

# **Probuphine for Maintenance Treatment of Opioid Dependence**

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Titan Pharmaceuticals, Inc.  
FDA Advisory Committee  
March 21, 2013

# Probuphine for Maintenance Treatment of Opioid Dependence

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Marc Rubin, M.D.  
Executive Chairman  
Titan Pharmaceuticals, Inc.

# Opioid Dependence is a Chronic Neurobiological Disease

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- Impacts patient, family and society
- Medication assisted treatment is viable option
- Medical treatments themselves can be subject to abuse, misuse or diversion
- One of the most challenging and complex diseases to manage

# Buprenorphine: An Established Treatment for Opioid Dependence

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- Used by many patients in US
- Sublingual BPN has increased access to care
- Used in office-based setting
  - Tablet for sublingual administration
  - Sublingual film
- Less reinforcing than methadone
- Additional treatment alternatives are needed

# Draft Guidance on Abuse-deterrent Opioids

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- Released by FDA on January 9, 2013
- Abuse-deterrent formulations include delivery systems
  - “...a subcutaneous implant can be more difficult to manipulate.”

# Probuphine: Formulation and Indication

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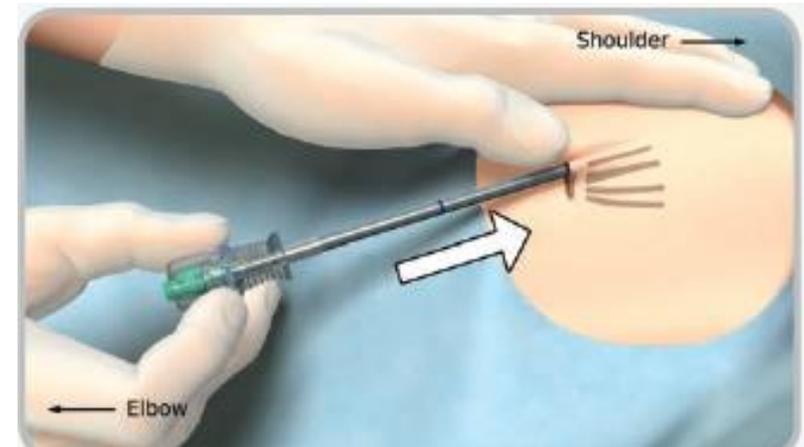
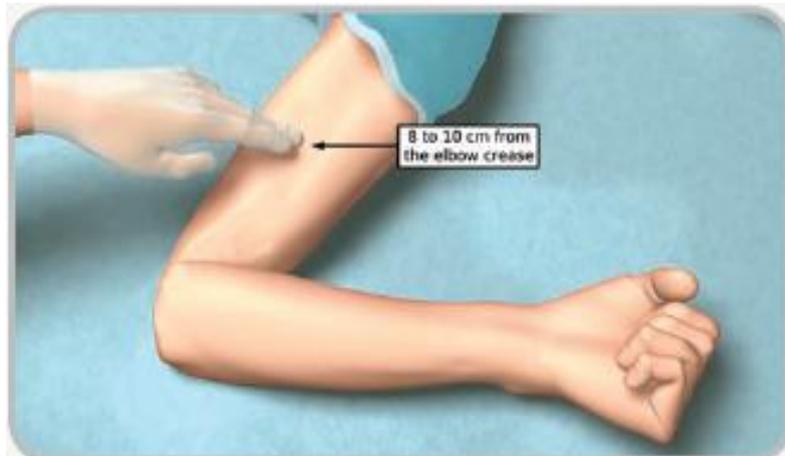
Buprenorphine  
HCL + EVA  
polymer →



- Sustained-release formulation of buprenorphine in ethylene vinyl acetate (EVA) matrix
  - 26 mm long, 2.5 mm diameter
  - 80 mg of buprenorphine
- EVA used in subdermal implants, ocular implants, vascular stents, IUDs
- No risk of drug “dumping”
- Six months of sustained drug delivery

# Probuphine Administration: Subdermal Placement in Minor Procedure

- Inserted under local anesthesia in brief office procedure
- After 6 months, implants removed
- New implants placed if indicated



# Goals of Probuphine Development Program

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- Provide safe and effective alternative delivery form of buprenorphine
- Address care of patient as well as public health
- Deliver long-term continuous treatment without interruption
- Minimize patient possession and chance of diversion (Prescription, Dispensing, Possession)
- Efficacy endpoint developed with FDA as a meaningful metric of opioid abuse

# Topics for Discussion

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- ❑ Efficacy for proposed indication and dose exploration
- ❑ Safety:
  - General safety in this population
  - Safety specific to the placement and removal of the implants
- ❑ REMS relevant to implant procedures
- ❑ Data and proposals to address:
  - Potential implant removal by non-medical personnel for the purpose of diversion
  - Potential long-term exposure to implant components
  - Use of multiple implant sites for continued treatment

# Agenda

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## Background and Medical Need

### **Andrea Barthwell, M.D., FASAM**

Former Deputy Director of Demand Reduction  
Office of National Drug Control Policy (ONDCP)  
Founder and CEO of Two Dreams

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## Clinical Efficacy

### **Katherine Glassman-Beebe, Ph.D.**

Executive VP and Chief Development Officer  
Titan Pharmaceuticals, Inc.

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## Clinical Safety

### **Steve Chavoustie, M.D., FACOG, CCRP**

PI, Segal Institute for Clinical Research  
Assistant Professor, Obstetrics and Gynecology, Family  
Medicine and Community Health, University of Miami,  
Miller School of Medicine

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## REMS

### **Garry Neil, M.D.**

Head of R&D, Braeburn Pharmaceuticals

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## Conclusion

### **Katherine Glassman-Beebe, Ph.D.**

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# Additional Experts

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**Karen L. Sees, D.O.**      **Independent Medical Consultant**

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**John Constant, Ph.D.**      **Vice President, Scientific Affairs**  
PRA International, Inc.

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**Deborah Leiderman, M.D., M.A.**      **CNS Drug Development and Regulatory Consultant**

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**Sidney Schnoll, M.D., Ph.D.**      **Vice President, Pharmaceutical Risk Management Services**  
Pinney Associates

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**Behshad Sheldon**      **Executive Vice President**  
Braeburn Pharmaceuticals

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**Alan Bye, Ph.D.**      **Independent Pharmacokinetic Consultant**

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# Opioid Dependence: Patient Care and Public Health Challenges

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Andrea Barthwell, M.D., FASM

Former Deputy Director of Demand Reduction  
ONDCP

Founder and CEO of Two Dreams

# Perspective on Opioid Dependence

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- Opioid abuse, misuse, diversion, overdose
- Goal/challenge of medication assisted treatment (MAT)
- Appropriate Probuphine patients

# Non-medical Prescription Opioid Use is a Major Public Health Problem

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- ~5.1 million in the US in 2011
  - 4.5 million non-medical use
  - 620,000 heroin
- ~2.2 million are opioid dependent
  - 1.8 million non-medical use
  - 369,000 heroin
- ~750,000 of non-medical users sought treatment for opioid dependence

# Opioid Dependence: A Chronic Disease

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- Dysfunction in circuits leads to
  - Bio-psycho-social changes
  - Pathologically pursuing reward
  - Relief by substance use
  - Disregard for consequences
- Physical dependence and need for opioid

# Opioid Dependence: A Potentially Fatal Disease

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- Increased risk of death
  - HIV AIDS
  - Suicide
  - Overdose
  - Infection
  - Trauma

# MAT Options for Opioid Dependence

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- Methadone, buprenorphine, buprenorphine/naloxone and Naltrexone
- Drug Abuse Treatment Act (DATA 2000) allowed medical office-based treatment of opioid dependence
- Available through Opioid Treatment Programs (OTP) certified by SAMHSA, office based opioid treatment (OBOT)

# Benefits of Medication Assisted Treatment

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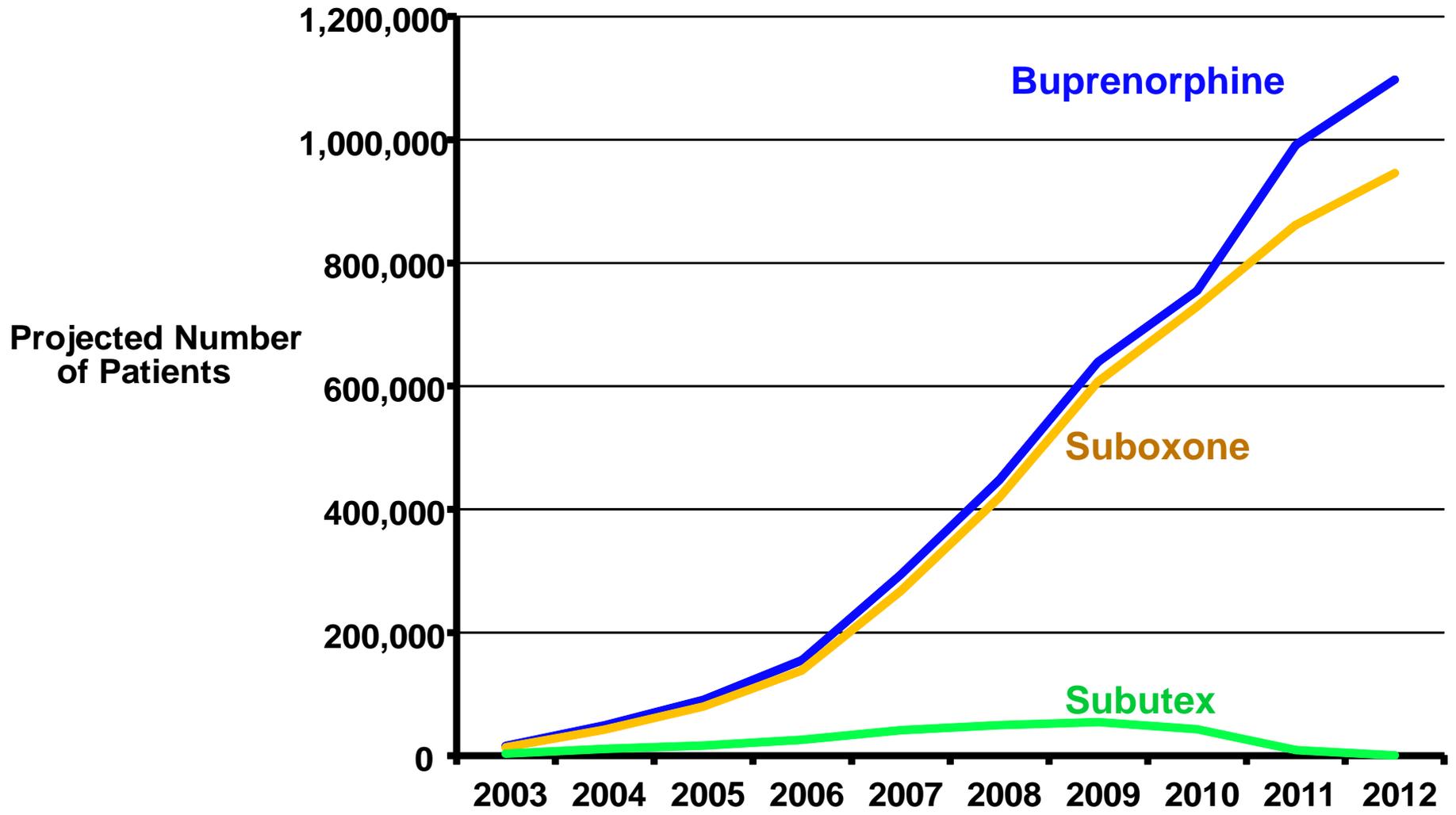
- Reduces high risk behavior, crime, drug use
- Positive health outcomes and psycho-social functioning
- Reduction in use correlates with retention in treatment
- Patients retained in MAT risk reduced by 75%

# Buprenorphine Treatment Paradigm

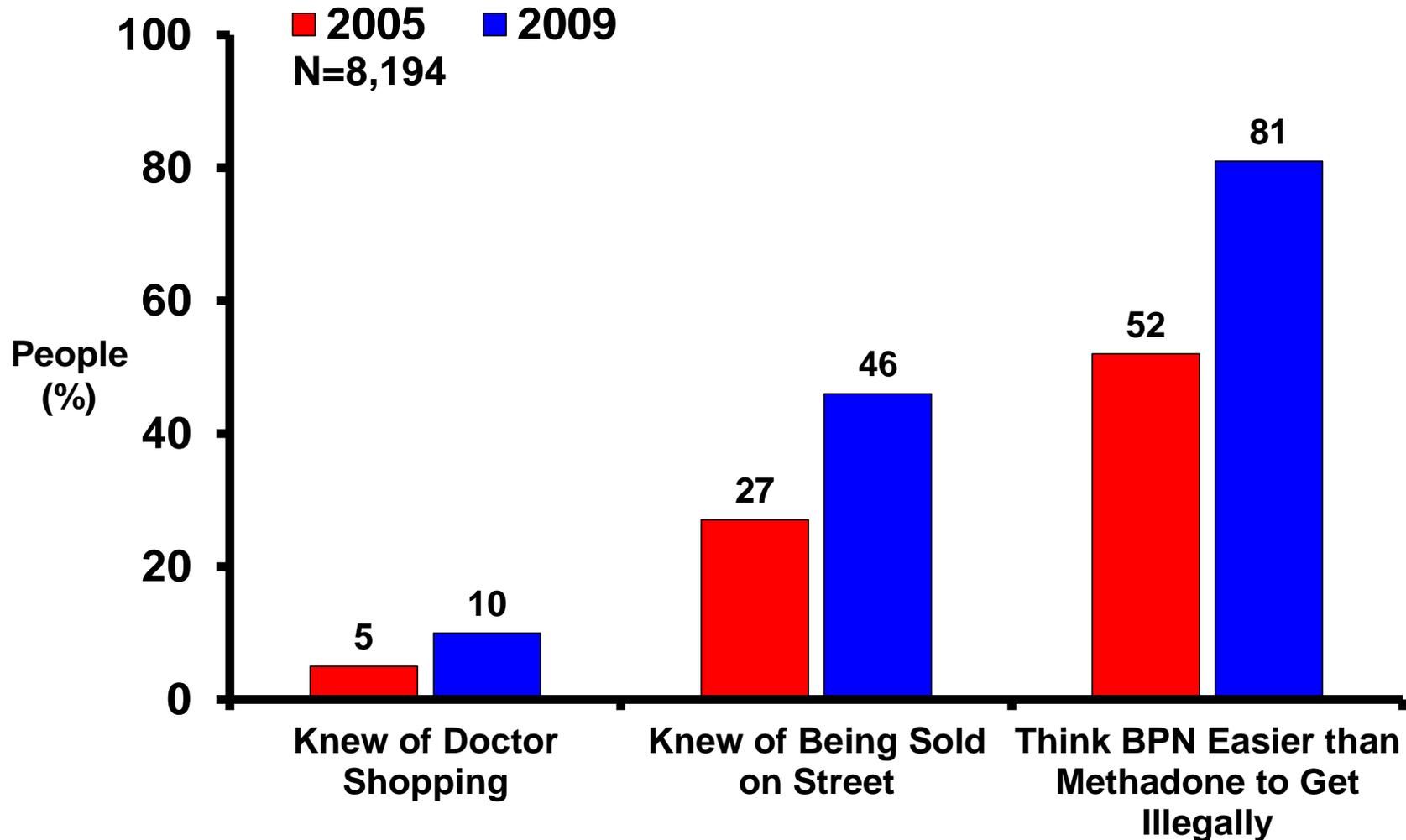
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- 3 phases of MAT
  - Induction
    - Goal: eliminate opioid withdrawal symptoms and achieve steady state
  - Stabilization
    - Goal: eliminate craving and extinguish drug-seeking
  - Maintenance
    - Goal: resume normal functioning and continue medication

