LONG-ACTING BUPRENORPHINE IMPLANTS FOR OPIOID USE DISORDER

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Disclosure Information

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Overview

- The Opioid Epidemic and Opioid Use Disorder (OUD) in the US
- The rationale for long-acting medications in OUD
- Buprenorphine implants
  - The evidence base
  - Most recent data
  - US FDA approval - May 2016
  - Implications

Opioid Abuse is Epidemic in the United States

In 2014:

- ~2 million Americans abused/dependent on prescription opioids
- >70% of abused opioids obtained from friends or family
- ~772,000 sought treatment for prescription pain meds
- Greatest increases in heroin use in groups with historically low rates:
  - Women, the privately insured, and people with higher incomes.
- Heroin increased >2X among 18 to 25 year olds in last 10 years
- In 2014, >14,000 people died from overdoses involving prescription opioids, and > 10,500 from heroin overdoses.

[1]2014 National Survey on Drug Use and Health: Detailed Tables, SAMHSA 2015 Retrieved from http:/www.samhsa.gov/data/ [2]Centers for Disease Control and Prevention. Vital Signs: Today's Heroin Epidemic – More People at Risk, Multiple Drugs Abused. MMWR 2015.

Nonmedical Pain Reliever Use among Nonmedical Psychotherapeutic Drug Users Aged ≥12 - 2014

- 6.5 Million Current Nonmedical Users of Psychotherapeutic Drugs
- 4.3 Million Current Nonmedical Users of Pain Relievers (66.2%)

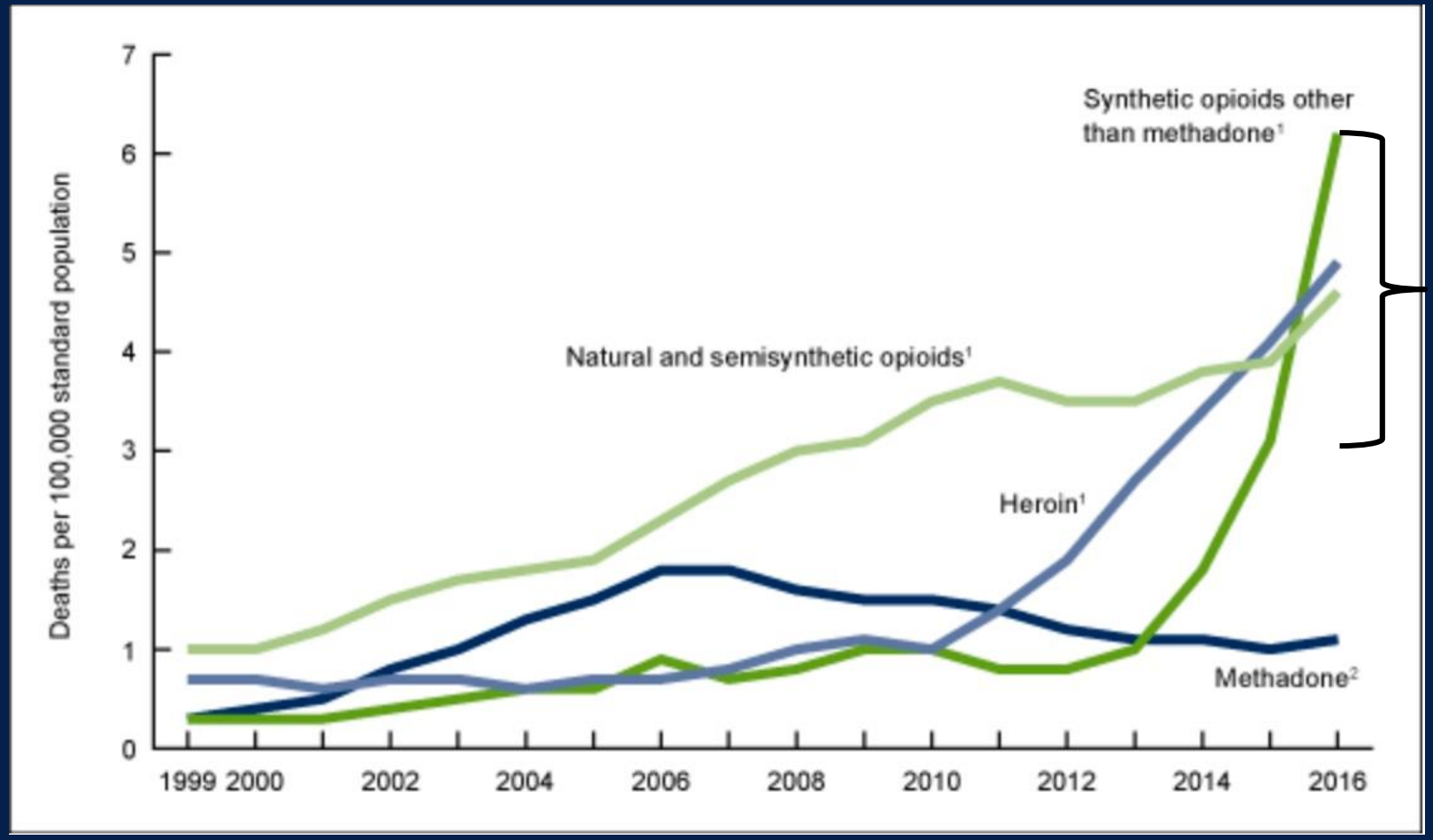
Center for Behavioral Health Statistics and Quality. (2015). Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUHSeries H-50). Retrieved from http:/www.samhsa.gov/data/

Drug Overdose Deaths Involving Opioids by Type of Opioid, United States, 1999–2016

