RUSH UNIVERSITY MEDICAL CENTER

Opioid Stewardship and Managing the Opioid Crisis: A Health-Care Perspective

February 13, 2018

Frank Vocci, PhD

New Therapies on the Horizon

The planners, editors, faculty and reviewers of this activity have no relevant financial relationships to disclose. This presentation was created without any commercial support.

Disclosures

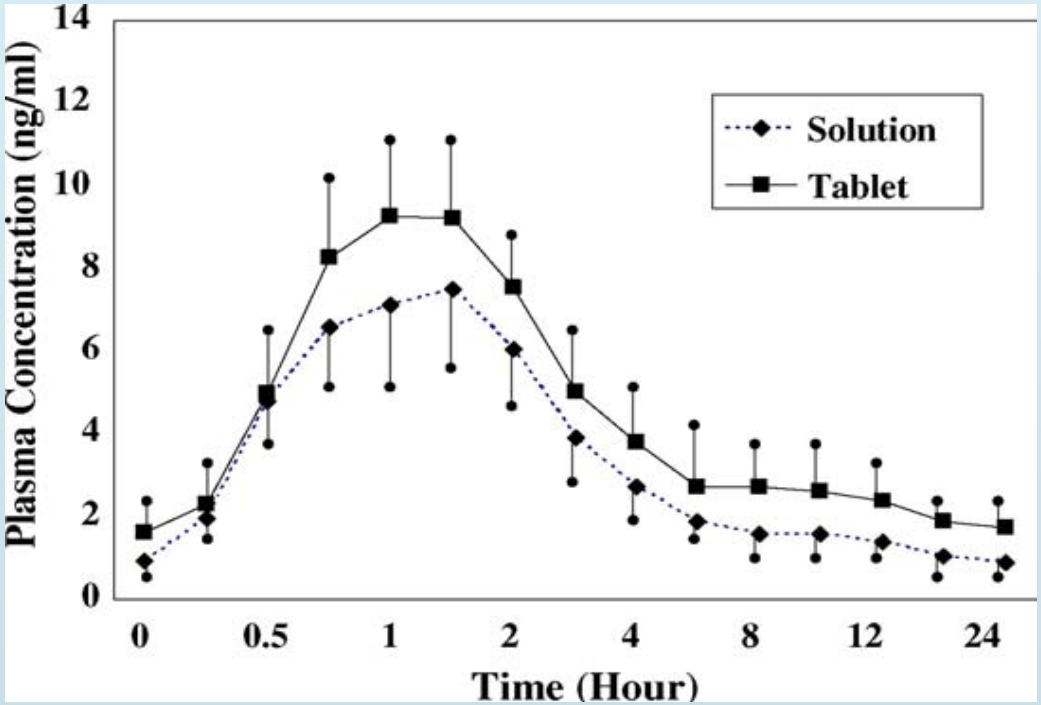
- I consult for Indivior, Braeburn Pharma, and generic buprenorphine manufacturers. I have been an investigator for Braeburn Pharma. All consulting fees for these efforts go to my employer. I also consult for IntraTab Labs, Inc. I am a minority owner in IntraTab Labs.

Organization of the Presentation

- Development of new buprenorphine dosage forms
- Buprenorphine pharmacodynamics and pharmacokinetics
- Probuphine (Implantable buprenorphine)
- SUBLOCADE™ (buprenorphine extended-release)
- Cam 2038 (Injectable buprenorphine)
- New naloxone formulations
- Abuse-deterrent opioid analgesic formulations

FDA Requirements for New Dosage Forms of Already Approved Drugs

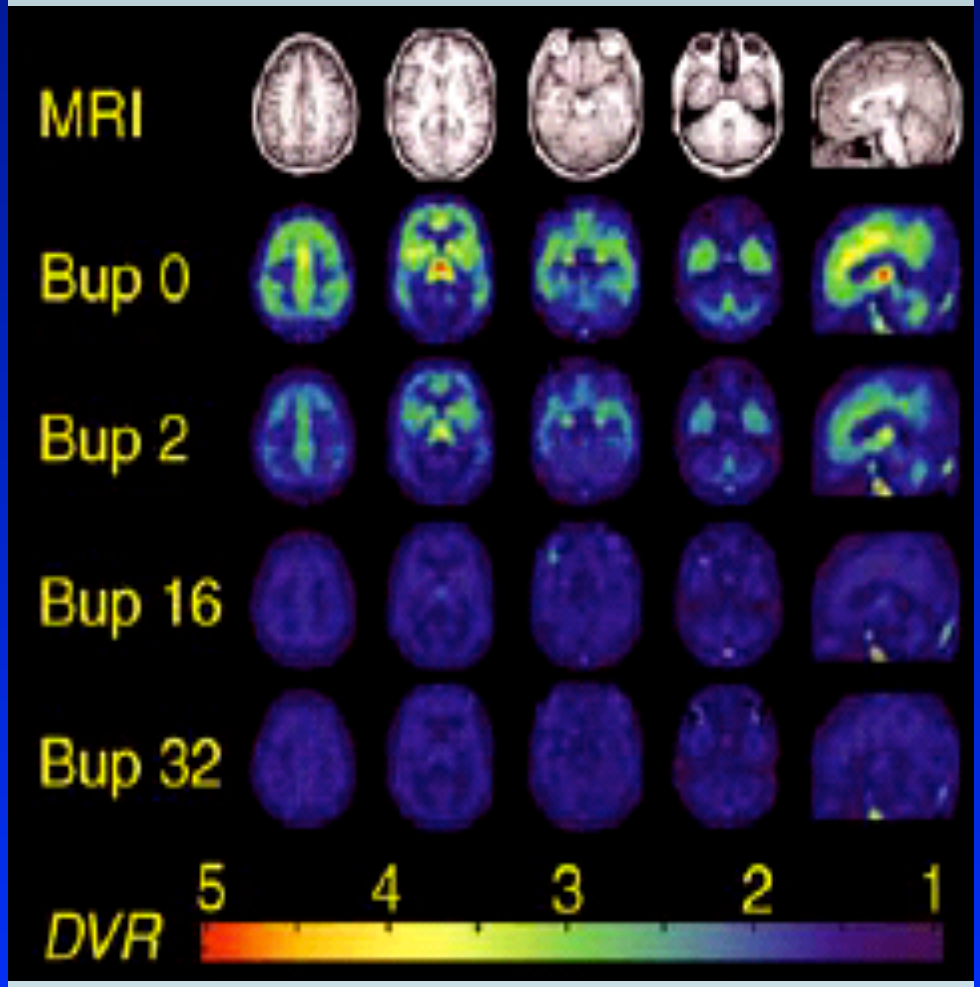
- FDA has a drug development pathway called 505 (b) 2 for new dosage forms of already approved drugs
- The streamlined pathway requires data on the chemistry and manufacturing controls data on the dosage form,
- minimal pre-clinical toxicology data,
- pharmacokinetics of the new dosage form,
- some other clinical pharmacology,
- and one or two efficacy studies

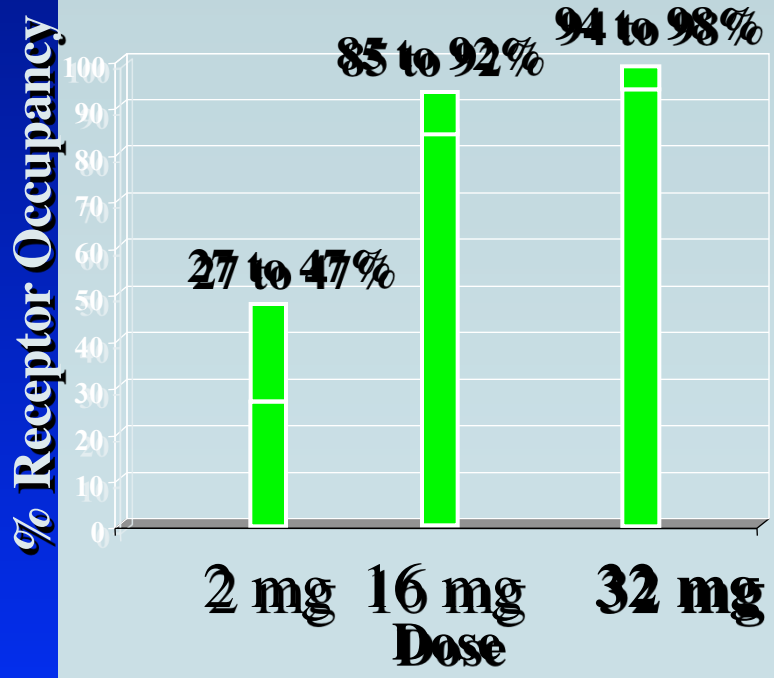


Mean and standard deviation of plasma buprenorphine concentration (ng/ml) for 8mg solution buprenorphine and 16 mg tablet buprenorphine on Day 10 (Bioavailability for the tablet is 71% of the solution formulation).

(Compton et al, Drug and Alcohol Dependence, 82, 25-31, 2006),

Effects of Buprenorphine Maintenance Dose on μμ-Opioid Receptor Availability





Source: Greenwald, MK et al, Neuropsychopharmacology 28, 2000-2009, 2003.

Buprenorphine Plasma PK –PD Relationships

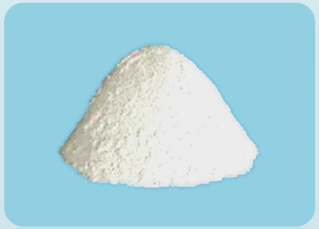
- A plasma level of 0.7 ng/ml is sufficient to block withdrawal symptoms (Kuhlman et al, 1998)
- An acute 16 mg sublingual dose is associated with a plasma level of 3.9 ng/ml (Greenwald et al, 2007)
- This is an opioid blocking concentration against hydromorphone 24 mg, im (Greenwald et al, 2007)
- A buprenorphine plasma concentration ≥ 3 ng/ml is considered sufficient to block opioid agonists and is associated with μ- receptor availability ≤ 20 % (Greenwald et al., 2014)

Probuphine

- Probuphine is an implantable formulation of buprenorphine (80 mg per implant) developed for the maintenance treatment of opioid dependence, following brief induction with sublingual buprenorphine
- Inserted subdermally in the inner side of upper arm
- Provides sustained release of buprenorphine for up to 6 months
- Dosage is 4 implants
- Must be inserted and removed only by clinicians who have completed the implant procedure training program