# Increasing Numbers of Buprenorphine Prescriptions

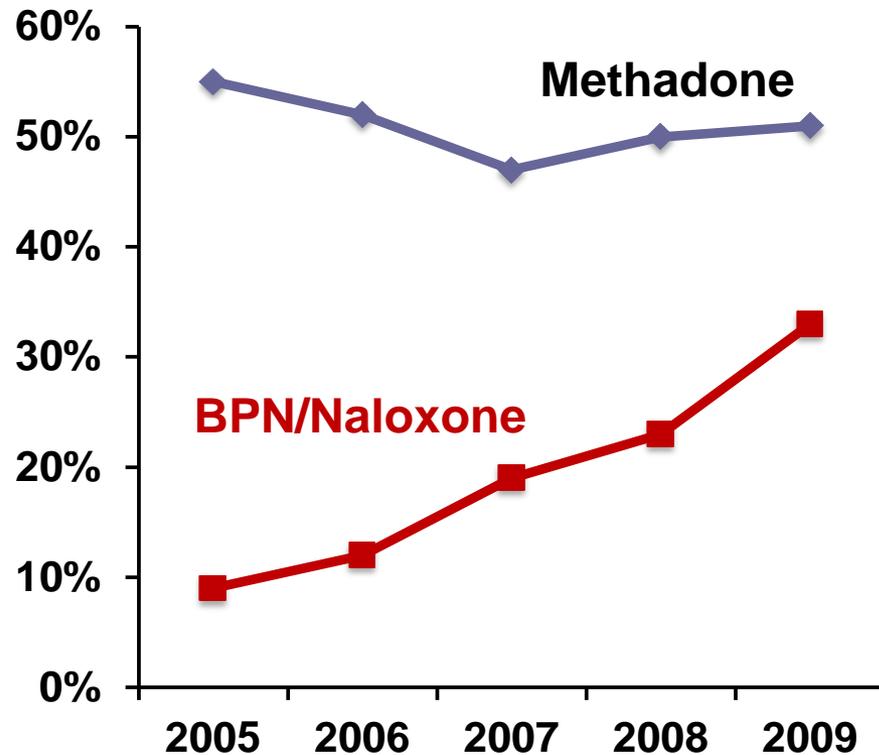


# Physician Knowledge of Buprenorphine Misuse and Diversion

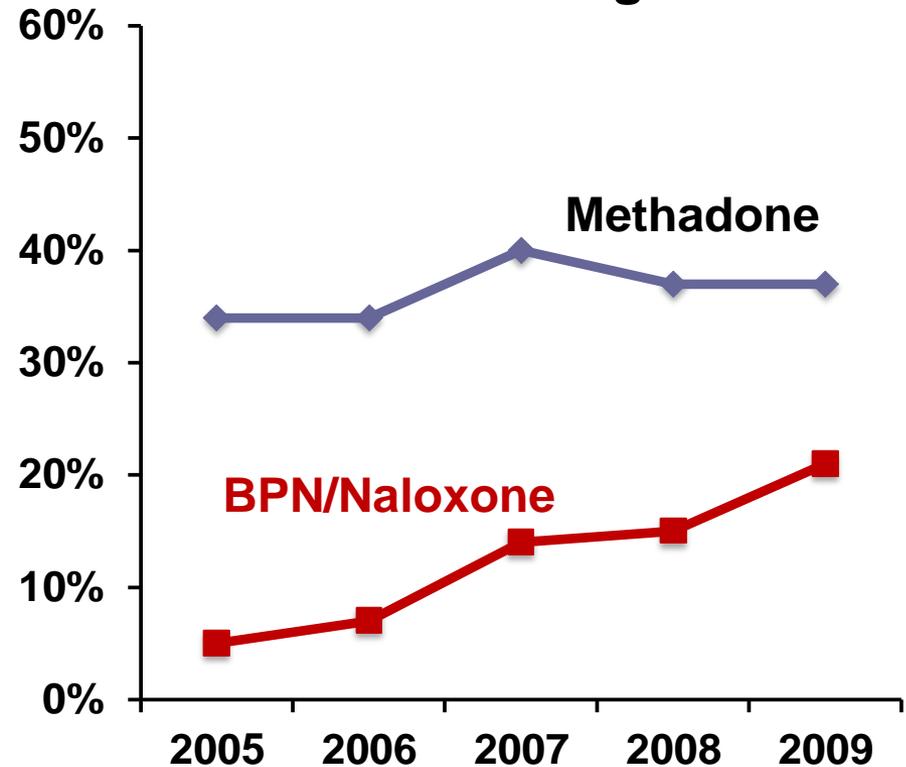


# Patient Knowledge of Buprenorphine Misuse and Diversion

## Knew Drug Being Sold on the Street



## Knew Drug Being Used to Get High



N=18,956

Adapted from Johanson et al. J. Drug and Alcohol Dependence 120:190-195, 2012

# Buprenorphine Ingestions by Children are Increasing

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- Increasing emergency department visits for buprenorphine ingestion
  - ~1,500 ED visits
- 9.5% of emergent hospitalizations for drug ingestion
  - 2.2% of opioid prescriptions

# Probuphine is an Alternative to SL BPN for Treatment of Opioid Dependence

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- A safe and effective product can
  - Minimize risk of accidental ingestion
  - Minimize misuse, abuse and diversion
  - Stabilize blood levels over 6 months
  - Reduce pill burden
  - Guarantee dose written is dose taken

## Patients who May Benefit from Probuphine

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- Households with children
- Risk of diversion
- Poor adherence
- Lack of MAT access
- Frequent travelers
- Stable patients who require less frequent office visits

# **Probuphine**

## **Pharmacokinetics and Efficacy**

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Katherine Glassman-Beebe, Ph.D.  
Executive Vice President and Chief  
Development Officer  
Titan Pharmaceuticals, Inc.

# Clinical Development Program: 6 Clinical Studies

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**Pharmacokinetic  
Study TTP-400**

**Bioavailability  
Study 810**

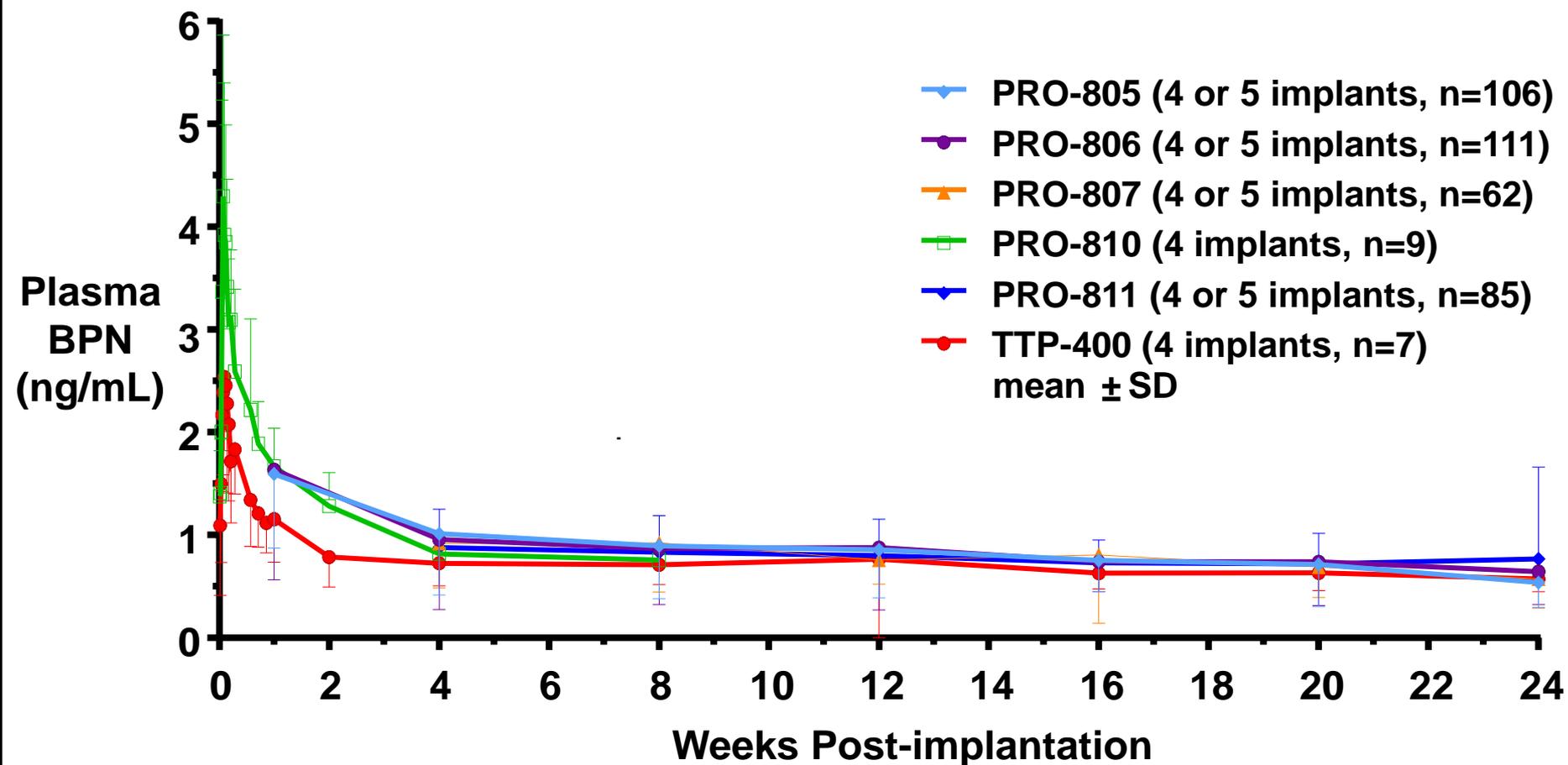
**Phase 3  
Study 805**

**Phase 3  
Study 806**

**Open-label  
Extension Safety  
Study 807**

**Open-label  
Extension Safety  
Study 811**

# Probuphine: Plasma Buprenorphine Concentration



## Phase 3 Study Design

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Double-blind, placebo controlled: 805 and 806

Open-label safety extensions: 807 and 811

# Phase 3 Study Design

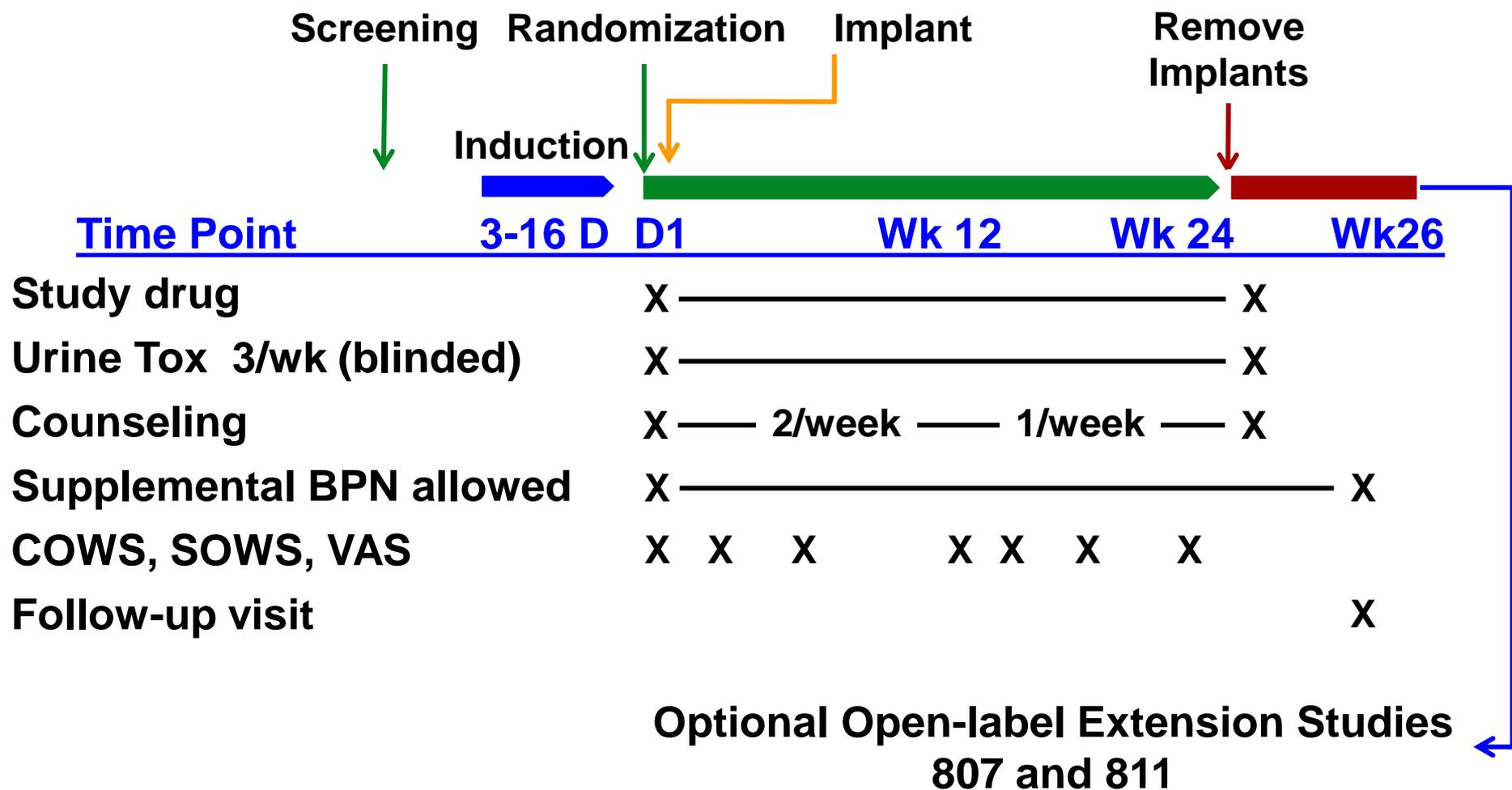
## Placebo-Controlled Studies

	<b>Study 805</b>	<b>Study 806</b>
<b>Number of Patients</b>	<b>163</b>	<b>287</b>
<b>Patient Population</b>	<b>Opioid-dependent adults</b>	<b>Opioid-dependent adults</b>
<b>Number of Sites</b>	<b>18</b>	<b>20</b>
<b>Design</b>	<b>Double-blind, randomized, placebo-implant-controlled</b>	<b>Double-blind, randomized, placebo-implant-controlled; Open-label active control (sublingual buprenorphine)</b>
<b>Randomization Scheme</b>	<b>2:1 Probuphine: Placebo implant</b>	<b>2:1:2 Probuphine: Placebo implant: Exploratory SL BPN</b>

Study 806 was partially funded through a grant from NIDA

# Study Procedures

## Studies 805 and 806



## Prospective Criteria for Dose Increase

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- Protocol required patients to receive 5<sup>th</sup> implant if
  - Supplemental buprenorphine required on  $\geq 3$  days per week for 2 consecutive weeks
  - Supplemental buprenorphine required on  $\geq 8$  days over 4 consecutive weeks
- Open-label Suboxone group (Study 806)
  - Daily dose not to exceed 16 mg
  - 1 dose reduction allowed
  - Daily dose not lower than 12 mg

# **Phase 3 Efficacy Endpoints and Analyses**

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Studies 805 and 806

# Primary Efficacy Endpoint

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- Primary efficacy outcome measure
  - Percentage of urine samples negative for opioids
  - Patient self-reported drug use

# Primary Analysis of Percent Opioid: Negative Urines in Studies 805 and 806

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- Percent of negative urine samples
  - Missing samples treated as positive
  - Negative sample treated as positive if patient self-reported opioid use
- Expressed as cumulative distribution function (CDF)
- Analyzed using stratified Wilcoxon test

# Secondary Endpoints: Efficacy Instruments Used in Phase 3 Studies

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- Subjective Opiate Withdrawal Scale (SOWS)
  - Score 0-64
  - Higher score = greater withdrawal
- Clinical Opiate Withdrawal Scale (COWS)
  - Score 0-44
  - Higher score = greater withdrawal
- Opiate Craving Visual Analog Scale (VAS)
  - 100 mm scale
  - 0 = no craving; 100 = highest possible craving
- Clinical Global Impression (CGI)

# Key Secondary and Exploratory Endpoints: Fixed Testing Sequences

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- Fixed testing sequence specified for each study to control for multiplicity
  - Each endpoint tested only if preceding endpoint(s) met statistical significance
  - All tested at  $\alpha=0.05$ , two-sided
- Prespecified sequences presented with efficacy results

# Key Inclusion and Exclusion Criteria

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- Key inclusions
  - Adults age 18-65
  - Current opioid dependence (DSM-IV-TR)
  - No MAT within 90 days
- Key exclusions
  - AIDS diagnosis
  - Serious medical or psychiatric diagnosis
  - Opioid use for chronic pain
  - Inadequate control of withdrawal symptoms post-induction
  - Significant craving post-induction
  - Pregnant or lactating women
  - Dependence on other substances

# Results

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Placebo-controlled Studies 805 and 806

# Patient Demographics Similar Between Studies

	Study 805		Study 806	
	Probuphine N=108	Placebo N=55	Probuphine N=114	Placebo N=54
	(%)	(%)	(%)	(%)
<b>Sex</b>				
Male	66.7	72.7	63.2	57.4
Female	33.3	27.3	36.8	42.6
Mean Age (yr)	35.8	39.3	36.4	35.2
<b>Race</b>				
Caucasian	75.9	72.7	83.3	83.3
Black	13.0	10.9	12.3	13.0
Asian	0	1.8	0	1.9
Other	11.1	14.5	4.4	1.9