2017 Estimate:

~ 50,000

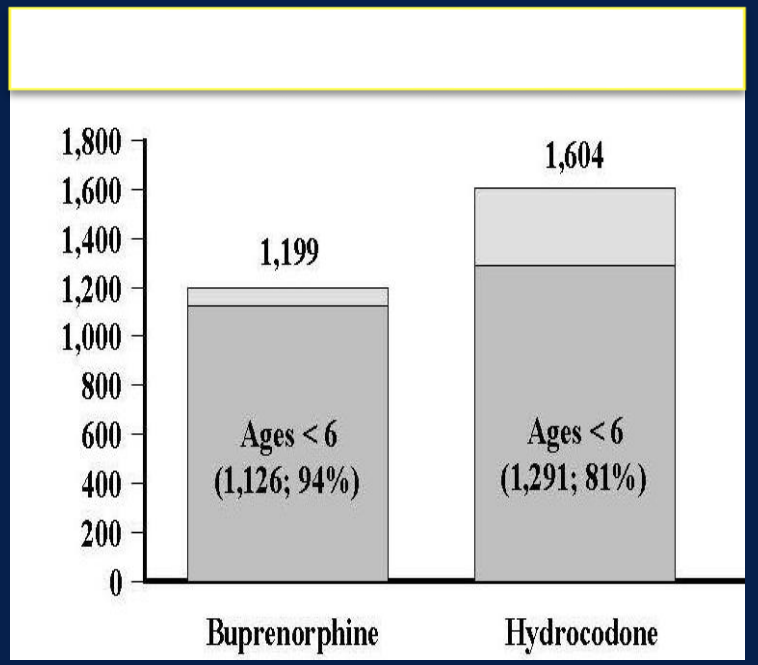
Hedegaard H, Warner M, Miniño AM. Drug overdose deaths in the United States, 1999–2016. NCHS Data Brief, no 294. Hyattsville, MD: National Center for Health Statistics. 2017.



[1]Significant increasing trend from 1999 to 2016 with different rates of change over time, $p < 0.05$.
[2]Significant increasing trend from 1999 to 2006, then decreasing trend 2006 to 2016, $p < 0.05$.

Buprenorphine: Limitations of Sublingual/ Buccal Transmucosal Formulations

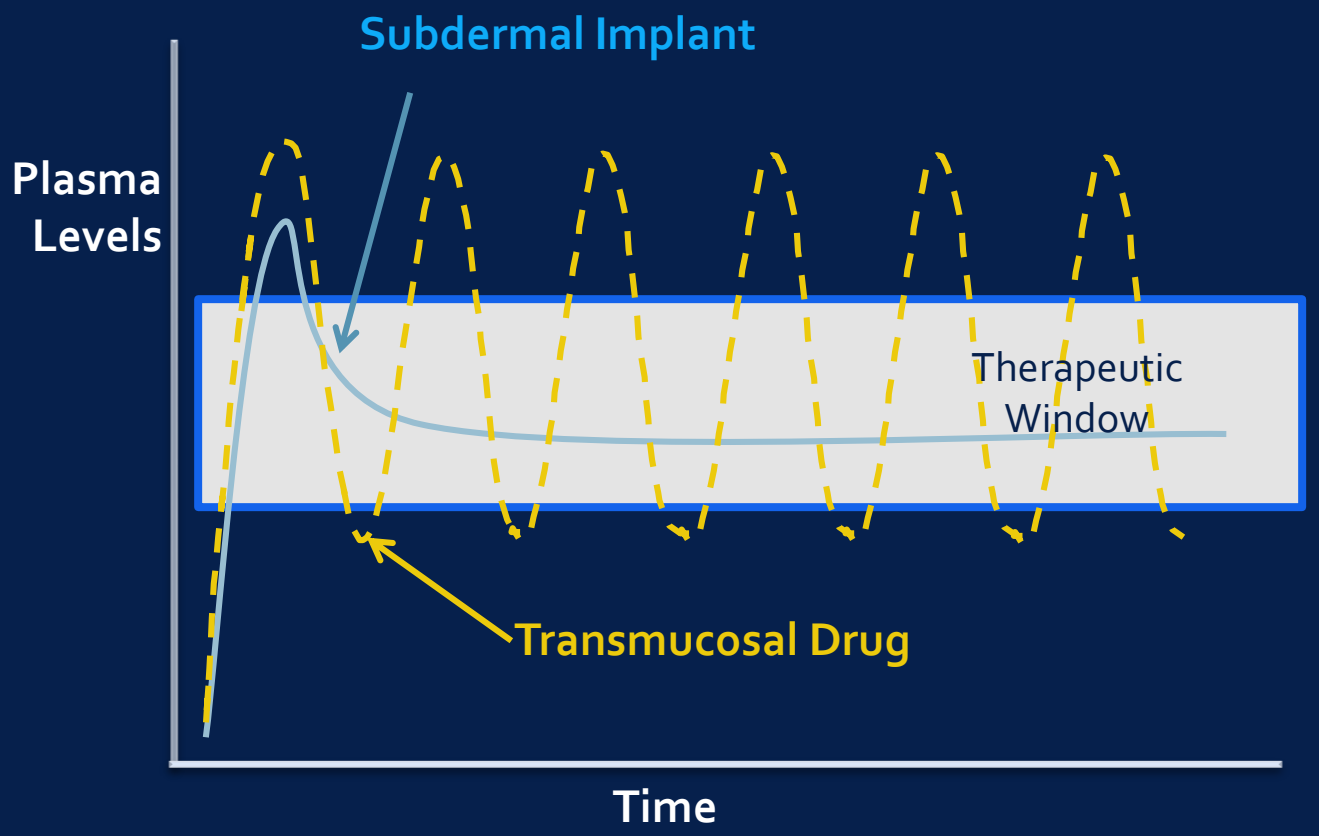
- Missed doses, low adherence to treatment
- Variable exposure with risk of withdrawal
- Abuse, theft, and intentional diversion
- Accidental exposure: especially increased child ED visits
  - ≈ 1,499 children <6 years evaluated in U.S. emergency departments for buprenorphine-product ingestions in 2010-11 (0 reported in 2004)
  - 9.5% of emergent hospitalizations for drug ingestion by children <6, greater proportion than any other medication



