Phase 3 Efficacy and Safety Results of Sufentanil Sublingual Tablet

2016 MHSRS Plenary Session

Pamela Palmer, MD PhD

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[1]
- Sublingual tissue perfusion maintained during shock[2]
- 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[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

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[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.

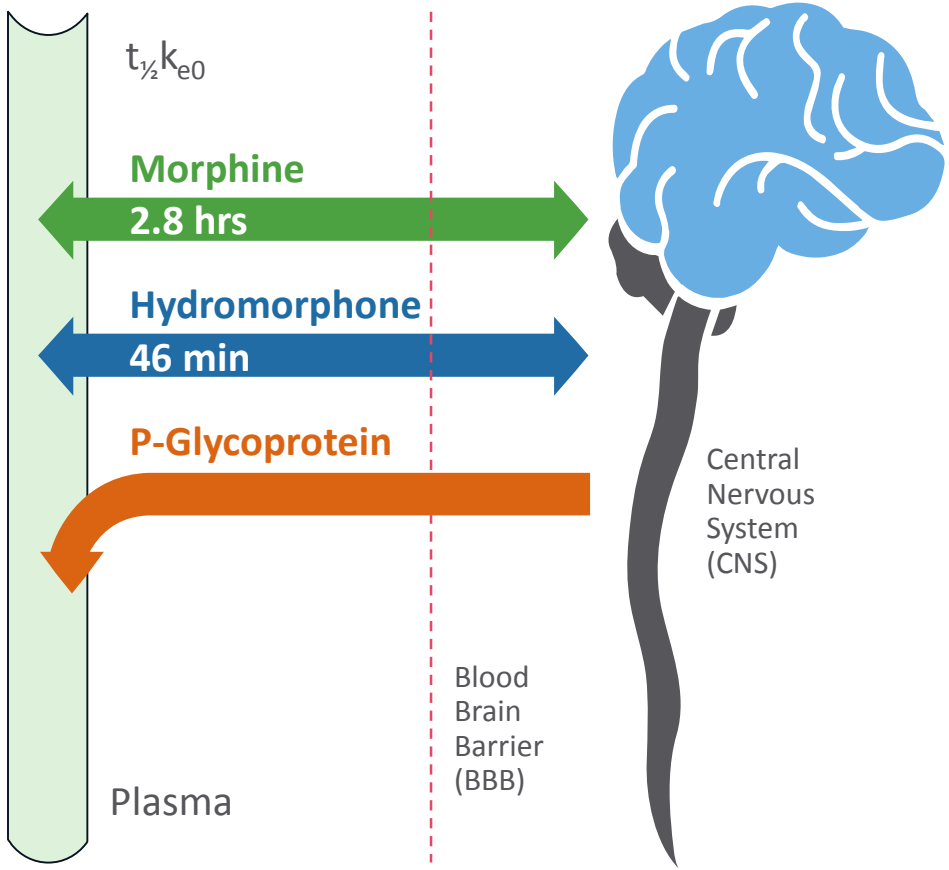
Sufentanil Penetrates CNS Due to Lipophilicity ($t_{½}k_{e0}$)

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]

