# BUPRENORPHINE IMPLANTS FOR THE MAINTENANCE TREATMENT OF OPIOID DEPENDENCE: TWELVE MONTH OUTCOMES

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# **ABSTRACT**

An implantable formulation of buprenorphine (BPN) has been developed that delivers constant, low levels of BPN for up to six months and offers potential advantages over sublingual BPN by ensuring subject compliance and limiting diversion. Five studies have demonstrated that treatment with buprenorphine implants (BI) is well-tolerated and effective; data from these studies will be presented in an overview fashion. The main objective of the study discussed in detail during this presentation is to assess longer-term safety and efficacy of implantable buprenorphine and report on subject satisfaction evaluations that were also conducted.

Eighty-five opioid-dependent subjects who had completed 6-months of double-blind treatment with either BI (n=57), placebo implants (PI) (n=8), or open-label sublingual buprenorphine/ naloxone (SL BPN) (n=20) at 18 US sites were enrolled in a second 6-month, open label trial in which all subjects received 4-5 buprenorphine implants. Results demonstrated that no treatment-emergent adverse events led to discontinuation or were considered related to study drug. The most common adverse events reported were minor and included headache (12%), upper respiratory infection (8%), back pain (6%), and urinary tract infection (6%). Opioid withdrawal symptoms and craving were well-controlled, with 79% of subjects completing the second 6 months of treatment. Among completers, the majority agreed (somewhat or strongly) with positive statements and disagreed (somewhat or strongly) with negative statements about their treatment experience over 12 months. Subjects treated with placebo or sublingual buprenorphine during the initial 6-month phase decreased their self-reported drug use by 25% and 20%, respectively, during the 6-month open-label phase when switched to buprenorphine implants. These data indicate that buprenorphine implants were well-tolerated and effective for up to 12 months, with high rates of treatment satisfaction reported by completers.

# BACKGROUND

- An implantable formulation of buprenorphine has been developed to address the problems of diversion and non-medical use, lack of compliance, and risk of accidental exposure that are evident with sublingually-administered buprenorphine naloxone products in the treatment of opioid dependence.
- The buprenorphine (BPN) implant is a polymeric matrix composed of ethylene vinyl acetate and buprenorphine that provides sustained release of BPN for 6 months.
- A total of 5 studies have demonstrated that treatment with buprenorphine implants welltolerated and effective treatment for opioid dependence

# **OBJECTIVE**

• To provide an overview of the efficacy and safety of Probuphine for the treatment of opioid dependence, with a focus on longer term efficacy and safety, as well as subject satisfaction

# METHODS

### **Study 1 Design and Treatment**

- Brief induction with sublingual buprenorphine/naloxone tablets (12-16 mg/day).
- Randomized to 24 weeks of double-blind buprenorphine implants (4 implants of 80 mg each), double-blind placebo implants, or open-label sublingual buprenorphine tablets.
- Supplemental sublingual buprenorphine/naloxone could be administered for opiate withdrawal or craving symptoms in 2 mg/d increments up to 16 mg/d.
- A dose increase of one additional implant was permitted for subjects who exceeded the protocol-specified allowance for rescue sublingual BPN.
- All subjects also received regular drug counseling.
- Blinded urine samples were collected thrice weekly, and routine assessments of other clinical symptoms of opioid dependence and safety were conducted.

#### Study 2 (Re-Treatment) Design

- At the end of 24 weeks, study completers were given the option of enrolling in a six-month, open-label buprenorphine implant re-treatment safety study.
- Subjects who received the BPN or placebo implants received four BPN implants in the opposite arm. Enrolled subjects from the sublingual BPN treatment arm in Study 1 and received implants for the first time.
- Subjects continued to be evaluated monthly with outcome measures used in Study 1

### Implantation Insertion and Removal Procedures

- Implants were administered subdermally in the inner, upper arms of subjects.
- The brief, in-office implant insertion and removal procedures were performed under local anesthetic using standardized equipment including a 10-gauge needle applicator for insertion and a modified vasectomy clamp for removal.

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### Table 1. Baseline Demographic and Clinical Characteristics

	Randomize	STUDY 2 Retreatment Pha (second 6 month		
	Buprenorphine Implants (N=114; double-blind)	Placebo Implants (N=54; double-blind)	Sublingual Buprenorphine (N=119; open-label)	Buprenorphine Implants (N=85; open-label)
Male, %	63.2%	57.4%	60.5%	65.9%
Age, years, mean	36.4	35.2	35.3	37.5
Race, %				
White	83.3%	83.3%	81.5%	84.7%
Black	12.3%	13.0%	13.4%	12.9%
Other	4.4%	3.8%	5.0%	2.4%
Time Since First Diagnosis of opioid dependence, % <sup>a</sup> ≤ 5 years > 5 years	74.6% 25.4%	77.8% 22.2%	68.9% 31.1%	69.4% 30.6%
Primary Opioid of Abuse, % Heroin Prescription analgesics	66.7% 33.3%	51.9% 48.1%	63.0% 37.0%	69.4% 30.6%

