RESULTS OF A SIX-MONTH, RANDOMIZED, CONTROLLED, PHASE 3 TRIAL COMPARING THE EFFICACY AND SAFETY OF PROBUPHINE™ TO PLACEBO IMPLANTS, AND SUBOXONE® FOR OPIOID ADDICTION

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ABSTRACT

Objectives: Sublingual buprenorphine-naloxone combination (Suboxone) is an effective and well-tolerated treatment for opioid addiction. However, daily sublingual dosing may hinder treatment compliance, and increases the risk of misuse and diversion. The objective of this Phase 3 study was to evaluate efficacy and safety of Probuphine, a subcutaneous implant that delivers a low, continuous level of BPN for 6 months with a single treatment, compared to placebo and to Suboxone.

Methods: Following brief induction with sublingual BPN (12-16 mg/day), opioid-dependent (DSM-IV-TR) outpatients at 20 US sites were randomized (2:1:2) to receive either 4 Probuphine (n=114), 4 placebo (n=54) implants, or open-label Suboxone (n=119). Subjects received a 5th Probuphine or placebo implant if the protocol-specified threshold for rescue with SL BPN was exceeded. Urine samples were collected 3 times weekly and analyzed for opioids. Assessments included standard safety measures, symptoms of opioid withdrawal and craving, self-reported illicit drug use, and clinical global improvement.

Results: Over the 24-week study, Probuphine was clinically and statistically superior to placebo on the percentages of opioid-negative urines ($p<0.0001$); trial retention [64% for Probuphine, 26% Placebo, ($p<0.0002$)], and was non-inferior to Suboxone in its ability to significantly reduce illicit opioid use using a pre-specified non-inferiority margin of -15%. Consistent with the first controlled trial, the rates of adverse events were low and similar between treatment groups. Implant insertion and removal procedures also were well-tolerated.

Conclusions: These data are consistent with previous trials and indicate that Probuphine is an effective and well-tolerated treatment option for patients with opioid addiction.

BACKGROUND

- Probuphine is an implantable formulation of buprenorphine HCL (80 mg) under development for the treatment of opioid dependence following induction with sublingual buprenorphine
- Probuphine is inserted subdermally into the inner side of the upper arm in a brief in-office procedure under local anesthetic, and provides sustained release of buprenorphine for 6 months
- At the end of treatment, Probuphine is removed in a brief, in-office procedure
- In a previously conducted 24-week, randomized, placebo-controlled trial, treatment with Probuphine was associated with:
  - A higher percentage of urines negative for illicit opioids: 40.4% vs. 28.3% ($P<0.05$)
  - A higher retention rate: 65.7% vs. 30.9% ($P<0.001$)
  - A lower incidence of clinician-rated ($P<0.001$) and patient-rated ($P=0.004$) withdrawal symptoms
  - Lower patient ratings of craving ($P<0.001$) (Ling et al, JAMA 2010;304:1576-83)
- The current study was designed to confirm the efficacy of Probuphine during 24 weeks of outpatient treatment

Study Objectives:

Primary

- To confirm the efficacy of Probuphine vs. placebo in opioid dependence over weeks 1-24 of outpatient treatment

Secondary

- To confirm the efficacy of Probuphine vs. placebo in opioid dependence over weeks 1-16, and 17-24 of outpatient treatment
- To demonstrate the non-inferiority of Probuphine vs. Suboxone in opioid dependence over weeks 1-24 of outpatient treatment

METHODS

Primary Efficacy Endpoints

- Cumulative Distribution Function (CDF) of % of urine samples negative for illicit opioids in Weeks 1-24
- Cumulative Distribution Function (CDF) of % of urine samples negative for illicit opioids, weeks 1-24, incorporating patient self-reported opioid use

Secondary Efficacy Endpoints

1. CDFs for Probuphine vs. placebo (Weeks 1-16, 17-24)
2. Non-inferiority of Probuphine vs. Suboxone
3. Proportion of study completers (retention)
4. Mean % negative urines (Weeks 1-24, 1-16, 17-24)
5. Clinician-rated Opioid Withdrawal Scale (COWS) and Subject-rated Opioid Withdrawal Scale (SOWS)
6. Opioid craving VAS
7. Clinician-rated Global Impression, Severity & Improvement (CGI-S; CGI-I)

