Phase 3 Results of Sublingual Sufentanil 30 mcg for the Management of Postoperative Pain following Abdominoplasty Surgery

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Disclosures

- **I am a Principal Investigator and Consultant for AcelRx Pharmaceuticals, the Sponsor of the study.**

ARX-04 (Sufentanil Sublingual Tablet 30 mcg) housed in Single-Dose Applicator

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

1. AcelRx data on file

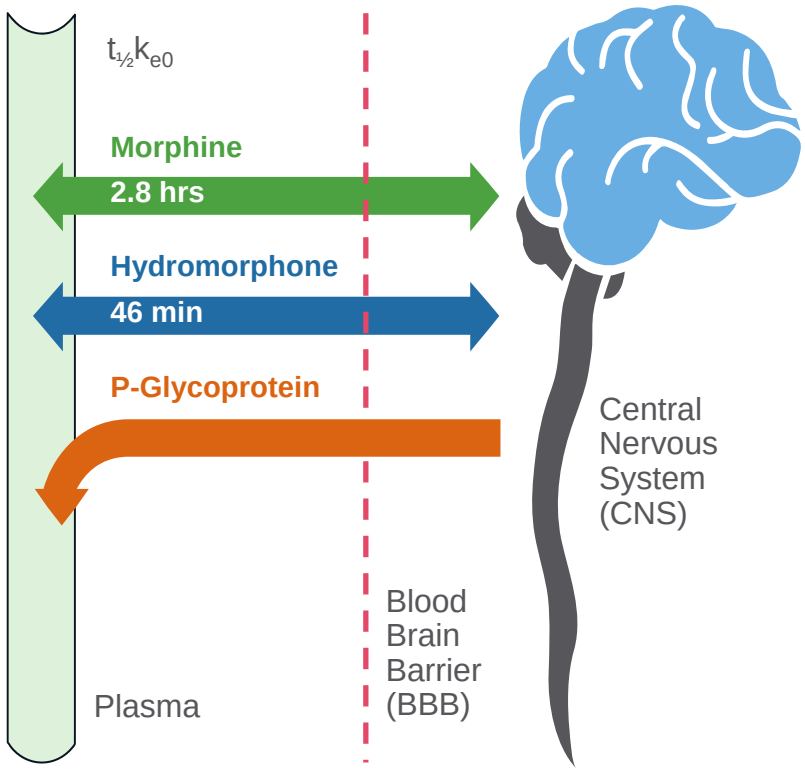
Sufentanil Penetrates CNS Due to Lipophilicity ($t_{½}k_{e0}$)

Commonly used IV opioids have a delayed equilibration time 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]

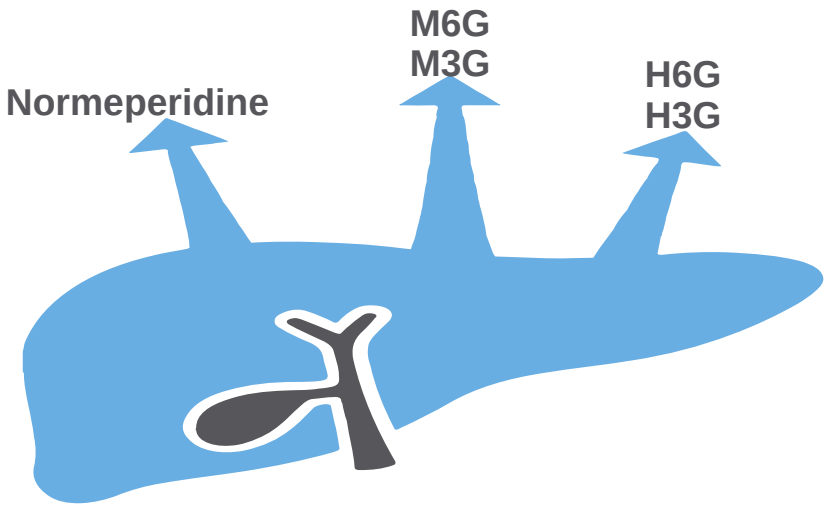


1. Lotsch et al., *Anesthesiol* 95:1329-38, 2001
2. Shafer et al., *Geriatric Anesthesiology*. 2nd ed. New York, NY: Springer; Chapter 15:209–28, 2007
3. Scott et al., *Anesthesiol* 74:34-42, 1991

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*

Pharmacokinetic Limitations of Current IV Opioid Therapy

IV morphine

- Delayed CNS penetration resulting in poor analgesic onset and slow offset which can delay discharge[1]
- Active metabolite morphine-6-glucuronide can cause delayed side effects[1]

IV hydromorphone

- Slightly more rapid onset than morphine but known for delayed and prolonged side effects (e.g., sedation, respiratory depression)[1]

IV fentanyl

- Lipophilic brain penetration results in rapid onset of analgesia but rapid alpha distribution of this lipophilic drug (1.7 minutes) results in quick offset and requires frequent re-dosing to maintain analgesia[2,3]
- Claxton et al, *Anesth Analg* 1997: “Evaluation of morphine versus fentanyl for postoperative analgesia after ambulatory surgical procedures” - postoperative pain returned 30 minutes after dosing with IV fentanyl