Emergency Department Visits and Hospitalizations for Buprenorphine Ingestion by Children — United States, 2010–2011. MMWR, Jan 25, 2013 / 62(03);56-56

Rationale for Sustained Release Implant Formulation

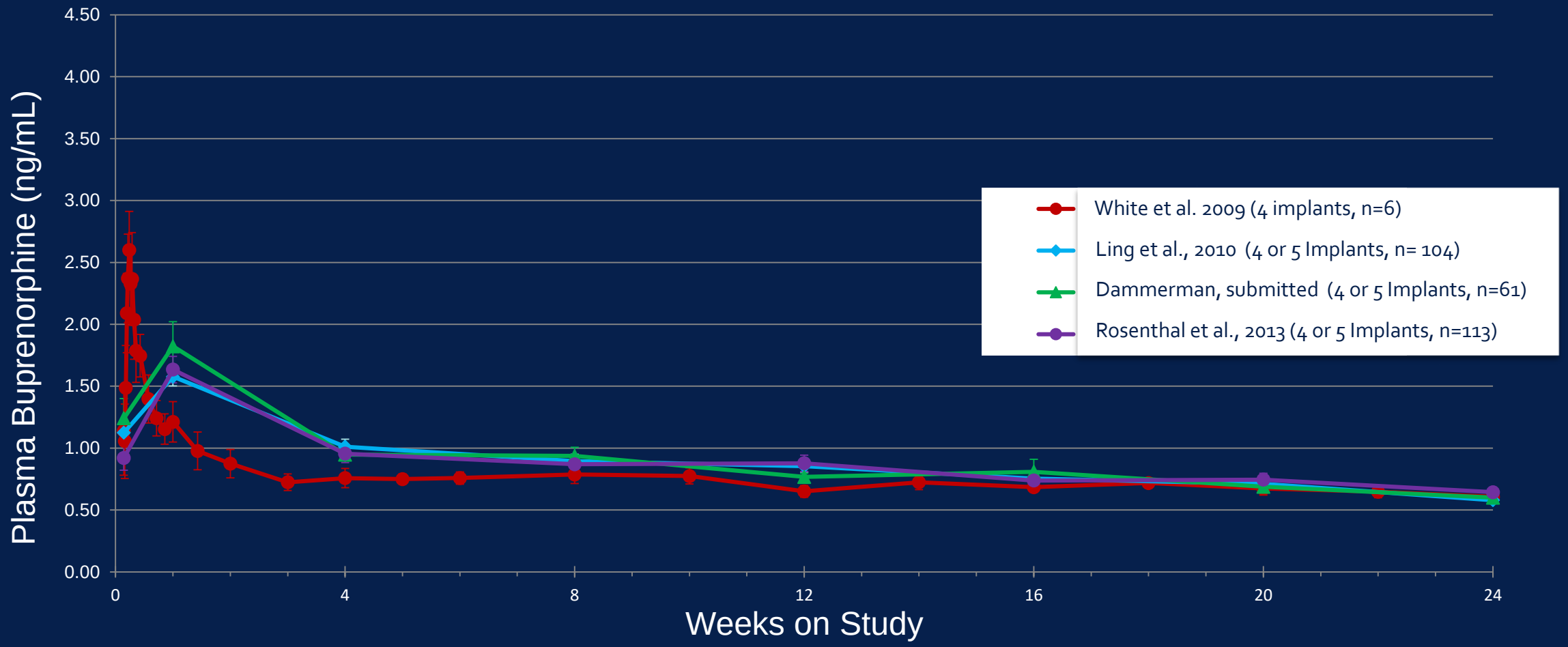
- Maintain efficacy, but minimize misuse/diversion
- Reduce dosing frequency
- Increase adherence
- Stabilize blood levels over 6 months