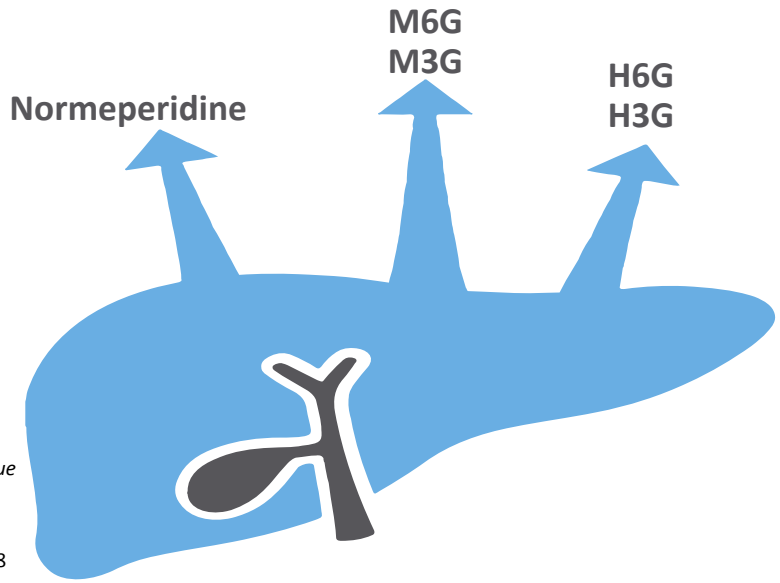


1. Lotsch et al., *Anesthesiol* 95:1329-38, 2001
2. Shafer et al., *Geriatric Anesthesiology*. 2nd ed. New York, NY: Springer; Chapter 15:209–28, 2007
3. Scott et al., *Anesthesiol* 74:34-42, 1991

Sufentanil: High Therapeutic Index and No Active Metabolites

Opioid	Therapeutic index [lethal dose (LD_{50})/effective dose (ED_{50}) in animal studies]
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