RESULTS

Figure 1. Study Design and Patient Disposition

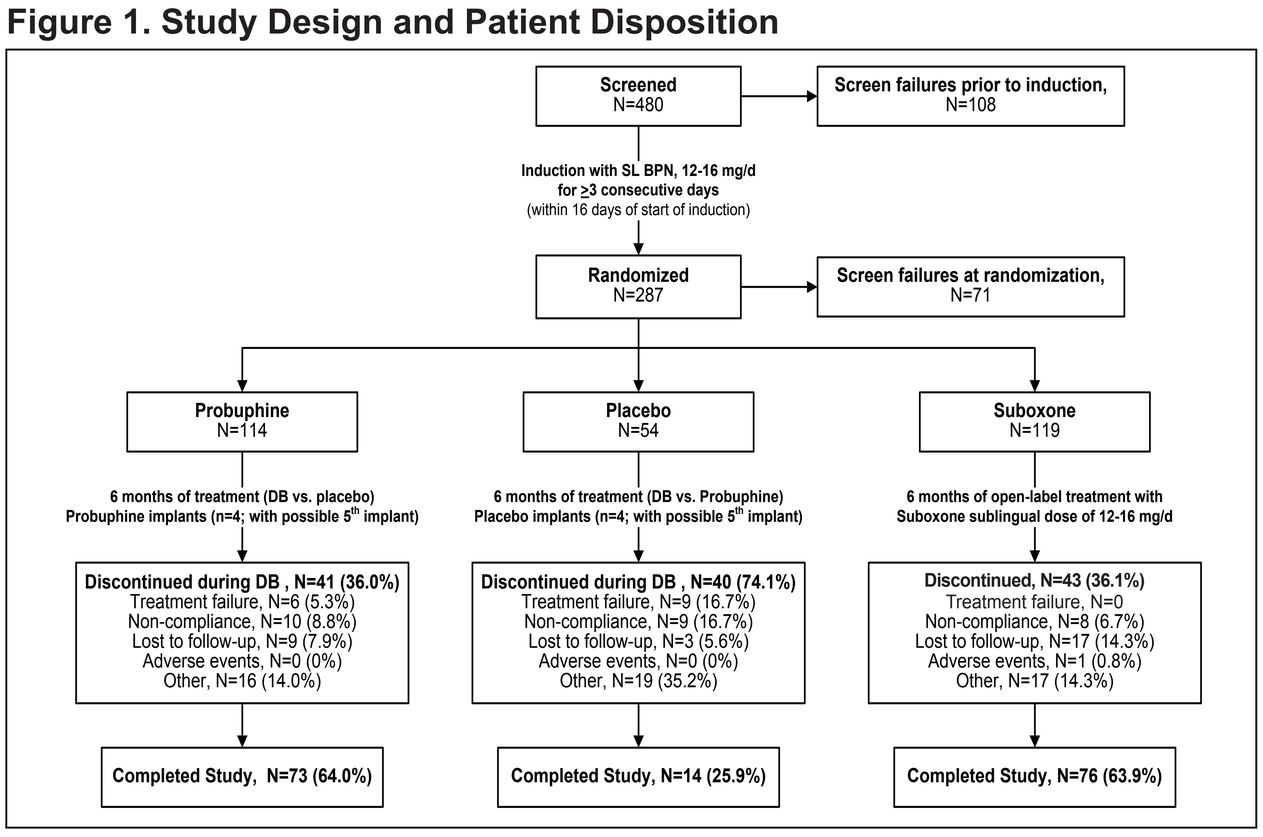

Table 1. Baseline Demographic and Clinical Characteristics

	Probuphine (n=114)	Placebo (n=54)	Suboxone (n=119)
Male, %	63%	57%	60%
Age, mean (SE)	36.4 (1.0)	35.2 (1.4)	35.3 (1.0)
White, %	83%	83%	81%
Hispanic, %	21%	20%	14%
Primary Opioid, % Heroin Prescription Opioid	67% 33%	52% 48%	63% 36%
Diagnosis in Past 5 yrs, %	75%	78%	69%
Prior Tx for Opioid Abuse, % *	55%	57%	57%

* Includes psychosocial and pharmacotherapy

DISCLOSURES

Dr. Beebe is a full-time employee of Titan Pharmaceuticals. Drs. Ling, Rosenthal, Bailey, Patkar, and Vocci are Probuphine Consortium Investigators and are non-paid consultants to Titan Pharmaceuticals.

