td>ED, upon discharge</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

ARX-04 Pivotal Efficacy Studies Completed
Remaining Trials are Open-Label Safety Studies

Pivotal Studies
- Positive Phase 2: SAP202 Bunionectomy Study
- Positive Phase 3: SAP301 Abdominal Surgery Study

Safety Studies
- SAP302: Emergency Room Study underway
- SAP303: Postoperative Elderly Patients and Patients with Comorbidities
ARX-04 Abdominal Surgery Study: SAP301
Postoperative Ambulatory Surgery Patients

**Surgery Types**
- Open Hernioplasty
- Abdominoplasty
- Laparoscopic Abdominal Surgery

**Study Details**
- Randomized 163 patients
- Randomized 2:1 active to placebo
- Completers = 24 hours in the study, extension to 48 hours if needed
- Primary endpoint: Sum of the pain intensity difference to baseline over the first 12 hours (SPID12)
ARX-04 Abdominal Surgery Study: SAP301
ARX-04 Superior to Placebo on Primary and Secondary Endpoints

- Significantly greater SPID12 compared to placebo
- ARX-04 also positive on secondary endpoints
- No difference in AE’s between ARX-04 and placebo
- AE’s typical of opioid therapy (nausea, headache, vomiting)

(p<0.001)
ARX-04 Abdominal Surgery Study: SAP301
SPID1 Statistically Better than Placebo after 15 Minutes

SPID Over First Hour of Treatment

Statistical separation at 15 minutes

ARX-04

Placebo

* p<0.01
** p<.001
ARX-04 Emergency Room Study: SAP302
Single-Arm, Open-Label

Single and multiple-dose treatment in patients presenting to the ER with trauma or injury associated with moderate-to-severe acute pain

Study Exclusions
- Pregnant
- Opioid-tolerant
  - (>15 mg oral morphine equivalent daily)
- Dependent on supplemental oxygen

Primary Efficacy Endpoint: SPID1
- Summed pain intensity difference to baseline
  - (over first hour after receiving ARX-04)

Key Safety Endpoints
- Six-item Screener
  - (cognitive impairment test: pre- and post-dosing)
- Adverse Events
- Vital Signs
ARX-04 Postoperative Study: SAP303
Single-arm, Open-label in Short-stay Postoperative Patients

- Post-surgical patients with moderate-to-severe acute pain
- Age 40 years or older, encourage enrollment of patients with comorbidities (renal impairment, liver impairment, etc.)
- ARX-04 30 mcg may be dosed once every 60 minutes, as needed, for up to 12 hours
- Expected to enroll up to 100 patients
- Multiple clinical sites experienced with sublingual sufentanil
- Represents another potential market segment for ARX-04
Zalviso™

Inpatient Surgeries requiring overnight stays

Development Status
- Approved in Europe
- Additional US study planned
- NDA resubmission planned H2 2016
Current Problems with IV PCA Devices and Delivery

Documented Problems with IV PCA$^{1,2,3}$

- User programming errors resulting in adverse events including death
- Proxy dosing can cause injury and death
- Infection risk
- Can limit ambulation
- Clear liquid drug can encourage drug diversion

1. Meissner, Hospital Pharmacy 44:312, 2009
2. ISMP: http://www.ismp.org/Newsletters/acutecare/articles/20070222.asp
Zalvisio:
Noninvasive Patient-Controlled Analgesia (PCA) Designed to Mitigate Issues with IV PCA

- **Decrease Medication Errors Associated with IV PCA:** Pre-programmed delivery/single-strength tablet
- **Reduce Proxy Dosing:** Patient RFID thumb tag required for dosing
- **Reduces Infection Risk:** Noninvasive sublingual delivery
- **Less Hampering of Ambulation:** Patient not tethered to Zalvisio
- **Multiple Anti-Diversion Features:**
  - RFID on cartridge provides full inventory tracking of tablets
  - HCP-controlled access, device tethered to bed, anti-diversion alarms

Investigational drug and delivery system not FDA approved for commercial use
The Opportunity for Zalviso is Geographically Concentrated

- Commercialization efforts specific to high-volume surgical specialists
- Original sales force size: ~65
- Profiling showed early opportunity in ~60 accounts