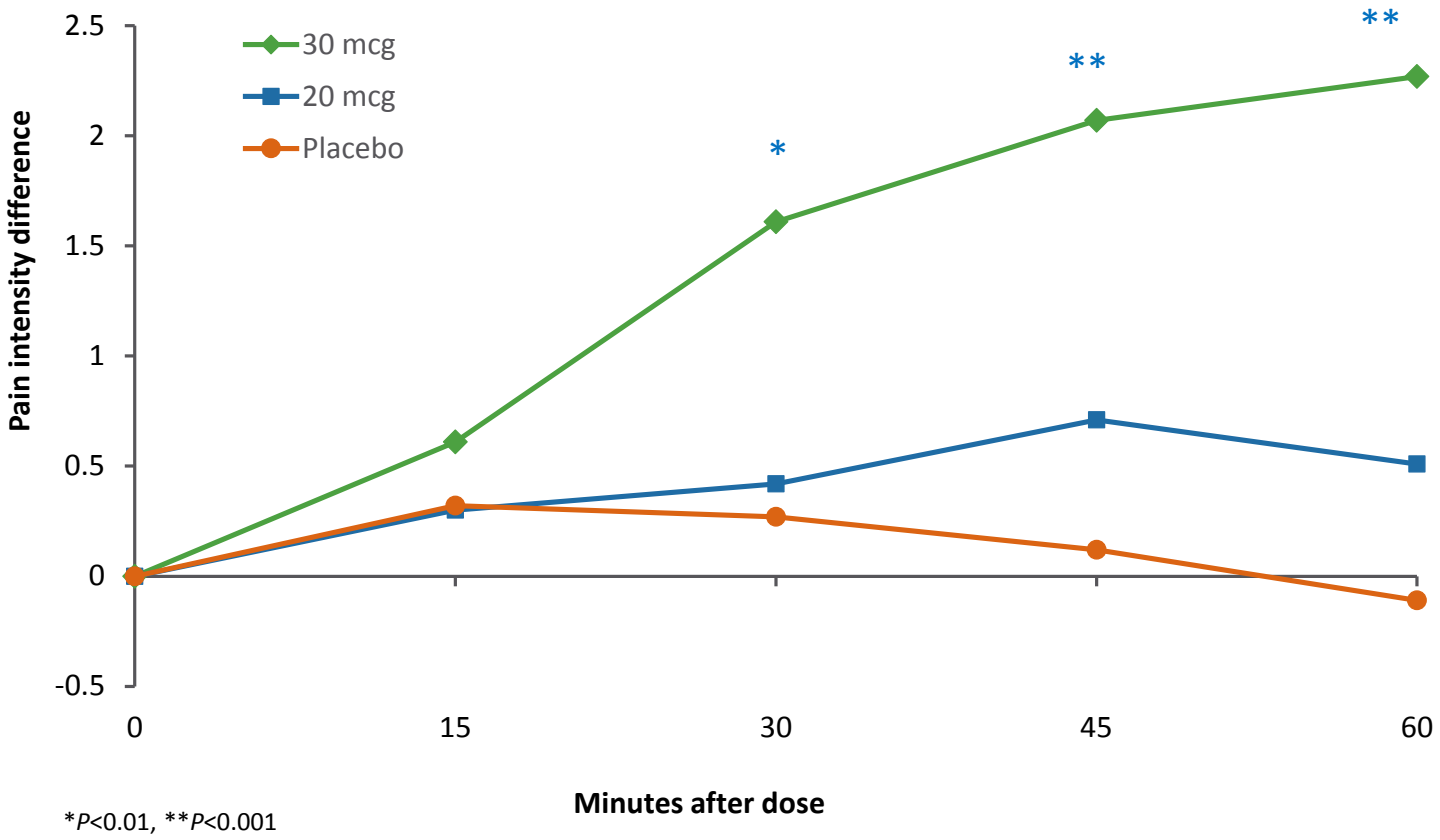
ARX-04 Clinical Studies

Study number	Phase #	Clintrials.gov NCT #	Patient population	Current status of study
SAP202	Phase 2 Dose-finding Pivotal	NCT01710345	Postoperative bunionectomy	Published 2014[1]
SAP301	Phase 3 Pivotal	NCT02356588	Ambulatory surgery -Postoperative abdominal	Completed 2015 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