<sup>a</sup> Patient self-report

Table 2. Incidence of Adverse Events (≥5% for buprenorphine implants)

	Rar (F	STUDY 2 (Second 6 Months)		
Event	Buprenorphine Implants (n=114)	Placebo Implants (n=54)	Sublingual Buprenorphine (n=119)	Buprenorphine Implants (n=85)
Headache	13.2%	9.3%	16.0%	11.8%
Upper respiratory infection	8.8%	7.4%	9.2%	8.2%
Mood symptoms	8.8%	5.6%	3.4%	4.7%
Sore throat	7.0%	1.9%	3.4%	
Nausea	6.1%	1.9%	6.7%	3.5%
Vomitting	6.1%	1.9%	4.2%	
Any "severe" event	7.9%	5.6%	11.8%	7.1%

Figure 1a. Probuphine Implant

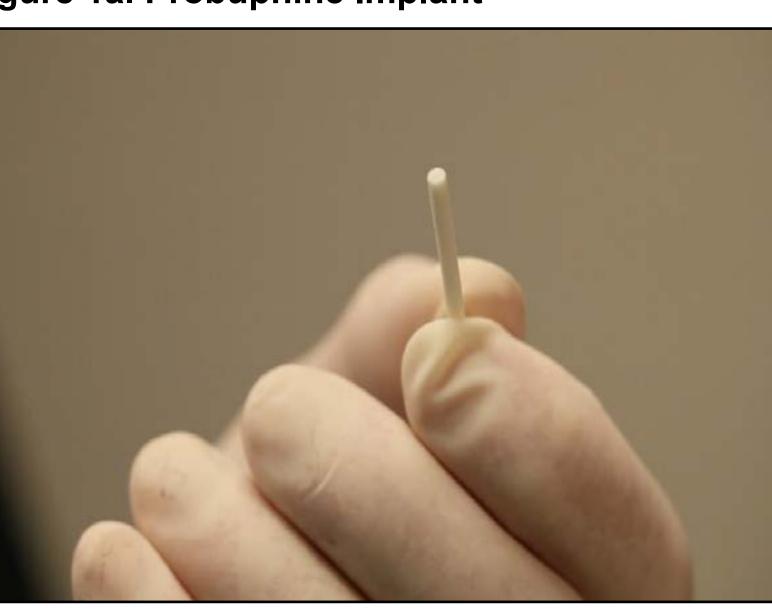
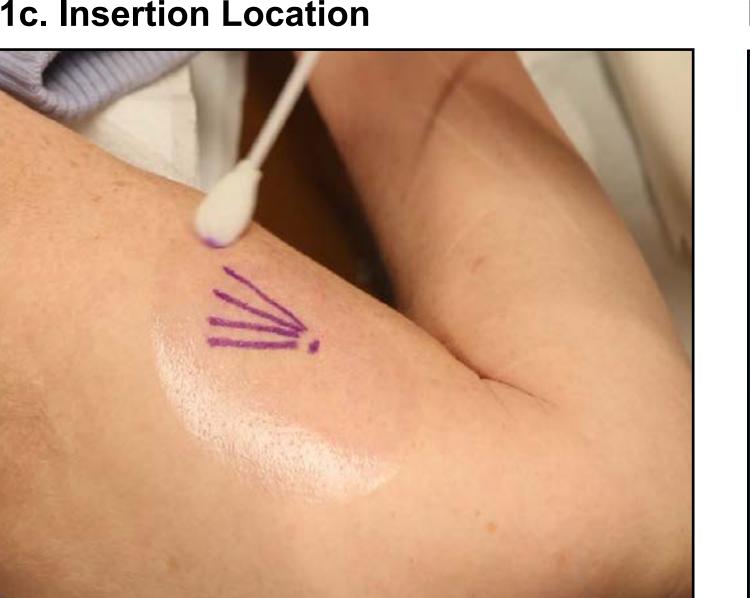