Solid Matrix Formulation Facilitates Long-Term Delivery

EVA polymer



Inert component of several approved products

+

Buprenorphine

Approved for treatment of opioid addiction, and acute and chronic pain

Blended & Extruded

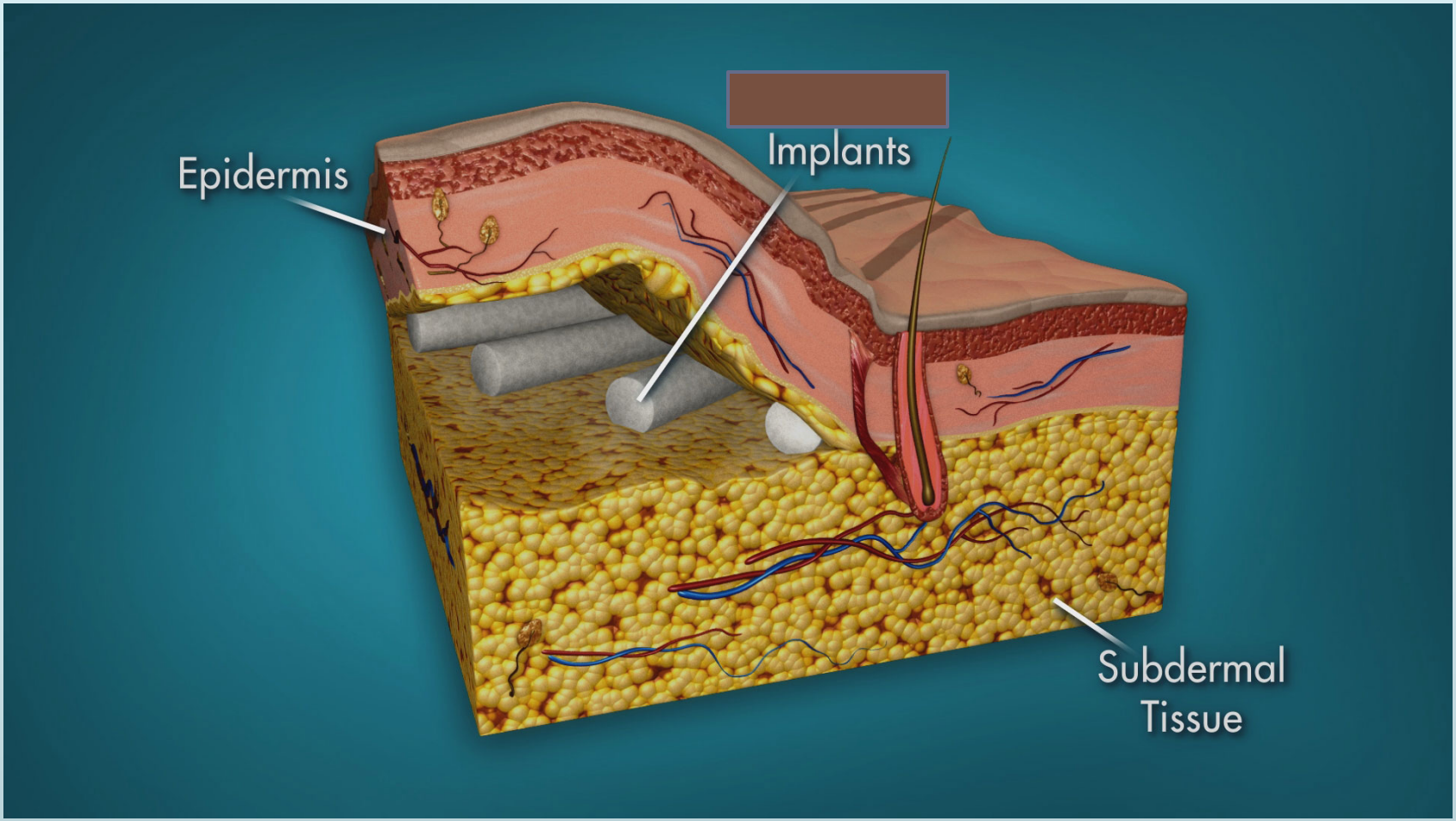
26 mm long, 2.5 mm diameter

Probuphine provides sustained release of buprenorphine for up to 6 months

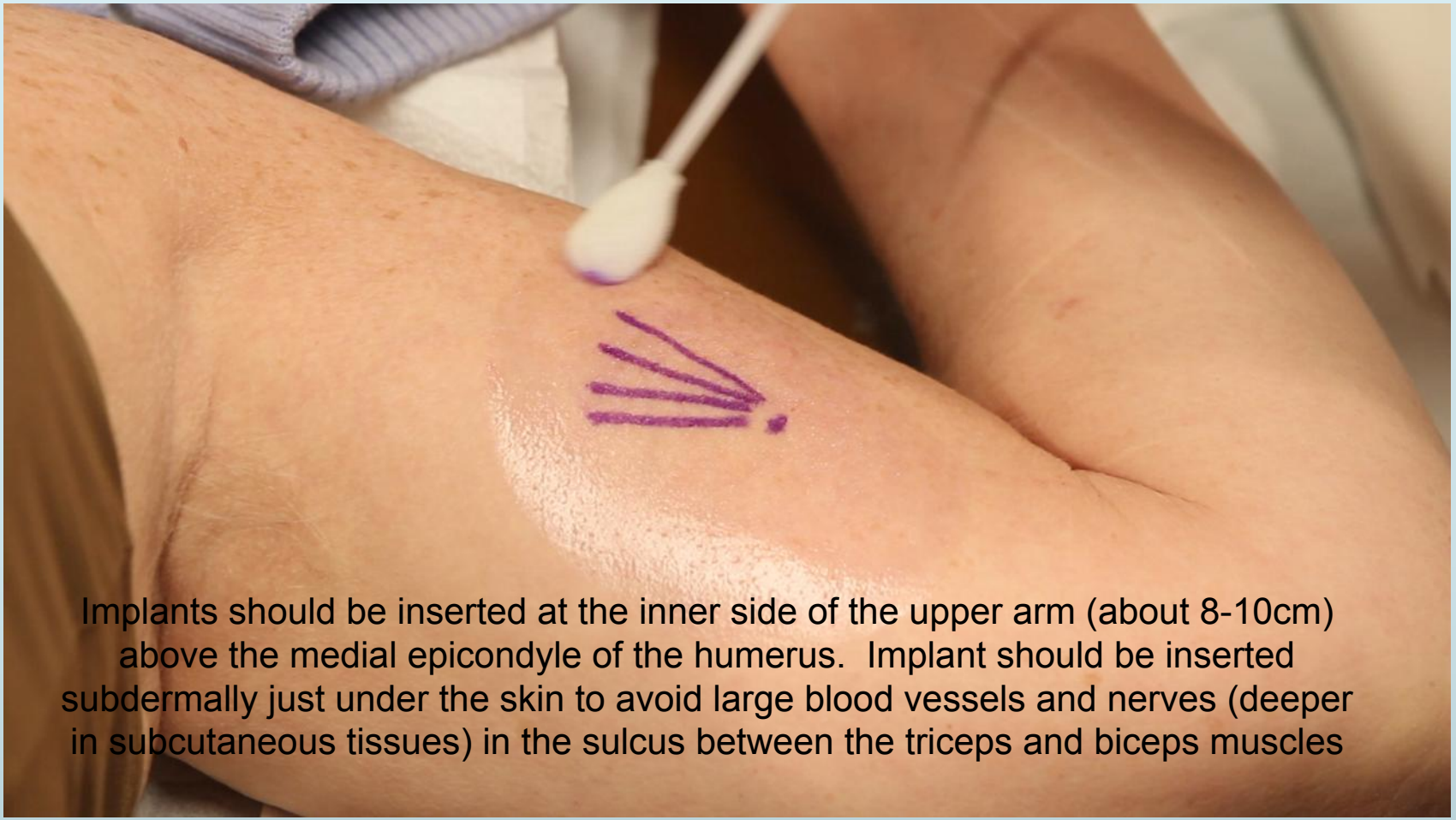
Probuphine is not radio-opaque

Insertion Applicator

Placement of Implants

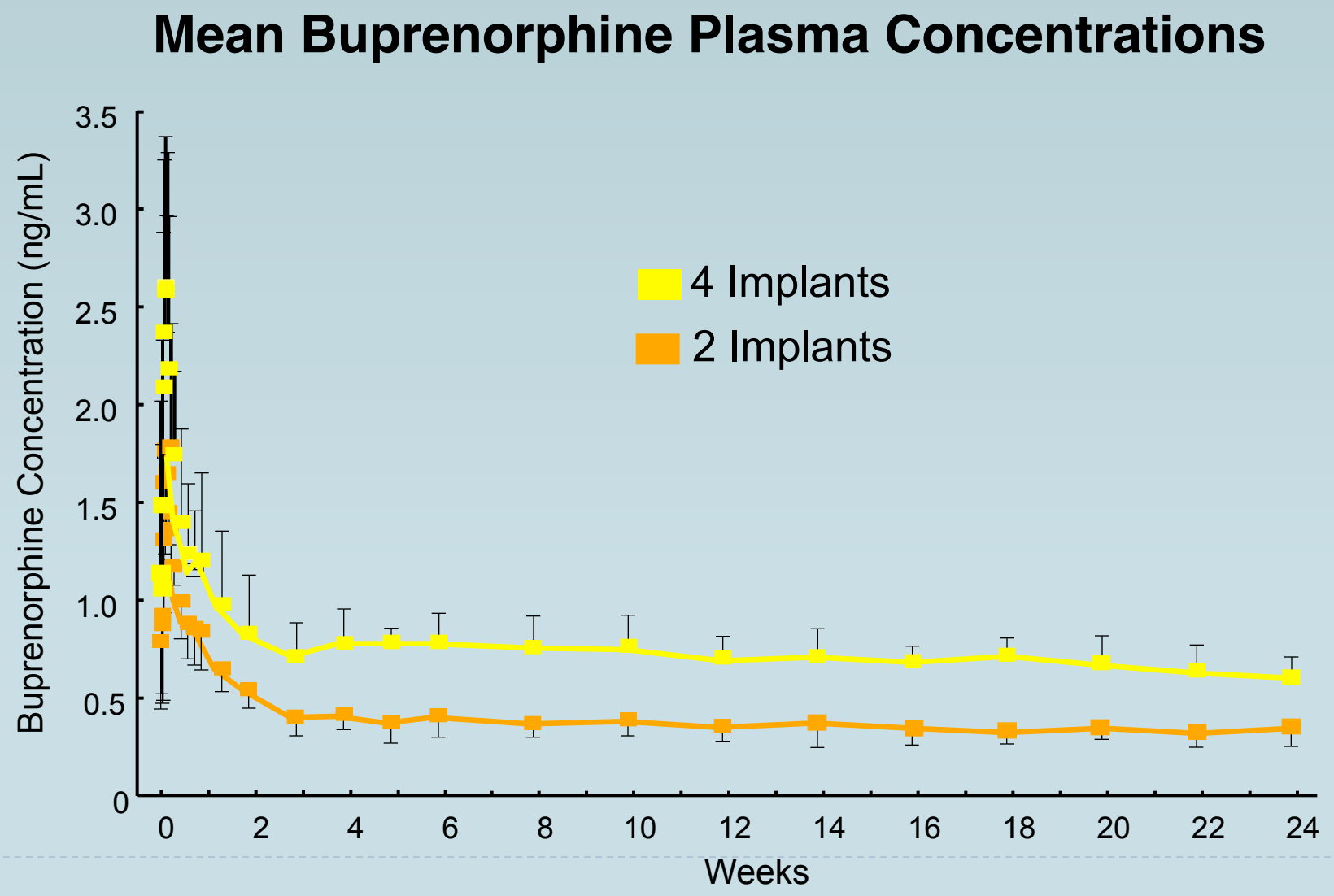


Insertion Location



Implants should be inserted at the inner side of the upper arm (about 8-10cm) above the medial epicondyle of the humerus. Implant should be inserted subdermally just under the skin to avoid large blood vessels and nerves (deeper in subcutaneous tissues) in the sulcus between the triceps and biceps muscles

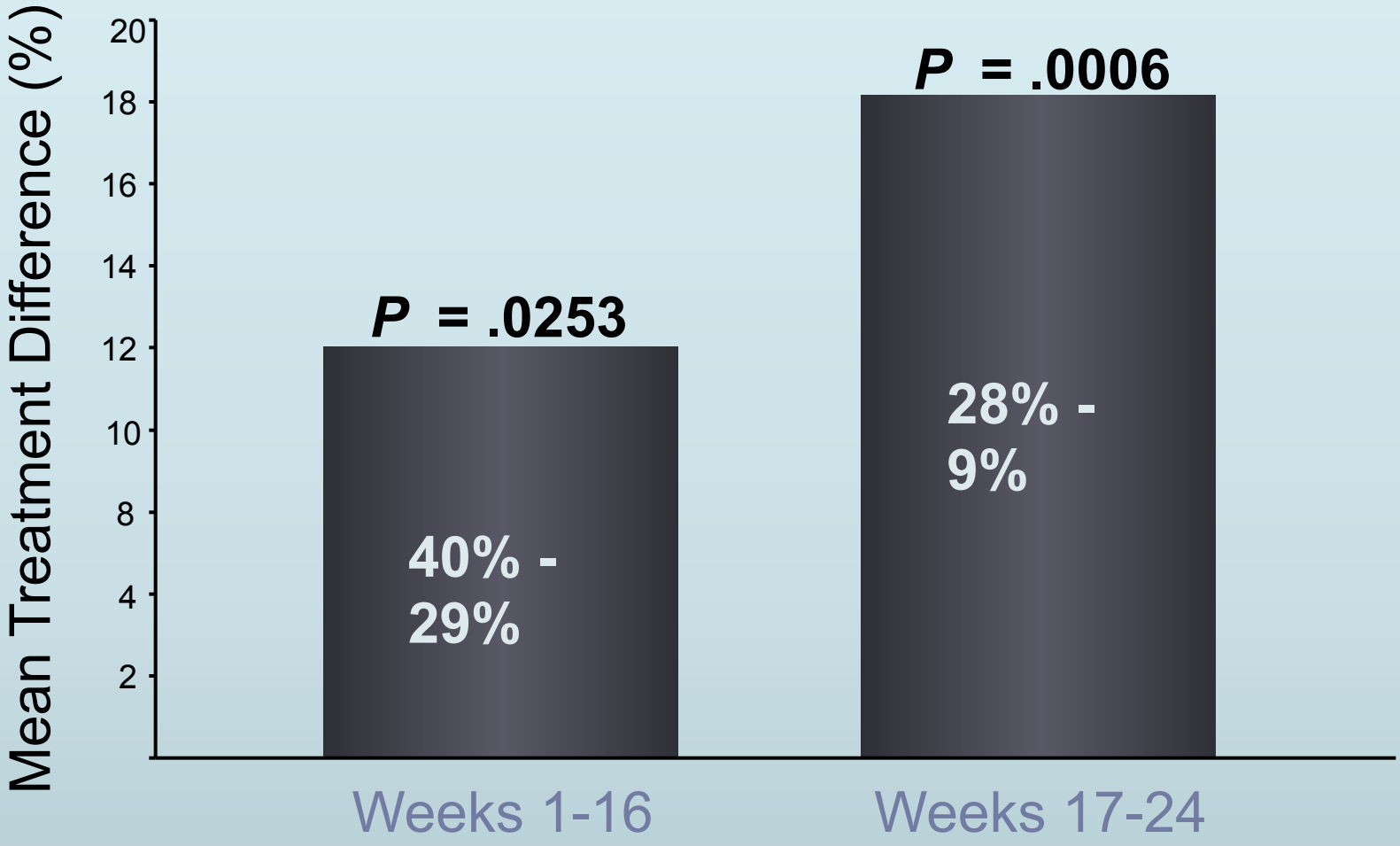
Probuphine Delivered Continuous, Low-Level Buprenorphine Plasma Concentrations for 6 months



Probuphine Initial Clinical Trials

- Compared opioid dependent participants randomized to Probuphine implants versus placebo implants under blinded conditions (Ling et al, 2010; Rosenthal et al, 2013)
- Supplemental sublingual buprenorphine was allowed
- Second study added an open-label buprenorphine arm
- Study population: Newly inducted participants received induction to 12-16 mg of sublingual buprenorphine over 2-3 days.
- Implantation occurred within the next 7-10 days
- Participants were followed for 24 weeks
- Urine samples were collected three times per week
- A cumulative distribution function of negative urines was the primary outcome measure