SAP202
ARX-04 Dose-Finding Study

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

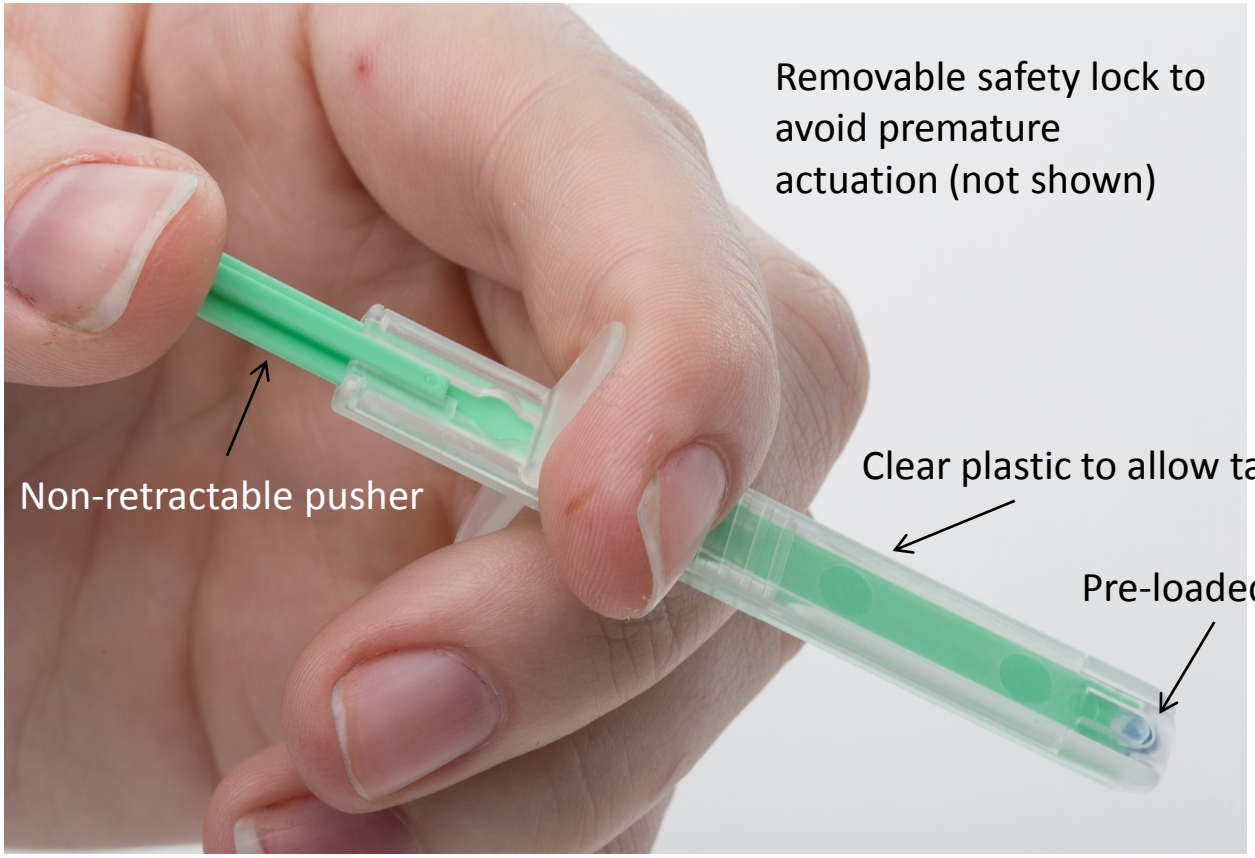


*P<0.01, **P<0.001

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

ARX-04 Single-Dose Applicator

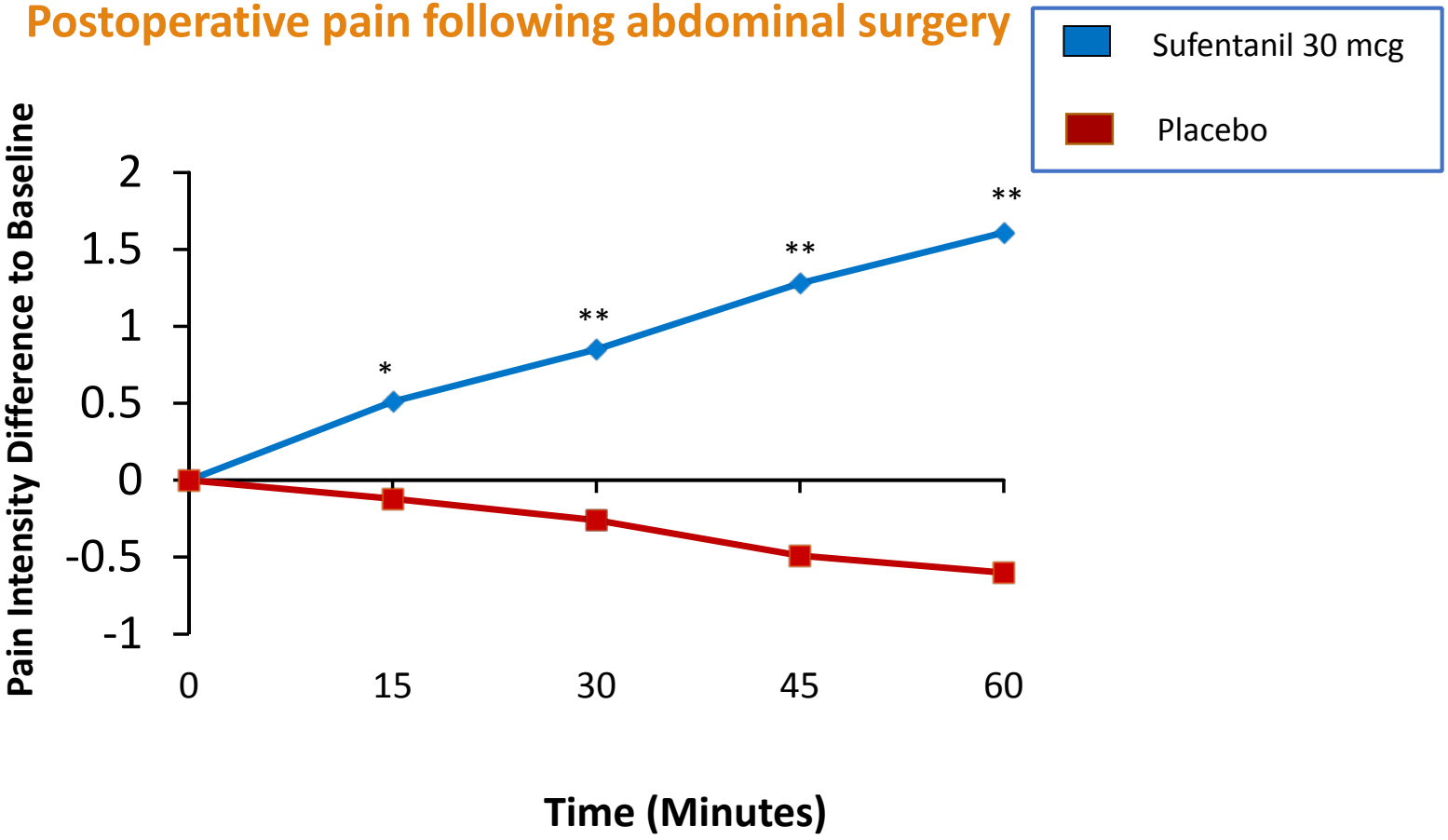
- **Designed in collaboration with DoD (light-weight, extreme-environment tested, easily handled with gloves)[1]**



