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

2016 International Society for Burn Injuries

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# 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]


1. Melson TI, Boyer DL, Minkowitz HS, et al (2014) Sufentanil sublingual microtablet system versus intravenous patient-controlled analgesia with morphine for postoperative pain control: a randomized, controlled trial. *Pain Pract* 14:679–688
2. de Moya, M. A. *Shock*. In Merck manual online, professional version. Retrieved from http://goo.gl/l8Xpa
3. Actiq package insert, Dec 2011, Cephalon, Inc.
4. Curran HV, Morgan C (2000) Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. *Addiction* 95:575-590

# 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 elctrolytes[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]


1. Norman, A and Judkins, K. Pain in the Patient with Burns, British Journal of Anaesthesia 2004;4(2):57-61.
2. Patterson, D and Sharar, *Burn Pain*, Em: Loeser, J. (Ed), Bonic's Management of Pain, 3rd ed. Philadelphia, PA: Lippincot, Williams and Wilkins, 2001, pp. 780-787
3. Srinivasa, N. *EVIDENCE FOR DIFFERENT MECHANISMS OF PRIMARY AND SECONDARY HYPERALGESIA FOLLOWING HEAT INJURY TO THE GLABROUS SKIN, Brain 1984;107:1179-1188*

# 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



1. Patterson, D and Sharar, *Burn Pain*, Em: Loeser, J. (Ed), Bonic's Management of Pain, 3rd ed. Philadelphia, PA: Lippincot, Williams and Wilkins, 2001, pp. 780-787
2. Norman, A and Judkins, K. Pain in the Patient with Burns, British Journal of Anaesthesia 2004;4(2):57-61.

# 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]

1. Patterson, D and Sharar, *Burn Pain*, Em: Loeser, J. (Ed), Bonic's Management of Pain, 3rd ed. Philadelphia, PA: Lippincot, Williams and Wilkins, 2001, pp. 780-787
2. Jellish et al. Effect of Topical Local Anesthetic Application to Skin Harvest Sites for Pain Management in Burn Patients Undergoing Skin-Grafting Procedures. Annals of Surgery 1999; 229:115-120
3. De Castro, R. et al. Pain Management in Burn Patients Rev Bras Anestesiol 2013; 63(1):149-158

# 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]

1. Stanley TH, Egan TD, Van Aken H. A tribute to Dr Paul AJ Janssen: entrepreneur extraordinaire, innovative scientist, and significant contributor to anesthesiology. Anesth. Analgesia. 2008;106(2):451–462
2. De Leon-Casasola et al. *Anesth Analg* 1996; 83:867-75.

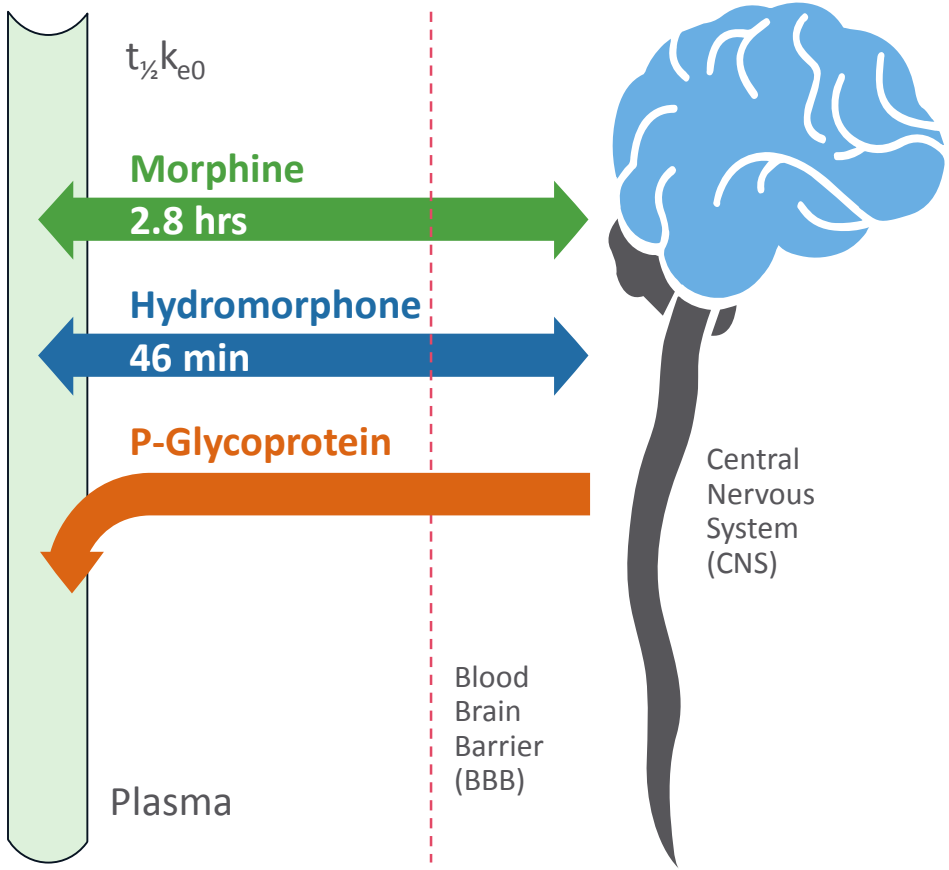
# Sufentanil Penetrates CNS Due to Lipophilicity ($t_{½}k_{e0}$)