Probuphine Implant Description

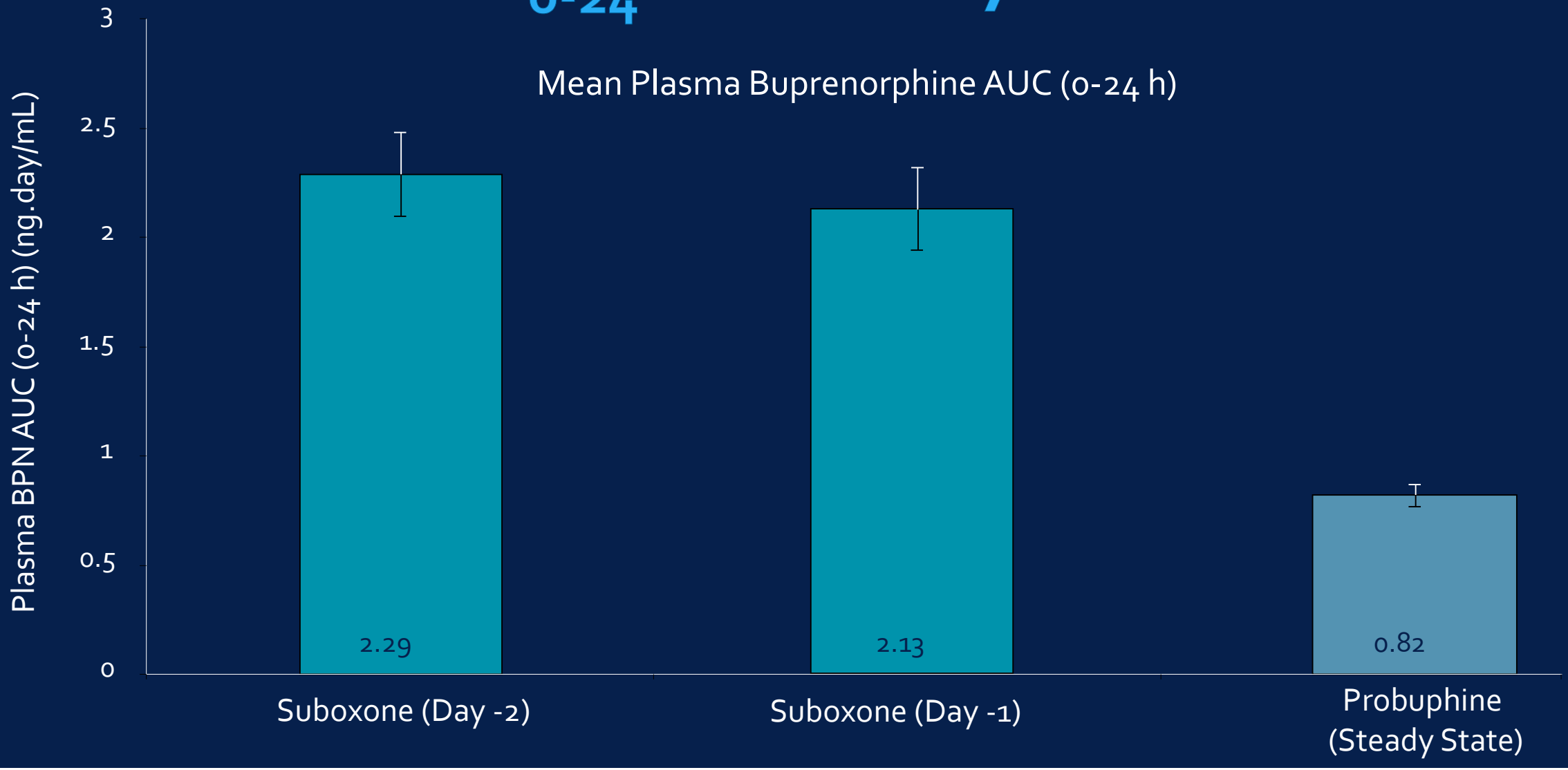
- Sustained-release polymeric matrix of buprenorphine in ethyl vinyl acetate (EVA)
  - Matchstick size: 26mm long
  - 80mg of buprenorphine
- Continuous buprenorphine levels for 6 months

Plasma Pharmacokinetics



White J,et al. *Drug and Alcohol Dependence* 2009;103:37-43; Ling W, et al. *JAMA.* 2010;304:1576-83; Dammerman R, et al. J Addict Behav Ther Rehabil 2017;6:1; Rosenthal RN, et al. *Addiction.* 2013;108:2141-9