Study 805: Difference in Mean % Negative Urines

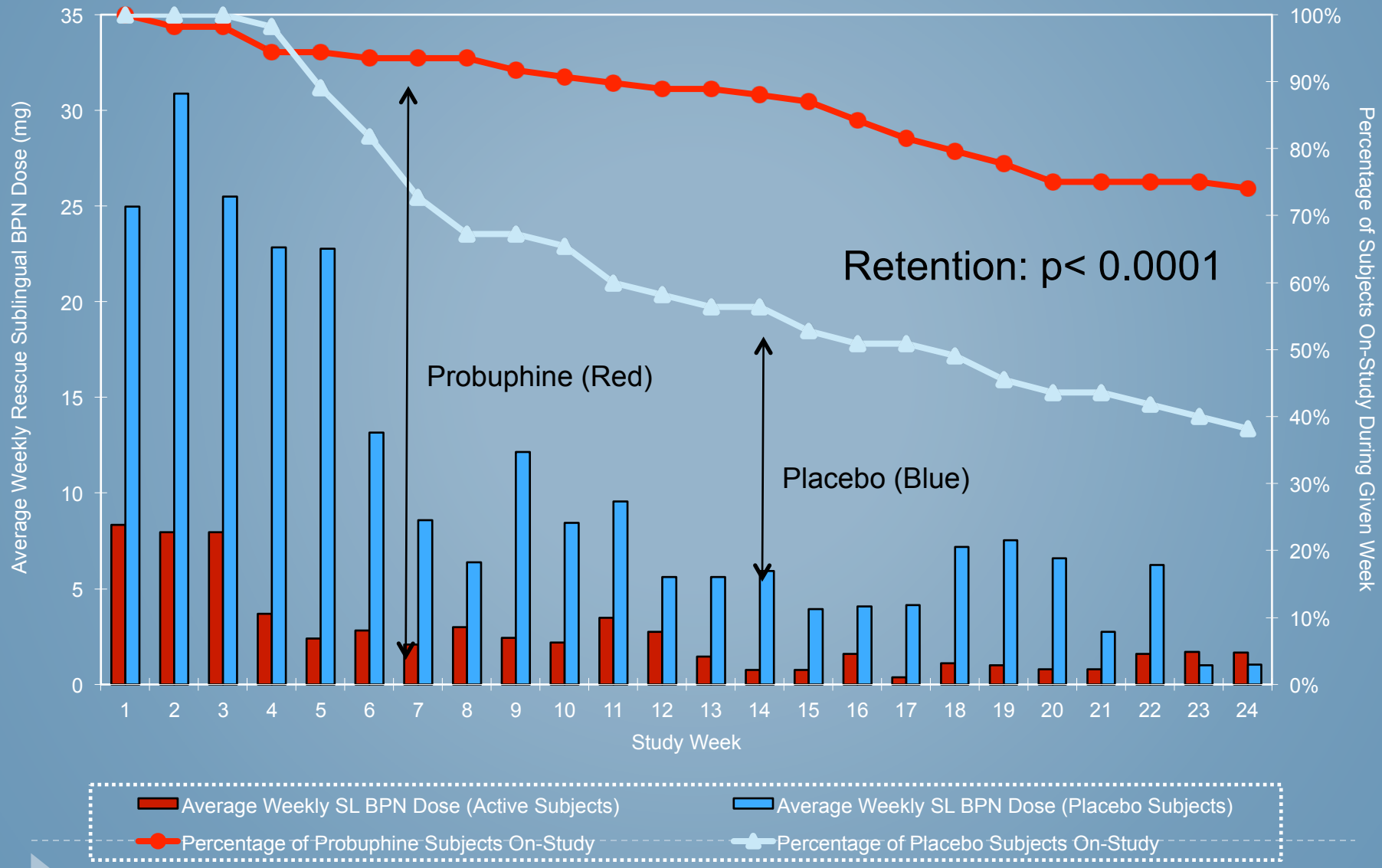


Study 805: Other Secondary Efficacy Results

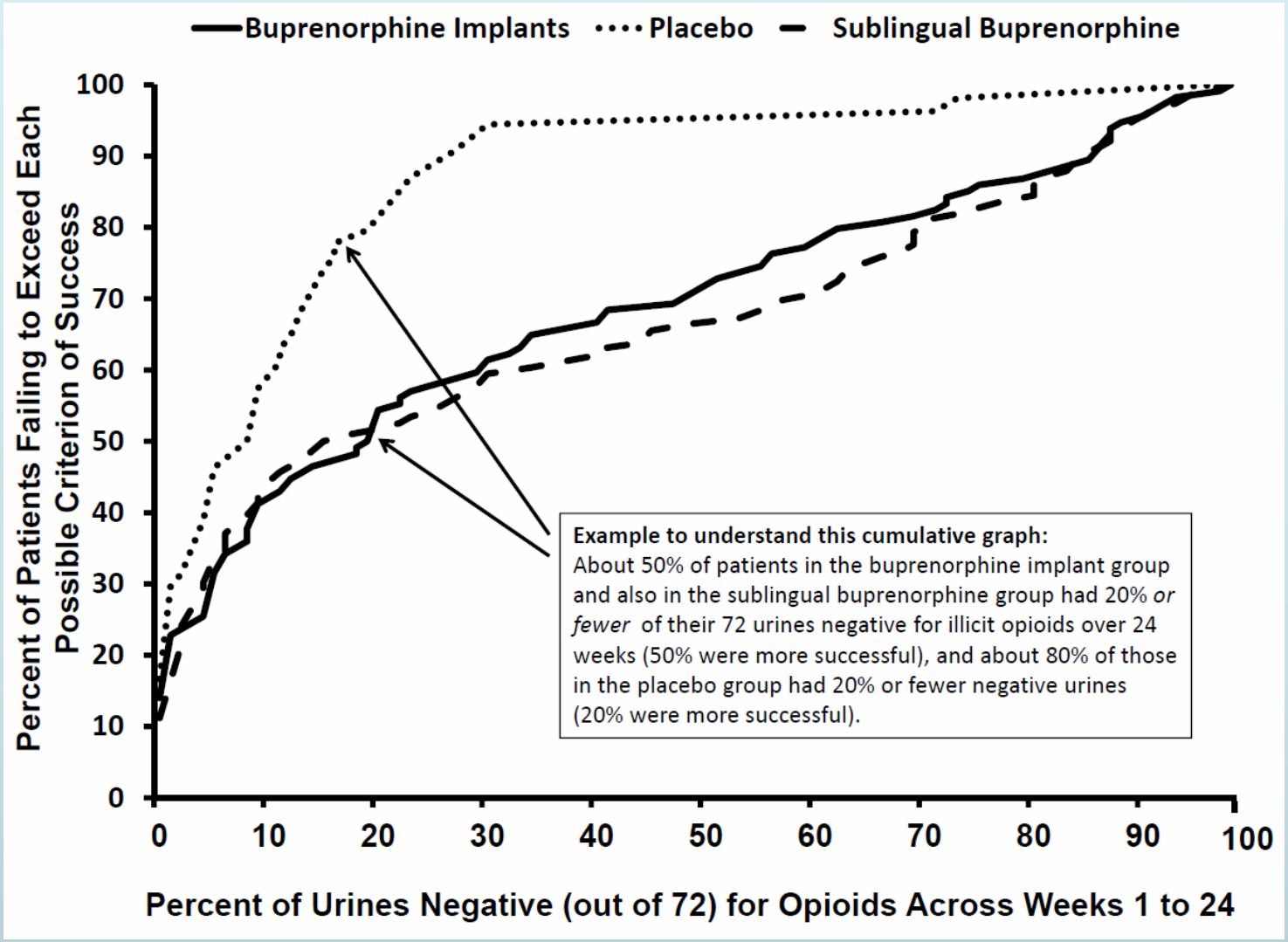
Outcome Measures (24 weeks)	Probuphine > Placebo
Treatment Retention	$p < .0001$
Patient-Rated Opioid Withdrawal	$p = .0005$
Clinician-rated Opioid Withdrawal	$p = .0008$
Global Improvement of Opioid Addiction (Clinician-Rated)*	$p = .0003$
Global Severity of Opioid Addiction (Clinician-Rated)*	$p = .0086$
Opioid Craving Visual Analog Scale (VAS)	$p = .0006$

* Responder Analysis

Study 805: Patient Retention vs. Rescue SL BPN

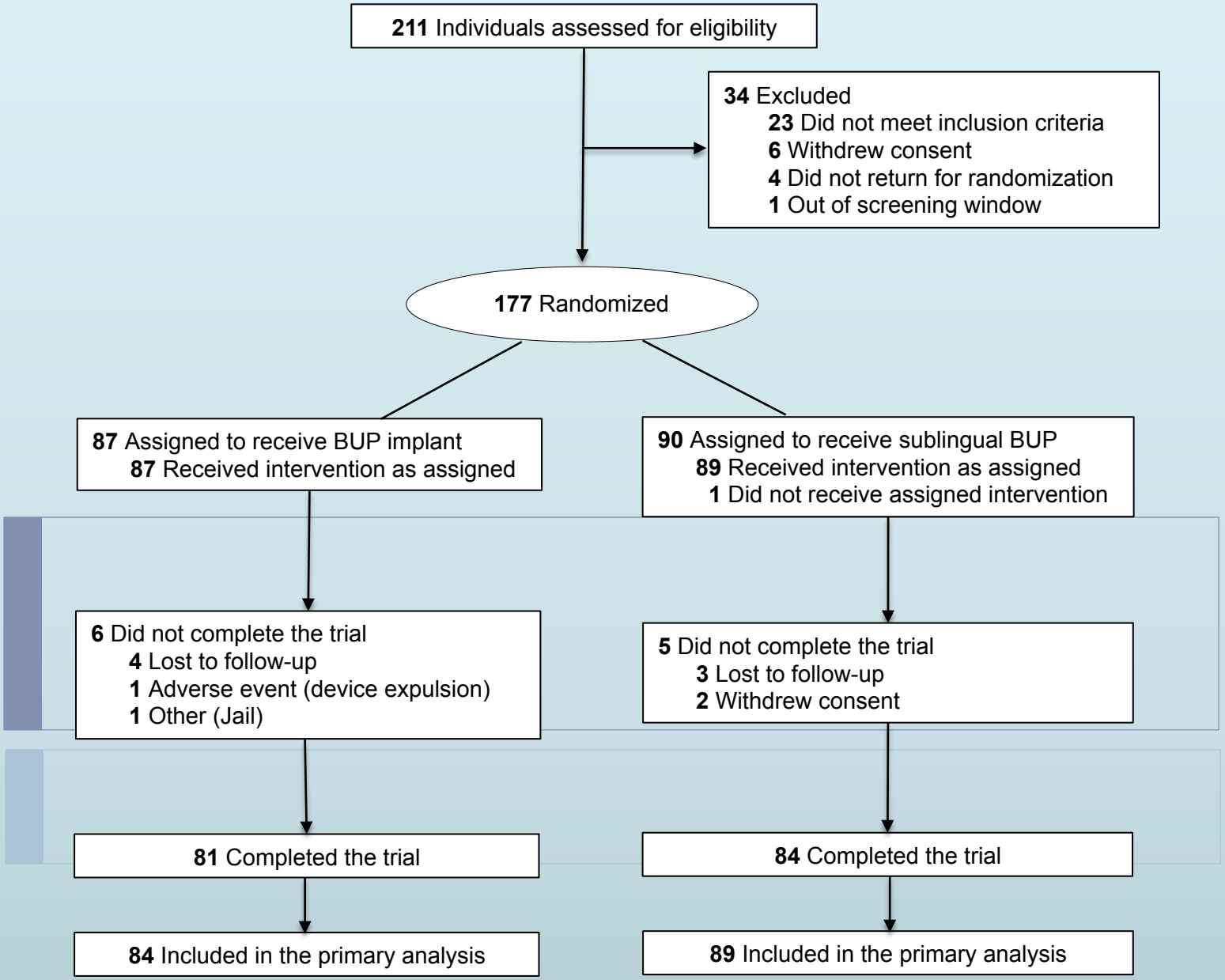


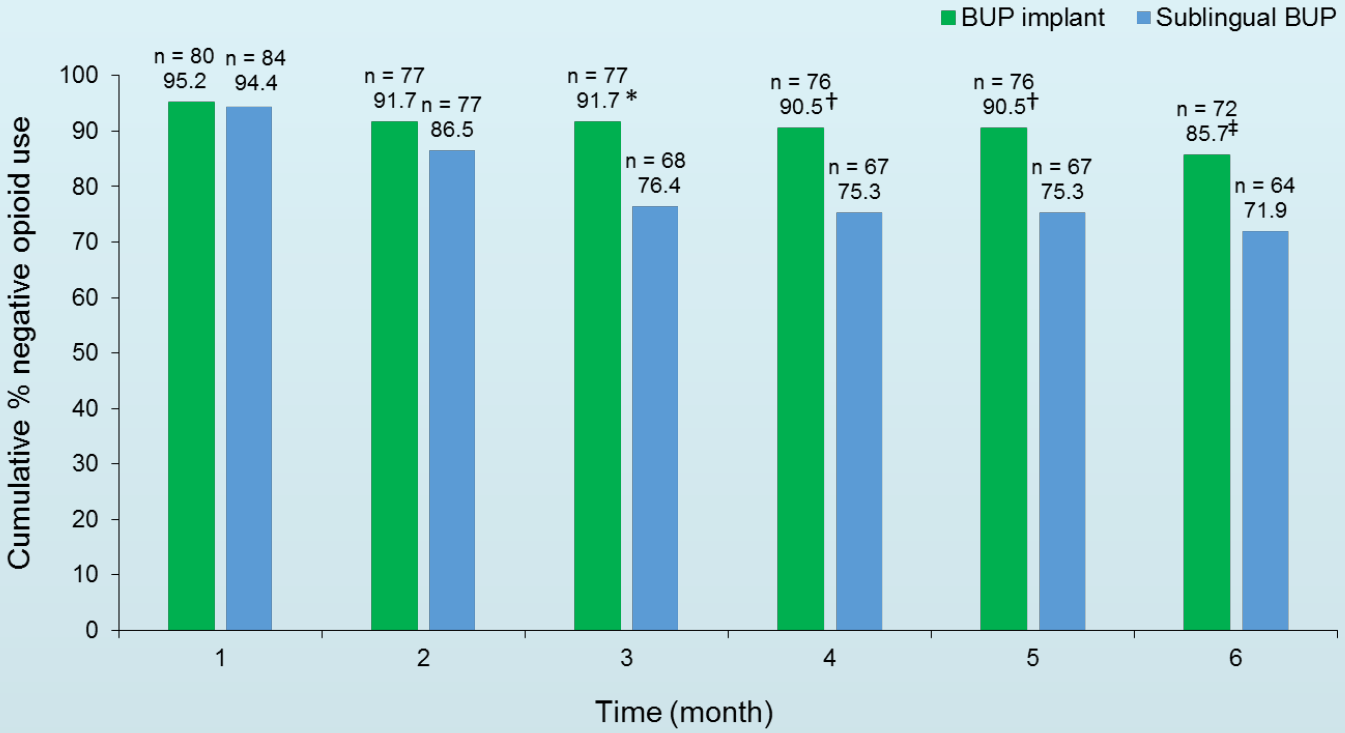
PRO-806 Study: Cumulative Distribution Function of Opioid Negative Urines

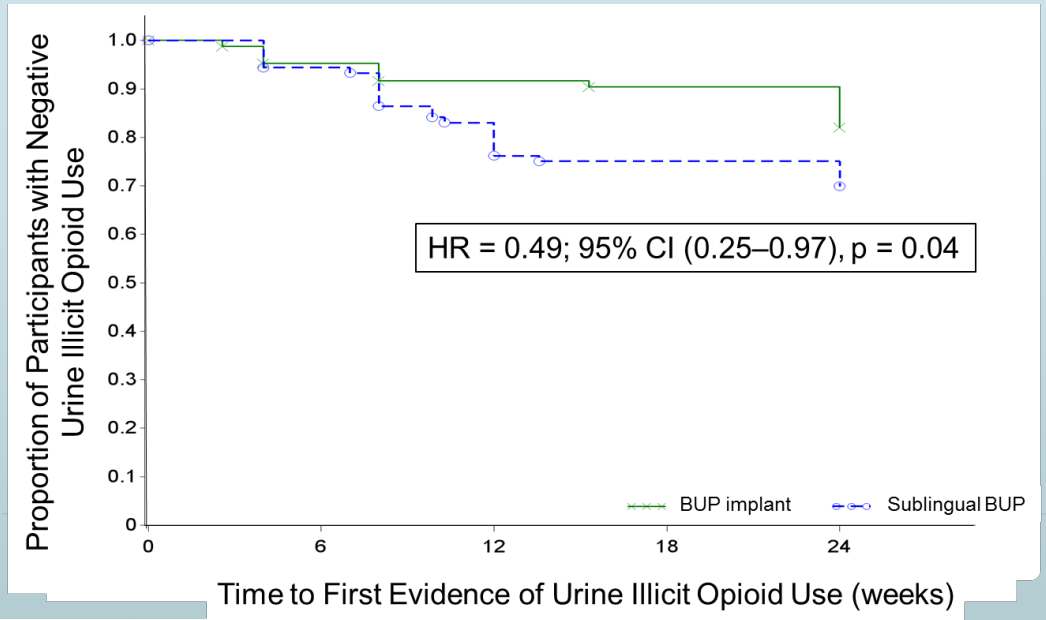


Third study (Rosenthal et al., 2016)

- The FDA was concerned that individuals on Probuphine were still using illicit opioids… although less so than those randomized to placebo
- An FDA Advisory Committee felt that there was an efficacy signal but did not know what patient population that Probuphine could be used in
- The FDA was concerned that the plasma level of buprenorphine obtained from the implants was insufficient to block the effect of exogenous opioids
- The FDA then asked that a non-inferiority study be performed in buprenorphine patients who were stable and not using illicit opioids
- Inclusion criteria: ≥ 24 weeks of sublingual bup (≤ 8 mg), no withdrawal, no illicit opioid use in the past 90 days.


