Phase 3 Efficacy and Safety Results of Sufentanil Sublingual Tablet

2016 MHSRS Plenary Session

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Chief Medical Officer, AcelRx Pharmaceuticals, Inc.
Treatment Considerations for Battlefield Acute Pain

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

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

Sublingual delivery of sufentanil offers potential for field-based analgesia

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

Issues with other current battlefield treatments

- IM morphine less effective during shock due to peripheral vasoconstriction
- Oral transmucosal fentanyl lozenge can take over 30 minutes to dissolve
- Ketamine can produce dissociative effects

Profile of Desired Battlefield Analgesic

Excerpted from - Combat Anesthesia: The First 24 Hours (eds. Buckenmaier C and Mahoney PF, 2015)$^1$

- Robust stability in the face of environmental challenges
- Straightforward method of delivery to increase potential caregivers
- Rapid onset with a rarity of adverse events
- Minimize altered mental status
- Large therapeutic index

1. Published by Office of the Surgeon General, United States Army, Falls Church, Virginia, p. 268
Why Sublingual Sufentanil?

Sufentanil first synthesized by Janssen in 1974

First approved in US for IV delivery in 1984

- Approved for induction of anesthesia
- Later approved for epidural delivery as an analgesic in combination with bupivacaine

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

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

Commonly used IV opioids have delayed equilibration between plasma and CNS

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

Sufentanil rapidly penetrates the CNS due to its very lipophilic nature

- Sufentanil $t_{1/2} k_{e0} = 6$ 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 [lethal dose (LD&lt;sub&gt;50&lt;/sub&gt;)/effective dose (ED&lt;sub&gt;50&lt;/sub&gt;) in animal studies]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>71&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>232&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>277&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>26,716&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>


Other Opioid Active Metabolites<sup>3-7</sup>
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>Bioavailability, %, mean</td>
<td>100</td>
<td></td>
<td>53</td>
</tr>
<tr>
<td>$C_{\text{max}}$ pg/mL, mean</td>
<td>1074</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>CST(\frac{1}{2}) h, median</td>
<td>0.1</td>
<td></td>
<td>2.3</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 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>

SAP202
ARX-04 Dose-Finding Study

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

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)
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. The graph indicates a significant increase in pain intensity for Sufentanil, with p<0.01 and p<0.001 for certain time points.

* p<0.01
** p<0.001

Sufentanil 30 mcg
Placebo
SAP302: Emergency Dept. Trauma Pain

Study Design

Inclusion/Exclusion

Inclusion:
- 18 years and older
- moderate-to-severe acute pain due 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

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)

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 Global Assessment
- Use of rescue medication
- Drop-outs due to inadequate analgesia

Safety Endpoints

- Adverse Events
- Vital Signs
- Six-item Cognitive Screener
- Concomitant Medications
### SAP302: Demographics (n=76)

<table>
<thead>
<tr>
<th>Category</th>
<th></th>
<th>Category</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male, %</td>
<td>61</td>
<td>BMI, %</td>
<td></td>
</tr>
<tr>
<td>Age, years, mean</td>
<td>42</td>
<td>&lt; 30kg/m²</td>
<td>61</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td>≥ 30kg/m²</td>
<td>39</td>
</tr>
<tr>
<td>Caucasian</td>
<td>59</td>
<td>ASA Classification, %</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>34</td>
<td>1</td>
<td>61</td>
</tr>
<tr>
<td>Native American</td>
<td>7</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td></td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>16</td>
<td>Baseline Pain</td>
<td>8.1/10</td>
</tr>
</tbody>
</table>
SAP302: Efficacy
Combined Cohorts (n=76)

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

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>

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)
SAP302: Safety
Six-Item Screener (SIS) Cognitive Test

Sublingual sufentanil not associated with cognitive impairment

- DoD requested cognitive test before and 1 hour after dosing of sublingual sufentanil 30 mcg
- Impaired cognitive skills a concern with other field-based analgesics used in the military (e.g., ketamine)\(^1\)
- A score of 4 or less has been validated as indicating cognitive impairment\(^2\)
- Only 2 of 76 patients had a drop on the SIS at one hour compared to baseline (6 $\gg$ 5; 5 $\gg$ 4)

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 and did not show cognitive impairment in this clinical study
- ARX-04 is still investigational, but if approved, could provide an analgesic option for opioid-naïve patients
- Additional research is indicated to assess safety and efficacy in actual field-based environments

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Thank you

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