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

SAP301:
PID Over First Hour

- Postoperative pain following abdominal surgery



* 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)

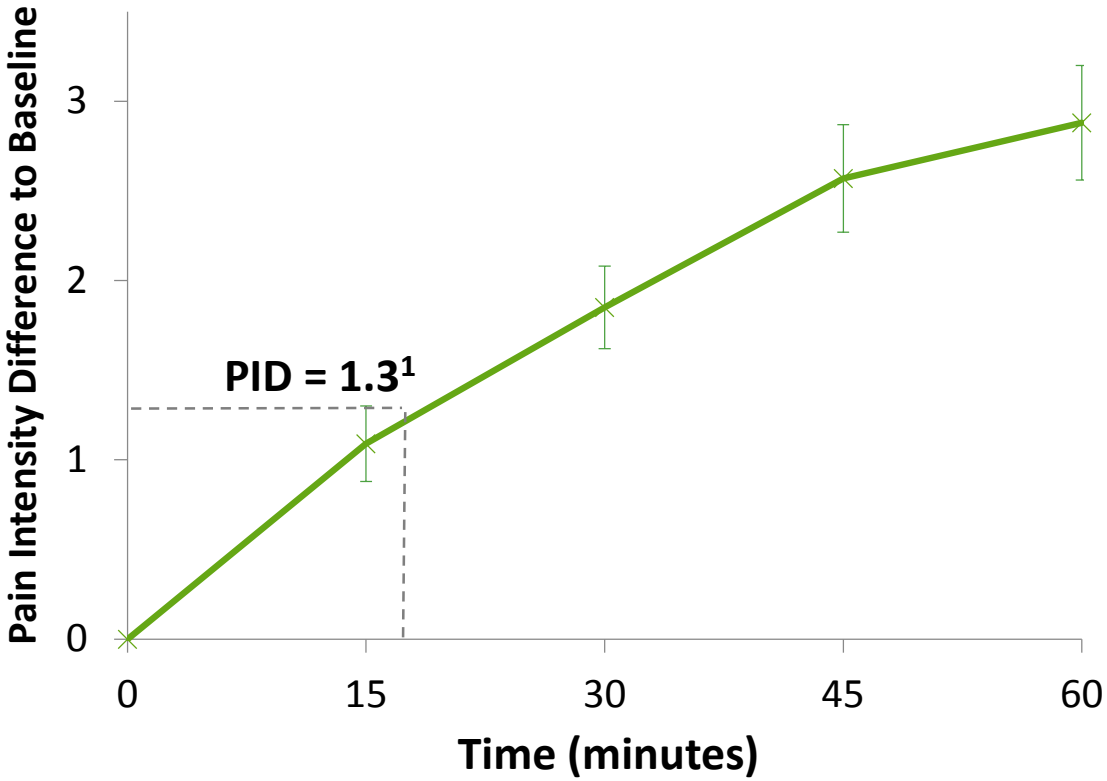
Primary Endpoint	Key Secondary Efficacy Endpoints	Safety Endpoints
▪ Sum of the pain intensity difference to baseline over the first hour of treatment (SPID1)	▪ PID assessments ▪ Patient and Healthcare Global Assessment ▪ Use of rescue medication ▪ Drop-outs due to inadequate analgesia	▪ Adverse Events ▪ Vital Signs ▪ Six-item Cognitive Screener ▪ Concomitant Medications