AUC_{0-24} at Steady State

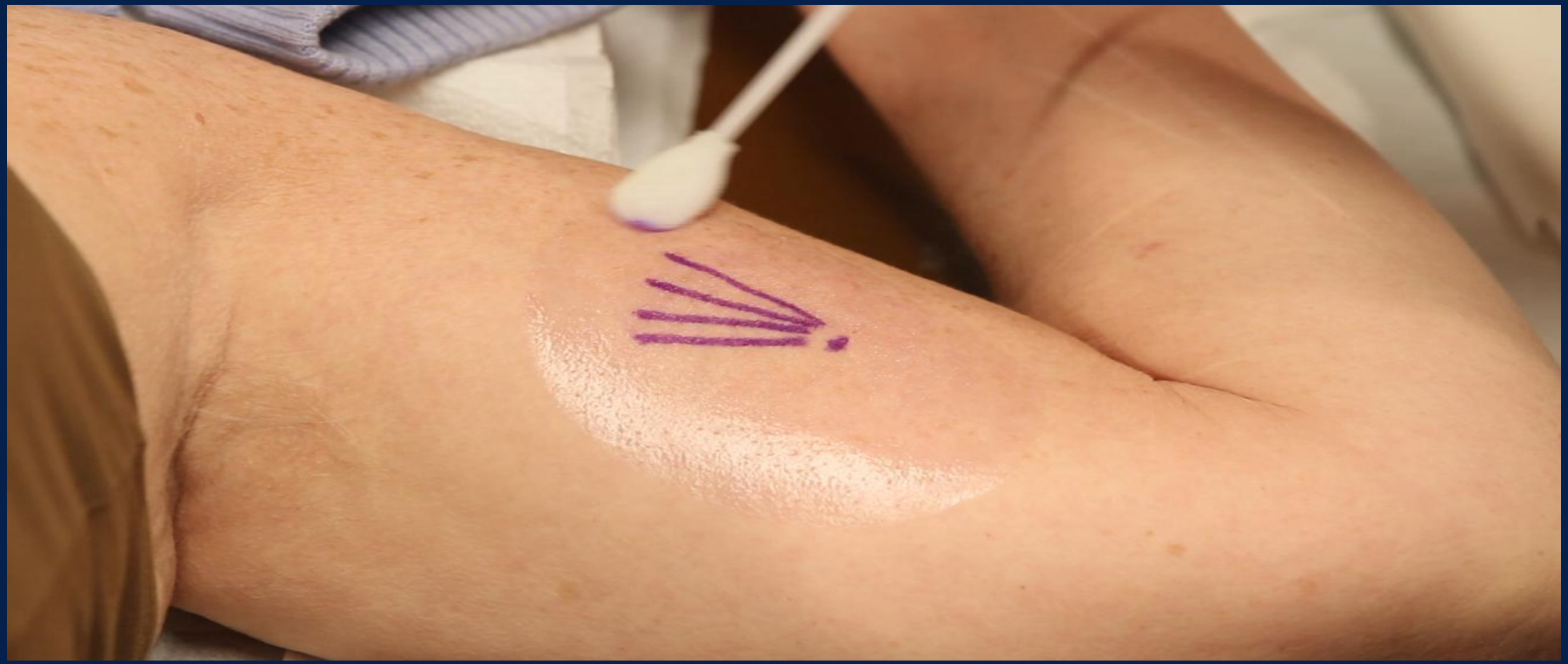


Implantation Procedure

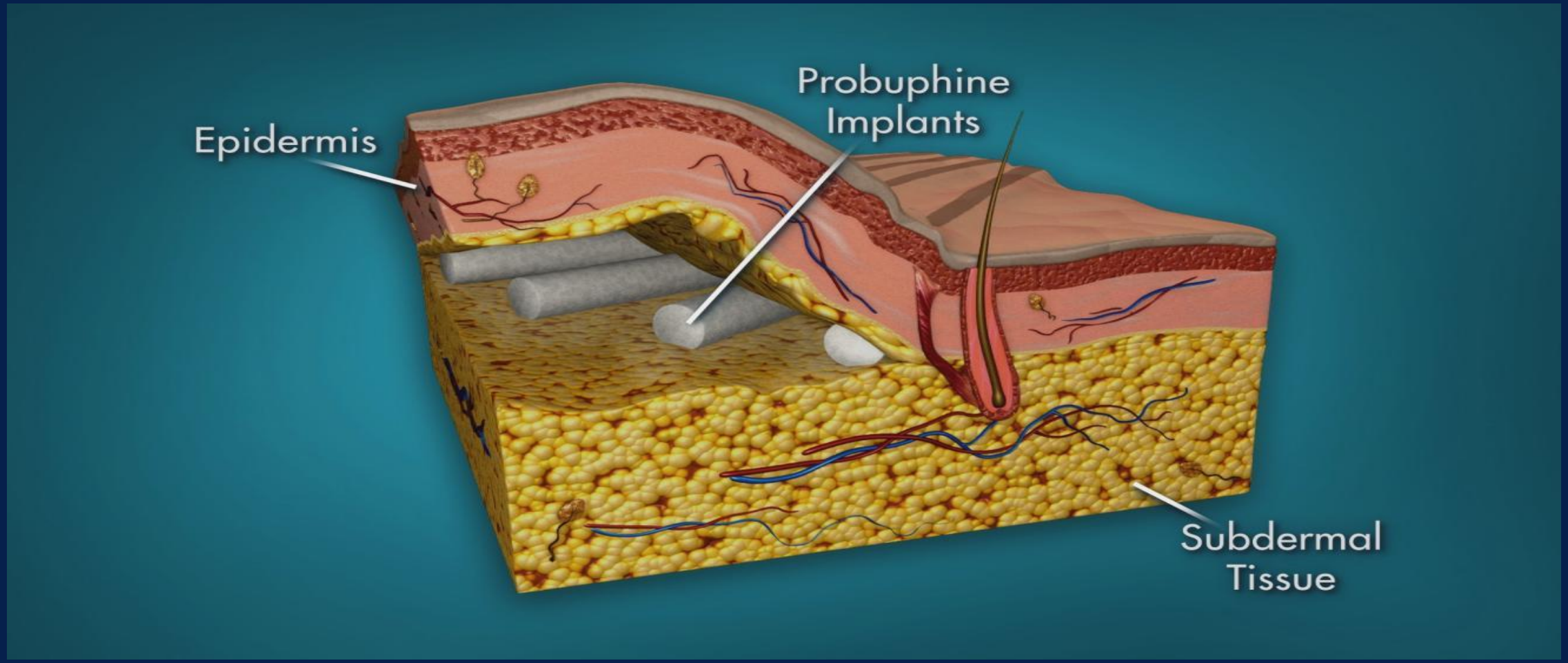
- Under local anesthesia implants are inserted subdermally into the inner side of the upper arm in a 10-15 minute in-office procedure
- Single 2.5- to 3-mm incision in the inner upper arm
- Implants inserted one at a time 2-3 mm below the skin using a custom-designed applicator
- 24 hour pressure dressing greatly reduces post-op adverse events
- Sustained release of buprenorphine for 6 months
- At the end of each 6-month period, implants are removed in a brief, in-office procedure using a custom-designed clamp

Insertion Applicator

Insertion Location

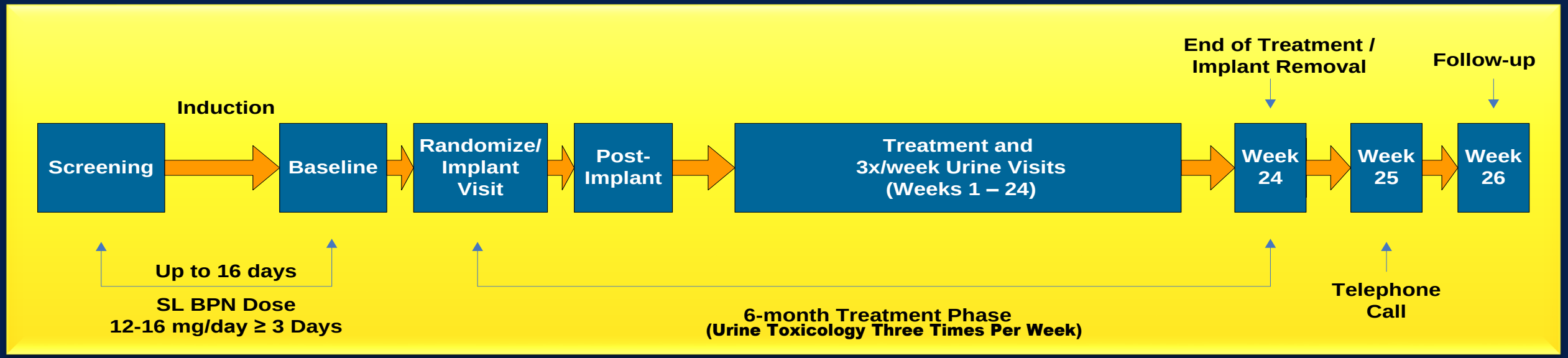


Placement of Implants



Removal Clamp

Two Phase 3 Controlled Studies



Study 1 (PRO-805):

- n = 163; 18 sites
- Two-arm: Double-blind randomized, placebo-controlled

Study 2 (PRO-806):

- n = 287; 20 sites
- Three-arm: Double-blind randomized, placebo-controlled and open-label active (Suboxone)

Ling W, et al. *JAMA.* 2010;304:1576-83.