Figure 1c. Insertion Location



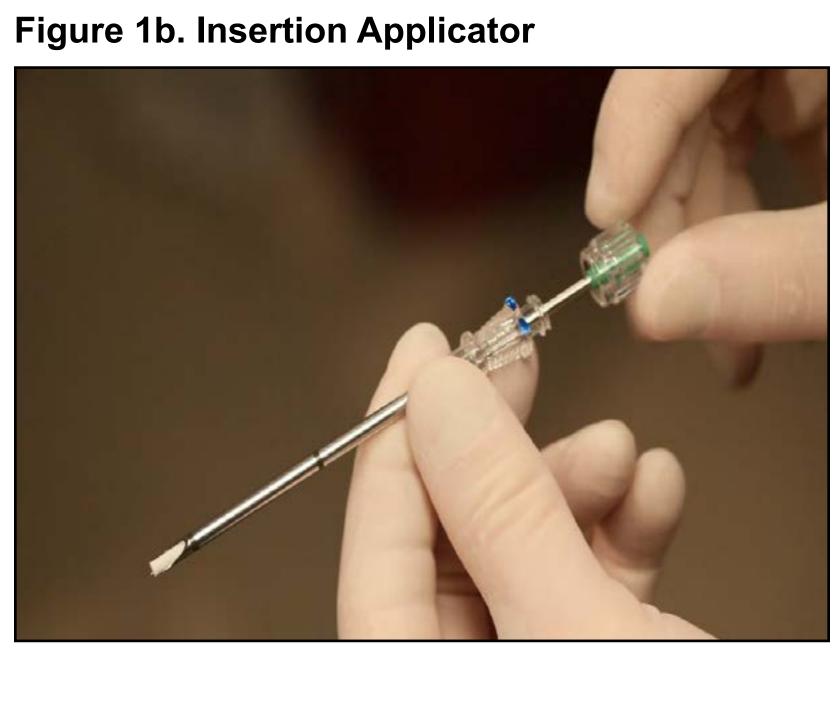
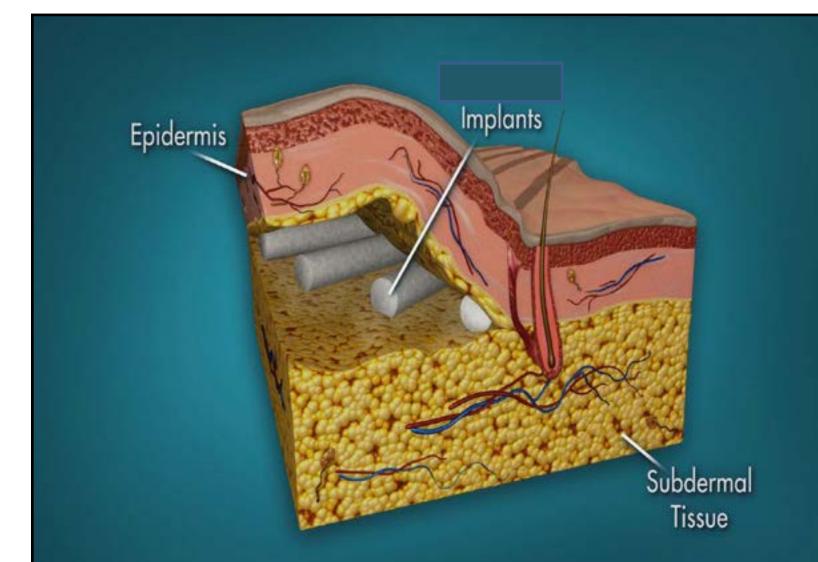