**Commonly used IV opioids have delayed equilibration between plasma and CNS**

- Morphine $t_{½}k_{e0}$ = 2.8 hours[1]
- Hydromorphone $t_{½}k_{e0}$ = 46 min[2]

**Sufentanil rapidly penetrates the CNS due to its very lipophilic nature**

- Sufentanil $t_{½}k_{e0}$ = 6 min[3]



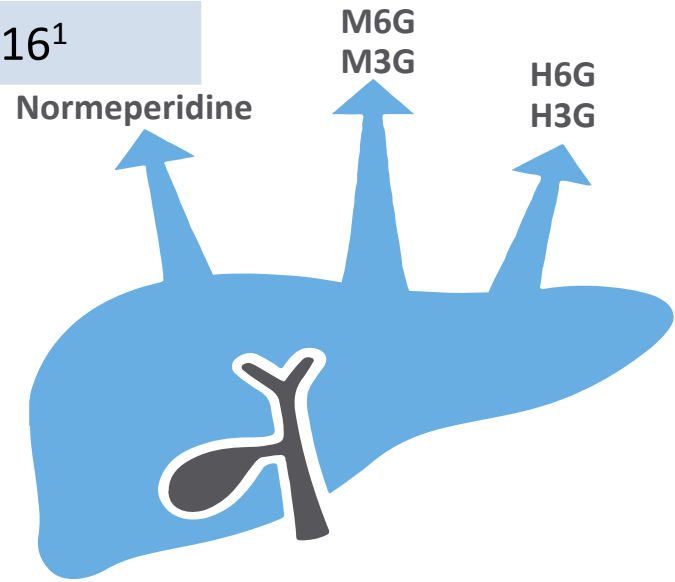


1. Lotsch et al., *Anesthesiol* 95:1329-38, 2001
2. Shafer et al., *Geriatric Anesthesiology*. 2nd ed. New York, NY: Springer; Chapter 15:209–28, 2007
3. Scott et al., *Anesthesiol* 74:34-42, 1991

# Sufentanil: High Therapeutic Index and No Active Metabolites

| Opioid | Therapeutic index [lethal dose ($LD_{50}$)/effective dose ($ED_{50}$) in animal studies] |
|---|---|
| Meperidine | 5[1] |
| Morphine | 71[1] |
| Hydromorphone | 232[2] |
| Fentanyl | 277[1] |
| Sufentanil | 26,716[1] |

**Other Opioid Active Metabolites[3-7]**





1. Mather, *Clin Exp Pharmacol Physiol* 1995; 22:833.
2. Kumar, *Eur J Pharmacol* 2008; 597:39 (ED50) and *Purdue Pharma MSDS*, 2009 (LD50)
3. Clark et al., *J Emerg Med 1995 ;*13:797–802
4. Smith et al., *Clin J Pain 2011;*27:824–38
5. Smith et al., *Clin Exp Pharmacol Physiol 2000;*27:524–8
6. Wright et al., *Life Sci 2001;*69:409–20
7. Smith, H. *Mayo Clin Proc 2009;84(7):613-614*

# Sufentanil Pharmacokinetics

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

| ARX-04 30 mcg | IV | Sublingual |
|---|---|---|
| Bioavailability, %, mean | 100 | 53 |
| $C_{max}$ pg/mL, mean | 1074 | 63 |
| $CST_{½}$ h, median | 0.1 | 2.3 |