SAP302: Demographics (n=76)

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: Efficacy
Combined Cohorts (n=76)

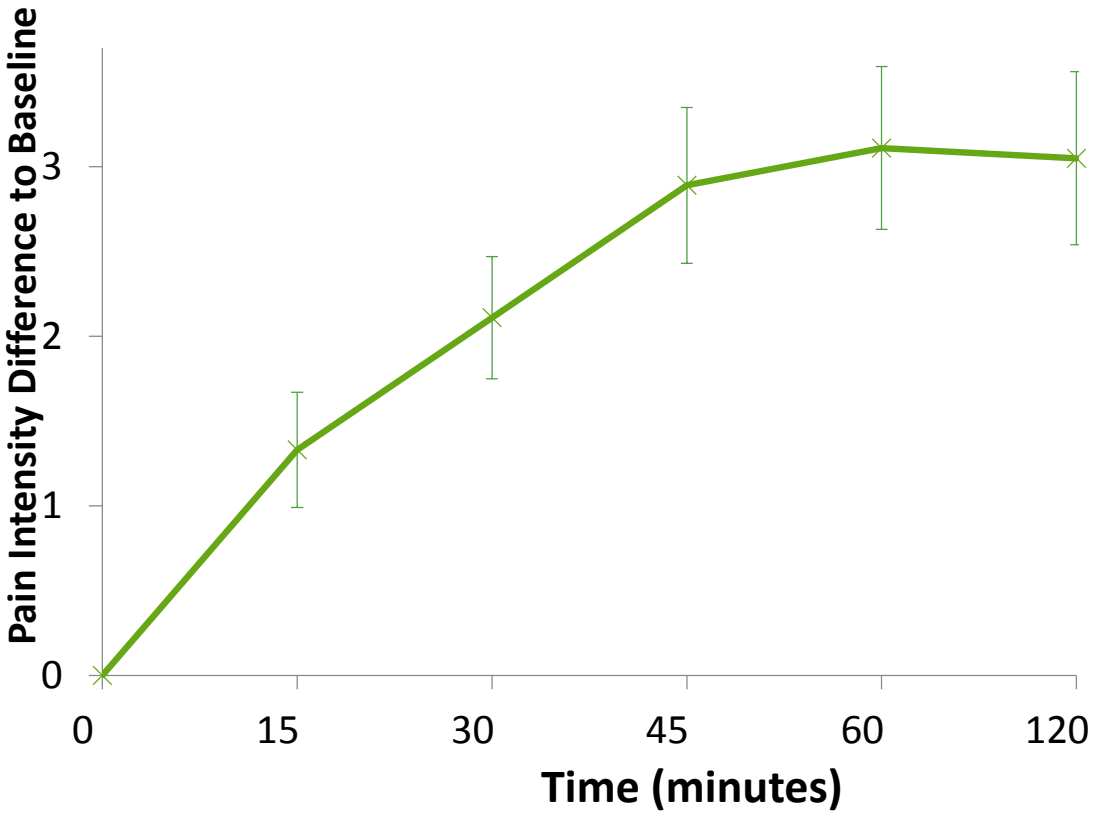
- Over 35% drop in pain intensity by 60 minutes[1]
- A clinically significant drop in pain intensity when administering 0-10 point numerical rating scale (NRS) to measure pain is 1.3[2]



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]

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 >> 5; 5 >> 4)

1. Green,et al., Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation: 2011 Update. Ann Emerg Med. 2011;57:449-461.
2. Callahan et al., Six-Item Screener to Identify Cognitive Impairment Among Potential Subjects for Clinical Research. Med Care. 2002;40:771-781.

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

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

Dr. Pamela Palmer

ppalmer@acelrx.com