# Baseline Characteristics

	Study 805		Study 806	
	Probuphine N=108	Placebo N=55	Probuphine N=114	Placebo N=54
	(%)	(%)	(%)	(%)
<b>Time Since First Diagnosis (patient-reported)</b>				
<5 years	72.2	72.7	74.6	77.8
5-10 years	15.7	7.3	11.4	11.1
>10 years	12.0	20.0	12.3	11.1
<b>Primary Opioid of Abuse</b>				
Heroin	63.9	61.8	66.7	51.9
Prescription analgesic	36.1	38.2	33.3	48.1

# Patient Disposition

	Study 805		Study 806	
	Probuphine N=108	Placebo N=55	Probuphine N=114	Placebo N=54
	n (%)	n (%)	n (%)	n (%)
ITT population	108 (100)	55 (100)	114 (100)	54 (100)
Completed study	71 (65.7)	17 (30.9)	73 (64.0)	14 (25.9)

# Patient Disposition

	Study 805		Study 806	
	Probuphine N=108	Placebo N=55	Probuphine N=114	Placebo N=54
	n (%)	n (%)	n (%)	n (%)
<b>Reasons for withdrawal</b>				
Treatment failure	0	17 (30.9)	6 (5.3)	9 (16.7)
Non-compliance	12 (11.1)	7 (12.7)	10 (8.8)	9 (16.7)
Patient request	8 (7.4)	9 (16.4)	5 (4.4)	9 (16.7)
Adverse event	4 (3.7)	0	2 (1.8)	2 (3.7)
Other	2 (1.9)	0	11 (9.7)	10 (18.5)
Lost to follow-up	10 (9.3)	4 (7.3)	9 (7.9)	3 (5.6)
Implant removal	1 (0.9)	0	0	0
Pregnancy	0	1 (1.8)	0	0

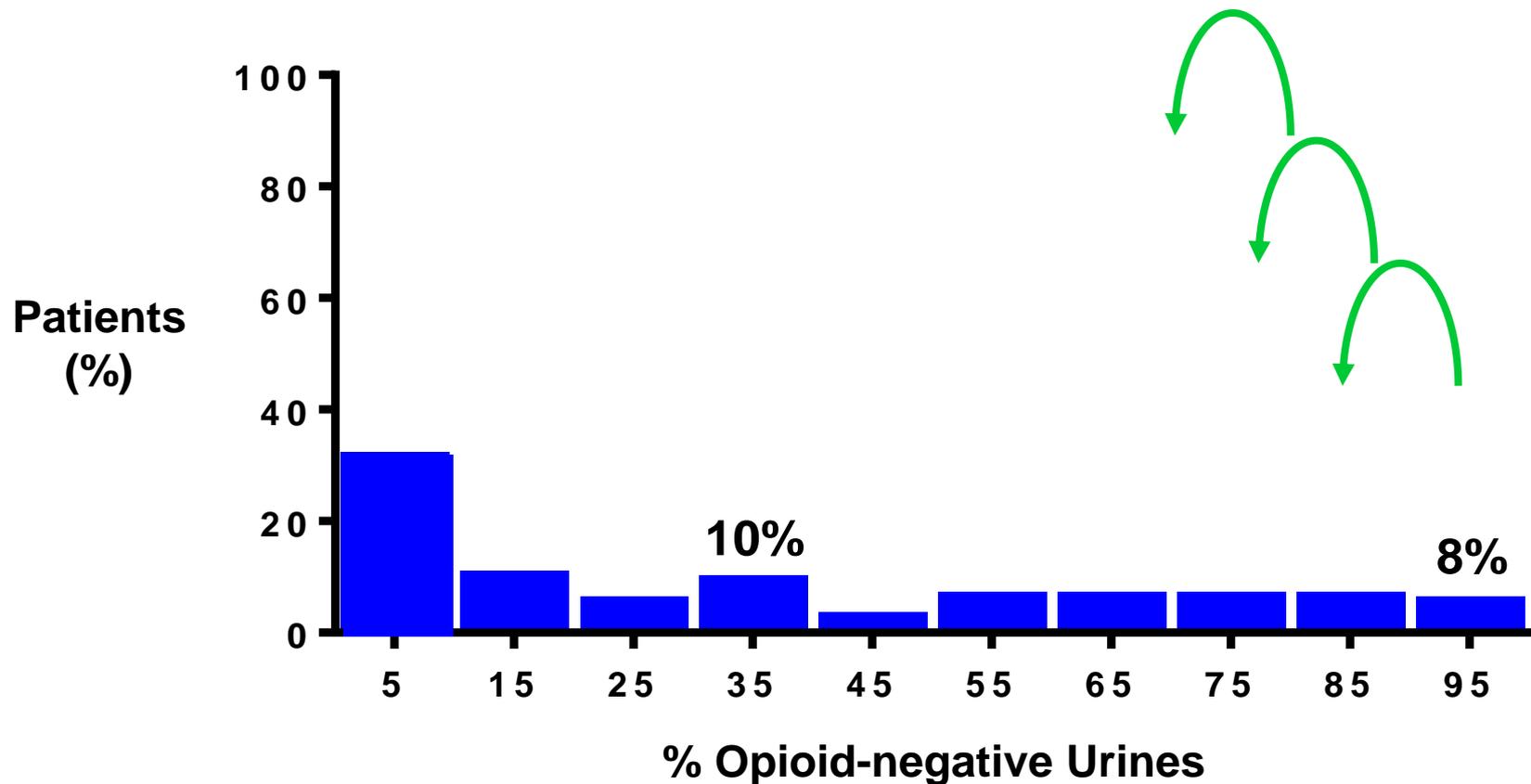
# **Efficacy Measures: Urine Drug Testing**

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## **Study 805**

# Study 805: Histogram of Percent-Negative Urines

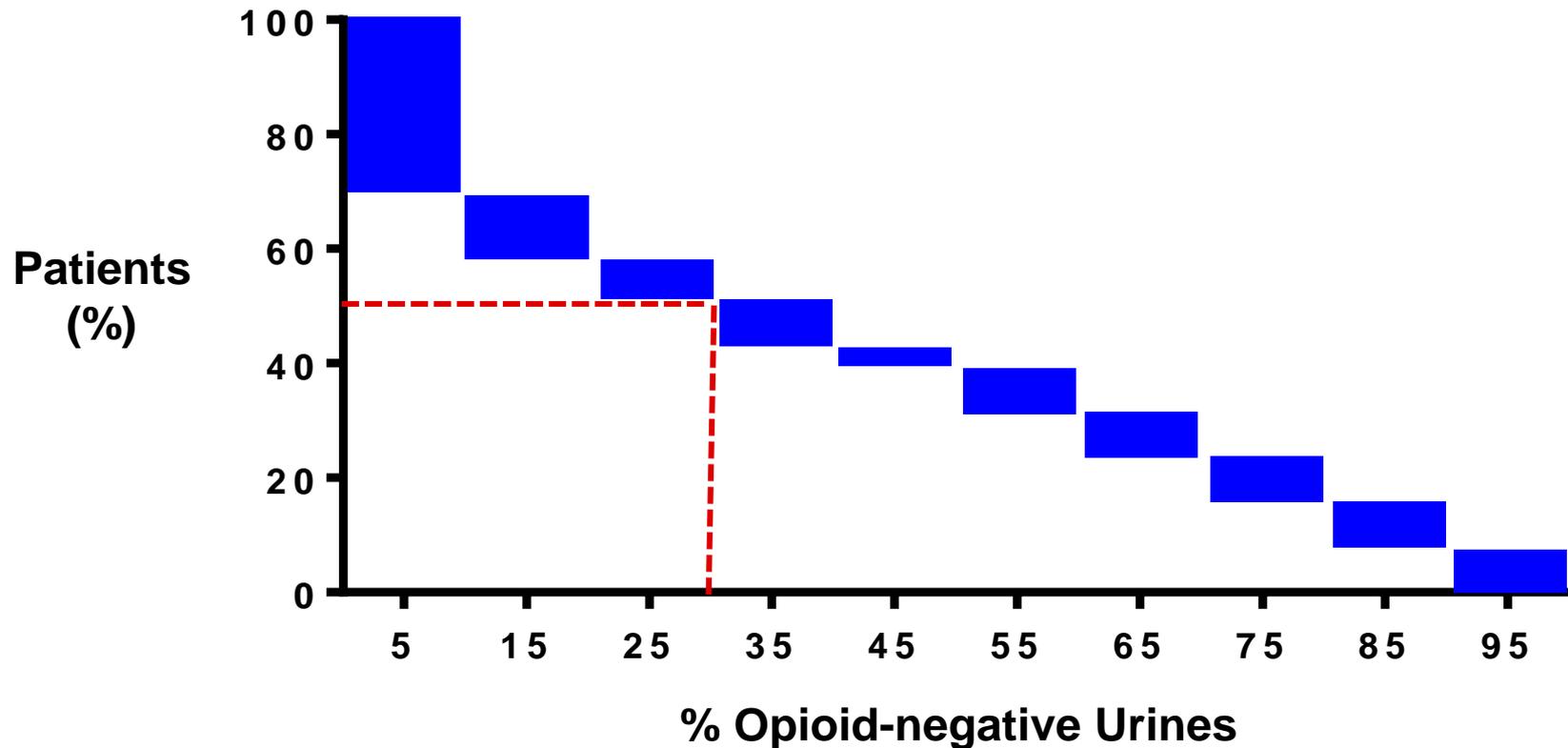
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Urine tested 3 times per week

# Study 805: Histogram of Percent-Negative Urines

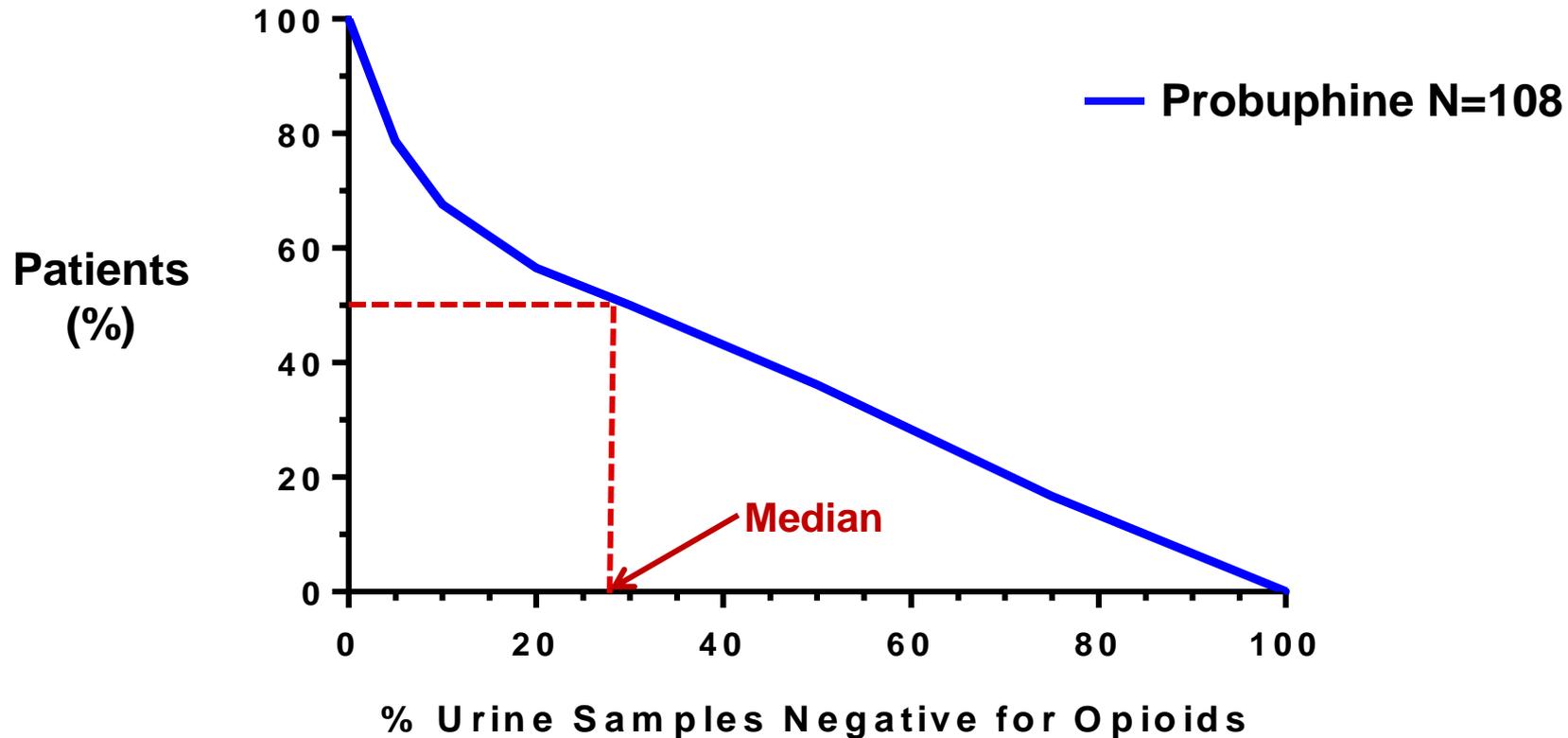
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Urine tested 3 times per week

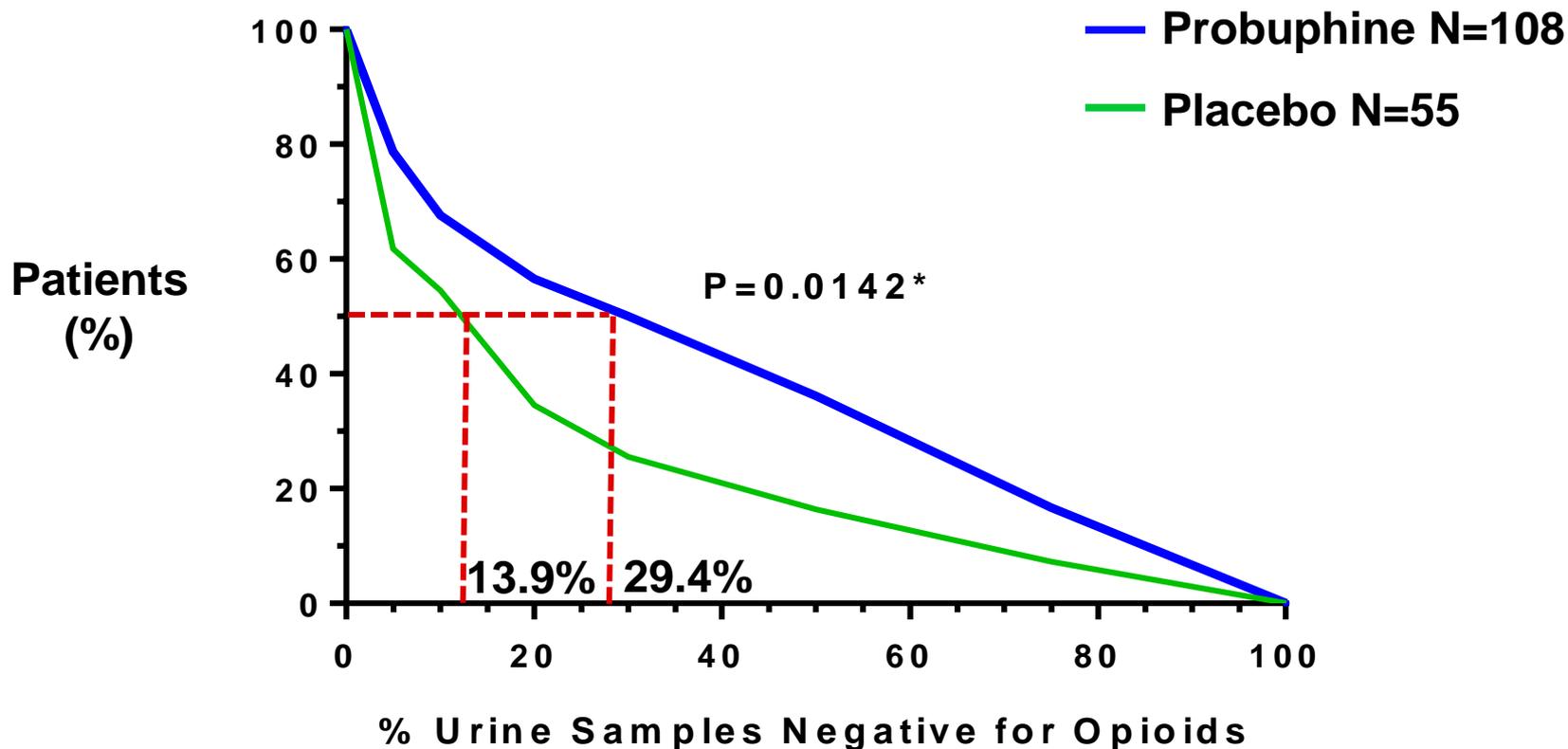
# Probuphine Superior to Placebo: CDF of % Negative Urines, Weeks 1-24, Study 805