Rosenthal RN, et al. *Addiction.* 2013;108:2141-9.

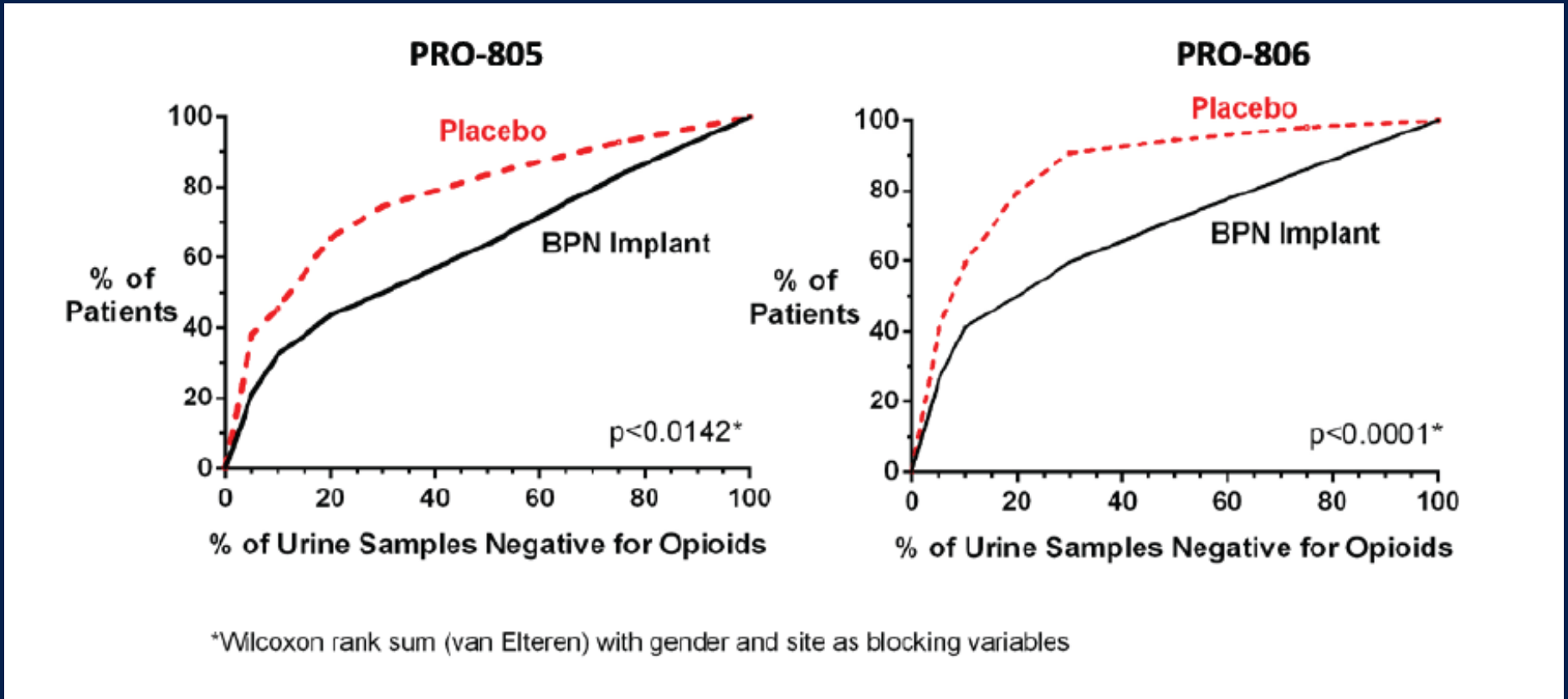
24-week Placebo Controlled Trials of BUP Implants

Summary of Significant Findings of Implant Against Placebo (2 trials):

- Higher mean % urines negative for illicit opioids, weeks 1-24
- Higher retention rate: 64-66 % vs. 26-31 %
- Lower incidence of clinician-rated and patient-rated opioid withdrawal symptoms
- Lower patient-rated opioid craving
- Greater change on the clinician global ratings of improvement
- Decreased Supplemental Buprenorphine Use

Ling W, et al. *JAMA.* 2010;304:1576-83. Rosenthal RN, et al. *Addiction.* 2013;108:2141-9.

Percentage of Urine Samples Opioid Negative Weeks 1–24 in 2 Placebo Controlled Trials



Includes imputation for Patient Illicit Opioid Self-Report

Ling W, et al. *JAMA.* 2010;304:1576-83.

Rosenthal RN, et al. *Addiction.* 2013;108:2141-9.

Extension Studies After 2 RCTs

- Two six-month, open-label, multicenter extension studies of BUP implants
  - Participants who had completed 24 weeks of treatment in the phase 3 trials received four 80mg implants
  - Supplemental 2mg BUP SL or fifth implant for patients meeting criteria for opioid craving or withdrawal, at investigator discretion
- Implant site-related AEs: 103/329 (31.3%) in Study 1, 19/57 (11.0%) in Study 2; Modification to implantation procedure after Study 1
  - Switch from blunt end to bevel-tipped applicator
  - Switch to removal with incision at implant mid point using 2.5mm vasectomy clamp

Dammerman R, et al. J Addict Behav Ther Rehabil 2017;6:1

Summary of Implant Site Adverse Events Frequency (≥ 10% in Any Treatment Group)

	PRO-805		PRO-807	PRO-806	
	Probuphine (n=108)	Placebo (n=55)	Probuphine (n=62)	Probuphine (n=114)	Placebo (n=54)
Erythema	25.0%	21.8%	25.8%	3.5%	0%
Edema	13.0%	9.1%	12.9%	1.8%	0%
Itching	25.0%	14.5%	19.4%	4.4%	3.7%
Pain	22.2%	10.9%	19.4%	8.8%	9.3%
Bleeding	12.0%	12.7%	16.1%	1.8%	3.7%
Bruising	5.6%	14.5%	9.7%	7.9%	11.1%
Scar	9.3%	12.7%	1.6%	0%	0%

Is Anyone Really Surprised?