Figure 1d. Placement of Implants



# Figure 2. Cumulative Distribution Function of Negative

RESULTS

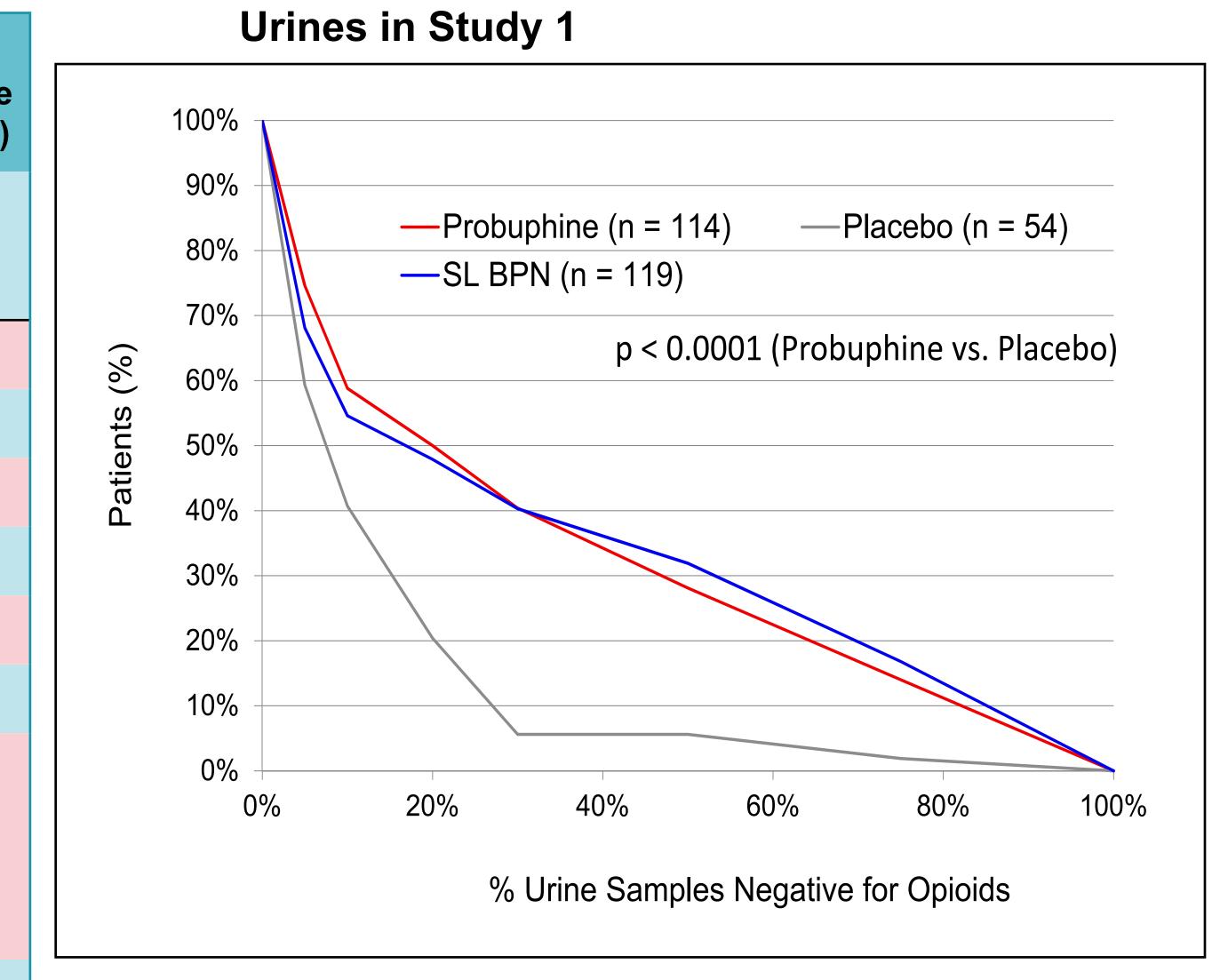


Figure 3. LS Mean Percent Opioid