CST½ = context-sensitive half-time (time from $C_{max}$ to 50% of $C_{max}$)

1. SAP101, data on file, AcelRx

# ARX-04 Clinical Studies

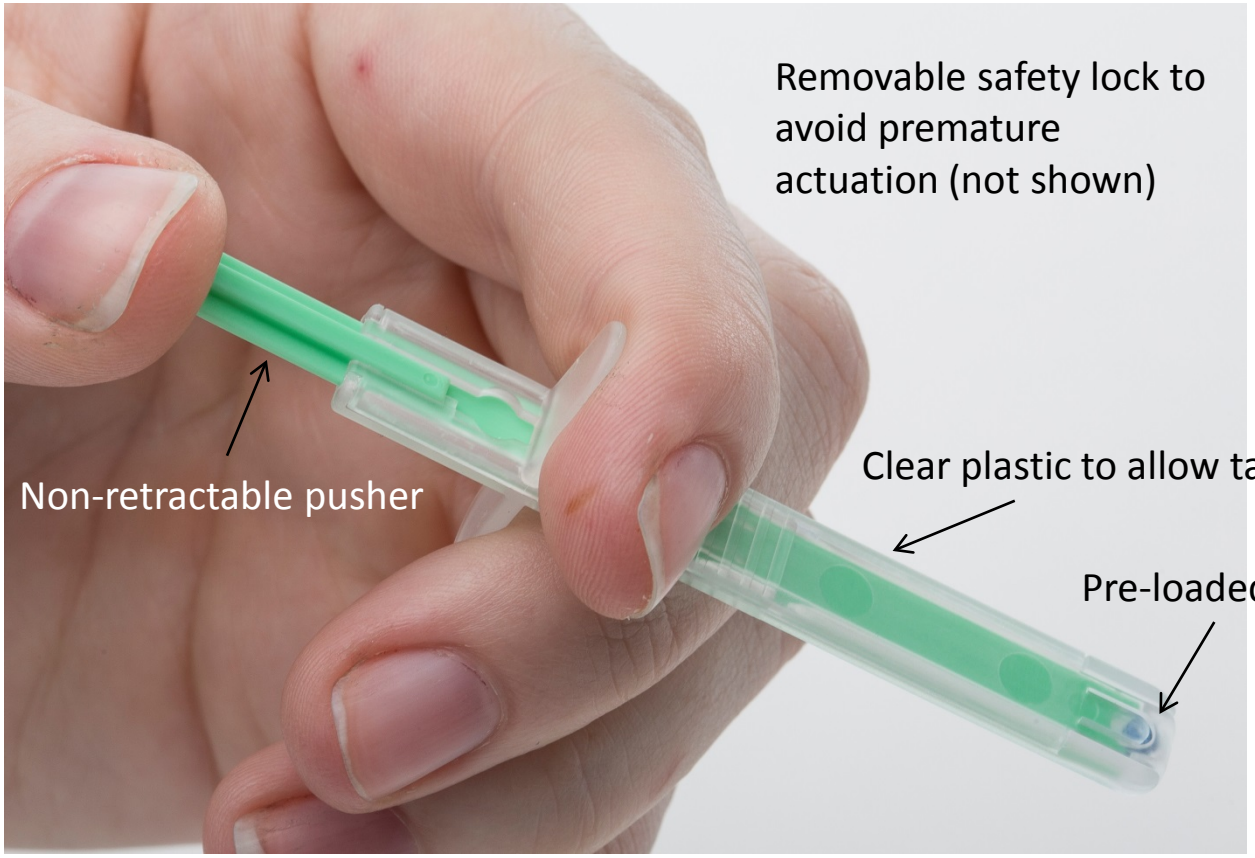
| Study number | Phase # | Clintrials.gov NCT # | Patient population | Current status of study |
|---|---|---|---|---|
| SAP202 | Phase 2<br>Dose-finding<br>Pivotal | NCT01710345 | Postoperative bunionectomy | Published 2014[1] |
| SAP301 | Phase 3<br>Pivotal | NCT02356588 | Ambulatory surgery<br>-Postoperative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



1. Singla NK, et al. A dose-finding study of sufentanil sublingual microtablets for the management of postoperative bunionectomy pain. *J. Trauma. Acute. Care. Surg*. 2014;77(3 Suppl 2):S198–S203

