Pharmacokinetics and Dose Proportionality of Sublingual Sufentanil NanoTab™ in Healthy Volunteers

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Sufentanil: A Superior Opioid

- Approved for intravenous (IV) and epidural administration\(^1\)
- High therapeutic index\(^2\)
- No active metabolites\(^3\)
- Rapid transmucosal uptake

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Therapeutic index(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>12</td>
</tr>
<tr>
<td>Meperidine</td>
<td>28</td>
</tr>
<tr>
<td>Morphine</td>
<td>70</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>232</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>300</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>25,000</td>
</tr>
</tbody>
</table>

Therapeutic index = median lethal dose (LD\(_{50}\))/lowest median effective dose (ED\(_{50}\))

NanoTab: Efficient Transmucosal Delivery

- NanoTab: a novel oral transmucosal dosage form
- Key attributes:
  - Bioadhesive
  - Low saliva response
    - Minimal swallowed drug
    - Enhanced transmucosal uptake
  - Consistent pharmacokinetics
  - High bioavailability
## AcelRx Development Programs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient acute postoperative pain</td>
<td></td>
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<tr>
<td><strong>ARX-01: Sufentanil NanoTab patient-controlled analgesia (PCA) System</strong></td>
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<td>Cancer breakthrough pain</td>
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<tr>
<td><strong>ARX-02: Sufentanil NanoTab breakthrough pain (BTP) Management System</strong></td>
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<tr>
<td>Procedural sedation anxiolysis and analgesia</td>
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<tr>
<td><strong>ARX-03: Sufentanil/Triazolam NanoTab</strong></td>
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</tbody>
</table>
Study Objective and Methods

Objective:
- To determine the pharmacokinetics and dose proportionality of varying strengths of sublingual Sufentanil NanoTabs

Methods:
- **Design:** open-label, single-dose, crossover design
- **24 healthy volunteers (12 males, 12 females, 18-45 years of age) in 2 cohorts**
- **Treatments:**
  - Cohort 1 (n = 12) received lower dosage strengths (2.5, 5, and 10 mcg)
  - Cohort 2 (n = 12) received higher strengths (10 and 80 mcg)
  - All subjects received IV sufentanil 5 mcg
  - All subjects were blocked with oral naltrexone 50 mg bid
- **Plasma sufentanil concentrations were determined for 640 minutes following Sufentanil NanoTab dosing**
Linear Dose Proportionality

10 mcg vs 80 mcg (80 mcg dose normalized to 10 mcg)

Sufentanil plasma concentration (pg/mL) vs Time (min)

- 10 mcg Sufentanil NanoTab
- 80 mcg Sufentanil NanoTab
Mean (± SD) $C_{\text{max}}$ of Sufentanil versus Dose

$C_{\text{max}} = 2.31 \times \text{dose} + 1.2$

$R^2 = 0.9852$

SD, standard deviation; $C_{\text{max}}$, maximum concentration.
Mean (± SD) $C_{\text{max}}$ of Sufentanil versus Dose

Cohort 2 $C_{\text{max}}$ Proportionality

$C_{\text{max}} = 1.67 \times \text{dose} + 5.95$

$R^2 = 0.9785$

SD, standard deviation; $C_{\text{max}}$, maximum concentration.
## Oral Transmucosal Products: Sufentanil vs Fentanyl

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>ARX-02 80 mcg</th>
<th>Actiq 400 mcg</th>
<th>Fentora 400 mcg</th>
<th>Onsolis 800 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>79%</td>
<td>47%¹⁺ ¹⁺</td>
<td>65%¹</td>
<td>71%³</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (range)</td>
<td>53 min (30-90)</td>
<td>91 min¹⁺ ¹⁺ (35-240)</td>
<td>47 min¹ (20-240)</td>
<td>60 min³ (45-240)</td>
</tr>
<tr>
<td>$t_{1/2}$ (range) (%CV)</td>
<td>4.23 h (2.89-5.79) (21%)</td>
<td>6.43 h² (NA) (115%)</td>
<td>11.09 h¹ (4.63-20.59) (NA)</td>
<td>14 h³ (NA) (NA)</td>
</tr>
</tbody>
</table>

$T_{\text{max}}$, time to maximum concentration; $t_{1/2}$, half-life; CV, coefficient of variation; NA, not available.

¹Dose adjusted (800 mcg to 400 mcg).

Sufentanil NanoTab BTP Management System

- First transmucosal formulation of sufentanil
  - Allows opioid rotation

- Highly consistent $C_{\text{max}}$ and $T_{\text{max}}$
  - Avoids dose stacking

- Shorter half-life than fentanyl products
  - More closely matches BTP episode

- Compact smart dispenser to monitor dosing in an outpatient setting
Thank You