Negative Urines in Study 1

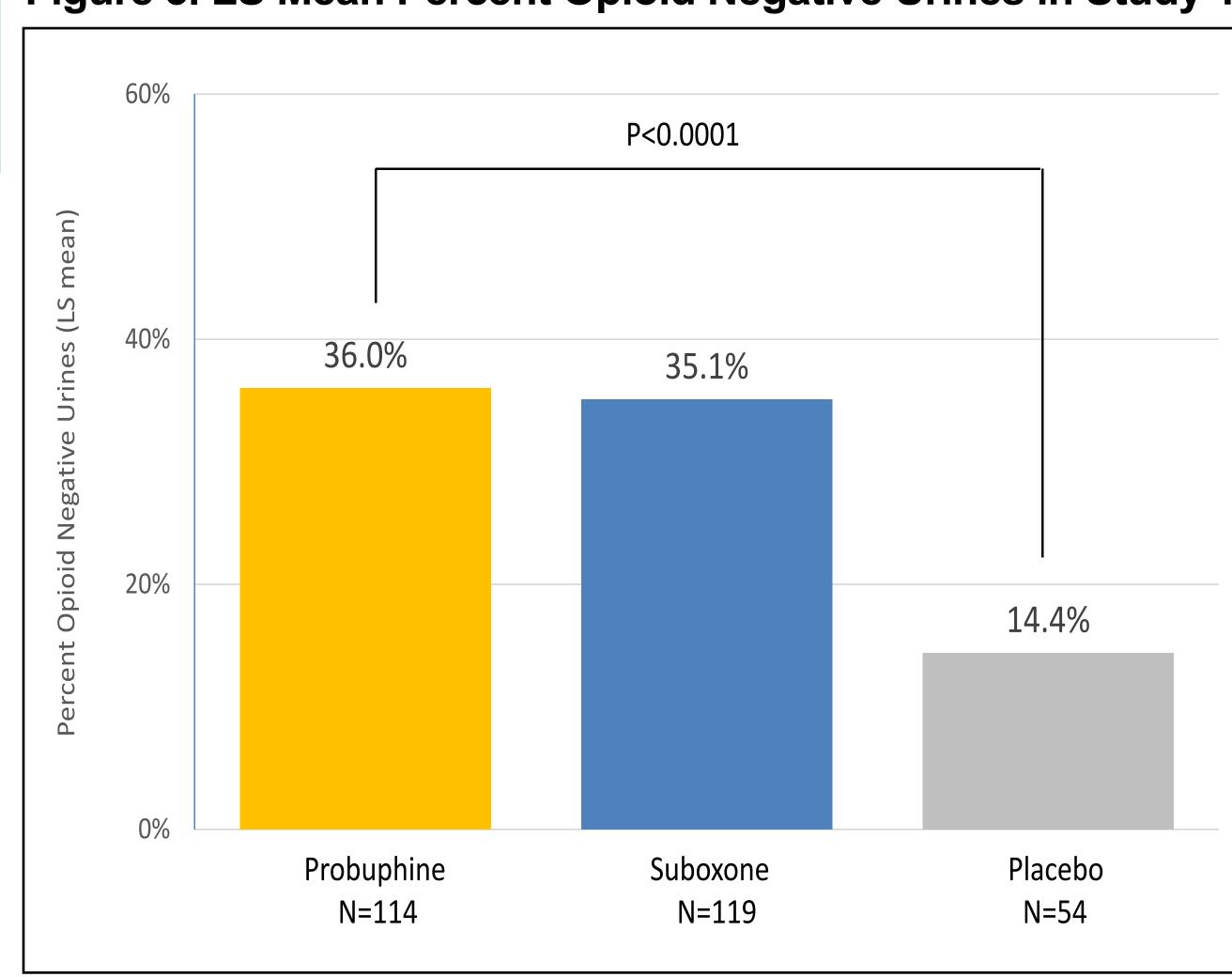


Figure 4. Study Retention Over 6 Months of Treatment in Study 1 and Study 2

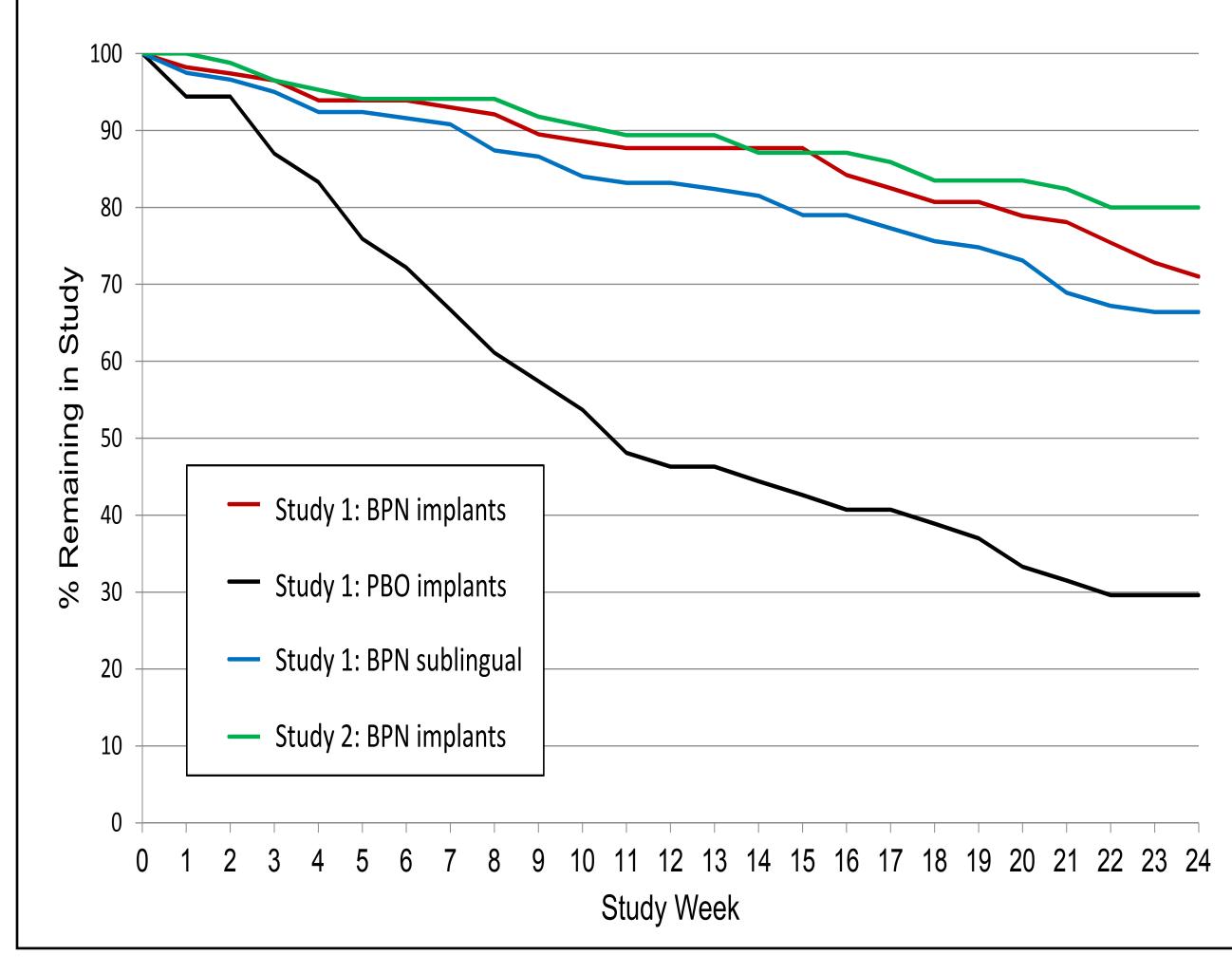