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With patient self-report imputation  
Urine tested 3 times per week

# Probuphine Superior to Placebo: CDF of % Negative Urines, Weeks 1-24, Study 805

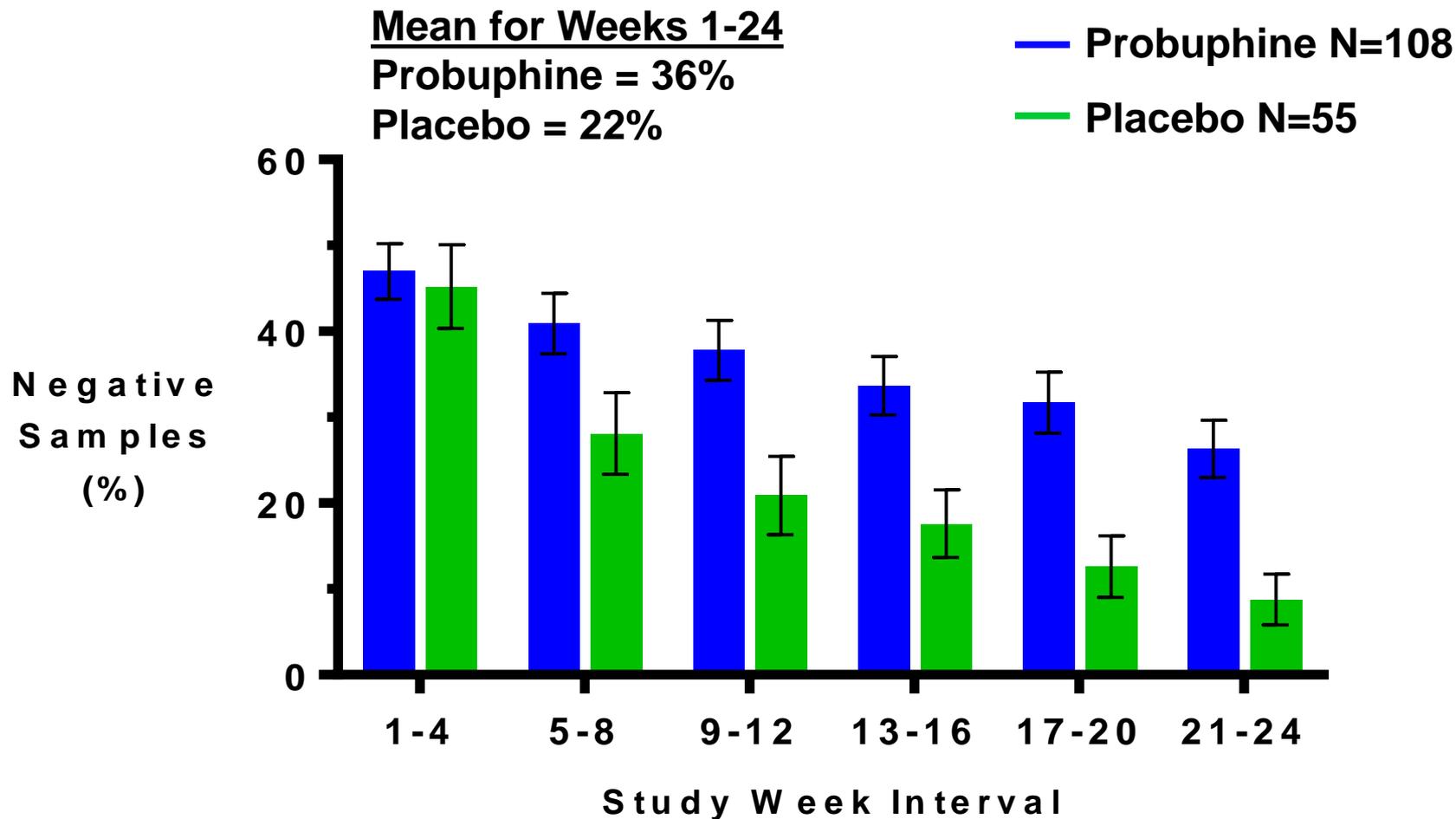


\*Stratified Wilcoxon rank-sum (van Elteren); ITT Population

With patient self-report imputation

Urine tested 3 times per week

# Probuphine Effective through 6 Months: Exploratory Analysis, Study 805



Urine tested 3 times per week

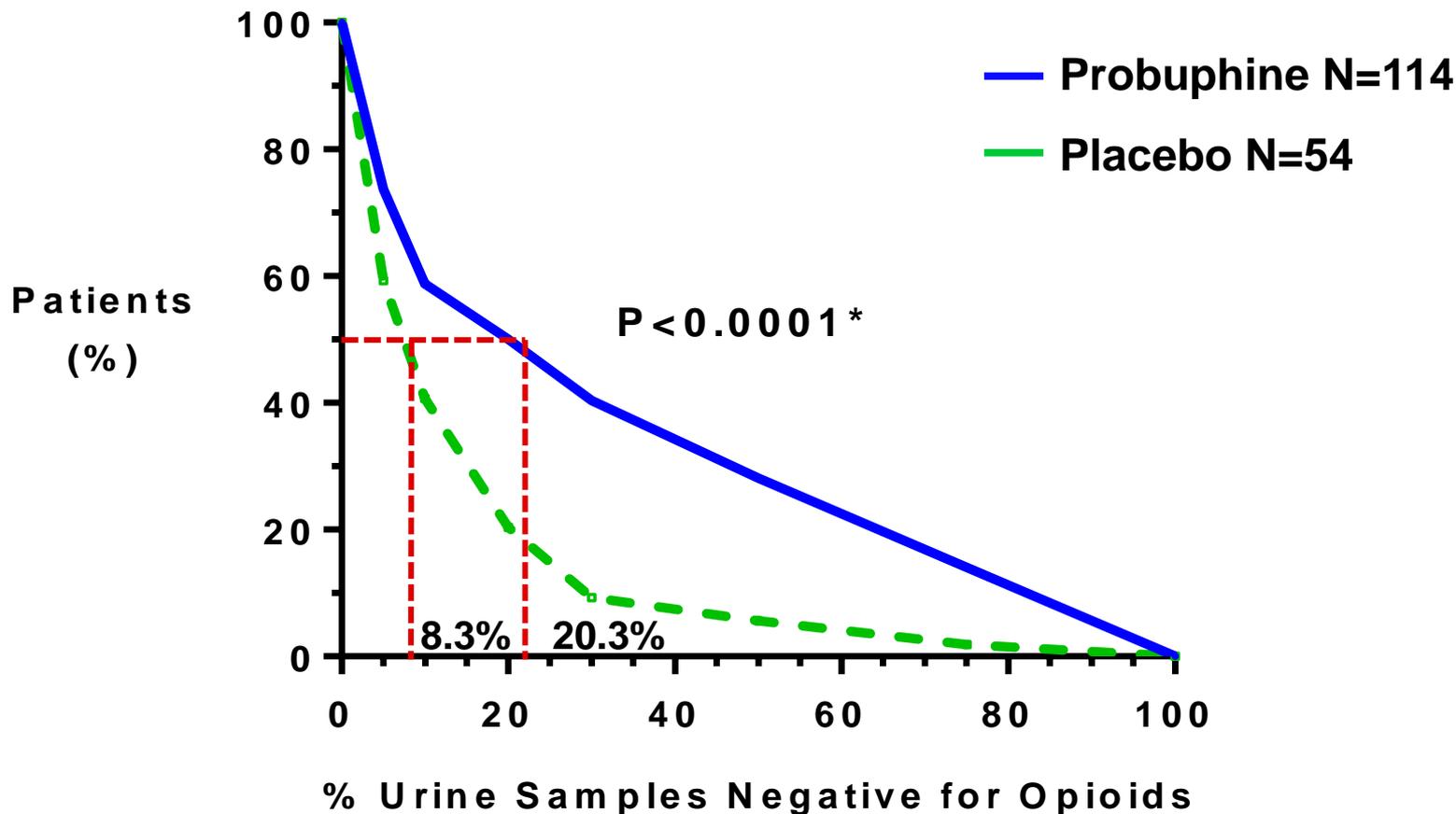
Data are mean  $\pm$  SEM; ITT population; missing values imputed as positive

# Efficacy Measures: Urine Drug Testing

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Study 806

# Primary Endpoint: Probuphine Superior to Placebo, Weeks 1-24, Study 806

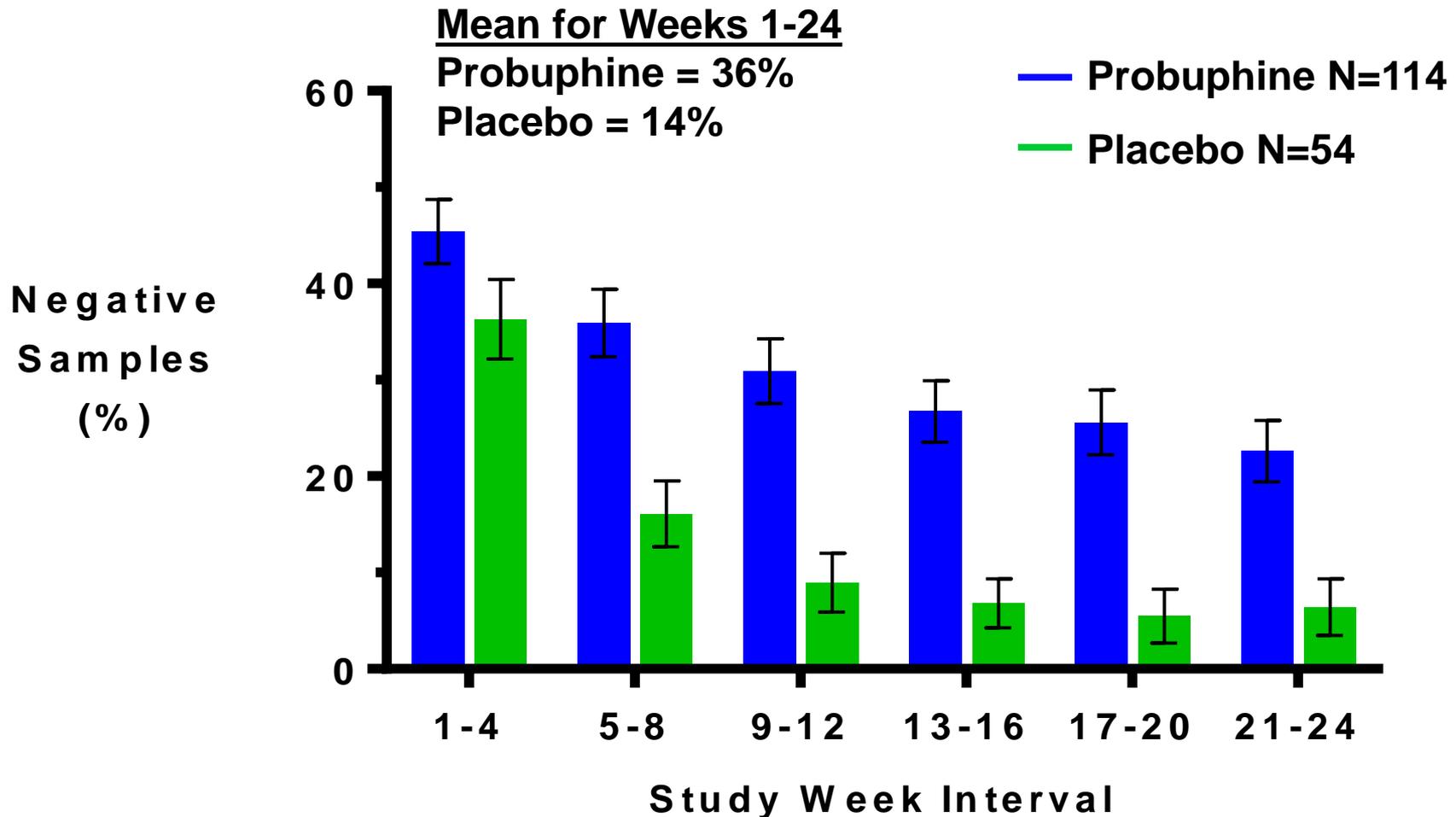


With patient self-report imputation

Urine tested 3 times per week

\*Stratified Wilcoxon rank-sum (van Elteren); ITT Population

# Probuphine Effective through 6 Months: Exploratory Analysis, Study 806



Urine tested 3 times per week

Data are mean  $\pm$  SEM; ITT population; missing values imputed as positive

## **Additional Efficacy Endpoints**

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Studies 805 and 806

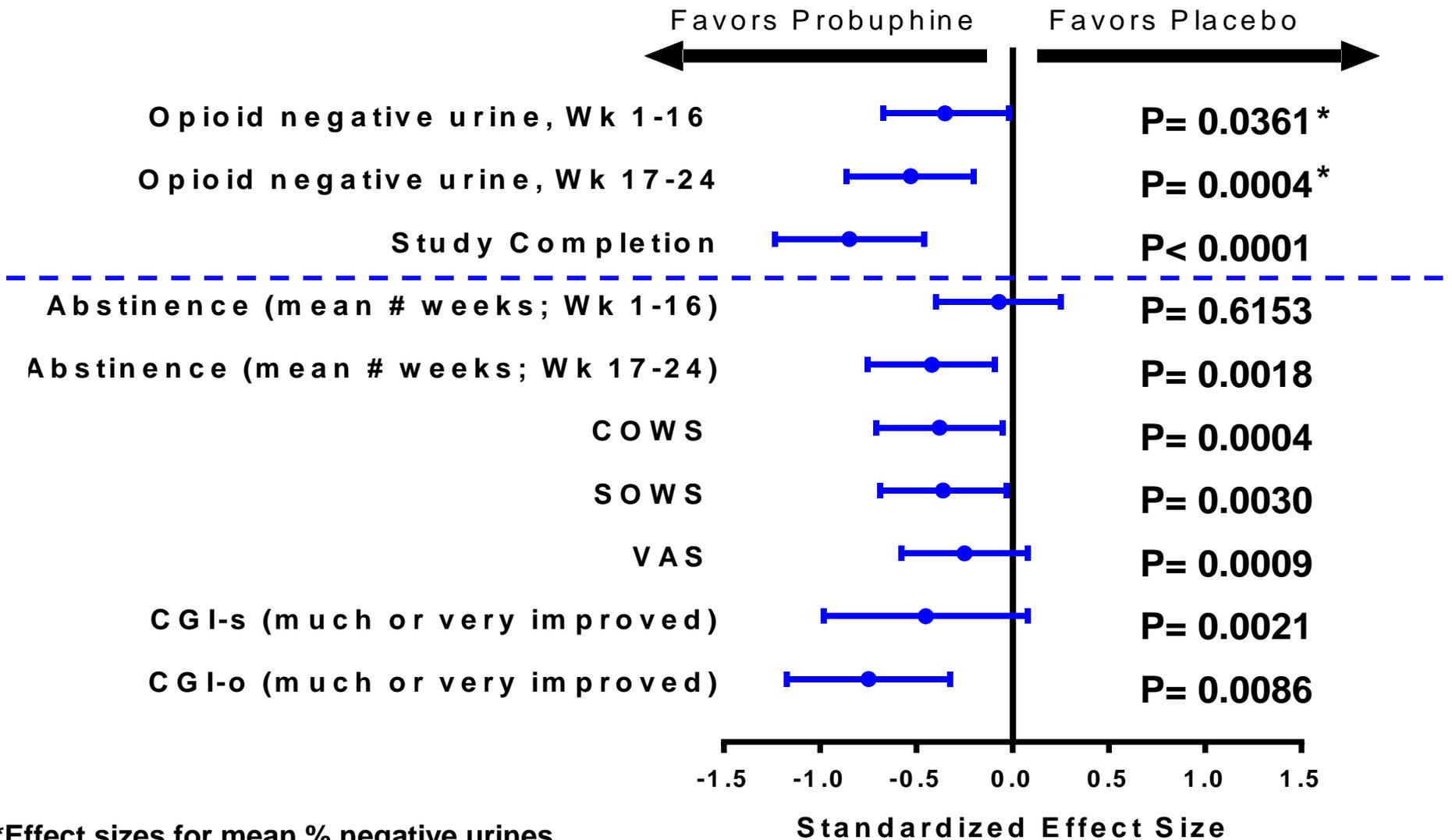
Presented in Order of Prespecified Fixed  
Analysis Sequence