211 Individuals assessed for eligibility
34 Excluded
23 Did not meet inclusion criteria
6 Withdrew consent
4 Did not return for randomization
1 Out of screening window
177 Randomized
87 Assigned to receive BUP implant
87 Received intervention as assigned
90 Assigned to receive sublingual BUP
89 Received intervention as assigned
1 Did not receive assigned intervention
6 Did not complete the trial
4 Lost to follow-up
1 Adverse event (device expulsion)
1 Other (Jail)
5 Did not complete the trial
3 Lost to follow-up
2 Withdrew consent
81 Completed the trial
84 Completed the trial
84 Included in the primary analysis
89 Included in the primary analysis


BUP implant
Sublingual BUP
Cumulative % negative opioid use
Time (month)
n = 80
95.2
n = 84
94.4
n = 77
91.7
n = 77
86.5
n = 77
91.7 *
n = 68
76.4
n = 76
90.5†
n = 67
75.3
n = 76
90.5†
n = 67
75.3
n = 72
85.7‡
n = 64
71.9


Proportion of Participants with Negative Urine Illicit Opioid Use
HR = 0.49; 95% CI (0.25–0.97), p = 0.04
BUP implant
Sublingual BUP
Time to First Evidence of Urine Illicit Opioid Use (weeks)

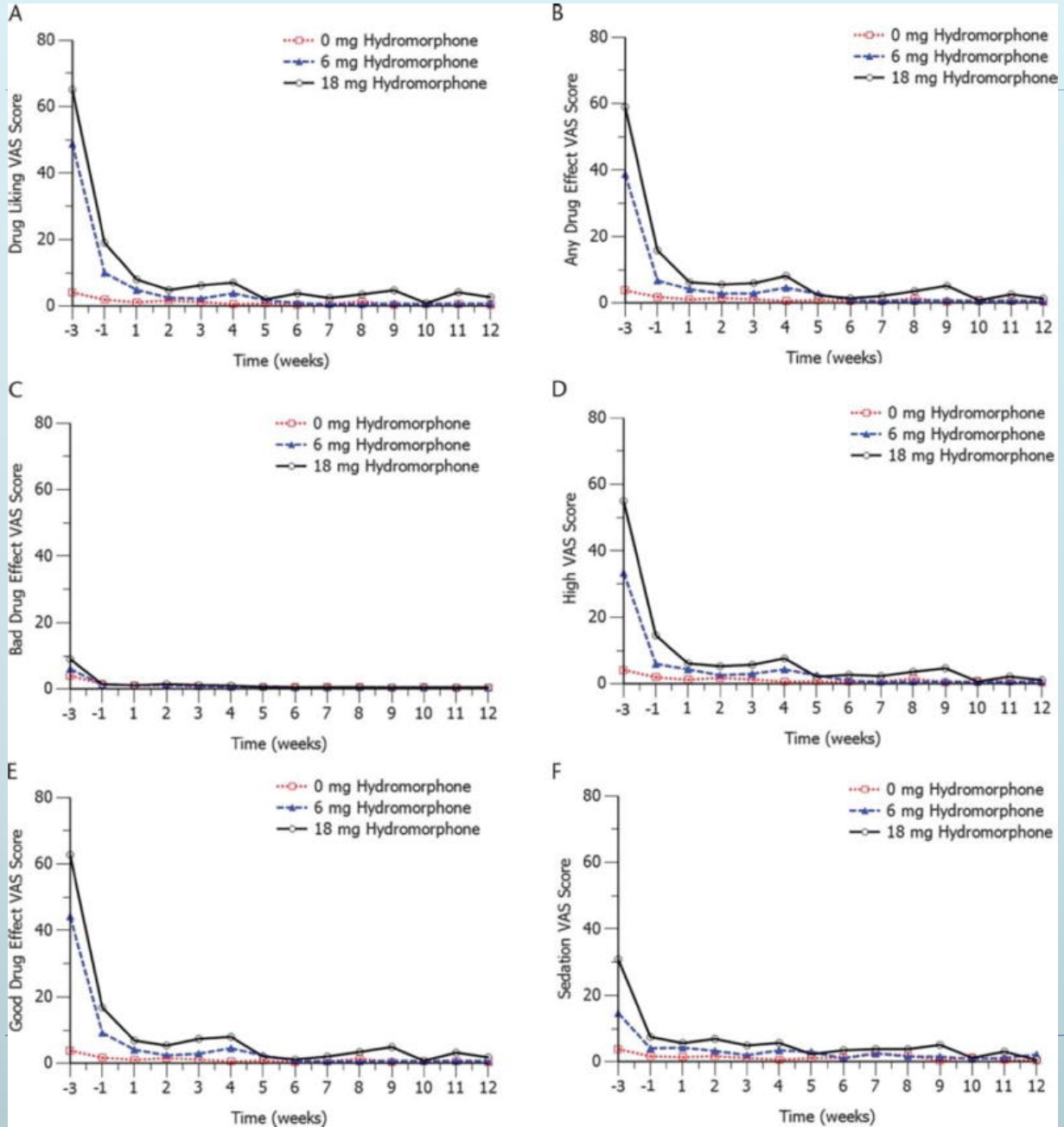
Probuphine Approval

- FDA Label:
- PROBUPHINE is indicated for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet or generic equivalent).
- PROBUPHINE should be used as part of a complete treatment program to include counseling and psychosocial support.
- PROBUPHINE is not appropriate for new entrants to treatment and patients who have not achieved and sustained prolonged clinical stability, while being maintained on buprenorphine 8 mg per day or less of a Subutex or Suboxone sublingual tablet equivalent or generic equivalent.

Buprenorphine Injection (SUBLOCADE)

- Monthly subcutaneous injection of Buprenorphine in patients who have been stabilized on ≥ 8 mg per day
- Clinical pharmacology blockade study was performed in study participants previously stabilized on 8-24 mg (Nasser et al, 2016)
- Two injections of 300 mg RBP-6000 (SUBLOCADE) were given on days 1 and 29 achieving plasma levels ≥ 5 ng/ml
- Participants were challenged with injections of 0, 6, or 18 mg of im hydromorphone prior to and after RBP-6000 injections on a weekly basis

VAS Scores Across Weeks

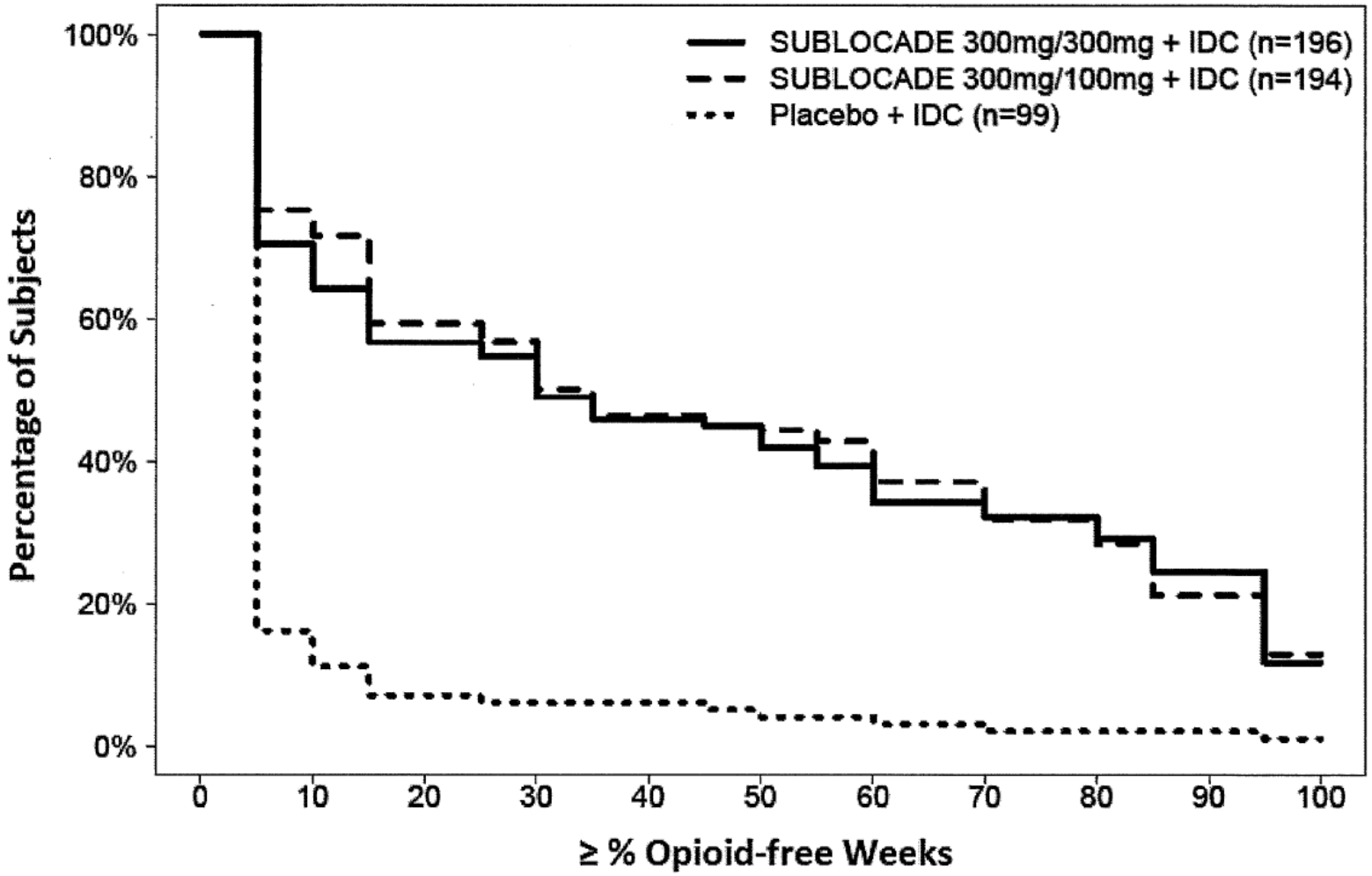


RBP-6000 Outpatient Study Design

- 24 week, randomized double-blind, placebo- controlled, multicenter trial in 504 individuals with opioid use disorder (DSM-5)
- Dosing regimens: 6 once-monthly, sc 300 mg doses, 2 once-monthly 300 mg doses followed by 4 once-monthly 100 mg doses, 6 once-monthly doses of placebo
- All participants received manual-guided psychosocial support
- Primary outcome measure was illicit opioid use, measured by weekly urine samples and self-report. This was reported as a cumulative distribution function.
- A treatment success metric, defined as ≥ 80% opioid free weeks, noted statistically significant differences between the RBP-6000 Groups (28.4 and 29.1%) versus 2% in the placebo group.

RBP-6000 Outpatient Study

Figure 12. Subjects Achieving Varying Percentages of Opioid-Free Weeks



SUBLOCADE Indication and Usage

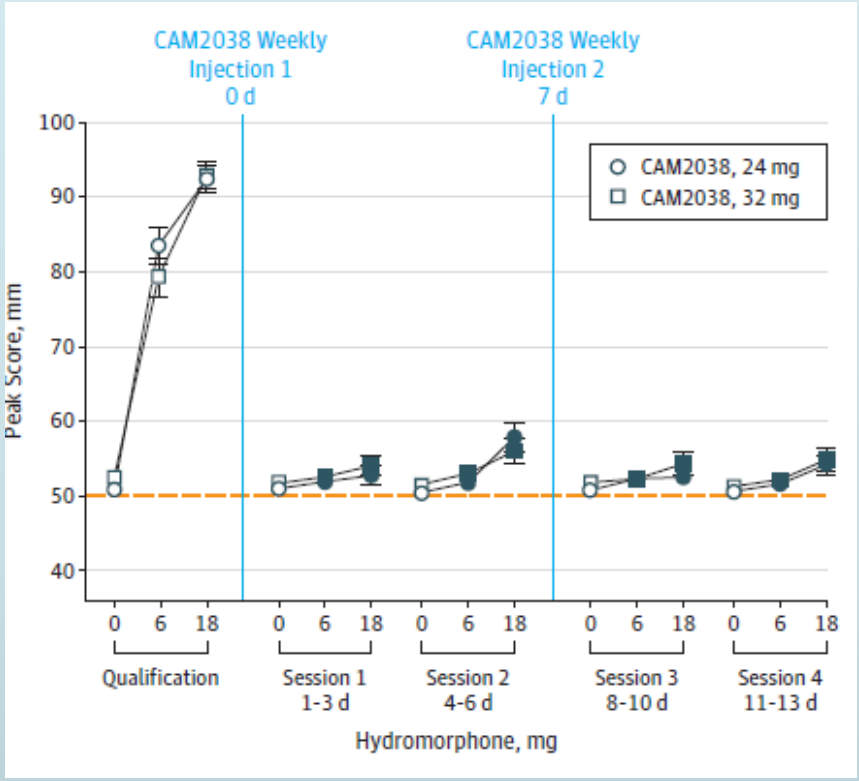
- SUBLOCADE is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product followed by a dose adjustment period for a minimum of seven days.