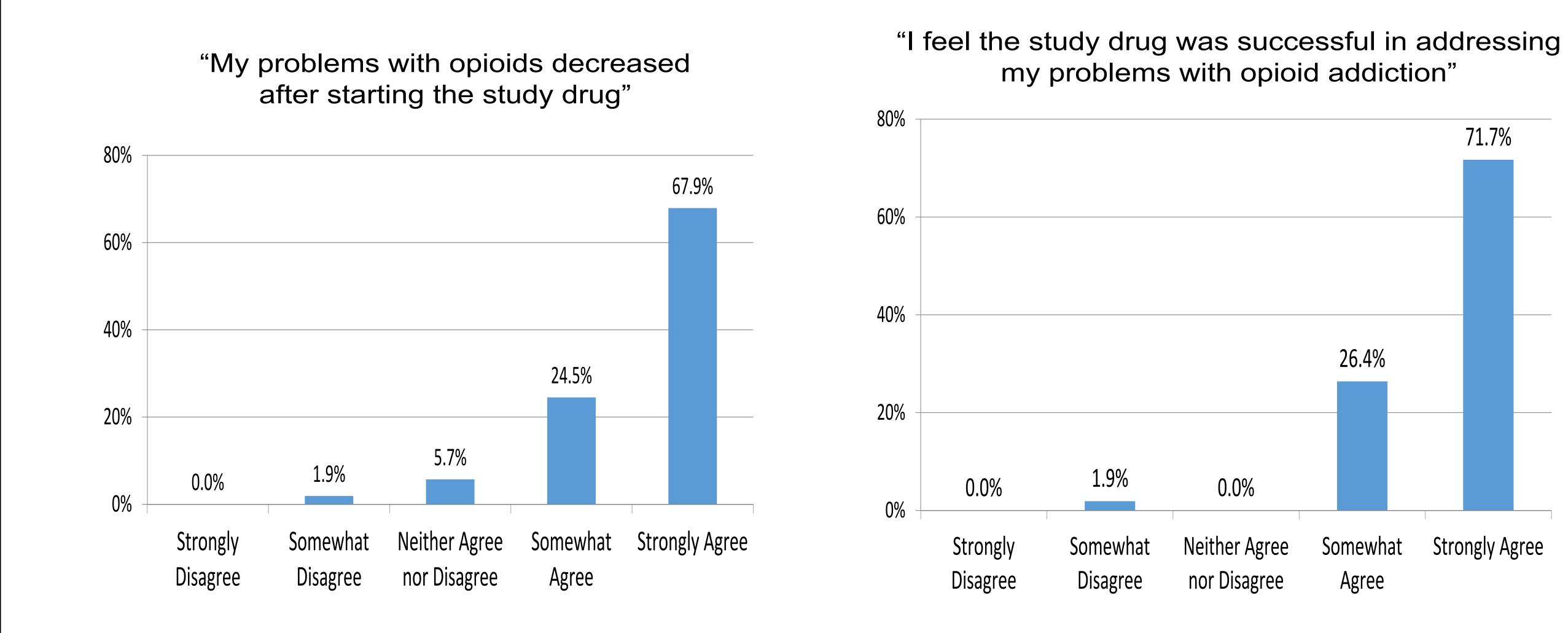
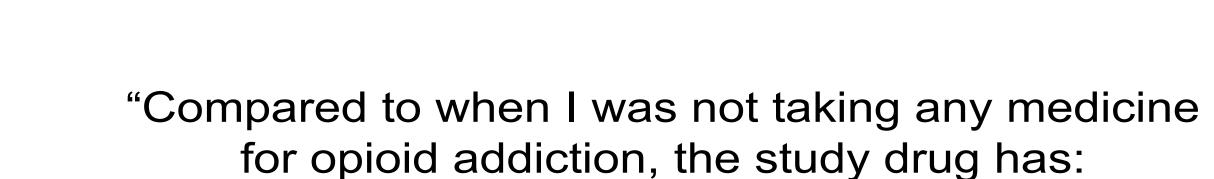


Figure 5. Subject Satisfaction Survey Administered at the End of Study 2 (N=53)

