Sufentanil Sublingual Tablet 30mcg
for Acute Traumatic Pain in the Emergency Department

2016 International Society for Burn Injuries

Karen DiDonato, MSN, RN
Disclosures

- AcelRx employee
ARX-04 Development

U.S. Department of Defense aware of our development of small sublingual sufentanil tablet for post-operative pain

- Requested durable, single-dose, easy to use applicator for field scenarios

Sublingual delivery of sufentanil offers potential for field-based, trauma-related analgesia

- Clinical data has shown greater pain intensity reduction in the first 4 hours compared to IV morphine\(^1\)
- Sublingual tissue perfusion maintained during shock\(^2\)
- Eliminate needle-stick injury and associated risk of infection

Issues with other current treatments for battlefield trauma

- IM morphine less effective during shock due to peripheral vasoconstriction\(^2\)
- Oral transmucosal fentanyl lozenge can take over 30 minutes to dissolve\(^3\)
- Ketamine can produce dissociative effects\(^4\)

Burn Trauma

- Burns caused by thermal, chemical, electrical or radiation insults
- Burn injury is one of the most painful and disfiguring forms of trauma, as it affects the skin, the largest and most visible organ\(^1\)
  - Cell destruction of the skin layers occurs, resulting in damage to nerve fibers as well as depletion of fluid and electrolytes\(^2\)
- Type of tissue damage caused by burns generates unusually high levels of pain
  - Pain-generating mechanisms in burns include nociception, primary and secondary hyperalgesia and neuropathy\(^3\)
  - Burn pain is long-lasting, often exceeding healing time
- Body’s response to the burn injury is systemic, affecting all major systems of the body\(^3\)
  - Arguably, most complicated form of acute pain to treat from any etiology\(^2\)

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Pain Management of Burns: Initial Challenges (EMS/ED)

- Energy from the burn source instantly causes cell damage and release of inflammatory mediators\(^1\)
  - Release of endorphins and other neurotransmitters triggered by the injury can cause initial stress-induced analgesia\(^2\)

- Hormonal response follows (elevated levels of cortisol, epinephrine, aldosterone), designed to protect vital organs\(^2\)
  - Goal of analgesia at this juncture is to prevent undesired consequences of stress response

- Potent opioids cornerstone of pharmacologic pain control\(^1\):
  - IV access difficult; painful, damaged tissue
  - IM or SC avoided; unreliable absorption through soft tissue as a result of unpredictable fluid shifts and muscle perfusion
  - Oral administration not recommended; possibility of GI dysfunction

Pain Management of Burns: Longer-Term Challenges (Hospital/Rehab)

- Burn patients at high risk for developing catheter-related sepsis\(^1\)
  - Physicians reluctant to maintain long-term IV access

- Drug pharmacokinetics can be altered in this population due to changes in volume distribution, unbound drug fraction and clearance half-life\(^2\)

- Nature of standard burn care (ie debridement, grafting procedures, dressing changes) worsens whatever pain is present\(^2\)
  - Wound care and therapies can generate pain that exceeds what patient experienced at the time of the injury

- Pain, in addition to being a source of outright suffering for patients, can interfere with wound treatment and lengthen hospitalization\(^1\)

- Well-documented association between insufficient pain relief and the onset of long-term psychiatric disorders such as PTSD and depression\(^3\)

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Rationale for Sublingual Sufentanil
Why Sublingual Sufentanil?

Sufentanil first synthesized by Janssen in 1974\(^1\)

First approved in US for IV delivery in 1984\(^1\)

- Approved for induction of anesthesia
- Later approved for epidural delivery as an analgesic in combination with bupivacaine\(^1\)

Sufentanil Physicochemical Properties

- Lipophilic: 1500 times more fat-soluble than morphine
- 20% non-ionized at physiological pH (fentanyl only 8%)
- Fat-soluble, non-ionized molecules = more rapid brain penetration than lipid-insoluble, charged molecules\(^2\)

Sufentanil Penetrates CNS Due to Lipophilicity ($t_{\frac{1}{2}}k_{e0}$)

Commonly used IV opioids have delayed equilibration between plasma and CNS

- Morphine $t_{\frac{1}{2}}k_{e0} = 2.8$ hours$^1$
- Hydromorphone $t_{\frac{1}{2}}k_{e0} = 46$ min$^2$