CAM2038 Buprenorphine injection

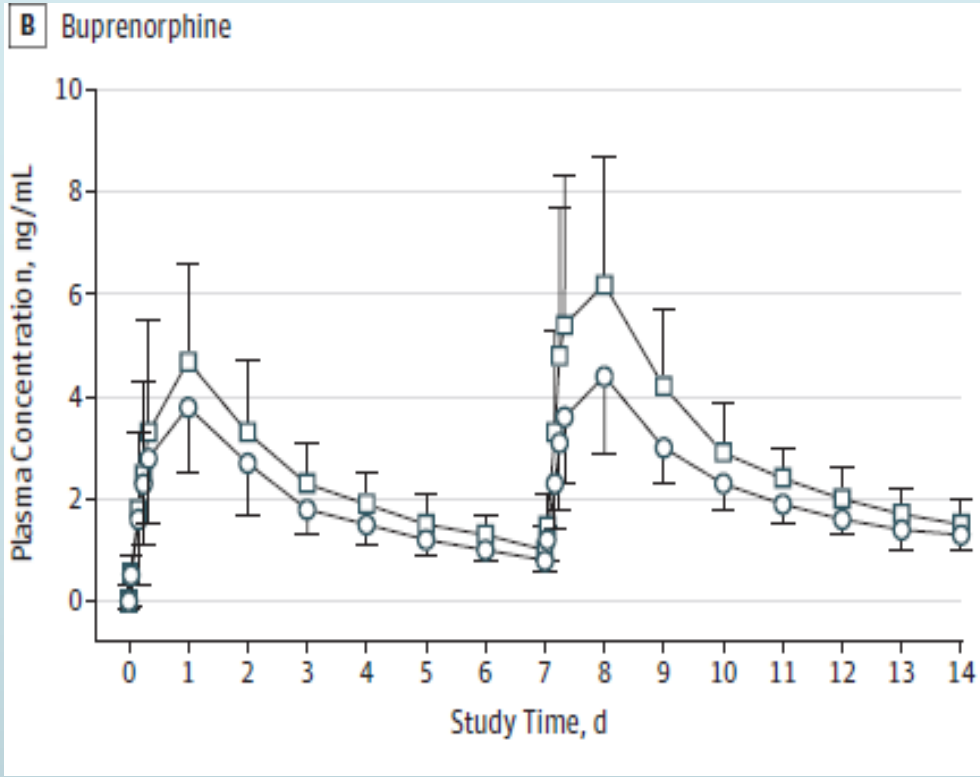
- Once-weekly injectable of buprenorphine at 24 or 32 mg dosage strengths
- Sc Injection is given in the buttocks, thigh, abdomen, or upper arm
- Tested in a clinical pharmacology study against 0, 6, and 18 mg im hydromorphone doses on days 1-3, 4-6, 8-10, and 11-13
- The primary outcome measure was drug liking as measured on a bipolar VAS scale
- Blood samples were taken for pharmacokinetic analysis

CAM2038 Injection Challenge Study

VAS Liking Scores



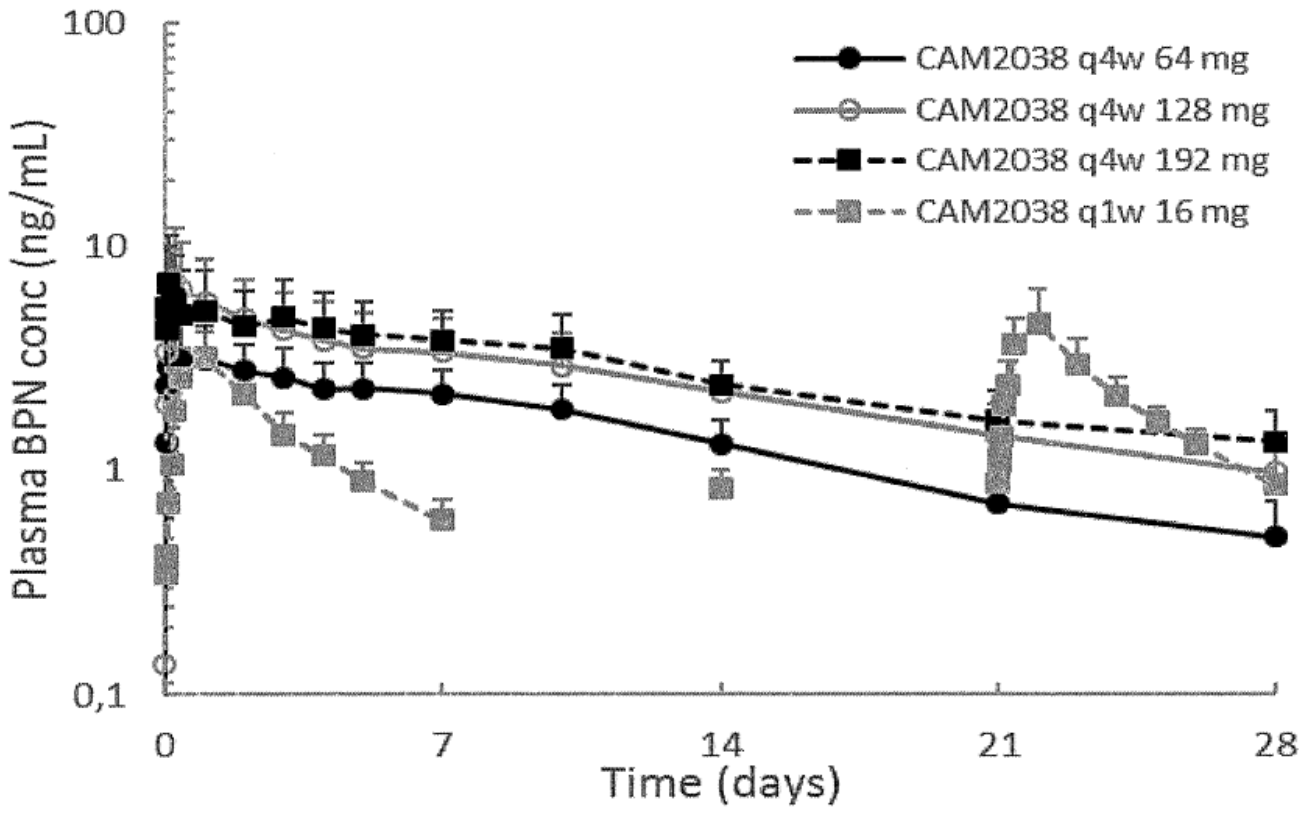
Plasma Levels



CAM2038 Efficacy Study Design

- Randomized, double-blind, active-controlled, double-dummy comparison of CAM 2038 (Varying doses for one week or one month) versus sublingual buprenorphine (range of 8 to 32 mg) for 24 weeks in 428 participants with DSM-5 moderate-to-severe OUD
- Responder defined as an individual having at least 1/3 of urines negative for opioids in the first 12 weeks (weekly visits) and 2/3 of urines negative for opioids in the following 12 weeks (monthly visits)
- A 10 % non-inferiority margin was selected
- CAM doses: 8,16, 24, and 32 mg for weekly injections and 64, 96, 128, 160 for monthly injections

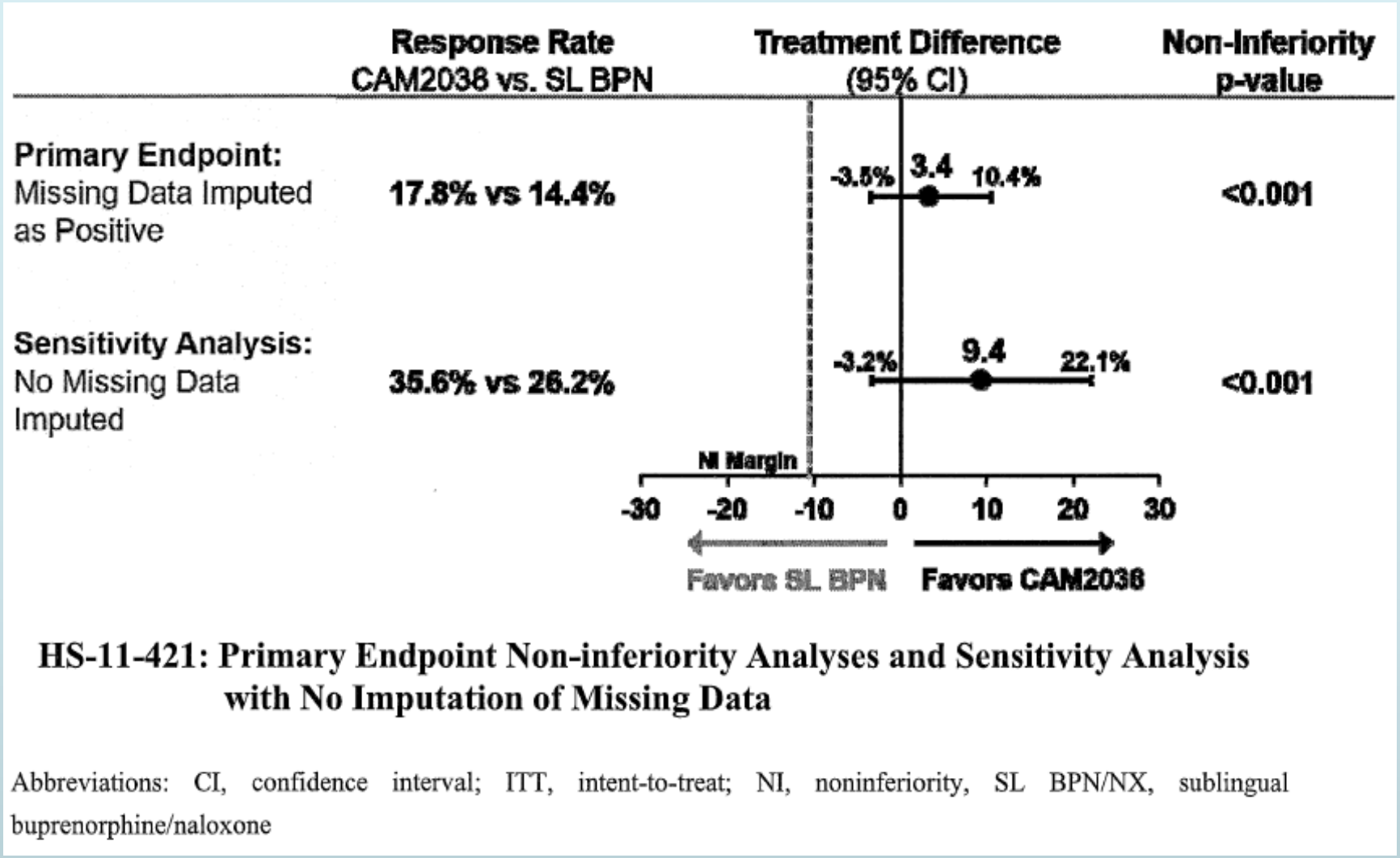
CAM 2038 Pharmacokinetics



Plasma Concentration Time Profiles of BPN After Single SC injection of CAM2038 q4w and at First and Fourth Repeated Weekly SC injections of CAM2038 q1w in study HS-13-487

Values are mean (+SD)

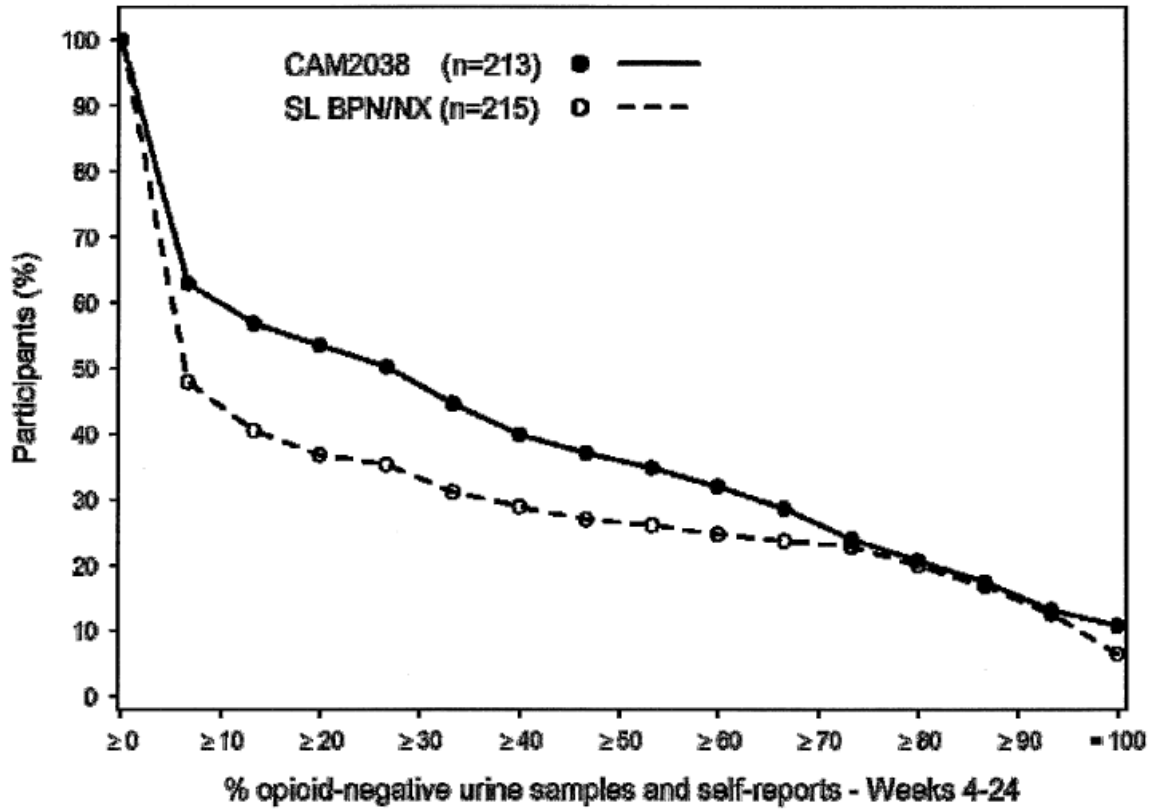
Non-Inferiority Results



HS-11-421: Primary Endpoint Non-inferiority Analyses and Sensitivity Analysis with No Imputation of Missing Data

Abbreviations: CI, confidence interval; ITT, intent-to-treat; NI, noninferiority, SL BPN/NX, sublingual buprenorphine/naloxone

Results Expressed as a CDF



Study HS-11-421: CDF of Percent of Urine Samples Negative for Illicit Opioids with Self-reports – Treatment Weeks 4 to 24 (ITT Population)

Abbreviations: CDF, cumulative distribution function; ITT, intent-to-treat; SL BPN/NX, sublingual buprenorphine/naloxone. Source: Extracted from summary of clinical efficacy, Figure 14

Proposed Dosing Transfer

Proposed Transfer from Daily Doses of SL BPN to Initial Weekly or Monthly Doses of CAM2038 q1w or CAM2038 q4w

Dose of daily SL BPN	Dose of weekly CAM2038 q1w
2-6 mg	8 mg
8-10 mg	16 mg
12-16 mg	24 mg
18-24 mg	32 mg
Dose of daily SL BPN	**Dose of monthly CAM2038 q4w**
8-10 mg	64 mg
12-16 mg	96 mg
18-24 mg	128 mg
26-32 mg	160 mg

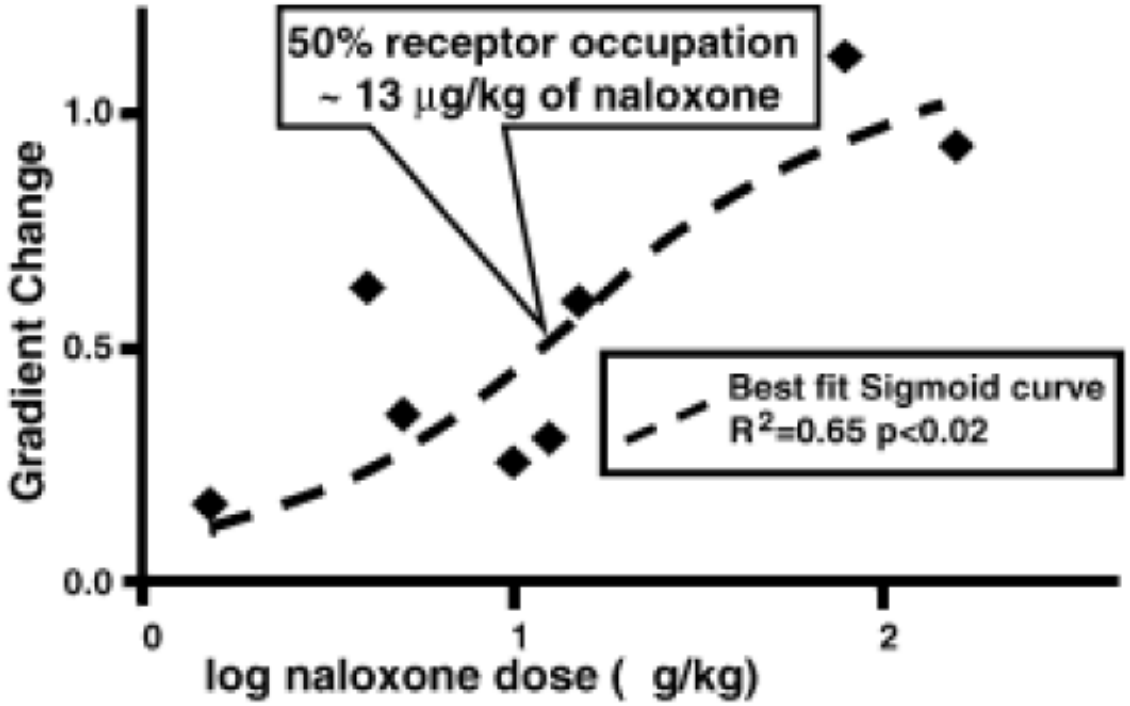
Abbreviation: SL BPN, sublingual buprenorphine

Source: Extracted from Summary of clinical pharmacology, Table 28

FDA Decision January 21, 2018

- Sent a Complete Response Letter requesting additional information
- Braeburn website states that no new studies are being requested

Naloxone for Opioid Overdose Reversal



Source: Melichar et al[7]; figure 2.