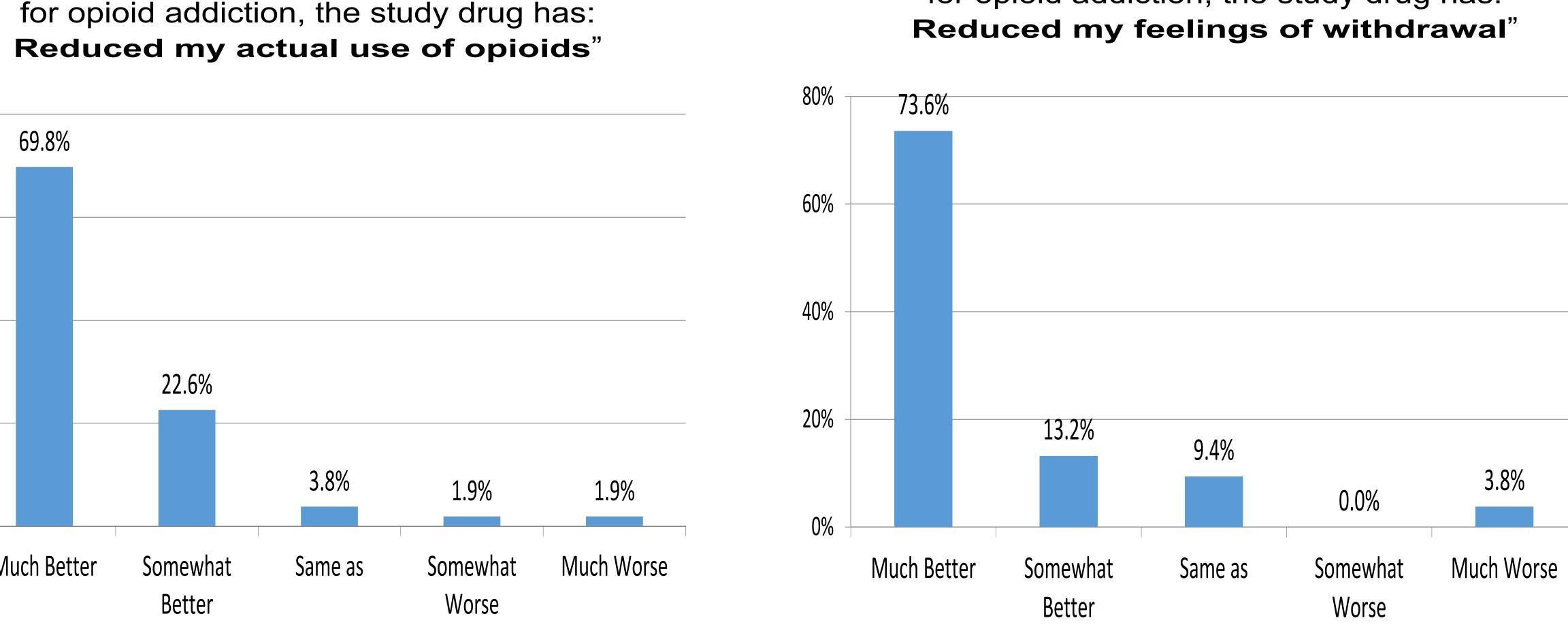


"Compared to when I was not taking any medicine



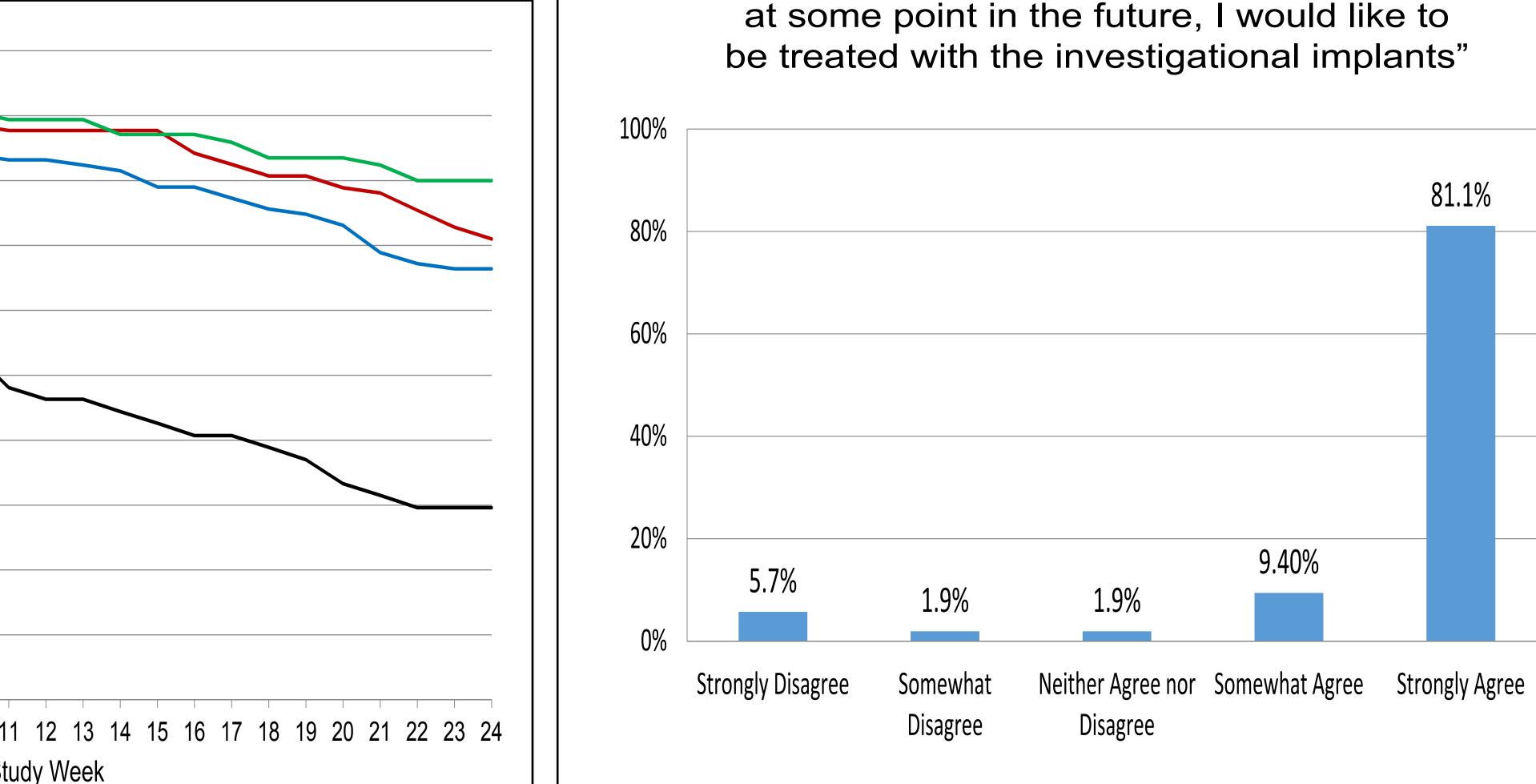
Somewhat Strongly Agree

my problems with opioid addiction"

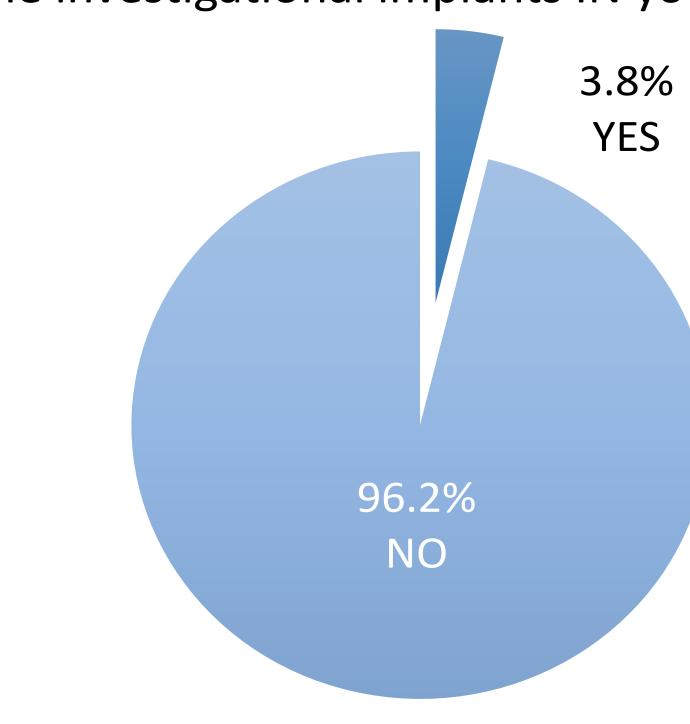


"If I needed to be treated for opioid addiction again

Bette



"Were you DISSATISFIED with the procedure used to put the investigational implants IN your arm?"



# REFERENCES

- Ling W, Casadonte P, Bigelow G, et al. Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. JAMA. 2010;304:1576-83.
- Rosenthal RN et al. Buprenorphine implants for treatment of opioid dependence. Addiction 2013 Aug 7. doi: 10.1111/ add.12315. [Epub ahead of print]

# DISCLOSURES

- Dr. Beebe is an employee of Titan Pharmaceuticals.
- Dr. Bailey's institution has received grant support from NIDA, Titan Pharmaceuticals, Inc., Alkermes, Inc., BioDelivery Sciences International, Inc. and Orexo. She has received travel support from Titan pharmaceuticals and is on the advisory boards of Braeburn Pharmaceuticals and BioDelivery Science International, Inc.

# SUMMARY

- Buprenorphine implants are in development for the treatment of opioid dependence.
- Results of these two studies confirm the 12-month safety and efficacy of BPN implants in the outpatient treatment of opioid dependence.
- The in-office procedures for implant insertion and removal were well-tolerated with relatively low risk of implant site adverse events.
- The durability of treatment over 12 months was demonstrated by high rates of subject retention, good control of opioid withdrawal and cravings, and high subject satisfaction with treatment.