Sufentanil rapidly penetrates the CNS due to its very lipophilic nature

- Sufentanil $t_{\frac{1}{2}}k_{e0} = 6$ min$^3$

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1. Lotsch et al., *Anesthesiol* 95:1329-38, 2001
# Sufentanil: High Therapeutic Index and No Active Metabolites

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Therapeutic index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine</td>
<td>5(^1)</td>
</tr>
<tr>
<td>Morphine</td>
<td>71(^1)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>232(^2)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>277(^1)</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>26,716(^1)</td>
</tr>
</tbody>
</table>

**Therapeutic index**

\[
\frac{\text{lethal dose (LD}_{50})}{\text{effective dose (ED}_{50})} \text{ in animal studies}
\]

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2. Kumar, *Eur J Pharmacol* 2008; 597:39 (ED50) and Purdue Pharma MSDS, 2009 (LD50)
Sufentanil Pharmacokinetics

- **Sublingual delivery of sufentanil blunts** $C_{\text{max}}$ **and extends** plasma half-time compared to IV administration$^1$

<table>
<thead>
<tr>
<th></th>
<th>ARX-04 30 mcg</th>
<th>IV</th>
<th>Sublingual</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability, %, mean</strong></td>
<td>100</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ pg/mL, mean</td>
<td>1074</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td><strong>CST$\frac{1}{2}$ h, median</strong></td>
<td>0.1</td>
<td>2.3</td>
<td></td>
</tr>
</tbody>
</table>

*CST$\frac{1}{2}$ = context-sensitive half-time (time from $C_{\text{max}}$ to 50% of $C_{\text{max}}$)*

1. SAP101, data on file, AcelRx
## ARX-04 Clinical Studies

<table>
<thead>
<tr>
<th>Study number</th>
<th>Phase #</th>
<th>Clintrials.gov NCT #</th>
<th>Patient population</th>
<th>Current status of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP202</td>
<td>Phase 2</td>
<td>NCT01710345</td>
<td>Postoperative bunionectomy</td>
<td>Published 2014(^1)</td>
</tr>
<tr>
<td></td>
<td>Dose-finding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pivotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP301</td>
<td>Phase 3</td>
<td>NCT02356588</td>
<td>Ambulatory surgery - Postoperative abdominal</td>
<td>Completed 2015 Manuscript Submitted</td>
</tr>
<tr>
<td></td>
<td>Pivotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP302</td>
<td>Phase 3</td>
<td>NCT02447848</td>
<td>Trauma/injury in the ED</td>
<td>Enrollment complete; topline data released</td>
</tr>
<tr>
<td>SAP303</td>
<td>Phase 3</td>
<td>NCT02662556</td>
<td>Postoperative; elderly and organ impaired</td>
<td>Enrollment complete; data under analysis</td>
</tr>
</tbody>
</table>

ARX-04 Single-Dose Applicator

- Designed in collaboration with DoD (light-weight, extreme-environment tested, easily handled with gloves)\(^1\)

1. Data on file, AcelRx (2015-2016)
**SAP202**

**ARX-04 Dose-Finding Study**

- **Postoperative bunionectomy patients**
- **ARX-04 30 mcg dose demonstrated superiority over placebo within 30 minutes**

![Graph showing pain intensity differences over time for 30 mcg, 20 mcg, and placebo doses.](image)

SAP301: PID Over First Hour

- Postoperative pain following abdominal surgery

![Graph showing pain intensity difference to baseline over time for Sufentanil 30 mcg and Placebo.]

- * p<0.01
- ** p<0.001
SAP302: Emergency Dept. Trauma Pain

**Study Design**

**Inclusion/Exclusion**

**Inclusion:**
- 18 years and older
- Moderate-to-severe acute pain due to trauma or injury

**Exclusion:**
- Opioid-tolerant (>15mg oral MSO₄ equivalent daily)
- Dependent on supplemental oxygen
- Pregnant

**Study Details**

- Multicenter, Single-Arm, Open-Label Study
- ARX-04 30 mcg

**Two Cohorts:**
- Single-dose (after 1 hour, other opioids administered if needed)
- Multiple-dose (up to 5 hours; rescue opioids allowed if study drug not effective)
SAP302

Outcome Measures

Primary Endpoint

- Sum of the pain intensity difference to baseline over the first hour of treatment (SPID1)

Key Secondary Efficacy Endpoints

- PID assessments
- Patient and Healthcare Practitioner Global Assessment
- Use of rescue medication
- Drop-outs due to inadequate analgesia