# ARX-04 Single-Dose Applicator

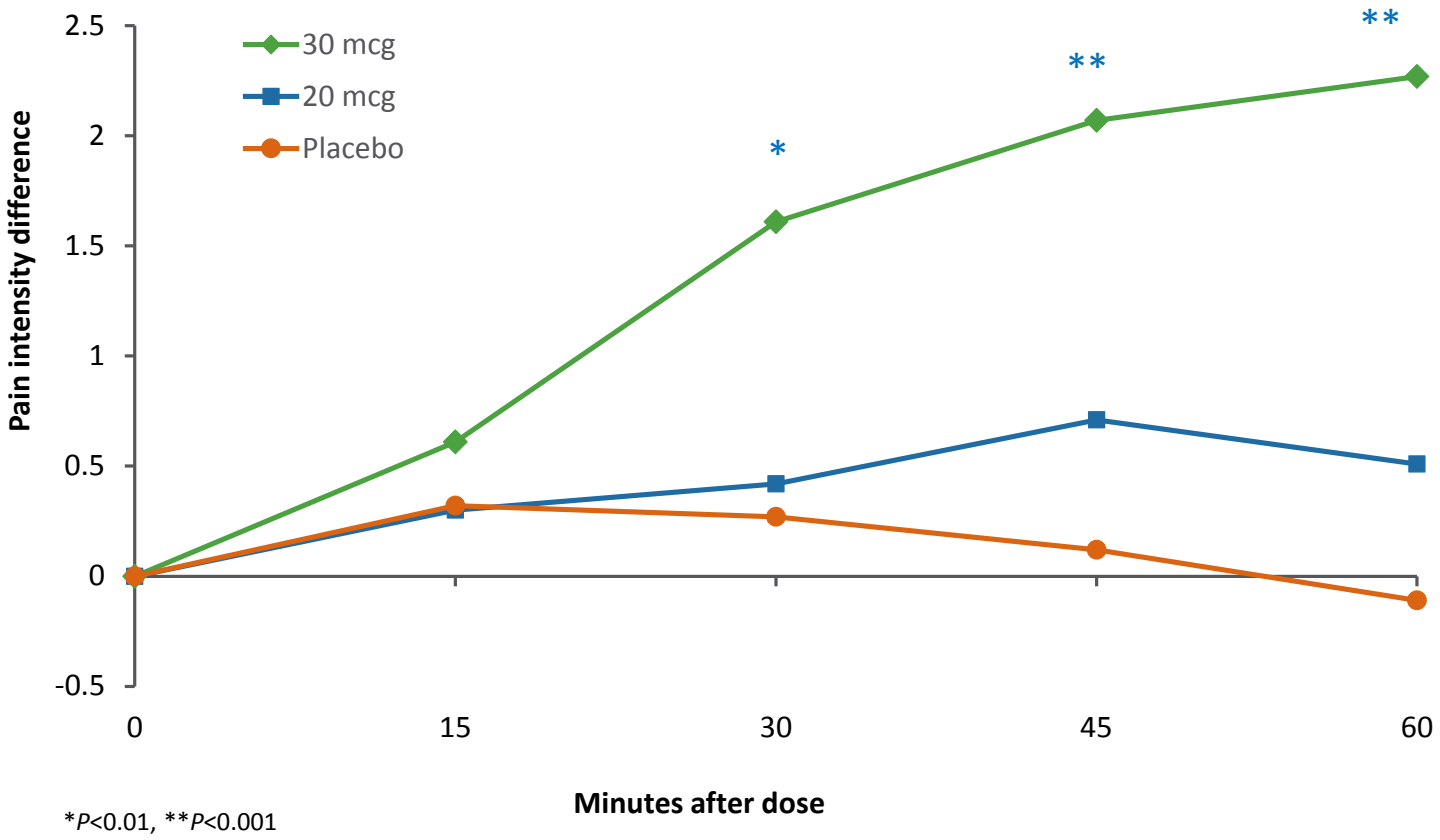
- **Designed in collaboration with DoD (light-weight, extreme-environment tested, easily handled with gloves)[1]**