- We already know that the Buprenorphine has efficacy for OUD compared to Placebo
- Only the delivery system was different from sublingual or buccal administration
- If the delivery system works, then it's a "no-brainer"
- So…

Open Label SL Buprenorphine

- In second trial, the implants were non-inferior to open label group continued at 12-16 mg SL Bup
- However:
  - increased subjective and objective withdrawal symptoms
  - Increased use of 2mg SL Bup rescue doses
- Unclear how transition to implants from SL Bup would affect clinical stability in patients who are already clinically stable

Rosenthal RN, et al. *Addiction.* 2013;108:2141-9.

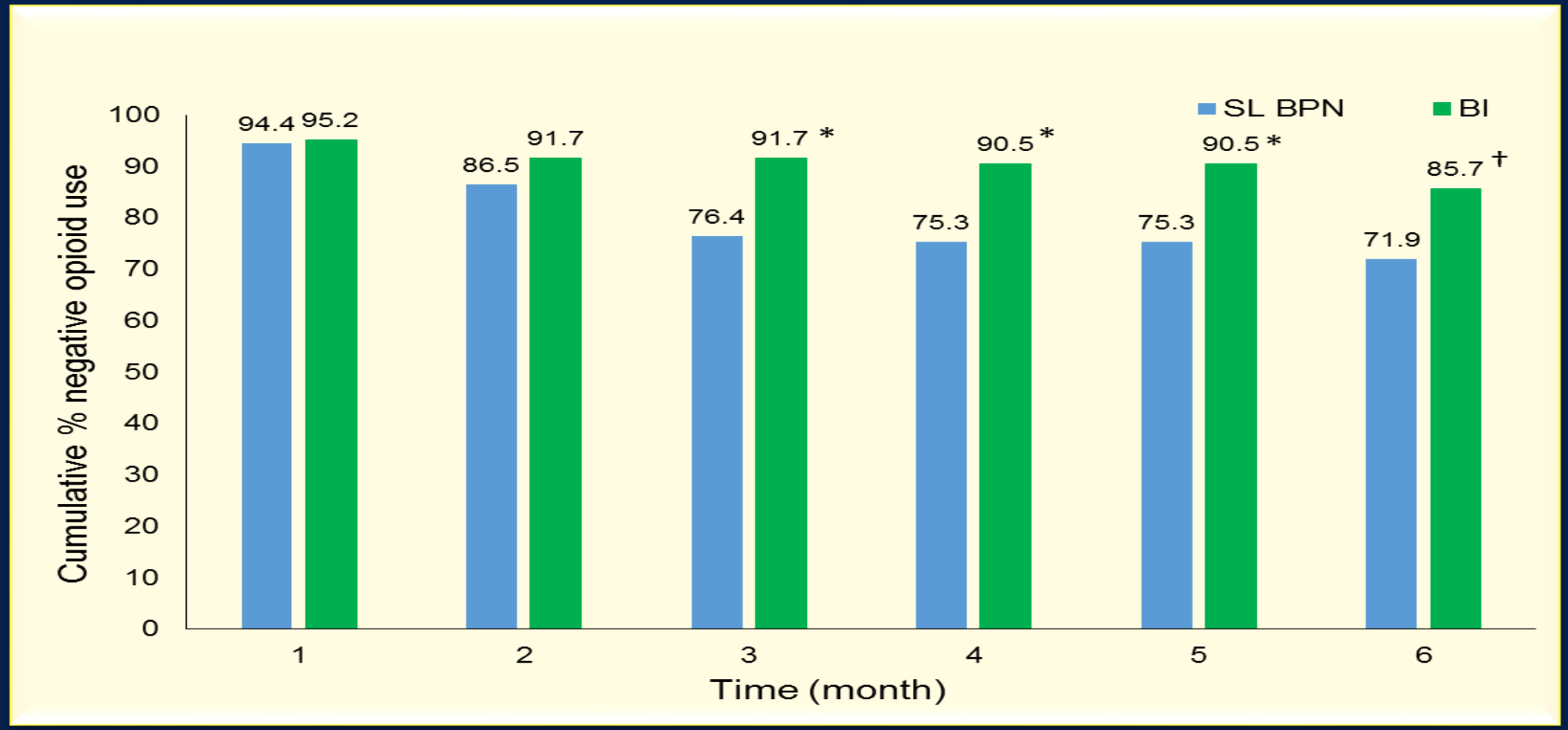
Double Blind Double Dummy Study of Buprenorphine Implants and SL Buprenorphine

Study:

- Head-to-head safety/efficacy trial of Bup implants and daily SL Bup on long-term remission in (N=177) patients stabilized on ≤8mg of SL Bup
- Responder rate defined as at least four of six study months with no evidence of illicit opioid use by either urine test or self-report

Rosenthal et al., *JAMA*. 2016;316(3):282-290. doi:10.1001/jama.2016.9382

Evidence of illicit opioid use by urine and self-report as a function of cumulative percentage of negative urine results



Rosenthal et al., *JAMA*. 2016;316(3):282-290. doi:10.1001/jama.2016.9382

Double Blind Double Dummy Study of Buprenorphine Implants and SL Buprenorphine

Summary:

- Transitioning to implants was not clinically destabilizing (e.g., increased craving or withdrawal symptoms).
- 96.4 vs 87.6% had no opioid-positive urine tests for at least four of the six study months (*P*< .001 non-inferiority; *P*=.03 superiority)
- Higher 6-month abstinence rate in the implant group 85.7% vs.71.9% in the SL Bup group (P< .03; NNT=7.25)

Rosenthal et al., *JAMA*. 2016;316(3):282-290. doi:10.1001/jama.2016.9382

Double Blind Double Dummy Study of Buprenorphine Implants and SL Buprenorphine

Implications:

- Bup implants effective for maintenance of abstinence in opioid-dependent adults clinically stable on ≤ 8mg/d SL Bup.
- Boost maintenance of abstinence in appropriate patients while reducing the risk of diversion and adverse events.
- Patients doing well at moderate SL doses in OTPs that could transition to office-based care.
- Proposed new targets: criminal justice, other hard-to-reach populations.[2]
- Issues with generalizability: most participants were white, domiciled, employed, ≥ HS education , and primarily prescription OUD.
- However, this is now the primary demographic for OUD in the US.