# Key Secondary and Exploratory Endpoints: Pre-specified Fixed Testing Sequence Study 805

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- Key Secondary Endpoints
  - CDF of % opioid-negative urines, weeks 17-24
  - Mean % opioid-negative urines, weeks 1-16, 17-24
  - Proportion of study completers
  - Mean total and maximal weeks of abstinence
  - Symptoms of opioid withdrawal total score, weeks 1-16, 17-24 (SOWS, COWS)
  - Opioid craving total score (VAS), weeks 1-16, 17-24
  - Clinical Global Improvement, weeks 1-16, 17-24
- Exploratory Endpoints
  - Supplemental buprenorphine use

# Summary of Key Secondary Endpoints in Study 805: Effect Size

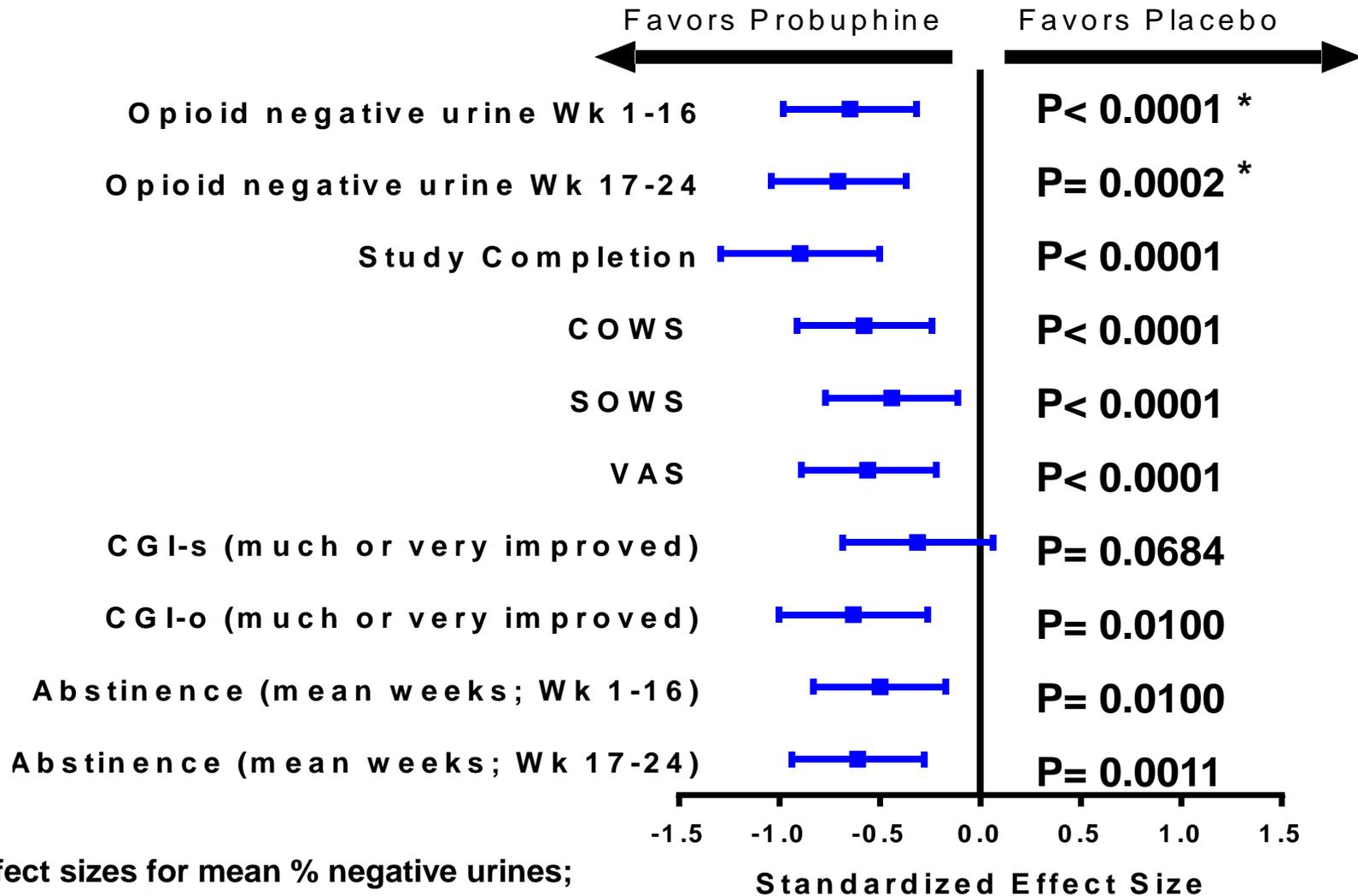


# Key Secondary and Exploratory Endpoints: Pre-specified Fixed Testing Sequence Study 806

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- Key Secondary Endpoints
  - CDF of % opioid-negative urines Weeks 1-16, 17-24
  - % opioid-negative urines, Probuphine vs. SL BPN
  - Proportion of study completers
  - Mean % opioid-negative urines Weeks 1-24, 1-16, 17-24
  - Symptoms of opioid withdrawal total score Weeks 1-16, 17-24 (SOWS, COWS)
  - Opioid craving total score (VAS) Weeks 1-16, 17-24
  - Clinical Global Improvement Weeks 1-16, 17-24
  - Probuphine vs. SL BPN for key secondary endpoints
  - Abstinence analyses
- Exploratory Endpoints
  - Supplemental buprenorphine use

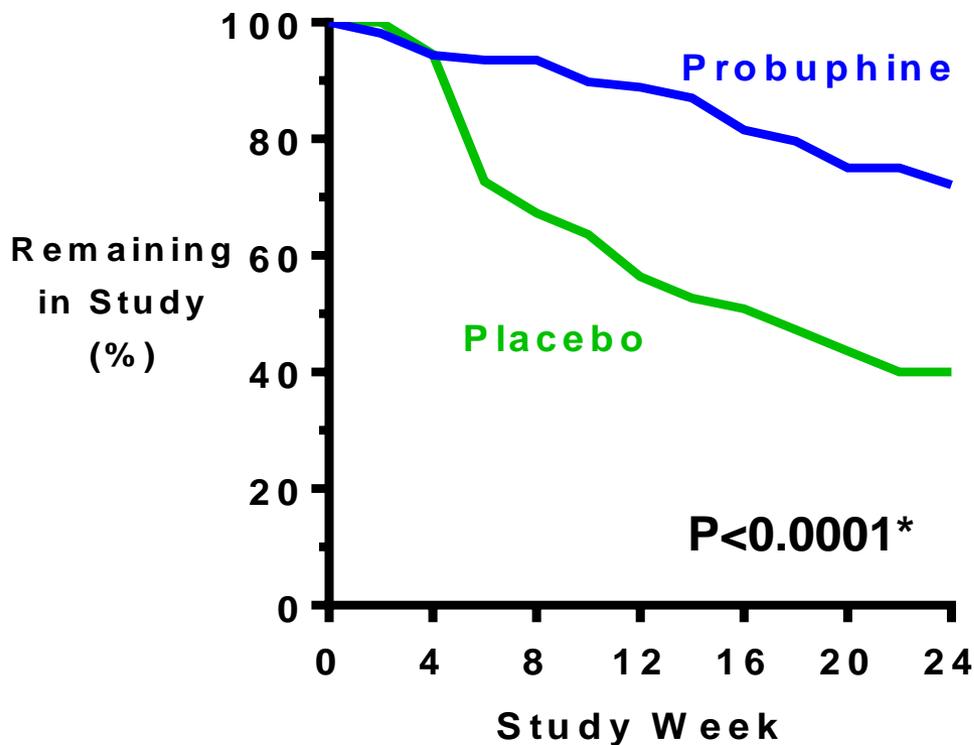
# Summary of Key Secondary Endpoints in Study 806: Effect Size



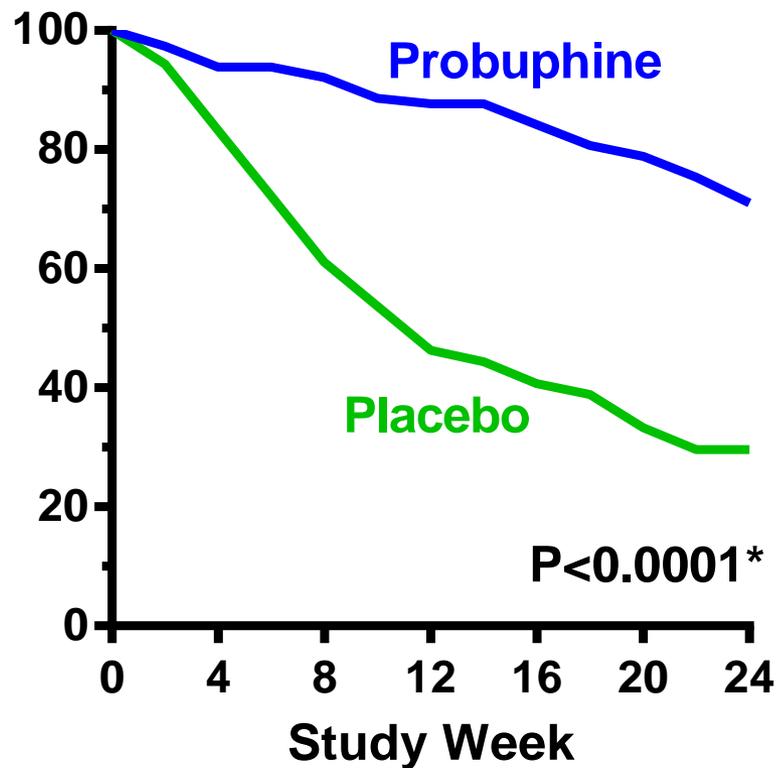
\*Effect sizes for mean % negative urines;  
P values: Wilcoxon rank sum test

# Probuphine Increased Study Completion. Studies 805 and 806

## Study 805



## Study 806



# Summary of Sublingual Rescue Medication Use in Probuphine Group

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- No rescue medication required
    - 63% of patients with 4 implants
    - 45% of patients after 5<sup>th</sup> implant
    - 79% of patients with 4 implants
    - 67% of patients after 5<sup>th</sup> implant
  - 41 of 83 (49%) patients who completed 2 sequential 24 week treatment periods required NO supplemental buprenorphine
- Studies 805 and 806
- Studies 807 and 811

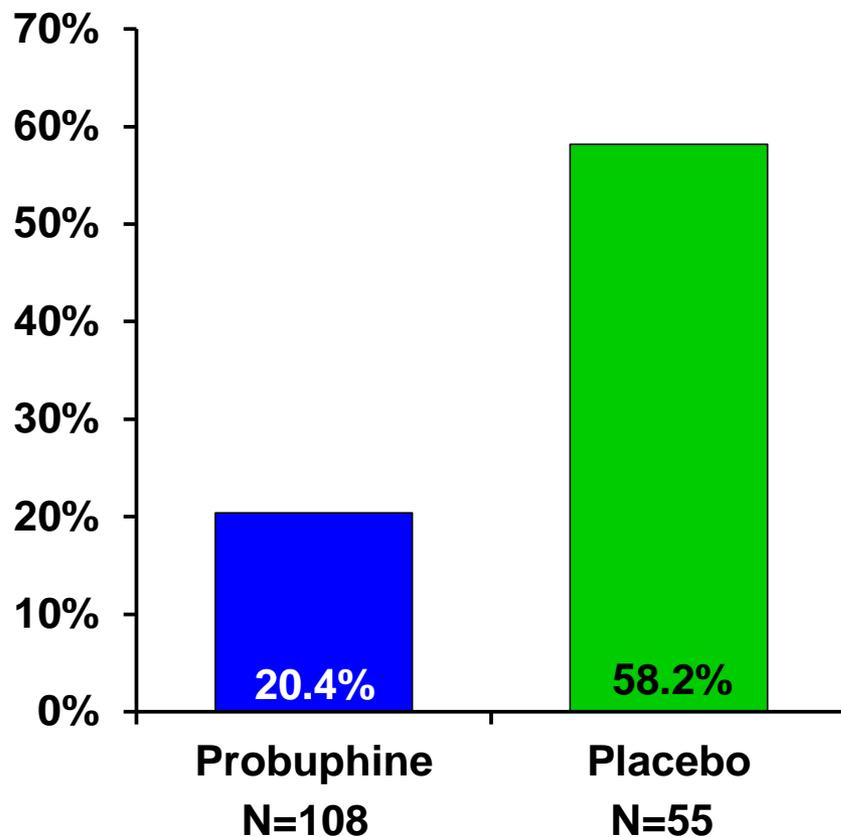
# Guidelines for Dose Increase and Treatment Failure

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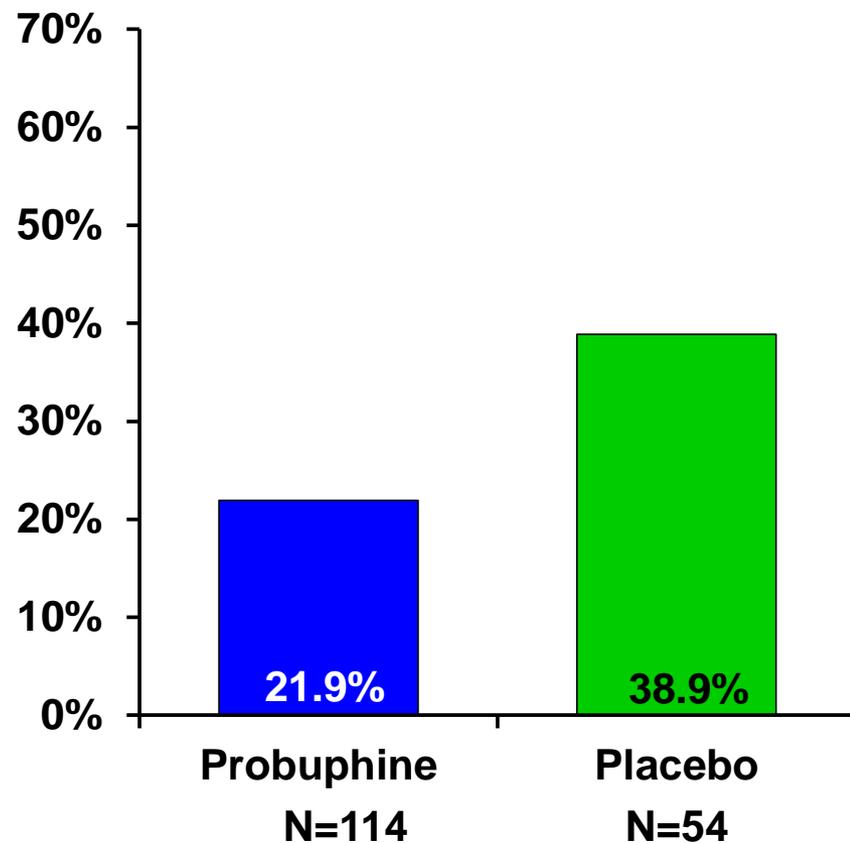
- Patients randomized to Probuphine or placebo required 5<sup>th</sup> implant (dose increase)
    - Took supplemental buprenorphine on  $\geq 3$  days per week for 2 consecutive weeks
- OR
- Took supplemental buprenorphine on  $\geq 8$  days over 4 consecutive weeks