1. Lötsch J. *J Pain Symptom Manage* 2005; 29(5 Suppl):S90-S103.
2. Scott JC, Cooke JE, Stanski DR. *Anesthesiol* 1991; 74:34–42.
3. Shafer, S and Varvel, J. *Anesthesiol* 1991; 74:53-63

SAP301
Study Design

Postoperative ambulatory surgery patients following abdominal surgery

- Abdominoplasty
- Open hernia repair
- Any laparoscopic abdominal surgery

Randomized 2:1, ARX-04:placebo

- ARX-04 30 mcg dosed “as needed” but no more than once per hour
- Rescue IV morphine 1 mg available upon patient request

Study completed at 24 hours after first dose

- Dosing could extend out to 48 hours if needed

Primary efficacy variable: Time-weighted SPID-12

- Essentially an area under the curve measurement of the drop in pain intensity from baseline over the first 12 hours of the study
- Pain intensity (PI) measured on a 0–10 NRS
  (0 = no pain, 10 = worst pain imaginable)

SAP301 Demographics

Category		Category	
Sex, female	68%	Surgery	
Age, years, mean	41	Abdominoplasty	50%
Race/ethnicity		Laparoscopic	30%
Caucasian	40%	Open hernia	20%
Hispanic	38%	ASA status	
African American	19%	1	64%
Asian	3%	2	32%
BMI <30	70%	3	4%

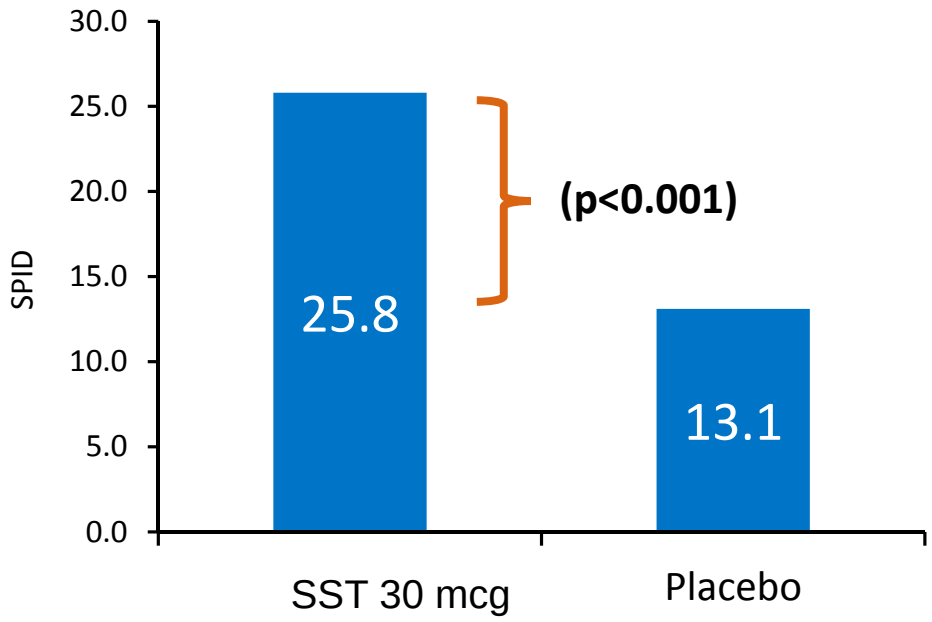
SAP301: Disposition over the 24-hour Study Period

Disposition	ARX-04 (n = 107)	Placebo (n = 54)	Total (n = 161)
Completed	95.3%	75.9%	88.8%
Discontinued	4.7%	24.1%	11.2%
Adverse event	0%	3.7%	1.2%
Lack of efficacy	3.7%	18.5%	8.7%
Protocol violation	0%	1.9%	0.6%
Withdrawal	0.9%	0%	0.6%

SAP301
Primary Endpoint: SPID-12

Pain intensity (PI) measured on a scale of 0–10

Assessment	ARX-04	Placebo	P-value
Baseline PI	5.6	5.5	NS
SPID-12	25.8	13.1	<0.001