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



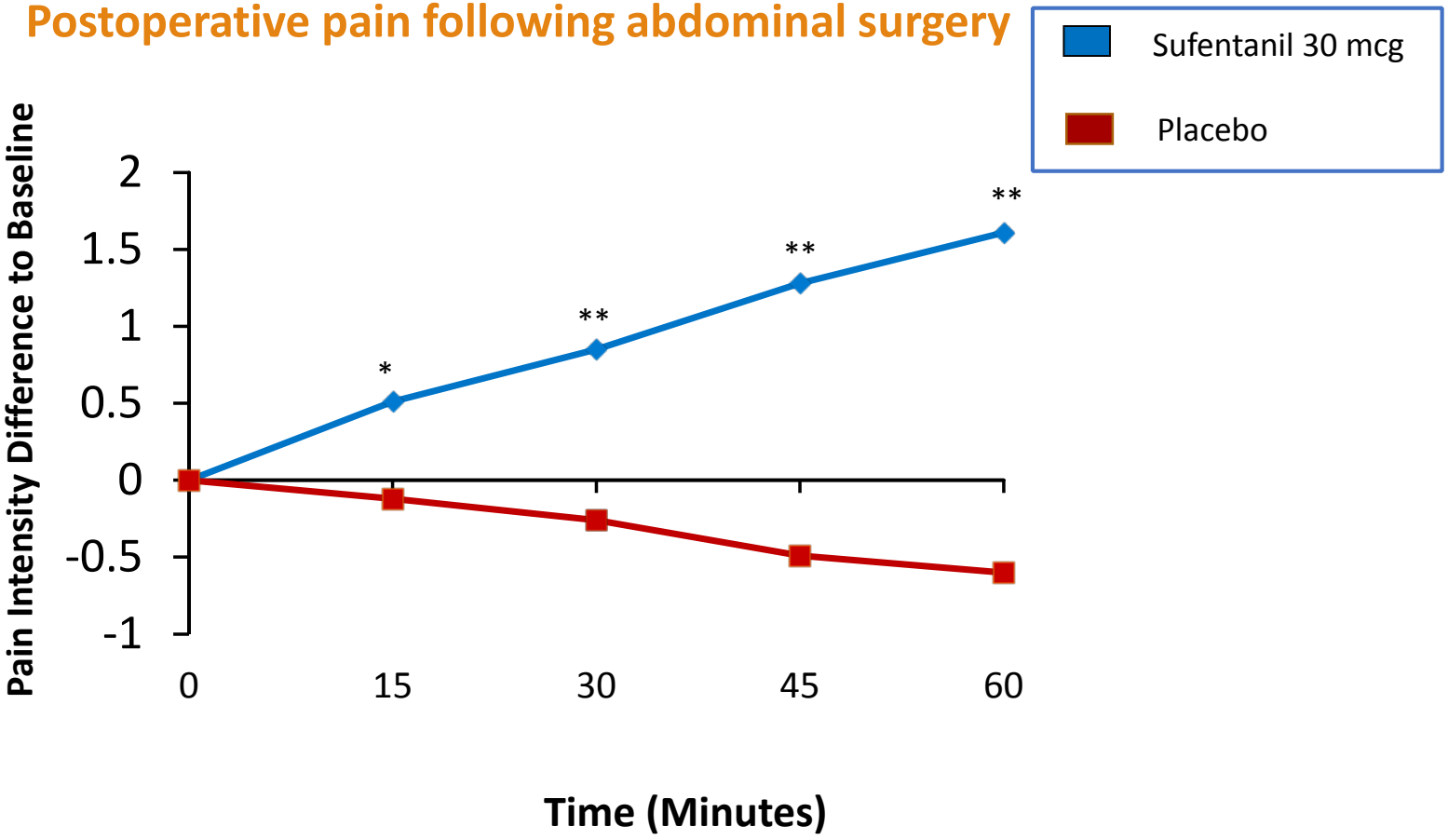

*$P$<0.01, **$P$<0.001



1. Singla NK, et al. A dose-finding study of sufentanil sublingual microtablets for the management of postoperative bunionectomy pain. *J. Trauma. Acute. Care. Surg.* 2014;77(3 Suppl 2):S198–S203

# SAP301: PID Over First Hour

- Postoperative pain following abdominal surgery




* 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 trauma or injury

**Exclusion:**

- Opioid-tolerant (>15mg oral $MSO_4$ 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 | Key Secondary Efficacy Endpoints | Safety Endpoints |
|---|---|---|
| ▪ Sum of the pain intensity difference to baseline over the first hour of treatment (SPID1) | ▪ PID assessments<br>▪ Patient and Healthcare Practitioner Global Assessment<br>▪ Use of rescue medication<br>▪ Drop-outs due to inadequate analgesia | ▪ Adverse Events<br>▪ Vital Signs<br>▪ Six-item Cognitive Screener<br>▪ Concomitant Medications |