# Fewer Probuphine Patients Required 5th Implant versus Placebo

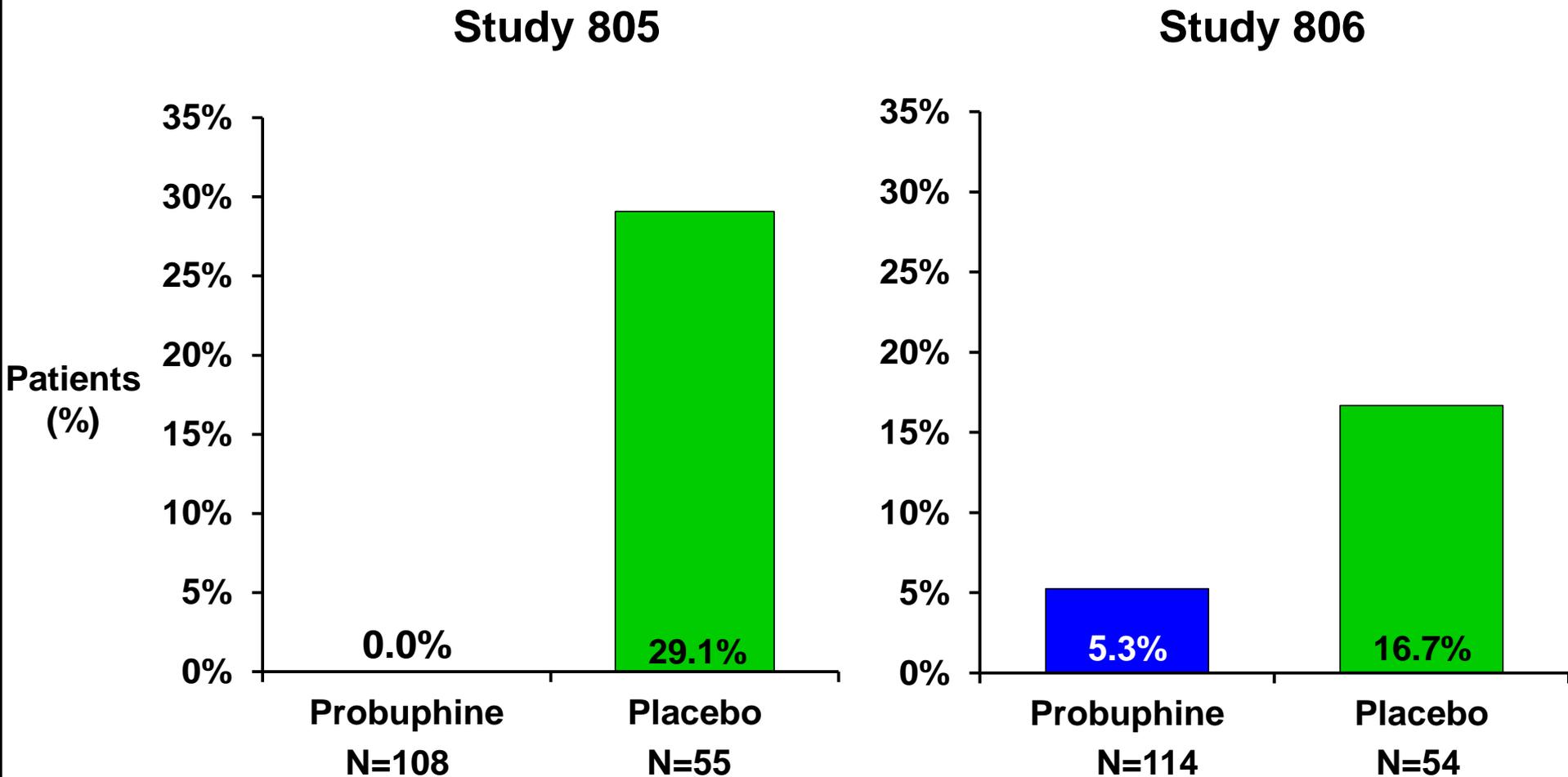
## Study 805



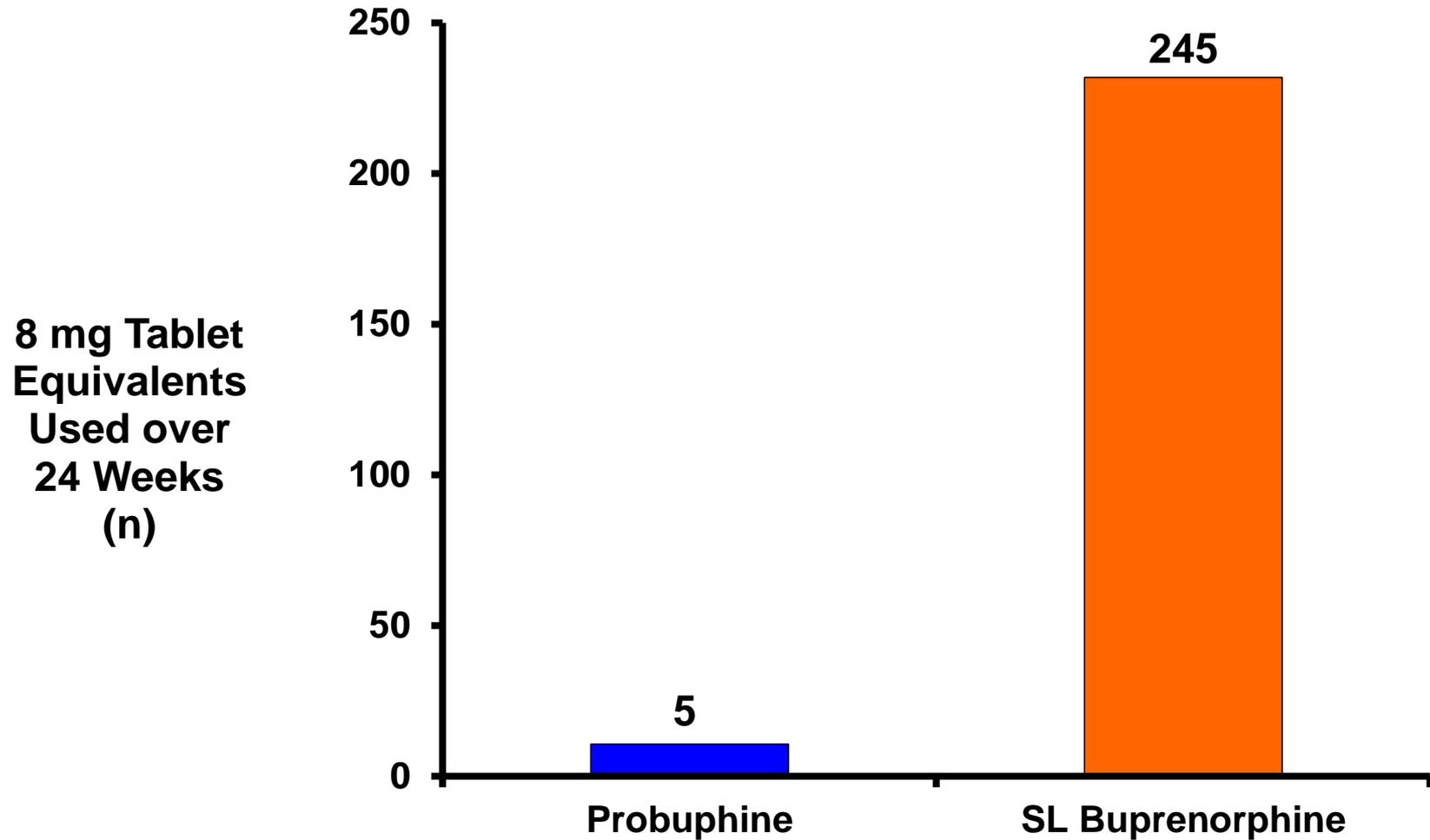
## Study 806



# Fewer Probuphine Patients Met Criteria for Treatment Failure



# Number of Sublingual Buprenorphine Tablets used by Probuphine Group and SL Buprenorphine Group



# Exploratory Comparison to Open-label SL Buprenorphine/ Naloxone

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Study 806

# Probuphine Efficacy Comparison with Open Label Sublingual Buprenorphine Arm

	Probuphine N=114	Placebo N=54	SL BPN N=119
<b>Percentage Opioid-negative urines, Weeks 1-24</b>			
<b>LS Mean</b>	<b>36.0</b>	<b>14.4</b>	<b>35.1</b>
<b>SEM</b>	<b>2.8</b>	<b>3.8</b>	<b>2.8</b>
<b>Treatment Difference; Probuphine vs. (95% CI)</b>		<b>21.6 (12.5, 30.8)</b>	<b>0.9 (-6.36, 8.2)</b>
<b>P-value</b>		<b>&lt;0.0001</b>	<b>0.8070</b>
<b>Study Completion (% of patients)</b>	<b>64.0</b>	<b>25.9</b>	<b>63.9</b>
<b>Discontinuation (% of patients)</b>	<b>36.0</b>	<b>74.1</b>	<b>36.1</b>

ANOVA test including treatment, (pooled) site and gender as a factors in the model.

# Response Analyses

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Post-hoc Analyses

# Response Analysis<sup>1</sup>

## Weeks 1-24, Studies 805 and 806

Response Definition (% Negative Urines)	Study 805	Study 806
	Probuphine N=108 (%)	Probuphine N=114 (%)
≥ 50	32	27
≤ 5	23	27
≥ 30	45	42

<sup>1</sup>Data presented in FDA briefing book

# Response Analysis

## Weeks 1-24, Studies 805 and 806

Response Definition (% Negative Urines)	Study 805			Study 806		
	Probuphine N=108 (%)	Placebo N=55 (%)	Effect Size (NNT)	Probuphine N=114 (%)	Placebo N=54 (%)	Effect Size (NNT)
≥ 50	32	16	7	27	6	5
≤ 5	23	40	6	27	43	7
≥ 30	45	27	6	42	7	3

# Exploratory Analysis of Continuous Abstinence, Pooled Studies 805 and 806

Numbers of Days	Study 805 + Study 806		P-value*
	Probuphine N=222 n (%)	Placebo N=109 n (%)	
7 days	154 (69.4)	61 (56.0)	0.0006
≥ 14 days	107 (48.2)	37 (33.9)	0.0086
≥ 21 days	81 (36.5)	24 (22.0)	0.0053
≥ 28 days	64 (28.8)	16 (14.7)	0.0055
≥ 35 days	42 (18.9)	8 (7.3)	0.0079
≥ 42 days	33 (14.9)	7 (6.4)	0.0424

\*Missing urines imputed as positive

Cochran-Mantel-Haenszel stratified on gender and site

# Efficacy Summary

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# Efficacy Summary: Probuphine Decreased Opioid Abuse Relative to Placebo

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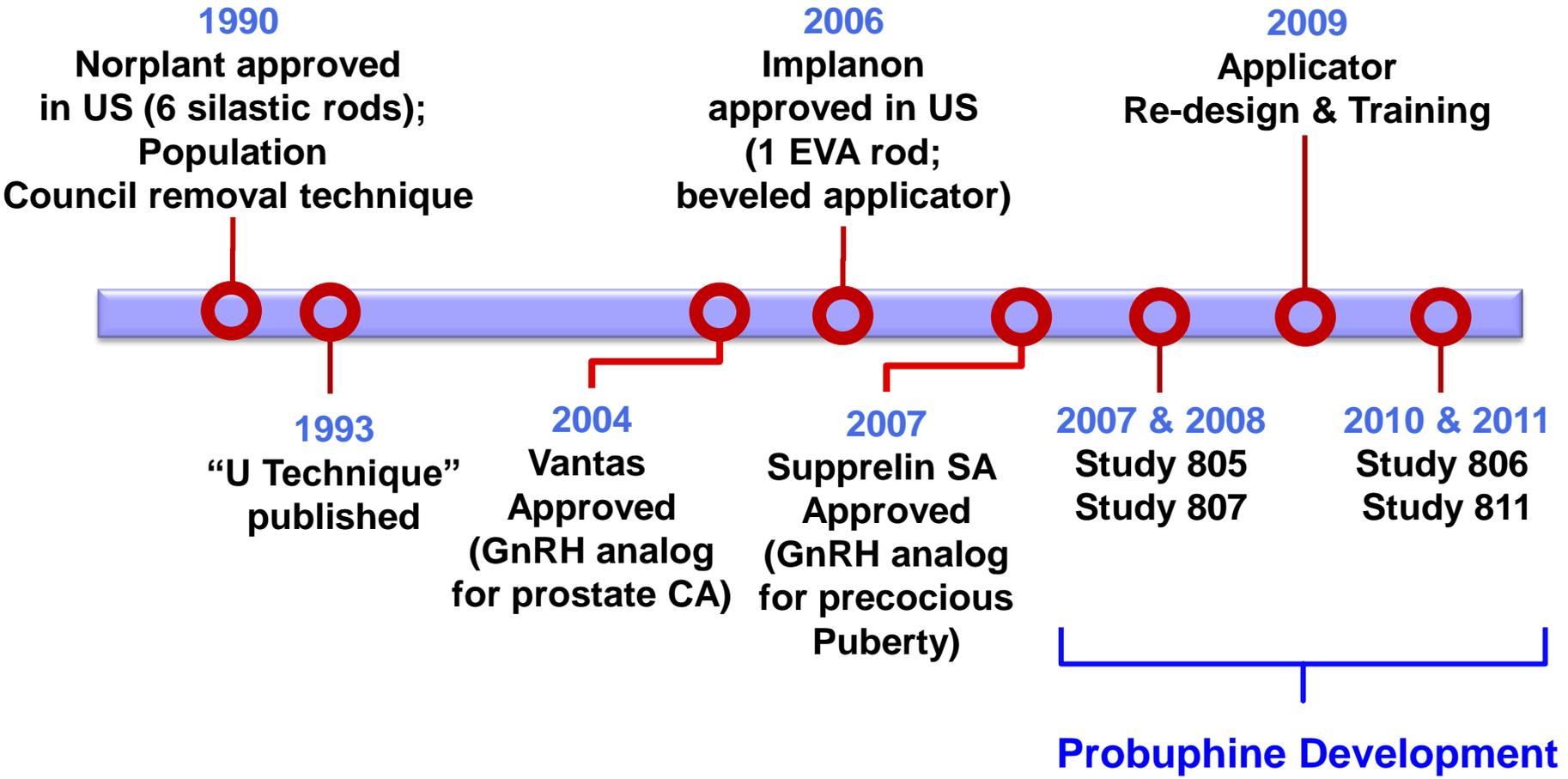
- Greater % of opioid-negative urine tests
- Greater study completion
- Sustained control of opioid withdrawal symptoms and cravings
- Exploratory comparison
  - Mean % opioid negative-urines similar with Probuphine and open-label sublingual buprenorphine
- ~80% of patients adequately treated with 4 implants

# **Probuphine Insertion and Removal: Background, Procedures and Training During Clinical Studies**

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Steve Chavoustie, M.D., FACOG  
Principal Investigator,  
Segal Institute for Clinical Research  
Assistant Professor, Obstetrics and Gynecology, Family  
Medicine and Community Health, University of Miami,  
Miller School of Medicine

# Chronology of Implantable Drug Products Approved in the US and Impact on Probuphine Development



# Equipment and Procedure Modifications

	<b>Studies 805 and 807</b>	<b>Studies 806 and 811</b>
<b>Applicator</b>	<b>Blunt</b>	<b>Beveled</b>
<b>Removal technique</b>	<b>Standard technique</b>	<b>“U” Technique</b>
<b>Removal clamp</b>	<b>Straight</b>	<b>Modified vasectomy clamp</b>

**Original  
Blunt-Tipped Applicator**



**Final  
Bevel-Tipped Applicator**



# Competency Based Training: Evolution from Study 805 to 806

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- Study 805/807
  - Instructional DVD
  - Self-guided written instructions
  - On-site training by implant medical monitor if needed
- Study 806/811
  - Training manual
  - Training video
  - Half-day training class
  - Hands-on training using a meat simulation model

# Implant Procedure Training

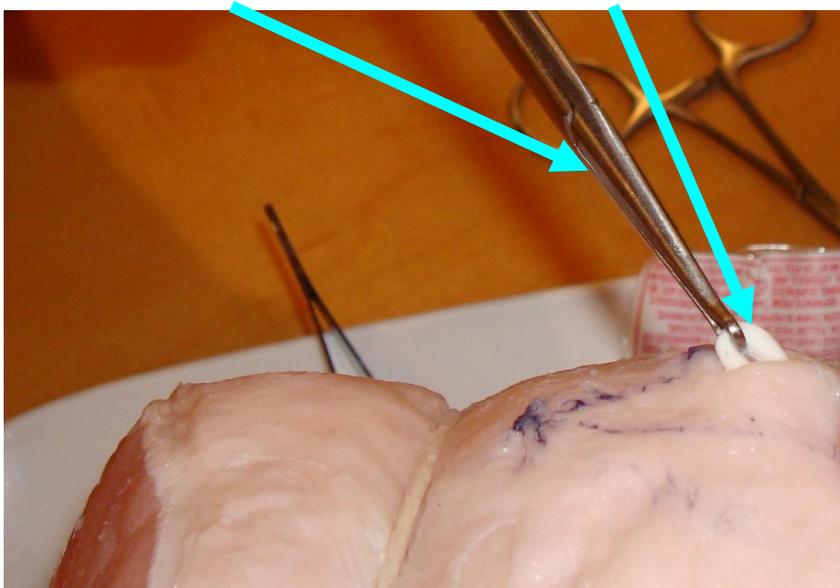
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# Implant Removal Training

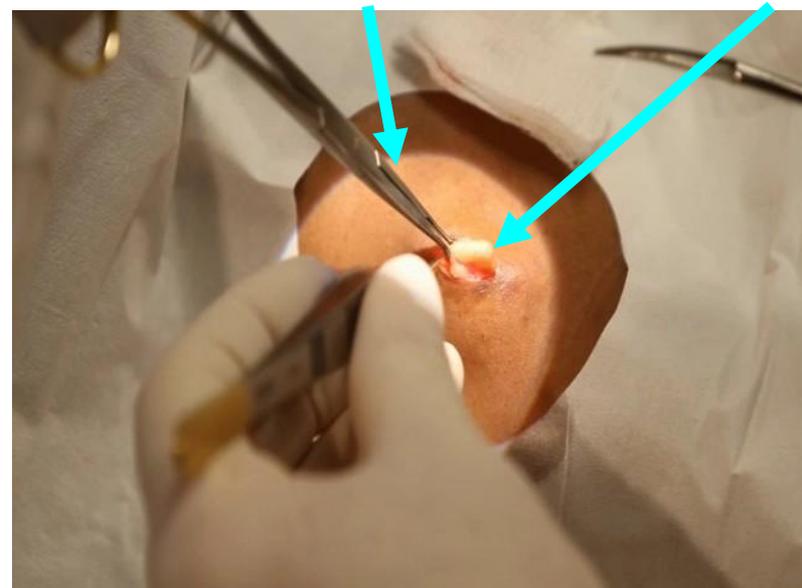
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**Specialized Clamp**      **Implant**