Naloxone-Current and Developing Dosage Forms

Fifty percent receptor occupancy by naloxone is needed to reverse an opioid overdose) Melichar et al, 2003)

A 1 mg dose of naloxone iv (~ 13 µg/kg) is needed to produce 50 percent receptor occupancy

A 2 mg dose of naloxone iv produces ~ 80 percent opioid receptor occupancy

Naloxone Current Routes of Administration

Nasal Spray

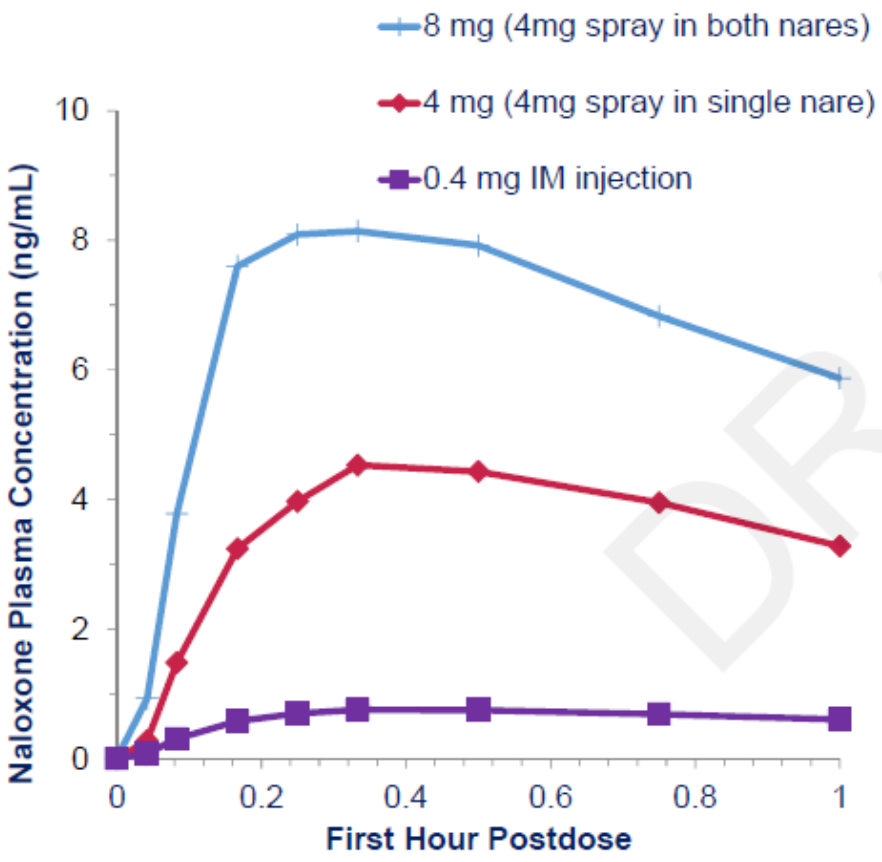
Nasal Injection Spray Kit

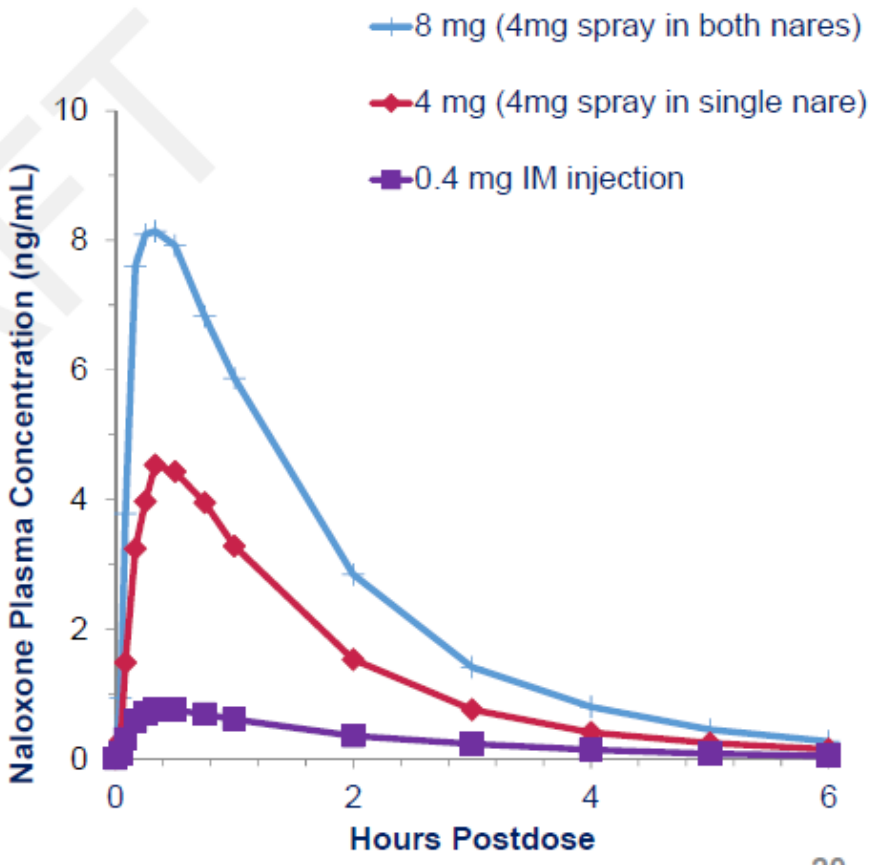
Auto Injector

Intramuscular Injection

IntraTab Labs

NARCAN NASAL RAPIDLY ACHIEVES HIGH NALOXONE EXPOSURE





NARCAN NASAL SPRAY 4MG HUMAN PHARMACOKINETICS

Geometric Mean Pharmacokinetic Parameters (CV%) of Naloxone Following Single Intranasal (IN) Administration and Intramuscular (IM) Injection of Naloxone to Healthy Subjects, Study Naloxone-Ph1a-002 (N=29)

Parameter	2mg IN Dose One Spray 20 mg/mL	4mg IN Dose Two Sprays 20 mg/mL	4mg IN Dose One Spray 40 mg/mL	8mg IN Dose Two Sprays 40 mg/mL	0.4mg IM Injection
$t_{½}$ (h)	1.81 (34.9)	2.23 (34.5)	2.08 (29.5)	2.10 (32.4)	1.24 (25.9)
t_{max} (h) †	0.33 (0.25, 1.00)	0.33 (0.17,0.57)	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)
C_{max} (ng/mL)	2.92 (34.3)	6.20 (31.9)	4.83 (43.1)	9.70 (36.0)	0.877 (30.5)
C_{max}/Dose (ng/mL/mg)	1.46 (34.3)	1.55 (31.9)	1.21 (43.1)	1.21 (36.0)	2.19 (30.5)
AUC_{0-t} (h*ng/mL)	4.51 (27.2)	9.32 (24.0)	7.87 (37.4)	15.3 (23.0)	1.72 (22.9)
AUC_{0-t}/Dose (h*ng/mL/mg)	2.25 (27.2)	2.33 (24.0)	1.97 (37.4)	1.91 (23.0)	4.29 (22.9)
AUC_{0-inf} (h*ng/mL)	4.56 (26.9)	9.43 (24.0)	7.95 (37.3)	15.5 (22.7)	1.76 (22.6)
AUC_{0-inf}/Dose (h*ng/mL/mg)	2.28 (26.9)	2.36 (24.0)	1.99 (37.3)	1.93 (22.7)	4.40 (22.6)
Relative BA (%) vs. IM	51.9 (21.7)	53.6 (22.5)	46.7 (31.4)	43.9 (23.8)	100

†: Median (minimum, maximum)

The relative bioavailability of IN-administered naloxone is based on the dose-normalized values of AUC_{0-inf} compared to the IM treatment

Field Experience with Narcan Nasal Spray

- 125,000 cartons (250,000 doses) dispensed in first 6 months
- Conducted survey to understand field experience of Narcan Nasal Spray Users
  - > Conducted interviews with 40 organizations that acquired 18,637 Narcan Nasal Spray cartons
  - > 15 organizations (that acquired 7,669 cartons) reported over 1,400 reversals with Narcan Nasal Spray
  - > A subset of 8 organizations provided case report summary data on 261 attempted reversals
  - > 1 dose was used 63% of cases and 2 doses in 30% of cases. Doses ranged from 4-16 mg.
  - > All but 3 attempts were successful, (in 2 cases product not administered in time, one event no information)
- Review of observations/adverse events conducted and no new safety concerns
- The vast majority of reported events were consistent with opioid withdrawal

New Standard for Naloxone Levels

Rapid Exposure and Higher Naloxone Dose Needed for Fentanyl ODs [4,5]

- Estimated to be 100 times more potent than morphine [1]
- Highly lipophilic [2] so peak respiratory depressive effects from 5 mins [1] v c.30 mins for morphine [3]
- Much of the fentanyl is illicitly manufactured and surreptitiously introduced to heroin /illicit narcotic pills

Lower Dose Naloxone Products May Deliver Too Little Too Late for Fentanyl

- Massachusetts EMS multiple naloxone administration incidents increased 40% (2015-v-2013) [6]
- CDC Health Advisory "…a higher dose or multiple number of doses per overdose event may be required to revive a patient due to the high potency of [fentanyl]". [7]
- Published case studies highlight need for higher and prolonger naloxone treatment [8]
- Hardest hit cities reporting need for 5-9 administrations of the improvised nasal naloxone product

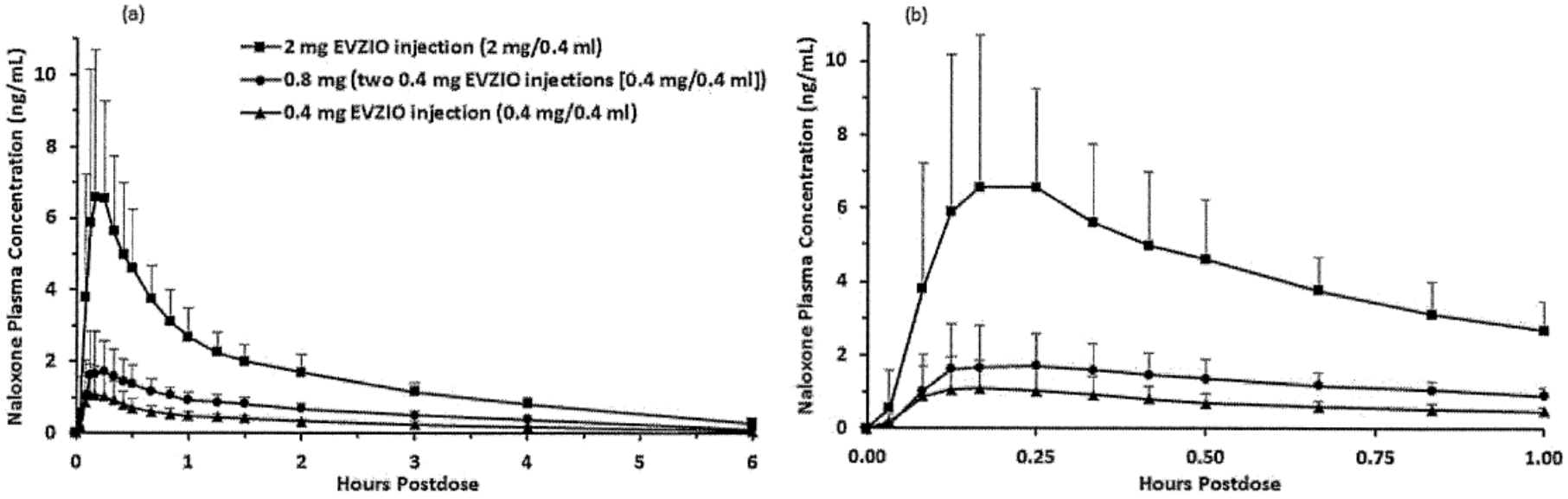
[1] Fentanyl Citrate Prescribing Information; [2] Volpe DA, McMahon Tobin GA, Mellon RD, et al. *Regul. Toxicol. Pharmacol.* Apr 2011;59(3):385-390.
[3] Olofsen E, van Dorp E, Teppena L, et al. Anesthesiology. Jun 2010;112(6):1417-1427. [4] Melichar et al 2003 EurJPharmacol. 459:217-219; [5] Kim HK, Nelson LS. *Exp Opin Drug Saf.* 2015;14(7):1137-1146. [6]. Opioid-related EMS Transports Massachusetts Residents: 2013-2015; [7] CDC HAN 00384 October 2015; [8] Sutter at al Acad Emer Med 2016 Jun 20