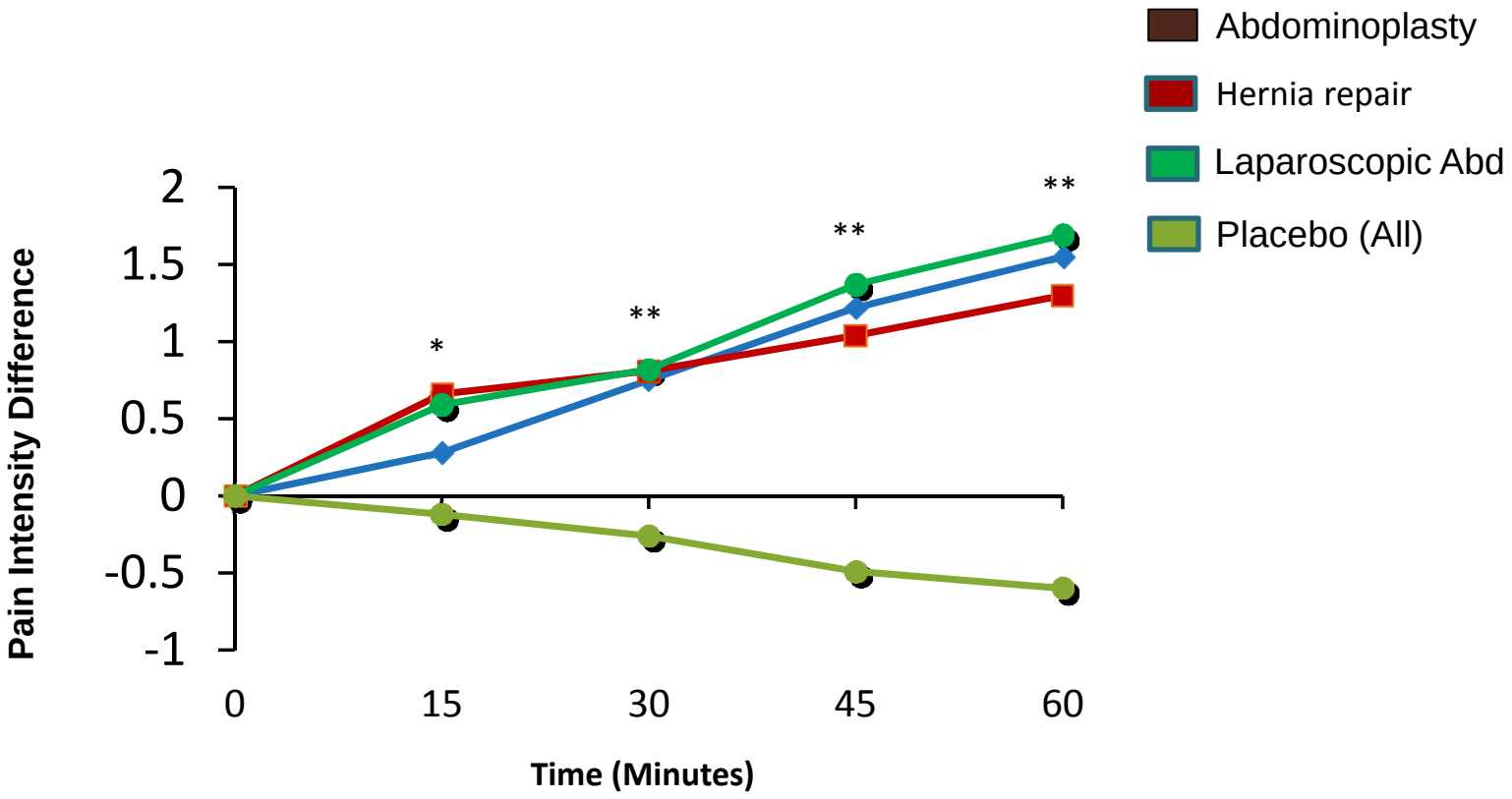


NS, not significant

SAP301:
SPID-12 by Surgical Subgroup

Type of Surgery	ARX-04 mean (SD)	Placebo mean (SD)	P-Value
Abdominoplasty	31.8 (2.3) n = 52	17.6 (3.1) n = 28	0.001
Laparoscopic abdominal surgery	21.4 (3.1) n = 32	8.2 (4.4) n = 16	< 0.05
Hernioplasty	18.6 (3.5) n = 23	7.7 (5.3) n = 10	NS

SAP301:
PID Over First Hour by Surgery Type



* p<0.01
** p<0.001

SAP301
Drug Utilization & Rescue

Number of 30 mcg tablets dosed

Time period	Number of tablets, median (range)	Inter-dosing interval, mean
0–12 Hours	4 (1–9)	185 minutes
0–24 Hours	7 (1–15)	221 minutes

Rescue Medication - 1mg IV Morphine

	ARX-04	Placebo	P-value
Patients using rescue, %	27.1	64.8	P<0.001

SAP301
Adverse Events (>3% in Either Group)

No statistical difference for ARX-04 compared to placebo

Adverse Event, %	ARX-04 (n=107)	Placebo (n=54)
No Adverse Event	42	37
Nausea/Procedural Nausea	36	35
Headache	20	19
Vomiting	8	2
Dizziness	6	4
Hypotension	5	4
Flatulence	4	7
Somnolence	3	4
Pruritus	2	4

SAP301
Abdominoplasty Adverse Events
(>5% in Either Group)

No statistical difference for ARX-04 compared to placebo

Adverse Event, %	ARX-04 (n=52)	Placebo (n=28)
No Adverse Event	25	21
Nausea/Procedural Nausea	48	43
Headache	29	21
Dizziness	12	7
Hypotension	10	7
Vomiting	8	4
Somnolence	6	7
Sinus Tachycardia	6	4
Pruritus	4	11
Flatulence	0	7

THANK YOU!