**Meat Practice Model**

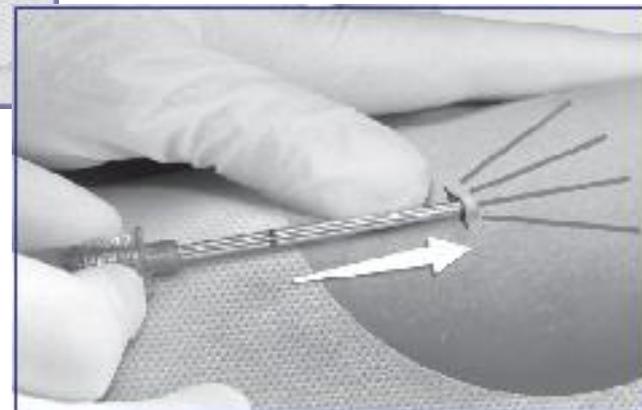
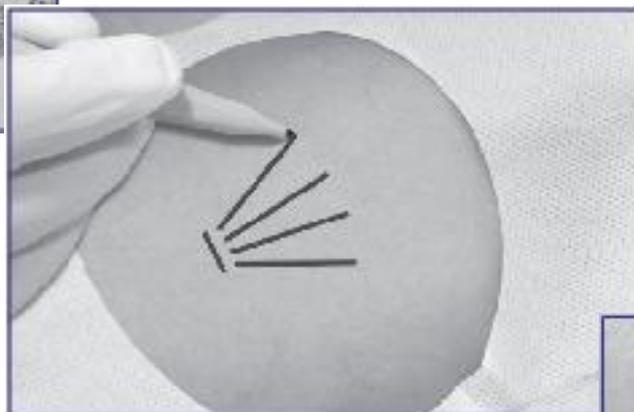
**Specialized Clamp**      **Implant**



**Implant Removal in  
a Patient**

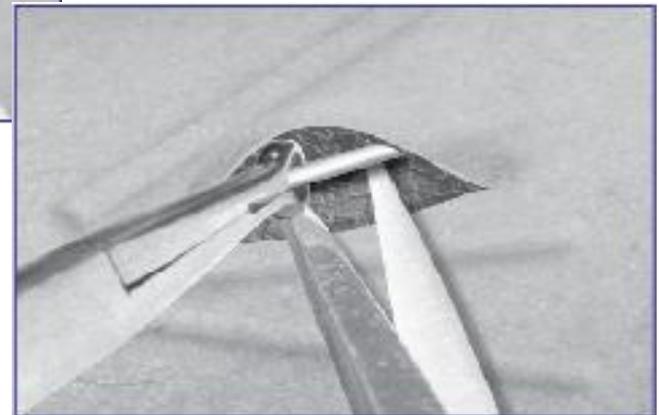
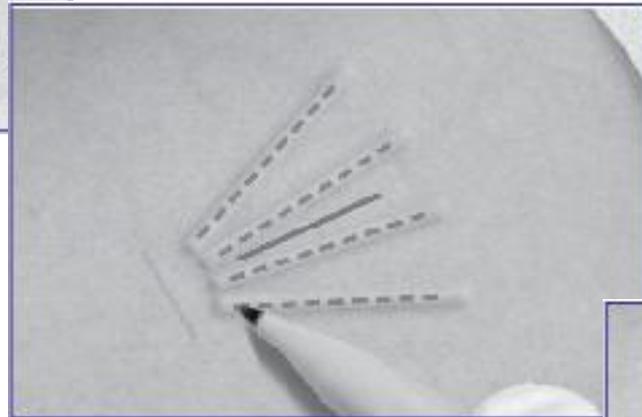
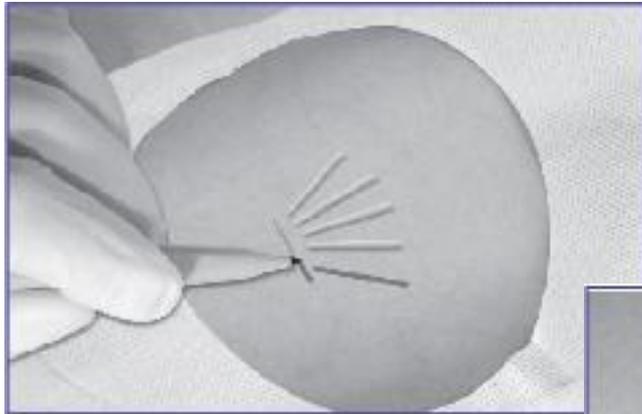
# Probuphine Implant Insertion

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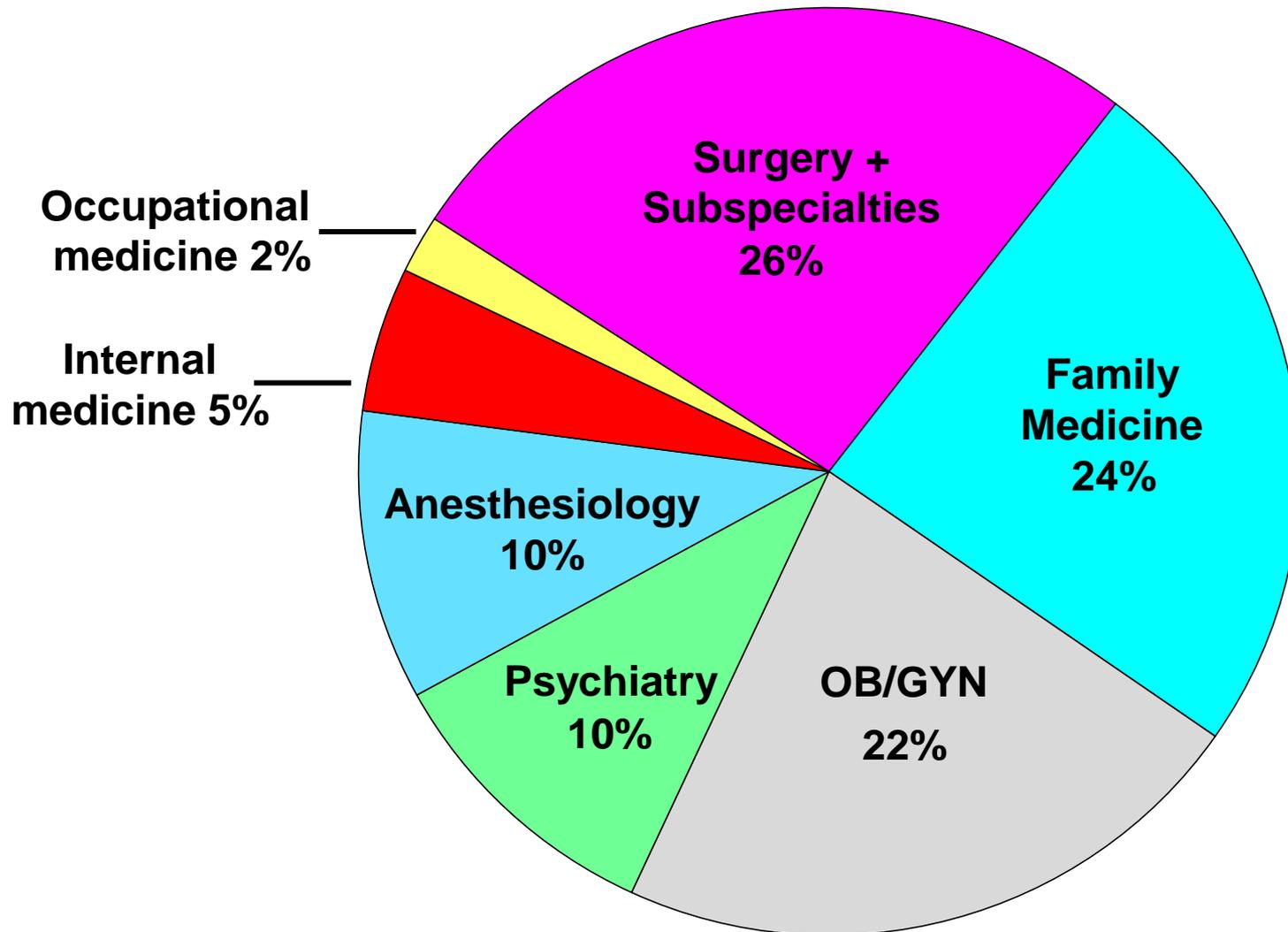
# Probuphine Implant Removal

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# Medical Specialties of Implanting Physicians

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# **Probuphine Safety: Studies 805, 806, 807, and 811**

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# Overview of Safety Presentation

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- Overview of exposure and adverse events (AEs)
- Serious Adverse Events (SAEs)
- Non-implant site AE summary
- Implant site AE summary

# Probuphine Exposure in Controlled and Open Label Studies

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	<b>N (%)</b>
<b>Total Patients Exposed</b>	<b>262</b>
<b>≥ 24 weeks</b>	<b>201 (76.7)</b>
<b>≥ 48 weeks</b>	<b>82 (31.3)</b>

# Overview of Safety During Double-blind Clinical Trials

	Study 805		Study 806		
	Probuphine N=108	Placebo N=55	Probuphine N=114	Placebo N=54	SL BPN N=119
	(%)	(%)	(%)	(%)	(%)
Any Adverse Event	86.1	81.8	71.9	66.7	71.4
Leading to discontinuation	3.7	0	1.8	3.7	4.2
SAE	1.9	7.3	5.3	5.6	5.9
Death	0	0	0	0	0.8

# Serious Adverse Events Possibly Related to Study Drug or Leading to Discontinuation, Studies 805 and 806

Number of Patients	Study 805		Study 806		SLBPN N=119
	Probuphine N=108	Placebo N=55	Probuphine N=114	Placebo N=54	
<b>Related or Possibly Related to Study Drug or Implant Procedure</b>					
Chronic obstructive pulmonary disease	1*	0	0	0	0
Pulmonary embolism	1*	0	0	0	0
Cellulitis (implant site)	0	1	0	0	0
<b>Leading to Study Discontinuation</b>					
Breast Cancer	0	0	1	0	0
Overdose	0	0	0	1	0

\*Same patient

# One Death: Study 806

## SL Buprenorphine Group

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- 29 year old woman
- Heroin overdose 3 days after she withdrew
- Randomized to SL BPN treatment group
- In treatment for ~3 months
- Last SL BPN dispensed
  - Fourteen 8 mg tablets 10 days before death
- Last counseling session
  - 8 days before death
- Medical examiner information not available

# **Non-Implant Site Related**

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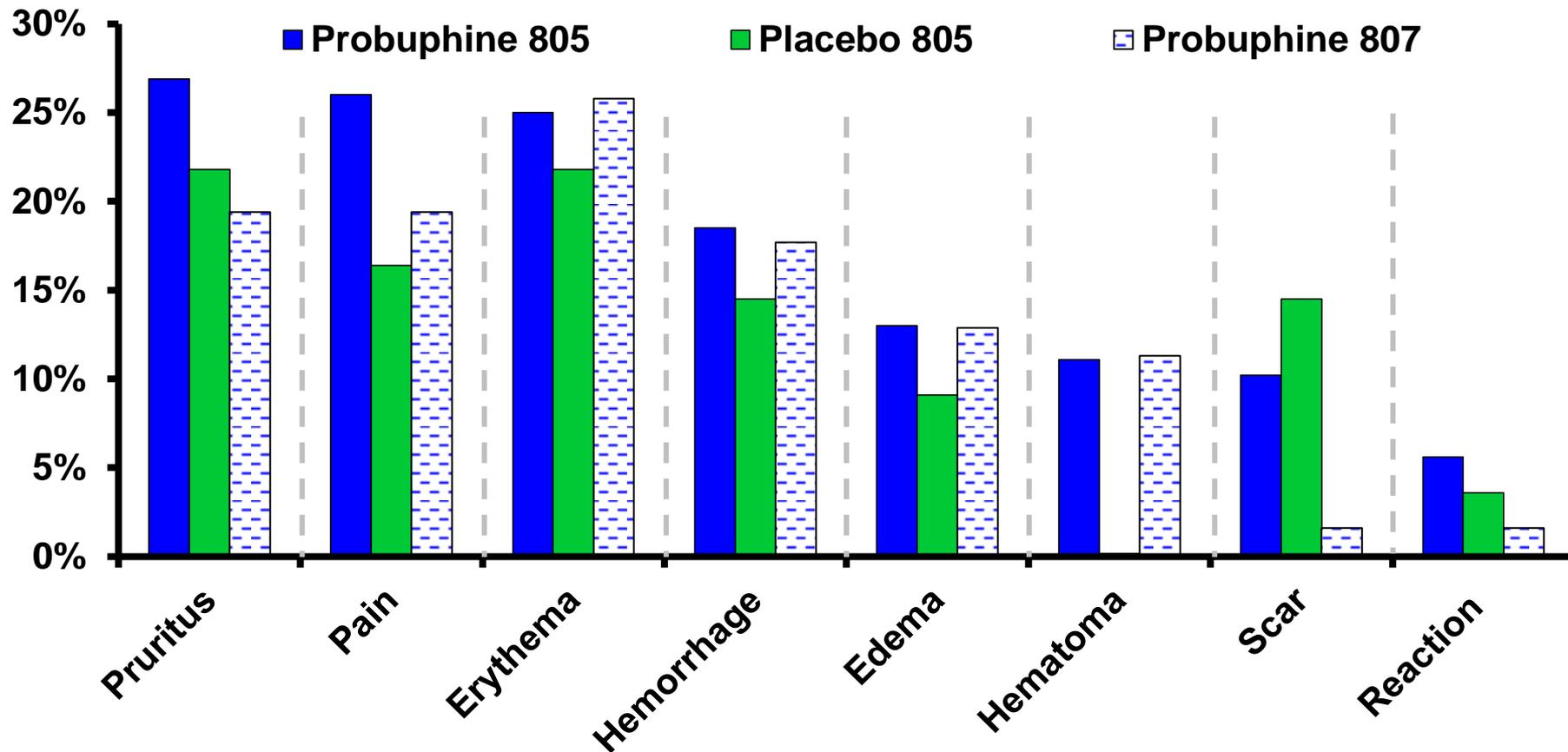
# Non-implant Site AEs in >5% of Patients: Similar to Marketed Buprenorphine Products

Preferred Term	Study 805		Study 806		
	Probuphine	Placebo	Probuphine	Placebo	SL BPN
	N=108 (%)	N=55 (%)	N=114 (%)	N=54 (%)	N=119 (%)
Headache	25	18.2	13.2	9.3	16
Nasopharyngitis	13.9	5.5	8.8	7.4	9.2
Nausea	13.9	12.7	5.3	5.6	10.1
Constipation	13.9	5.5	6.1	1.9	6.7
URI	13.0	10.9	5.3	5.6	5.9
Back pain	12.0	5.5	4.4	1.9	4.2
Toothache	11.1	5.5	6.1	1.9	4.2
Anxiety	10.2	9.1	8.8	3.7	2.5
Upper abdominal pain	9.3	1.8	3.5	1.9	4.2
Vomiting	7.4	7.3	7.0	1.9	3.4
Oropharyngeal pain	6.5	5.5	1.8	1.9	4.2
Fatigue	5.6	3.6	3.5	1.9	0
Cough	5.6	3.6	1.8	5.6	5.0
Depression	4.6	5.5	3.5	0	2.5