# SAP302: Demographics (n=76)

## *Baseline characteristics*

| Category | | Category | |
|---|---|---|---|
| Sex, male, % | 61 | BMI, % | |
| Age, years, mean | 42 | < 30kg/m$^2$ | 61 |
| Race, % | | ≥ 30kg/m$^2$ | 39 |
| Caucasian | 59 | ASA Classification, % | |
| African American | 34 | 1 | 61 |
| Native American | 7 | 2 | 33 |
| Ethnicity, % | | 3 | 7 |
| Hispanic/Latino | 16 | **Baseline Pain** | **8.1/10** |

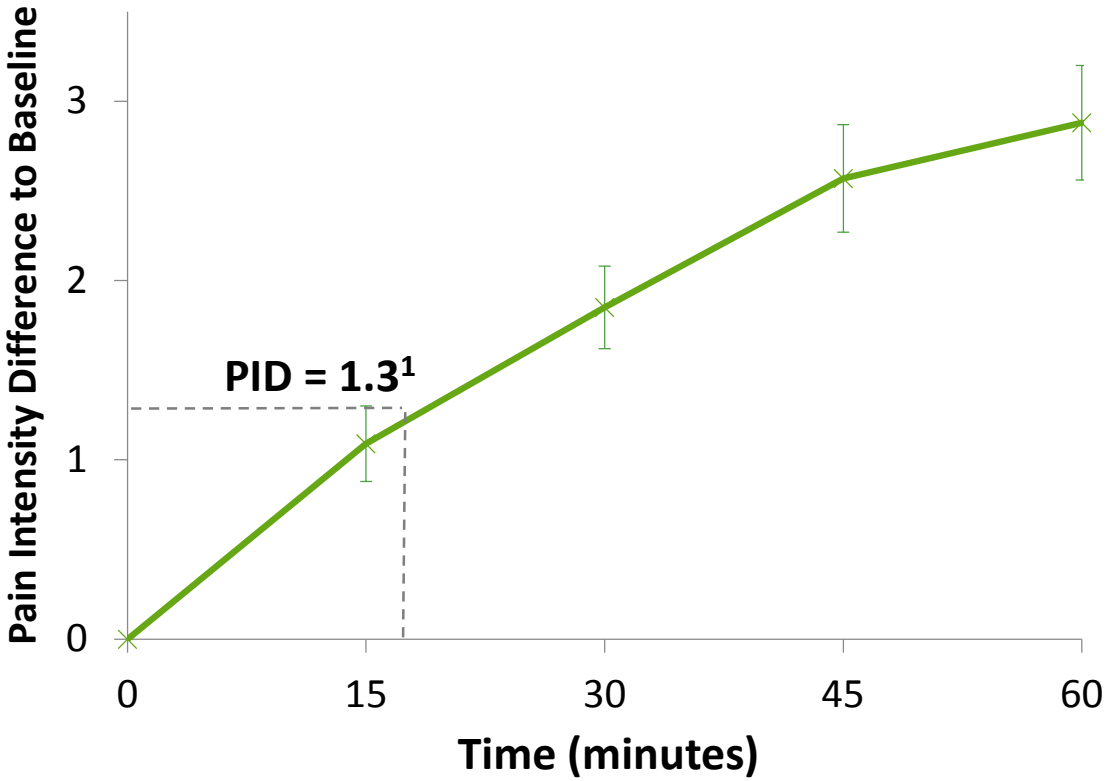
# SAP302: Demographics (n=76)

## *Trauma presentation*

| Injury Type | Number | Percent Total |
|---|---|---|
| Fractures | 25 | 32.9% |
| Sprains/strains | 23 | 30.3% |
| Contusion/hematoma (soft tissue) | 13 | 17.1% |
| Laceration | 8 | 10.5% |
| Joint dislocation | 4 | 5.3% |
| Burns | 2 | 2.6% |
| Infections | 1 | 1.3% |