<table>
<thead>
<tr>
<th>CBSA Relevant Procedure Volume</th>
<th># of CBSAs</th>
<th># of accounts</th>
<th>% of relevant procedure volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>100K+</td>
<td>6</td>
<td>591</td>
<td>19%</td>
</tr>
<tr>
<td>50K – 100K</td>
<td>13</td>
<td>570</td>
<td>18%</td>
</tr>
<tr>
<td>10K – 50K</td>
<td>88</td>
<td>1,191</td>
<td>34%</td>
</tr>
<tr>
<td>1K – 10K</td>
<td>367</td>
<td>1,238</td>
<td>25%</td>
</tr>
<tr>
<td>0-1K</td>
<td>473</td>
<td>623</td>
<td>4%</td>
</tr>
</tbody>
</table>

1. In-house commissioned market research. ZS Associates “Go-to-Market Support Hospital and Physician Segmentation” March 2014
2. Data on File, Symphony Health Solutions, 2014
Zalviso Pivotal Studies: Positive versus Placebo and Active Comparator

Placebo-Controlled Studies

- Study IAP310: postoperative pain after abdominal surgery
- Study IAP311: postoperative pain after total hip or knee surgery

Zalviso vs. IV PCA morphine (IAP309)

- Zalviso superior as measured by Patient Global Assessment (PGA) and onset of analgesia
- Easier to use as rated by patients and healthcare professionals
Zalviso: Studies Demonstrate Ability to Treat Moderate to Severe Acute Pain

Pain Intensity Difference to Baseline for Phase 3 Studies

Patient Pain Intensity Difference

Time from first dose of study drug (hours)

- Zalviso 309
- Zalviso 310
- Zalviso 311
- IV PCA MS 309
Final Phase 3 Study IAP312: 
Open-Label, Single-Arm
Designed to Evaluate Device Performance

IAP312 Multicenter Study

- Study designed specifically to address remaining FDA questions
- Protocol reviewed by FDA
- Revised protocol includes FDA comments
- Planned to enroll ~310 patients
- 24- to 72-hour duration
- Single-arm, open-label, various postsurgical settings
- Study will collect device failure rate
- Nurses will actively look for dropped tablets
- Multimodal analgesia allowed
Approved in Europe: Grunenthal Preparing for a 1H 2016 launch

**Commercial rights to European Union**

**Collaboration Details**

- $30M upfront received
- $5M on MAA filing received
- $15M on MAA approval received
- $28.5 in R&D milestones remain
- $166 commercial milestones remain (20% of first four worth $44.5M in total retained as part of PDL deal)
- Royalties from mid teens to mid twenties expected over life of agreement (25% retained as part of PDL deal)
- Peak Revenues in EU expected to be $150M
Issued Patents on Both Device and Drug Formulations

**IP Strategy**
- Drug-device combination allows for broad patent coverage
- Integrated IP and regulatory strategy designed to minimize ANDA exposure

**IP Portfolio**
- 12 US patents issued on NanoTab
  7 US patents issued on Devices
  Coverage through 2027 - 2031
- 3 EU patents issued on NanoTab
  2 EU patents issued on Device
  Coverage through 2027 - 2029
- 19 issued patents in other territories
- 11 US applications plus 30+ foreign applications in late stage prosecution
Projected to End 2015 with $100+ million in cash

- Cash on hand at September 2015: $104 million
- EU approval milestone (received Q4 2015): $15 million
- Projected cash balance Dec 31, 2015: $100+ million
- Outstanding Loan Amount: $21 million
- Shares Outstanding: 45 million
Achievement of Significant Milestones Anticipated in 2016

<table>
<thead>
<tr>
<th>Completed in 2015</th>
<th>Anticipated in 2016</th>
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<tr>
<td>ARX-04 DoD Contract Executed</td>
<td>ARX-04 ER Study Results</td>
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<tr>
<td>ARX-04 SAP301 Topline Data</td>
<td>Q2</td>
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<tr>
<td>Completed $65M Royalty Deal</td>
<td>ARX-04 Post-op Study Results</td>
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<tr>
<td>Zalviso MAA Approval</td>
<td>Q2</td>
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<td>ARX-04 Pre NDA Meeting</td>
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<td>FDA comments on IAP312</td>
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<td>Zalviso EU Commercial launch</td>
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<td>Zalviso Single-arm Study Results</td>
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AceldRx Pharmaceuticals, Inc.
Thank you for listening

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