# Implant Site Adverse Events

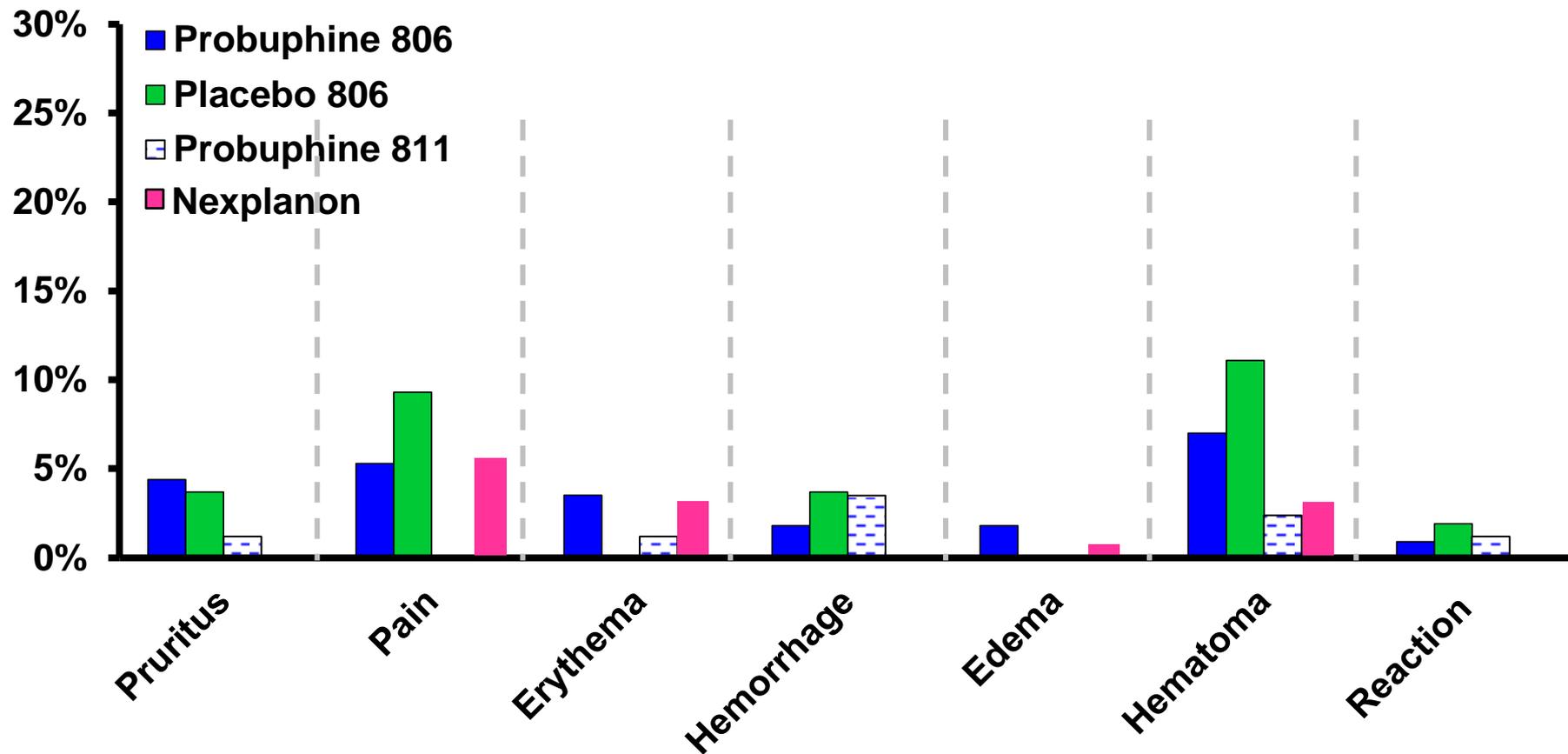
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# Study 805/807: Most Common Implant Sites AEs



Incidence >5% for any group

# Study 806/811: Incidence of AEs Decreased with Changes in Equipment, Procedures and Training



Incidence >5% for any group and preferred terms from Studies 805 and 807

# Implant Site Infections Occurred Infrequently

	Study 805		Study 807		Study 806		Study 811
	Probuphine	PBO	Probuphine	Probuphine	PBO	Probuphine	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Any implant site Infection	4 (3.7)	1 (1.8)	4 (6.5)	1 (0.9)	2 (3.7)	4 (4.7)	
Implant site infection	4 (3.7)	1 (1.8)	3 (4.8)	1 (0.9)	2 (3.7)	1 (1.2)	
Implant site cellulitis	0	1 (1.8)	1 (1.6)	0	0	0	
Post-operative wound infection	0	0	0	0	1 (1.9)	0	
Subcutaneous abscess	0	0	0	0	0	1 (1.2)	
Cellulitis	0	0	0	0	0	1 (1.2)	
Implant site abscess	0	0	0	0	0	1 (1.2)	

# Studies 805 and 807: Implant Site Adverse Event Intensity

	Study 805		Study 807
	Probuphine N=108	Placebo N=55	Probuphine N=65
	(%)	(%)	(%)
Any Implant Site AE (% of randomized)	57.4	45.5	45.1
Intensity (% of Implant Site AEs)			
Mild	79.1	87.9	71.4
Moderate	19.3	12.1	25.0
Severe	1.6	0	3.6

## Severe Intensity AEs:

805: Probuphine; implant site pain and infection (not SAE)

807: Probuphine; erythema, edema, pain, reaction, hematoma (not SAE)

# Studies 806 and 811: Implant Site Adverse Event Intensity

	Study 806		Study 811
	Probuphine N=114	Placebo N=54	Probuphine N=88
	(%)	(%)	(%)
Any Implant Site AE (% of randomized)	27.2	25.9	14.1
Intensity (% of Implant Site AEs)			
Mild	74.3	50.2	25.0
Moderate	25.7	42.9	66.7
Severe	0	7.3	8.3

## Severe Intensity AEs:

806: Placebo implant; implant site pain (not SAE)

811: Probuphine; reaction (not SAE)

# Probuphine Expulsions and Extrusions Reported as AEs

Patient	Study	Study Day	Implant Site AEs and Comments
<b>Studies 805 and 807</b>			
1	805	83	Itching, erythema, edema, pain, bleeding, scar, hemorrhage (all mild-moderate)
	807	74	Itching, pain, erythema, impaired healing (all mild-moderate); 3 replacements
2	805	31	Pain, erythema, itching, infection (all mild)
3	805	223	Implant fragment surfaced (post-removal)
4	807	105	Erythema, pain, bleeding, necrosis, scar (mild-moderate)
5	805	21	Erythema, itching, pain, bleeding, bruising, rash, impaired healing (all mild)
<b>Studies 806 and 811</b>			
6	806	21	Infection (moderate); 1 implants expelled, 1 lost

# Discontinuations due to Adverse Events

## Studies 805 and 806

	Study 805		Study 806	
	Probuphine N=108	Placebo N=55	Probuphine N=114	Placebo N=54
	(%)	(%)	(%)	(%)
Any AE	3.7	0	1.8	3.7
Implant site AE	2.8	0	0	0
Non-implant site AE	0.9	0	1.8	3.7
AE possibly related/ related to study drug and/or procedure	3.7	0	0	0

# Summary of Implant Procedure Safety

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- Studies 805 and 807
  - Implant site AEs common
  - Majority were mild
- Study 806 and 811
  - Implant site AEs less common
  - Majority mild or moderate
- Few discontinuations
- Decreased after equipment, procedure and training modifications

# Safety Conclusions

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- Well-characterized safety profile
- Overall safety comparable to approved BPN
- Adverse events as expected for buprenorphine
- Implant-related adverse events manageable

# Probuphine Care Model and Proposed REMS

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Garry Neil, M.D.

Head of R&D

Braeburn Pharmaceuticals

# Compliance with Existing Regulations

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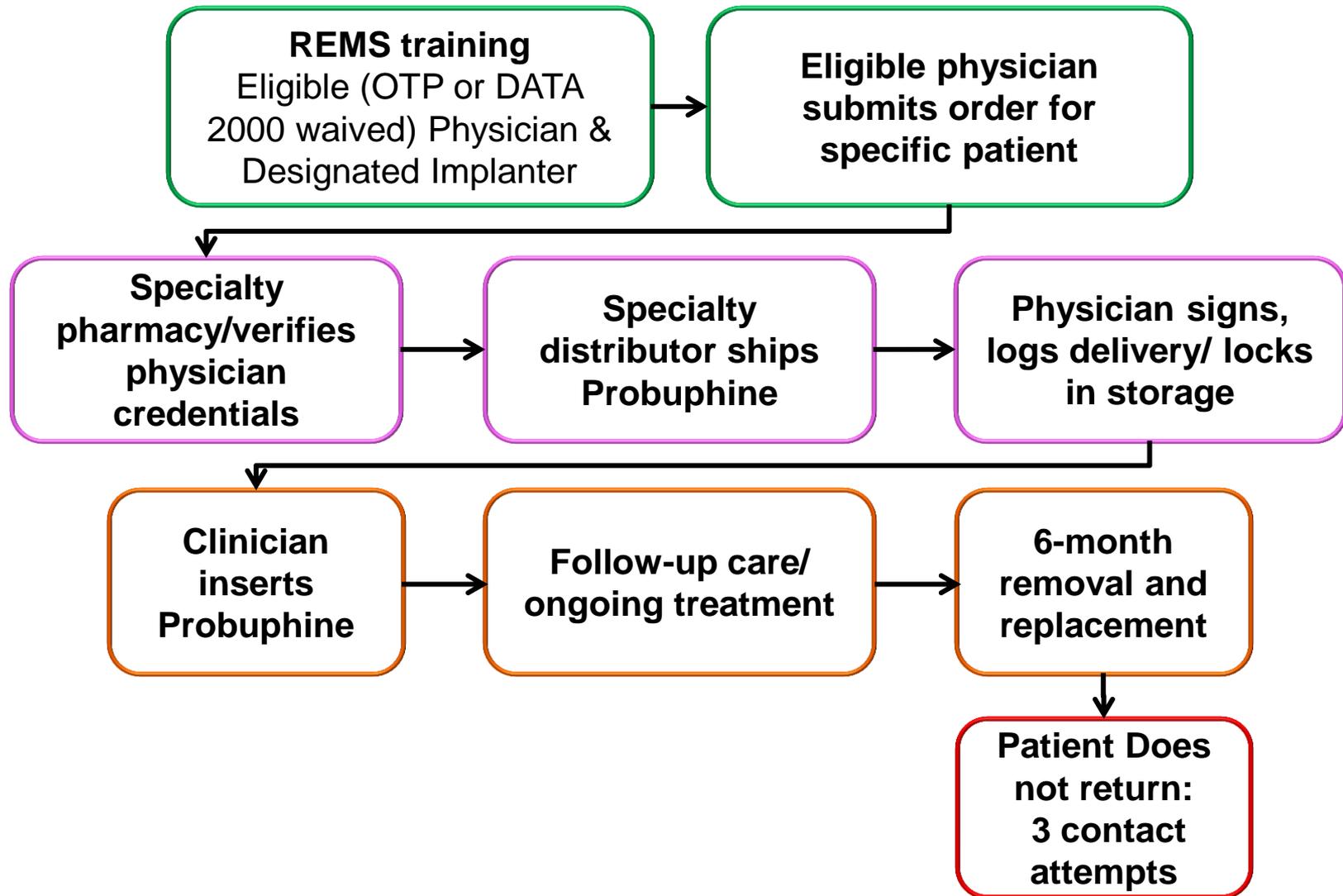
- Meeting with DEA
  - Model of care conforms with CSA requirements
- DEA scheduling (approved BPN products CIII)
- Drug Addiction Treatment Act of 2000 (DATA 2000)

# Proposed Care Model and REMS Addresses FDA's Concerns

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- Non-surgical medical specialties can be successfully trained
- Model of Care supports
  1. Treating physician performs procedure
  2. Treating physician contracts with implanting clinician
- Treated patients always under care of eligible physicians
- Only trained clinicians will implant and remove

# Model of Care and Distribution System



# Goals of REMS

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- Assure benefits outweigh risks
  - Assure patient access
  - Used only by trained qualified clinicians
  - Minimize burden on healthcare system
  - Minimize risk of accidental poisoning, overdose
  - Minimize risks of misuse, abuse, diversion

# REMS Components

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- Medication Guide
- Communication Plan
- Elements to Assure Safe Use (ETASU)
  - REMS training for treating physicians and implanting clinicians
  - Closed distribution system
  - Informed consent and wallet card for patients

# REMS Communication Plan

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- Intended to
  - Make HCPs aware of Probuphine
  - Support REMS implementation
- Communication Letters sent post approval
  - DATA 2000 waived physicians
  - Physicians practicing in a registered OTP
  - Addiction medicine professional societies
  - Emergency medicine physicians

# REMS Elements to Assure Safe Use (ETASU): REMS TRAINING (Part A)

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- REMS training components
  - REMS Training Part A: Clinical Training
    - Clinical data
    - Patient selection
    - Patient education
    - Incision care
    - Medication Guide
    - Access to Probuphine

# REMS Elements to Assure Safe Use (ETASU): REMS TRAINING (Part B)

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- REMS training components
  - REMS Training Part B: Procedure Training
    - Anatomy, insertion, localization, removal, management
    - REMS Training Kit: DVD, slides
- Treating physician: Part A
- Implanting clinician: Part A & B
- Supervising physicians: Part A & B



# Probuphine Training Program

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- Steering Committee
- Master Trainers (n=50)
  - 20 certified implanters from clinical trials
  - 30 additional physicians trained
- 2,000 implanters trained over 12 months
  - 20-30 regional meetings
  - 50-100 trainees per meeting
    - 1 trainer: 10 trainees
  - Each master trainer to instruct 4 meetings

# Medication Guide, Informed Consent and Wallet ID Card

## Medication Guide

**PROBUPHINE®**  
(pro-bü-feen)  
(buprenorphine implant)  
(CIII)

### IMPORTANT:

Read this Medication Guide before you start taking PROBUPHINE and each time you receive a PROBUPHINE treatment. There may be new information. This Medication Guide does not take the place of talking to your doctor. Talk to your doctor if you have questions about PROBUPHINE.

Share the important information in this Medication Guide with members of your household.

PROBUPHINE® (buprenorphine implant)  
Subdermal Use Only

### PROBUPHINE INFORMED CONSENT FORM

I have read and understand the Medication Guide for PROBUPHINE. I have discussed PROBUPHINE with my physician who answered all my questions. I understand that there are benefits as well as risks with using PROBUPHINE. I understand that there are other treatment options for opioid dependence and that each has its own benefits and risks. I understand that I need to sign this form to show that I am making an informed and careful decision to use PROBUPHINE, and that I have read and understand the following points:

- I understand that PROBUPHINE implants contain the opioid buprenorphine that may cause physical dependence.
- I have completed induction with sublingual buprenorphine and have discontinued sublingual buprenorphine for 12-24 hours before the implants will be placed in my arm.
- I understand that the implants will be placed under the skin of my arm during a procedure done in my physician's office. There is a slight risk of getting a scar or an infection from this procedure.

Initial Insertion Date (4 Rods)

Dose Titration Date (5th Rod)

6-Month Removal Date

Arm

Left  Right

Distributed by: Braeburn Pharmaceuticals, Inc.,  
an Apple Tree Consolidated company

Rx only

**Probuphine®**  
(buprenorphine implant) 

80 mg per implant For subdermal use only

**Important notice: The holder of this card is using a buprenorphine-only subdermal implant**

**Probuphine implants are located at the inner side of the upper arm. For additional information, please call toll (1-800 number) or visit website**



Rx only

**Probuphine®**  
(buprenorphine implant) 

80 mg per implant For subdermal use only

Inserted by:

Contact Phone Number:

Patient's Name:

Lot Number (four implants)

Lot Number (complete if fifth implant is inserted)

# REMS: Monitoring and Assessment

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- Healthcare professionals who completed REMS training (Part A and Part B)
- Orders filled by the Specialty Distributor
- Orders rejected
- Adverse events (AE) reported by prescribers, inserting providers or patients
- Formal assessments submitted to FDA post-launch at
  - 18 months
  - 3 years
  - 7 years

# Summary:

## Patient Care Model and REMS

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- Care model and REMS designed to assure safe use and minimize diversion
  - REMS training for health care providers
  - Controlled closed distribution
  - Effective clinical training for implantation and removal
  - Patient will not be given a prescription, dispensed medication, or be in possession until implanted

# **Benefit/Risk and Conclusion**

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**Kate Glassman-Beebe, Ph.D.**

# Improved Treatments Needed for Opioid Dependence

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- Opioid abuse growing problem in US
- Sublingual buprenorphine improved treatment, but current formulations are associated with
  - Misuse and abuse
  - Diversion
  - Unintentional ingestion

# Topics for Discussion

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- ☑ Efficacy for proposed indication and dose exploration
- ☑ Safety:
  - General safety in this population
  - Safety specific to the placement and removal of the implants
- ☑ REMS relevant to implant procedures
- ☑ Data and proposals to address:
  - ☑ Potential implant removal by non-medical personnel for the purpose of diversion
  - ☑ Potential long-term exposure to implant components
  - ☑ Use of multiple implant sites for continued treatment

# Probuphine has a Favorable Benefit-Risk Profile

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- No direct patient access to drug
- Efficacious for 6 months with single administration
- Safety profile consistent with buprenorphine formulations
- Implant insertion and removal well tolerated
- Needed treatment option for selected patients

# **Probuphine for Maintenance Treatment of Opioid Dependence**

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Titan Pharmaceuticals, Inc.  
FDA Advisory Committee  
March 21, 2012