# SAP302: Efficacy
# Combined Cohorts (n=76)

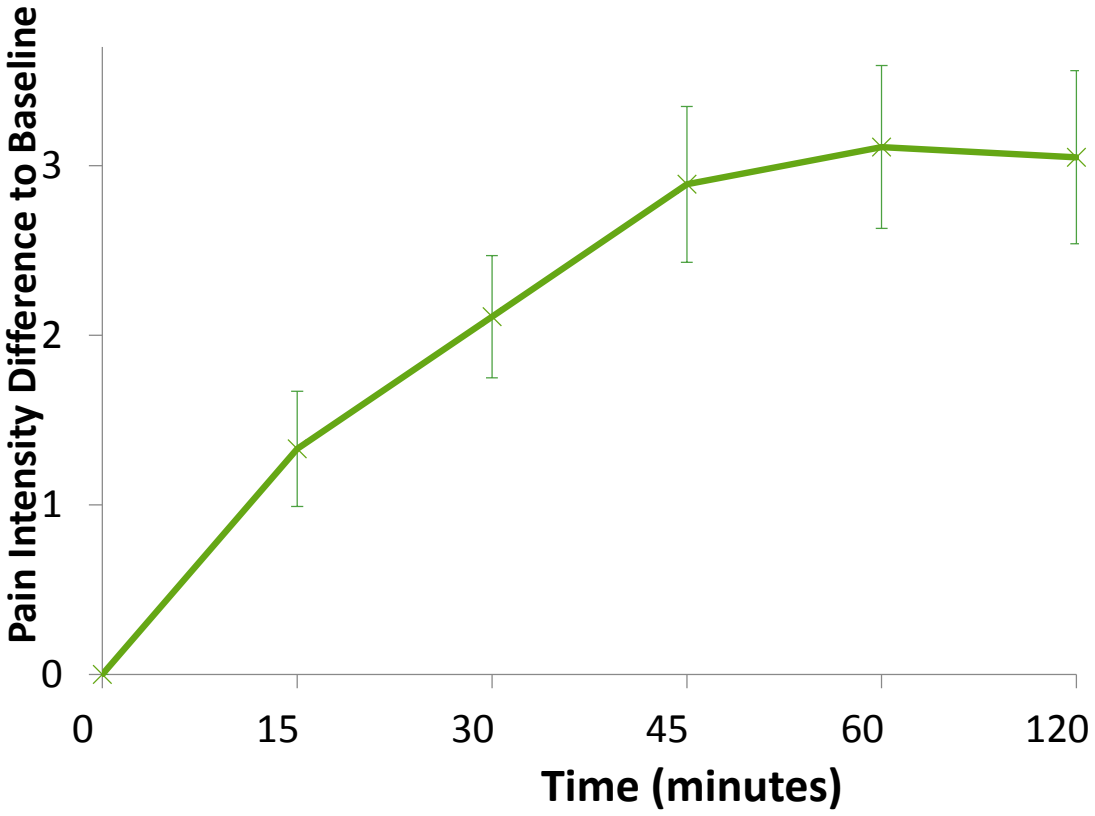
- Over 35% drop in pain intensity by 60 minutes[1]
- A clinically significant drop in pain intensity when administering 0-10 point numerical rating scale (NRS) to measure pain is 1.3[2]




1. Mean reduction in pain intensity of 2.88 from a baseline of 8.08
2. Bijur, Polly E., et al.. Validation of a Verbally Administered Numerical Rating Scale of Acute Pain four Use in the Emergency Department. Academy Emergency Medicine. 2003;10: 390-392

# 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**

| Study Period | Patients Requiring Use of Rescue Opioid | |
|---|---|---|
| | Single-Dose Cohort (n = 40) | Multiple-Dose Cohort (n = 36) |
| Use in First Hour | 7.5% | 0% |
| Use after First Hour | NA | 8.3% |

# SAP302: Safety
## Adverse Events (≥ 2% of patients)

- **Majority of patients experienced no side effects**

| Adverse Event, n (%) | ARX-04 (30 mcg) n=76 |
|---|---|
| **No Adverse Event** | **79%** |
| Nausea | 9% |
| Somnolence | 5%[1] |
| Vomiting | 4% |
| Oxygen Desaturation | 3%[2] |

- **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

1. Bijur, Polly E., et al.. Validation of a Verbally Administered Numerical Rating Scale of Acute Pain four Use in the Emergency Department. Academy Emergency Medicine. 2003;10: 390-392.

# Thank you

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