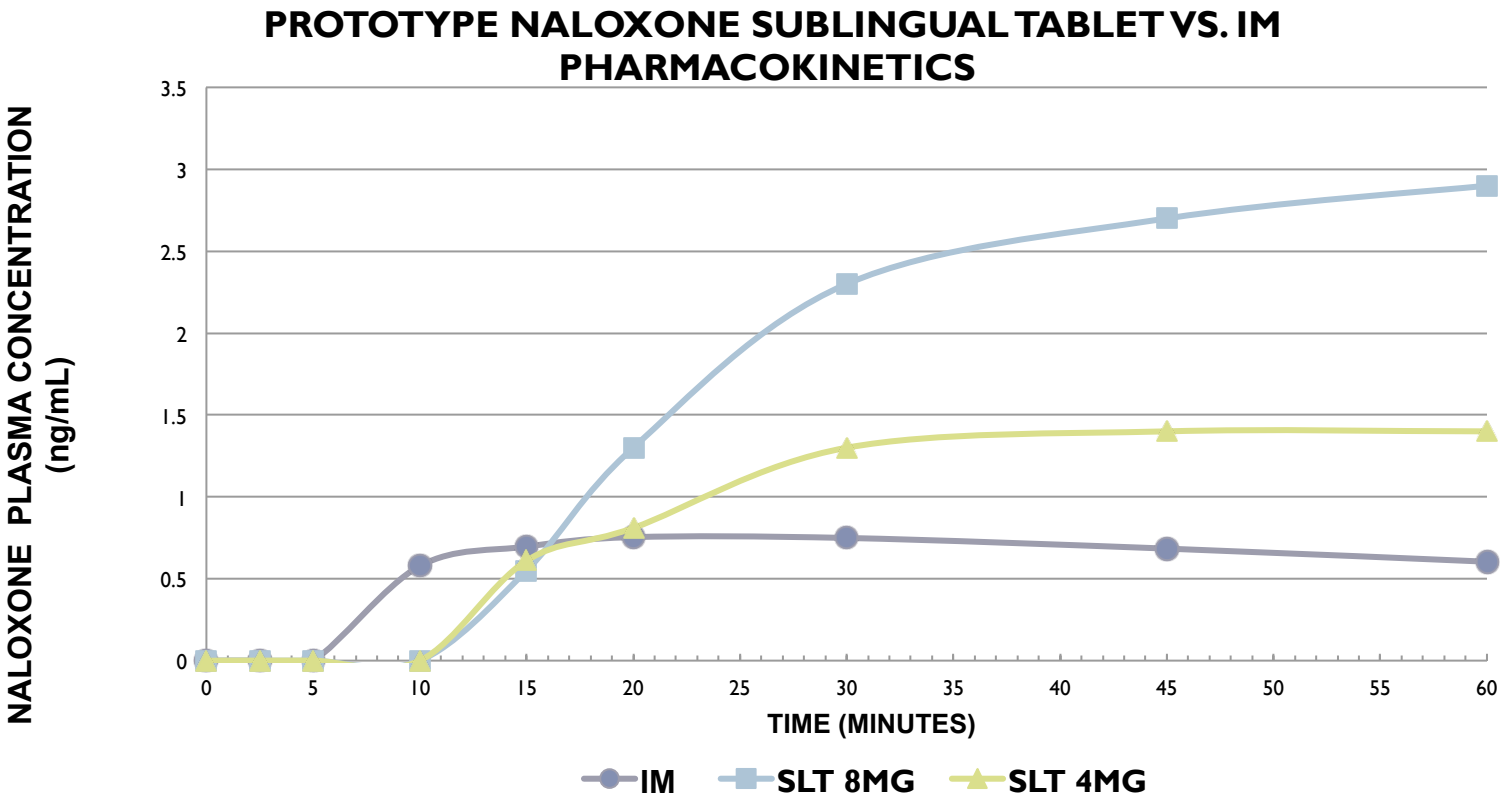
IN Cmax at 2 mg may become the new FDA Standard for Approval

Variable	Intranasal 2mg	Intramuscular 0.4 mg
T max	0.33	0.38
C max (ng/ml)	2.92	0.877
AUC (h x ng/ml)	4.51	1.72
Relative BA (%)	51	100

Evzio Auto-injector

Figure 1 Mean ± SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intramuscular/Subcutaneous Administration using EVZIO





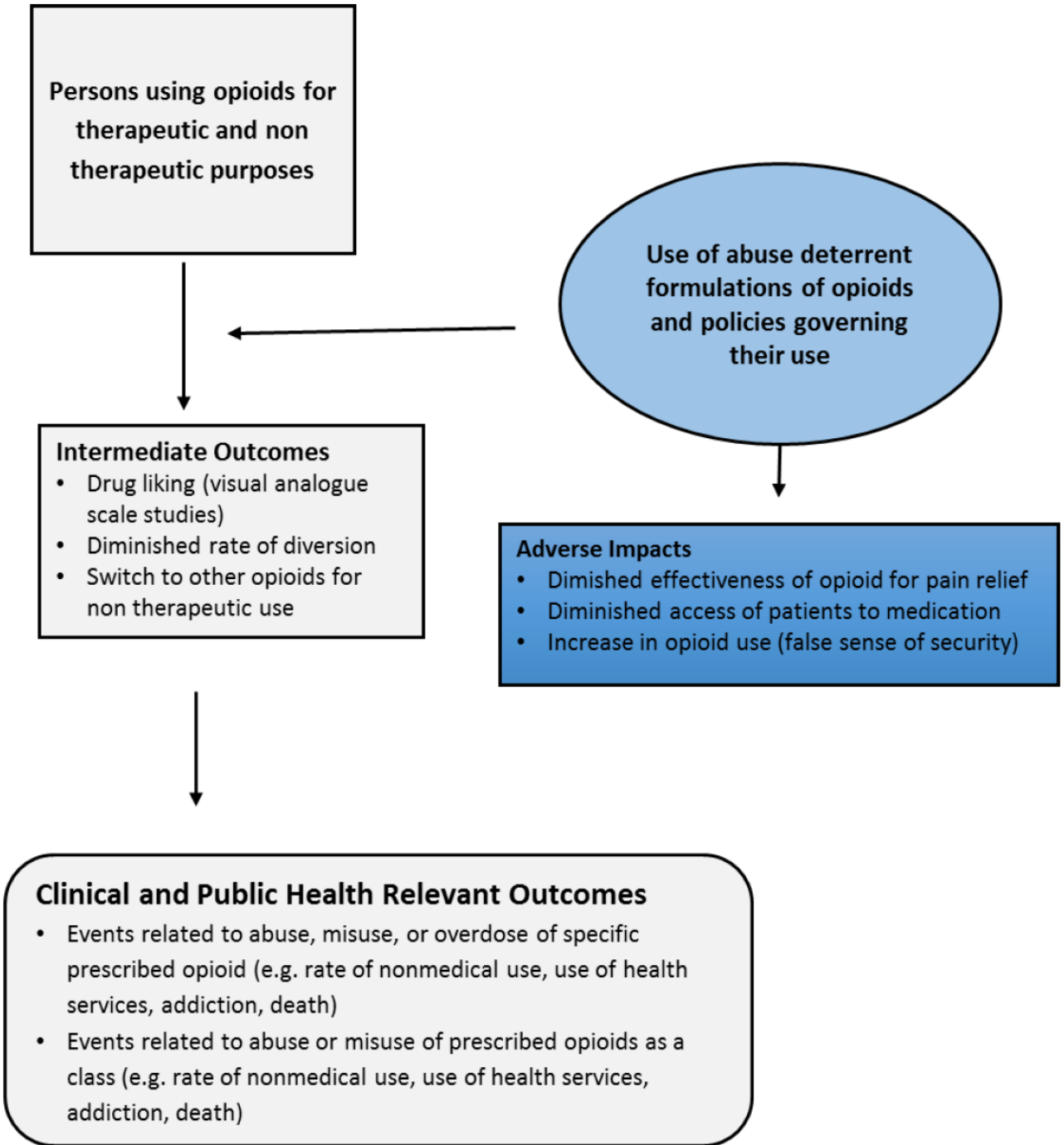
Note Limits of quantification in PK study was 0.5ng/mL, thus early time points were not quantifiable

IM data from Narcan SBA

Abuse Deterrent Opioids

- FDA has a 4 part process for determining the effect of abuse-deterrent opioids
- Laboratory manipulation and extraction studies
- Pharmacokinetic studies
- Clinical abuse liability studies
- Post-marketing studies

Figure 1: Analytic Framework: Abuse-deterrent Formulation of Opioids in Pain Management



Currently Marketed and Investigational Abuse-deterrent Formulations

Oxycodone:

- Oxycontin® (oxycodone extended release, available on the market)
- Xtampza™ (oxycodone extended release, available on the market)
- Troxyca® ER (oxycodone + naltrexone extended release; approved, but currently not available on the market)
- Remoxy™ (oxycodone extended release [Investigational])

Hydrocodone:

- Hysingla® ER (hydrocodone extended release; available on the market)
- Vantrela™ ER (hydrocodone extended release [Investigational])

Morphine:

- Embeda® (morphine + naltrexone extended release; available on the market)
- Morphabond™ (morphine extended release; approved, but currently not available on the market)
- Arymo™ ER (morphine extended release [Investigational])

ICER

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Abuse-Deterrent Formulations of Opioids: Effectiveness and Value

Final Evidence Report

August 8, 2017

Brand Name	Type of Opioid	Year of Approval	Reported Abuse-Deterrence Mechanism	Commercially Available±
OxyContin® (reformulated)	Oxycodone	2010	When dissolved, forms a viscous gel that is difficult to inject through a hypodermic needle.	Yes
Embeda®	Morphine	2014	Capsules of ER morphine pellets that contain a sequestered core of naltrexone; if the pellets are swallowed, the morphine is gradually released and absorbed, while the naltrexone core passes through the gut intact. If the pellets are crushed, chewed, or dissolved, the naltrexone is released, blocking morphine-induced euphoria.	Yes
Targiniq® ER	Oxycodone	2014	Combination pill containing extended-release (ER) oxycodone and naloxone; if the formulation is crushed and administered intravenously or intranasally, high naloxone concentrations block opiate-induced euphoria and can induce withdrawal symptoms.	No
Hysingla® ER	Hydrocodone	2015	When dissolved, forms a viscous gel that is difficult to inject through a hypodermic needle	Yes
MorphaBond®	Morphine	2015	Formulated with inactive ingredients that make the tablet harder to adulterate while maintaining ER characteristics if the tablet is subjected to physical manipulation or chemical extraction.	No
Xtampza® ER	Oxycodone	2016	Capsules containing microspheres formulated with oxycodone base and inactive ingredients that make the formulation harder to manipulate.	Yes
Troxyca® ER	Oxycodone	2016	Contains pellets that consist of oxycodone that surround sequestered naltrexone. When taken orally, the naltrexone is intended to remain sequestered and patients receive ER oxycodone. When the pellets are crushed, the naltrexone is released and counteracts the effects of oxycodone.	No
Arymo® ER	Morphine	2017	A polymer matrix tablet technology with controlled-release properties as well as physical and chemical barriers that resist manipulation. The technology results in a viscous hydrogel on contact with liquid, making the product very difficult to draw into a syringe.	Yes
Vantrela® ER	Hydrocodone	2017	Incorporates abuse-deterrent technology designed to resist drug extraction through the most common routes: oral, intranasal, and intravenous.	No
****RoxyBond®**	Oxycodone	2017	Includes inactive ingredients that make the tablets harder to misuse by physical manipulation, chemical extraction, or both; in vitro data suggest physicochemical properties that are expected to make abuse through injection difficult.	No

*Modified from Becker, 2017.[20] **Only ADF approved as immediate-release. ±As of June 28, 2017.

Intranasal Abuse Liability Comparisons

ADF (n)	Dose	Crushed ADFs & active comparators¥	VAS score, E_{max}		
			Drug liking	Take drug again	Overall drug liking
Extended-release (ER)					
OxyContin[49] (n=30)	**30mg**	OxyContin- crushed	NR	64*	69.7*
		Original OxyContin- crushed	**NR**	**89.6**	**87.4**
		Oxycodone IR powder	**NR**	**86.6**	**84.8**
Xtampza ER[50] (n=39)	**40mg**	Xtampza ER- crushed	NR†	47.8†	48.2†
		Oxycodone IR- crushed	**NR**	**71.3**	**71.8**
Troxyca ER[51] (n=28)	**30mg**	Troxyca ER- crushed	60.5†	58.9*	60.2*
		Oxycodone IR- crushed	**92.8**	**88.4**	**85.4**
Targiniq ER‡[42] (n=23)	**40mg**	Targiniq ER-Crushed	59.1	42.6	NR
		Oxycodone IR powder	**94.8**	**93.6**	**NR**
Hysingla ER[52] (n=25)	**60mg**	Hysingla ER- crushed	66.8†	34.6†	NR
		Hydrocodone powder	**90.4**	**83.9**	**83.4**
Vantrela ER[41] (n=45)	**45mg**	Vantrela ER- crushed	72.8*	NR	68.5*
		Hydrocodone powder	**80.2**	**NR**	**77.1**
		Zohydro	**83.2**	**NR**	**79.8**
Embeda[53] (n=33)	**30mg**	Embeda- crushed	69.6†	60.6†	60.8†
		Morphine sulfate ER- crushed	**87.6**	**84.9**	**83.8**
Morphabond ER[54] (n=25)	**60mg**	Morphabond ER- crushed	71.1*	NR*	NR†
		Morphine sulfate ER- crushed	**84.8**	**NR**	**NR**
Arymo ER[55] (n=46)	**60mg**	Arymo ER- crushed	52.5†	50†	50.5†
		Morphine sulfate ER- crushed	**77.5**	**73**	**71**
Immediate-release (IR)					
RoxyBond IR‡[56] (n=29)	**30mg**	RoxyBond IR - crushed	71.1†	62.2	NR
		Oxycodone IR - crushed	**82.9†**	**82.1**	**NR**

¥: Placebo arms not included in table, non-ADF comparator arms indicated by bold font;‡: Data from Targiniq FDA label *p≤0.05 vs. active comparator; †p≤0.001 vs. active comparator

Abuse Liability Studies of Oral Products

ADF (n)	Dose	Intact & crushed ADFs & active comparators¥	VAS score, E_{max}		
			Drug liking	Take drug again	Overall drug liking
Extended-release (ER)					
OxyContin	--	***No oral abuse potential study***			
Xtampza ER[43] (n=38)	**40mg**	Xtampza ER- intact	68.8*	70.2*	69.4*
		Xtampza ER- crushed	73.4*	73.7*	74.2*
		IR oxycodone- crushed	**81.8**	**75.4**	**76.2**
Troxyca ER[44] (n=41)	**60mg**	Troxyca ER- intact	59.3*	48.7*	53.3*
		Troxyca ER- crushed	74.5*	72.5	74.3
		IR oxycodone- crushed	89.8	81.5	81.8
Targiniq ER‡[45] (n=29)	--	Targiniq ER-intact	54.7	38.5	NR
		Targiniq ER-chewed	54.6	32.6	NR
		Oxycodone IR solution	**77.9**	**61.4**	**NR**
Hysingla ER[39] (n=35)	**60mg**	Hysingla ER- intact	63.3†	32.6†	54.9†
		Hysingla ER- crushed	69†	43†	56.8†
		Hydrocodone IR solution	**94**	**86.7**	**84.1**
Vantrela ER[46] (n=41)	**45mg**	Vantrela ER- intact	53.9†	46.4†	49.2†
		Vantrela ER- crushed	66.9†	58.7†	59†
		Hydrocodone IR	**85.2**	**75.2**	**75**
Embeda[47] (n=33)	**120mg**	Embeda- crushed	65.2†	57.7†	58.6†
		Morphine sulfate ER- crushed	**80.8**	**70.7**	**69.8**
Embeda[48] (n=32)	**120mg**	Embeda- intact	67.6†	NR	NR
		Embeda- crushed	68.1†	NR	NR
		Morphine solution	**89.5**	**NR**	**NR**
Morphabond ER	--	***No oral abuse potential study***			
Arymo ER[40] (n=38)	**60mg**	Arymo ER- intact	62†	56†	57†
		Arymo ER- crushed	67*	61.5*	63.5
		Morphine sulfate ER- crushed	**74**	**68**	**67.5**
Immediate-release (IR)					
RoxyBond IR	--	***No oral abuse potential study***			