Safety Endpoints

- Adverse Events
- Vital Signs
- Six-item Cognitive Screener
- Concomitant Medications

Study sites

- Hennepin County Medical Center, Minneapolis, MN (James Miner, MD)
- Memorial Hermann-Memorial City Medical Center, Houston, TX (Harold Minkowitz, MD)
- Baylor College of Medicine, Ben Taub General Hospital, Houston, TX (Zubaid Rafique, MD)
# SAP302: Demographics (n=76)

## Baseline characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Category</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male, %</td>
<td>61</td>
<td>BMI, %</td>
</tr>
<tr>
<td>Age, years, mean</td>
<td>42</td>
<td>&lt; 30kg/m²</td>
</tr>
<tr>
<td>Race, %</td>
<td>34, 7</td>
<td>≥ 30kg/m²</td>
</tr>
<tr>
<td>Caucasian</td>
<td>59</td>
<td>ASA Classification, %</td>
</tr>
<tr>
<td>African American</td>
<td>34, 7</td>
<td>2</td>
</tr>
<tr>
<td>Native American</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td>16</td>
<td>Hispanic/Latino</td>
</tr>
<tr>
<td>Baseline Pain</td>
<td>8.1/10</td>
<td></td>
</tr>
</tbody>
</table>
## SAP302: Demographics (n=76)

**Trauma presentation**

<table>
<thead>
<tr>
<th>Injury Type</th>
<th>Number</th>
<th>Percent Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractures</td>
<td>25</td>
<td>32.9%</td>
</tr>
<tr>
<td>Sprains/strains</td>
<td>23</td>
<td>30.3%</td>
</tr>
<tr>
<td>Contusion/hematoma (soft tissue)</td>
<td>13</td>
<td>17.1%</td>
</tr>
<tr>
<td>Laceration</td>
<td>8</td>
<td>10.5%</td>
</tr>
<tr>
<td>Joint dislocation</td>
<td>4</td>
<td>5.3%</td>
</tr>
<tr>
<td>Burns</td>
<td>2</td>
<td>2.6%</td>
</tr>
<tr>
<td>Infections</td>
<td>1</td>
<td>1.3%</td>
</tr>
</tbody>
</table>
SAP302: Efficacy
Combined Cohorts (n=76)

- Over 35% drop in pain intensity by 60 minutes\(^1\)
- A clinically significant drop in pain intensity when administering 0-10 point numerical rating scale (NRS) to measure pain is 1.3\(^2\)

1. Mean reduction in pain intensity of 2.88 from a baseline of 8.08
SAP302: Efficacy
Multiple-Dose Cohort (n=36)

- Re-dosing allowed hourly if needed
- 75% of patients did not require re-dosing
SAP302: Efficacy
Use of Rescue

- Low rate of rescue opioid usage

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Patients Requiring Use of Rescue Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single-Dose Cohort (n = 40)</td>
</tr>
<tr>
<td>Use in First Hour</td>
<td>7.5%</td>
</tr>
<tr>
<td>Use after First Hour</td>
<td>NA</td>
</tr>
</tbody>
</table>
SAP302: Safety
Adverse Events (> 2% of patients)

- Majority of patients experienced no side effects

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>ARX-04 (30 mcg) n=76</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Adverse Event</td>
<td>79%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5%(^1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4%</td>
</tr>
<tr>
<td>Oxygen Desaturation</td>
<td>3%(^2)</td>
</tr>
</tbody>
</table>

- Only 2 of 76 patients had a drop on the SIS at one hour compared to baseline (6 >> 5; 5 >> 4)

1. All 4 patients with somnolence were rated as mild
2. Two patients experienced transient room air oxygen desaturations below 95% (88% and 94% which immediately improved with nasal cannula oxygen)
ARX-04: Positive Phase 3 Data in the Treatment of Moderate-to-Severe Acute Pain

- Single dose of ARX-04 30 mcg results in approximately a 3-point drop in pain intensity within 60 minutes, with clinically meaningful analgesia in < 20 minutes\(^1\)

- ARX-04 is well-tolerated in post-surgical and emergency medicine patients, with no evidence of cognitive impairment reported.

- ARX-04 is still investigational, but if approved, could offer an analgesic alternative to IV/IM or PO opioid dosing.

- Additional research is indicated to assess safety and efficacy in burn patients, specifically through the various stages of treatment and rehabilitation.

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Thank you

Karen DiDonato
 kdidonato@acelrx.com