[1]Rosenthal et al., JAMA. 2016;316(3):282-290. [2]Compton & Volkow JAMA. 2016;316(3):277-79

PRO-814 Demographic Characteristics

Variable	Value	Probuphine® n=87	SL BPN n=89	Total n=176
Sex	Male	59.8%	58.4%	59.1%
	Female	40.2%	41.6%	40.9%
Age (yrs)	Mean (SD)	38 (11.2)	39 (10.8)	39 (11.0)
Race	White	94.3%	95.5%	94.9%
	Black	3.4%	2.2%	2.8%
	Asian	1.1%	0.0%	0.6%
	Other	1.1%	2.2%	1.7%
Ethnicity	Hispanic or Latino	3.4%	3.4%	3.4%
	Not Hispanic or Latino	96.6%	96.6%	96.6%

PRO-814 Demographics (Cont.)

Variable	Value	Probuphine® n=87	SL BPN n=89	Total n=176
Time Since First Diagnosis (subject-reported, yrs)	Mean (SD)	6.2 (5.93)	6.2 (6.95)	6.2 (6.45)
Primary Opioid of Abuse	Heroin	17.2%	24.7%	21.0%
	Rx Opioid Pain Reliever	75.9%	73.0%	74.4%
	Other	5.7%	2.2%	4.0%
Daily Dose of Buprenorphine at Time of Randomization	2 mg	6.9%	3.4%	5.1%
	4 mg	13.8%	16.9%	15.3%
	6 mg	9.2%	4.5%	6.8%
	8 mg	70.1%	75.3%	72.7%

Table 3: Adverse Events, Implant-site related

System Organ Class	Preferred Term	Sublingual BPN (n=89)	Probuphine (n=87)	Total
AT LEAST ONE AE PER SYSTEM ORGAN CLASS	**TOTAL**	**12 (13.5%)**	**20 (23.0%)**	**32 (18.2%)**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**TOTAL**	**7 (7.9%)**	**12 (13.8%)**	**19 (10.8%)**
	IMPLANT SITE PAIN	4 (4.5%)	4 (4.6%)	8 (4.5%)
	IMPLANT SITE PRURITUS	1 (1.1%)	4 (4.6%)	5 (2.8%)
	IMPLANT SITE BRUISING	1 (1.1%)	1 (1.1%)	2 (1.1%)
	IMPLANT SITE ERYTHEMA	1 (1.1%)	1 (1.1%)	2 (1.1%)
	IMPLANT SITE HAEMORRHAGE	0 (0.0%)	1 (1.1%)	1 (0.6%)
	OEDEMA PERIPHERAL	0 (0.0%)	1 (1.1%)	1 (0.6%)
	DEVICE EXPULSION	1 (1.1%)	0 (0.0%)	1 (0.6%)
	IMPLANT SITE DISCOLOURATION	1 (1.1%)	0 (0.0%)	1 (0.6%)
INFECTIONS AND INFESTATIONS	**TOTAL**	**3 (3.4%)**	**3 (3.4%)**	**6 (3.4%)**
	CELLULITIS	1 (1.1%)	1 (1.1%)	2 (1.1%)
	INCISION SITE INFECTION	1 (1.1%)	0 (0.0%)	1 (0.6%)
	PURULENT DISCHARGE	0 (0.0%)	1 (1.1%)	1 (0.6%)
	WOUND INFECTION	1 (1.1%)	1 (1.1%)	2 (1.1%)

Table 3: Adverse Events, Implant-site related

System Organ Class	Preferred Term	Sublingual Buprenorphine (n=89)	Probuphine (n=87)	Total
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**TOTAL**	**3 (3.4%)**	**2 (2.3%)**	**5 (2.8%)**
	DERMATITIS CONTACT	2 (2.2%)	1 (1.1%)	3 (1.7%)
	RASH	0 (0.0%)	1 (1.1%)	1 (0.6%)
	SKIN IRRITATION	1 (1.1%)	0 (0.0%)	1 (0.6%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**TOTAL**	**1 (1.1%)**	**2 (2.3%)**	**3 (1.7%)**
	CONTUSION	1 (1.1%)	0 (0.0%)	1 (0.6%)
	INCISION SITE COMPLICATION	0 (0.0%)	1 (1.1%)	1 (0.6%)
	POSTOPERATIVE WOUND COMPLICATION	0 (0.0%)	1 (1.1%)	1 (0.6%)
NERVOUS SYSTEM DISORDERS	**TOTAL**	**1 (1.1%)**	**1 (1.1%)**	**2 (1.1%)**
	PARAESTHESIA	0 (0.0%)	1 (1.1%)	1 (0.6%)
	PERIPHERAL SENSORY NEUROPATHY	1 (1.1%)	0 (0.0%)	1 (0.6%)

Risk Evaluation and Mitigation Strategy

- Required REMS for Providers: probuphinerems.com
- DEA Waiver to prescribe or dispense BUP Implant.
- Must have performed at least one qualifying surgical procedure in the last 3 months under local anesthesia using aseptic technique, including, at a minimum, making skin incisions, or placing sutures.
- Prior to performing insertions or prescribing BUP implants Providers must successfully complete a live training program on the insertion and removal procedures and become certified in the PROBUPHINE REMS program.