¥: Placebo arms not included in table, non-ADF comparator arms indicated by bold font; *p≤0.05 vs. active comparator; †p≤0.001 vs. active comparator; ‡ study conducted in opioid-dependent population

Changes in Abuse Patterns

Data source	Timeframe compared		Change in abuse pattern of OxyContin‡		% change of comparators	
	Prior to reformulation	Post-reformulation	Outcome (population)	% change	Heroin	Prescription opioids (excludes OxyContin)
RADARS Poison center[59]	4Q08 - 3Q10	4Q10 - 1Q12	Quarterly rates of cases at poison control centers (U.S. population)	-38*	NM	All other opioids: NS
RADARS Poison center[57]	3Q09 - 2Q10	1Q11 - 2Q15	Quarterly rates of cases at poison control centers (U.S. population)	-75*	NM	All other opioids: -33*
RADARS Poison center[60]	3Q09 - 2Q10	1Q11- 4Q13	Quarterly rates of cases at poison control centers (U.S. population)	-55*	NM	All other opioids: -7*
RADARS SKIP[61,62]	1Q09 - 2Q10	1Q11 – 2Q14	Past month prevalence (Patients with primary diagnosis of opioid abuse)	-42*	+100	ER oxymorphone: +38*
RADARS SKIP[60]	3Q09 - 2Q10	1Q11- 4Q13	Past month prevalence (Patients with primary diagnosis of opioid abuse)	-30*	NM	All other opioids: +16*
RADARS SKIP[63]	4Q09 – 3Q10	4Q10 – 1Q12	Past month prevalence (Patients with primary diagnosis of opioid abuse)	-37	+78¥	All other opioids: +5¥
NAVIPPRO[58]	2Q09 – 3Q10	3Q10 – 2Q12	Past month prevalence (Patients entering substance use disorder treatment)	-41*	NM	ER oxymorphone: +246* ER morphine: NS
NAVIPPRO[64]	1Q08 – 3Q10	3Q10 – 4Q11	Past month prevalence (Patients entering substance use disorder treatment)	-22*	-11*	ER oxymorphone: +191* ER morphine: NS
NAVIPPRO[60]	3Q09 - 2Q10	1Q11- 4Q13	NC	-48*	NM	All other opioids: -3*
NSDUH[65]	1Q09 – 4Q09	1Q13 – 4Q13	Past year prevalence (US household survey-12 years and older)	-28¥(NS)	NM	--
NSDUH[66]	1Q09 – 4Q09	1Q13 – 4Q13	Past year initiation rate (US household survey-12 years and older)	-28¥†	NM	--
NPDS[67]	3Q09 – 2Q10	3Q10 – 3Q12	Quarterly rates of calls to poison control centers (U.S. population)	-36*	+42*	Other single entity oxycodone +20*
Claims data[68]	3Q09 – 3Q10	4Q10 – 4Q13	Diagnosed rate (Patients on OxyContin and comparator opioids)	-35*	NM	ER oxymorphone: +236* ER morphine: +44* IR oxycodone: +36*
Kentucky cohort[69]	Pre-3Q10	4Q10 – 1Q11	Past month prevalence (recreational users)	-55†	NM	IR oxycodone: +23
Canada cohort[70]	1 year prior	3Q12-4Q12	Positive urine drug screen (recreational users)	-12*	NM	ER morphine: NS
Australia cohort[71]	1Q14-1Q14	2Q14 – 3Q14	Past month prevalence (recreational users)	-57*	NM	Other opioids: NS

*p<0.01; † value not reported; ¥estimated; NM-not measured; NC-not clear; NS-Not significant; ‡There were some differences in the operational definition of abuse across sources (Table 10).

Cost Benefit and Potential Impact of ADFs

- What are the potential costs and outcomes of using ADFs versus non-ADFs?
- What level of effectiveness in abuse reduction and in price difference would be needed for ADF opioids to achieve cost neutrality or net savings relative to non-ADF opioids?

Cost-Benefit Model

- A weighted average of daily opioid cost for ADF and non-ADF opioids was calculated using market share data combined with opioid cost in the Federal Supply Schedule
- Daily cost was estimated to be $11.60 for ADFs and $5.82 for non-ADFs
- Health care costs were obtained from the Mass Health Policy Commission for commercially insured patients; no data available for Medicare or Medicaid patients
- $19,285 per year for therapeutic users
- $31,005 for those abusing opioids

Outcomes and Costs of Treating 100,000 Chronic Pain Patients

Table ES6. Abuse-Related Outcomes for ADF and Non-ADF Opioid Cohorts of 100,000 Chronic Pain Patients with ER Opioid Prescriptions

Outcome (at 5 years)	ADF cohort	Non-ADF cohort	Increment (ADF cohort – Non-ADF cohort)
New case of abuse	8,229	10,532	-2,303
Person-years of abuse	23,322	29,943	-6,621
Overdose deaths	1.38	1.77	-0.39

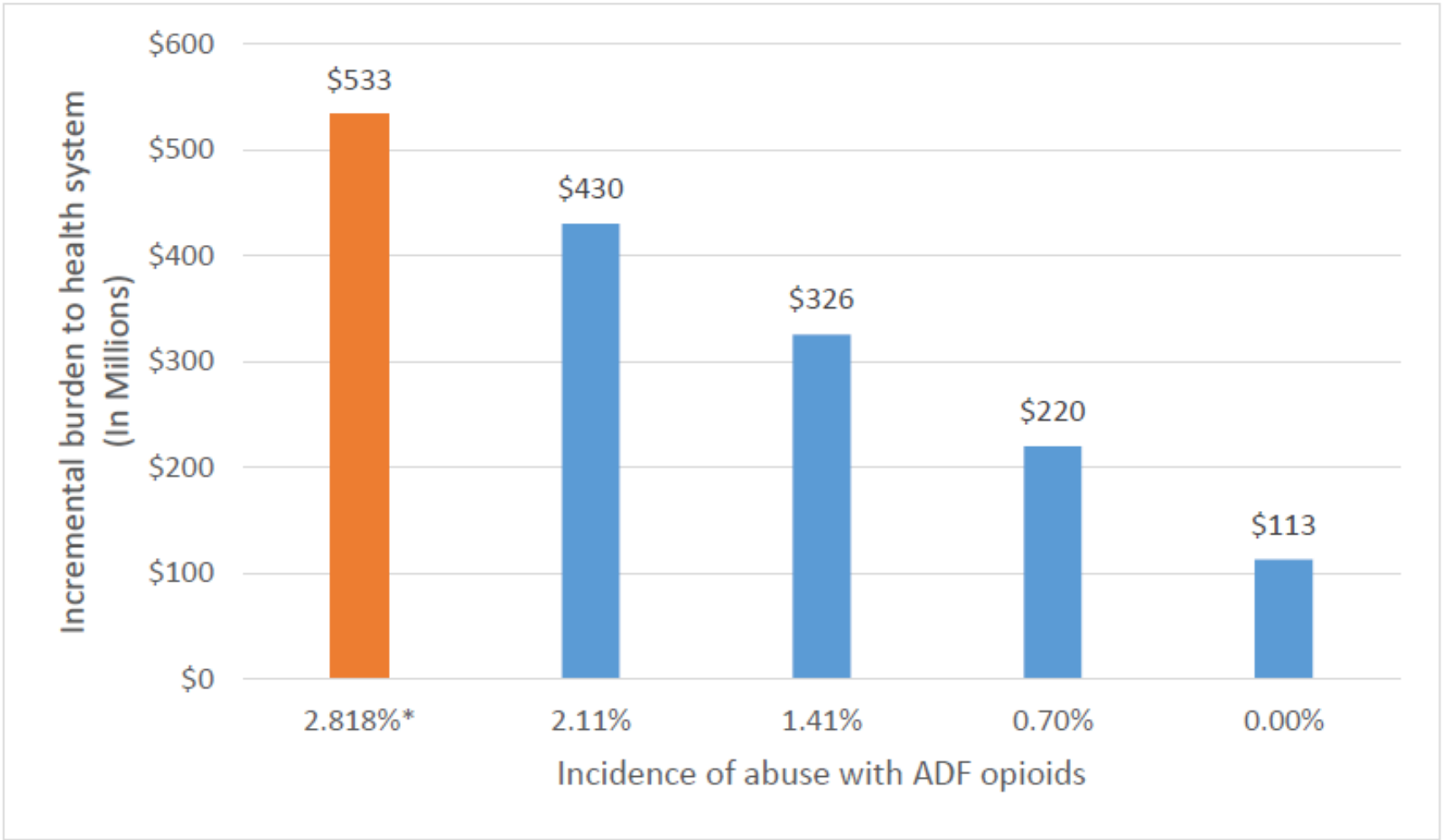
Table ES7. Total Estimated Health-Care Costs of Patients Prescribed ADF and Non-ADF Opioids Over Five Years

	ADF opioids	Non-ADF opioids	Difference (ADF – non-ADF)
Therapeutic use*	$7,845,606,246	$7,692,466,543	$153,139,703
Abuse*	$939,121,323	$1,205,748,255	-$266,626,932
Prescription opioid costs (entire cohort)	$1,303,908,313	$657,301,870	$646,606,443
Total	$10,088,635,882	$9,555,516,668	$533,119,214

Table ES8. Cost Per Incremental Outcome of ADF Opioid versus Non-ADF Opioid

Incremental outcome	Cost
To prevent one new abuse case	$231,514
To prevent one new abuse year	$80,517
To prevent one overdose death	$1,362,339,569

Figure ES2. Incremental Health System Cost of ADFs at Increasing Levels of Effectiveness (Decreasing Incidence of Abuse)



Costs of Converting 173,000 Non-Cancer Pain Patients to ADFs for One Year

Table ES9. Outcomes When Converting All Non-Cancer Chronic Pain Patients with Prescription ER Non-ADF Opioids to ADF Opioids in Massachusetts in One Year

	Mixed ADF/non-ADF opioid use	All ADF opioid use	Difference
Abuse cases	5,229	4,387	-842
Prescription opioid costs	$489,925,522	$1,002,689,521	$512,763,999
Abuse-related costs*	$224,828,862	$203,548,318	-$21,280,544
Total healthcare costs	$5,331,764,758	$5,806,899,717	$475,134,959
Cost to prevent one new case of abuse using ADF opioids	--	--	$599,131

*Combination of prescription (opioid and non-opioid) and resource utilization costs

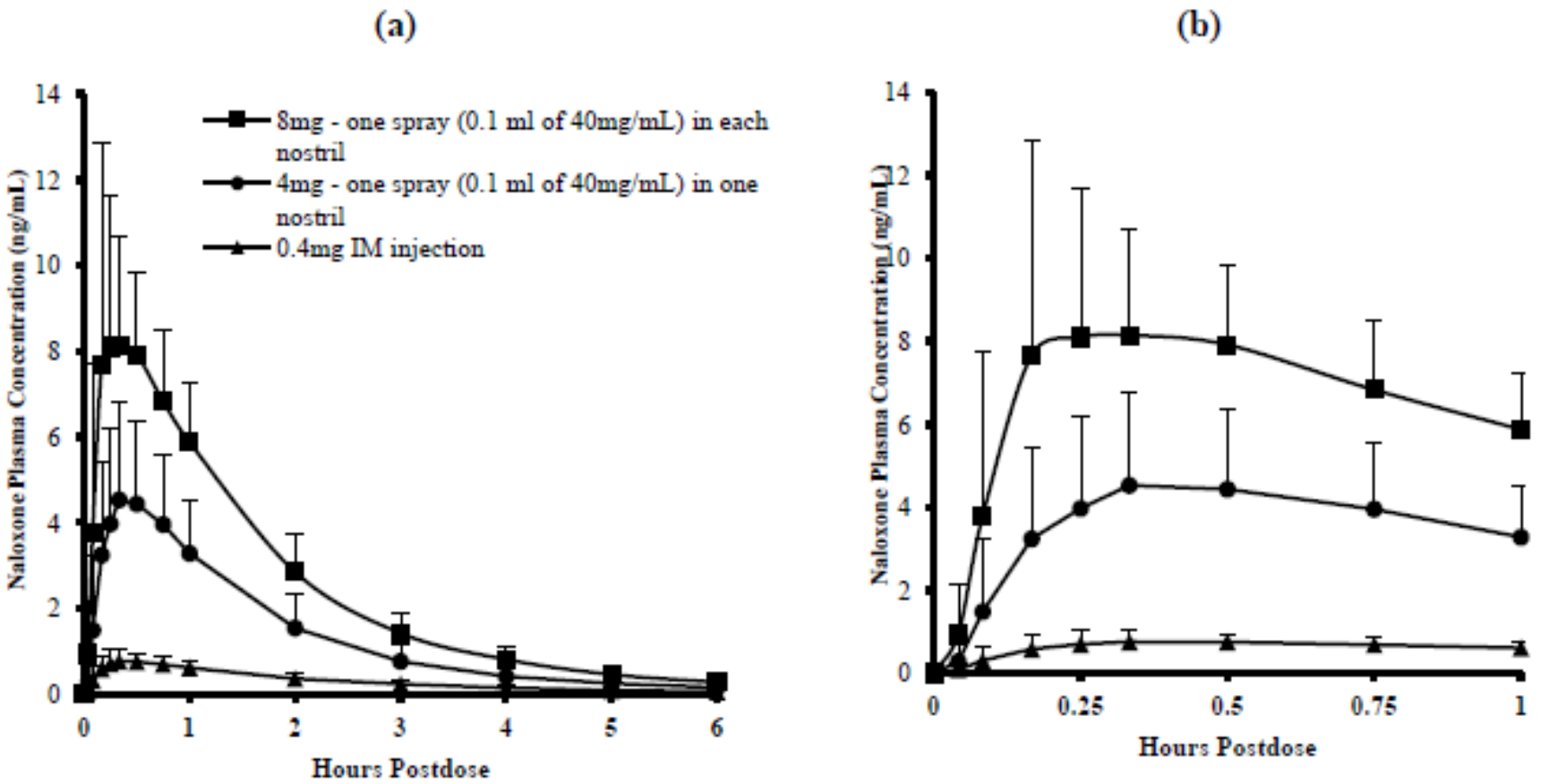
Summary

- FDA is relying on PK-PD relationships, opioid blockade studies, and non-inferiority studies for evaluation and approval of new, long-acting buprenorphine dosage forms
- Labeling will be dependent on whether a blocking dose of buprenorphine is being administered
- Several new naloxone formulations have been introduced into the market
- Newer naloxone formulations may need to have a Cmax approaching 3 ng/ml
- ADF opioids can reduce cases of abuse but at a very high cost per case, thus limiting the applicability of this strategy
- Cost Neutrality could only be achieved if the cost of ADF opioids were reduced at least 41 %

Thanks for your Attention

Intranasal Naloxone Pharmacokinetics

Figure 1 Mean ± SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intranasal Administration and Intramuscular Injection



Buprenorphine Implant