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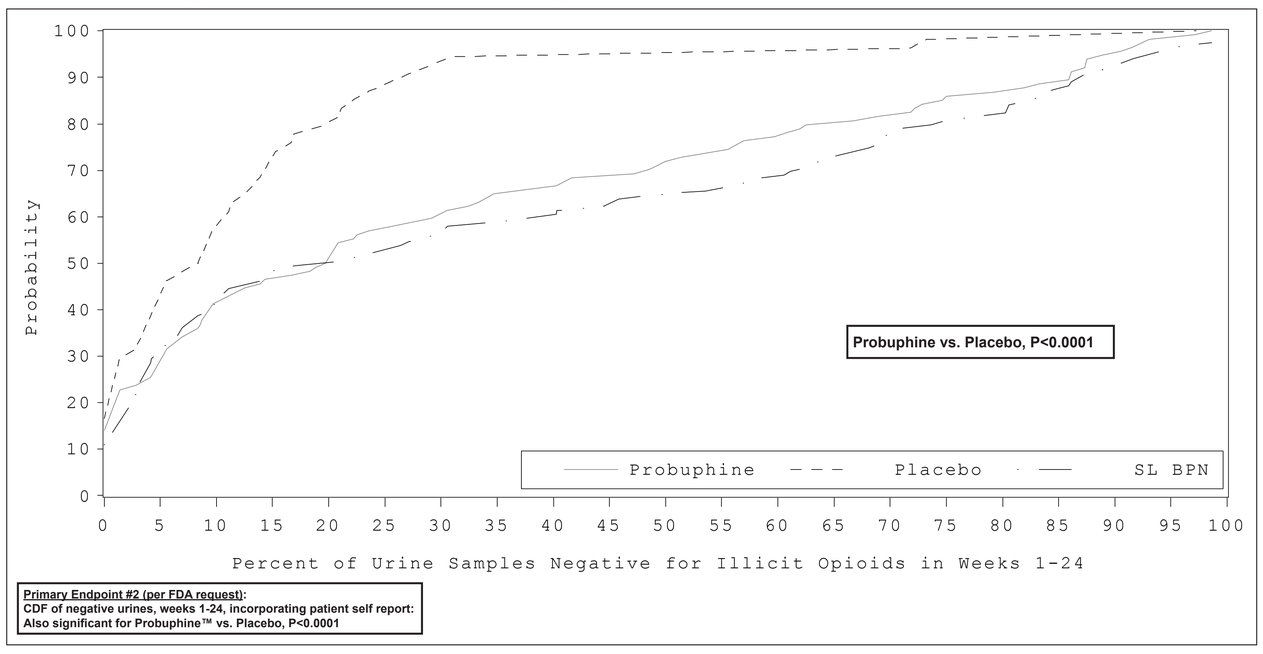
RESULTS (cont.)

EFFICACY

Figure 2. Primary Efficacy Endpoint #1: Cumulative Distribution Function (CDF) of Percentage of Urine Samples Negative for Illicit Opioids in Weeks 1-24



Non-Inferiority Comparison (-15% Margin):

- Probuphine, 31% vs. Suboxone, 33%
- 95%-CI of the difference score: (-10.7, 6.2)

Least-Squared Means (SE) Comparison:

- Probuphine, 36% (2.8) vs. Suboxone, 35% (2.8)
- 95%-CI of the difference score: (-6.4, 8.0)

Figure 3. LS Means of the % Negative Urines (Weeks 1-24; Weeks 1-16; Weeks 17-24)

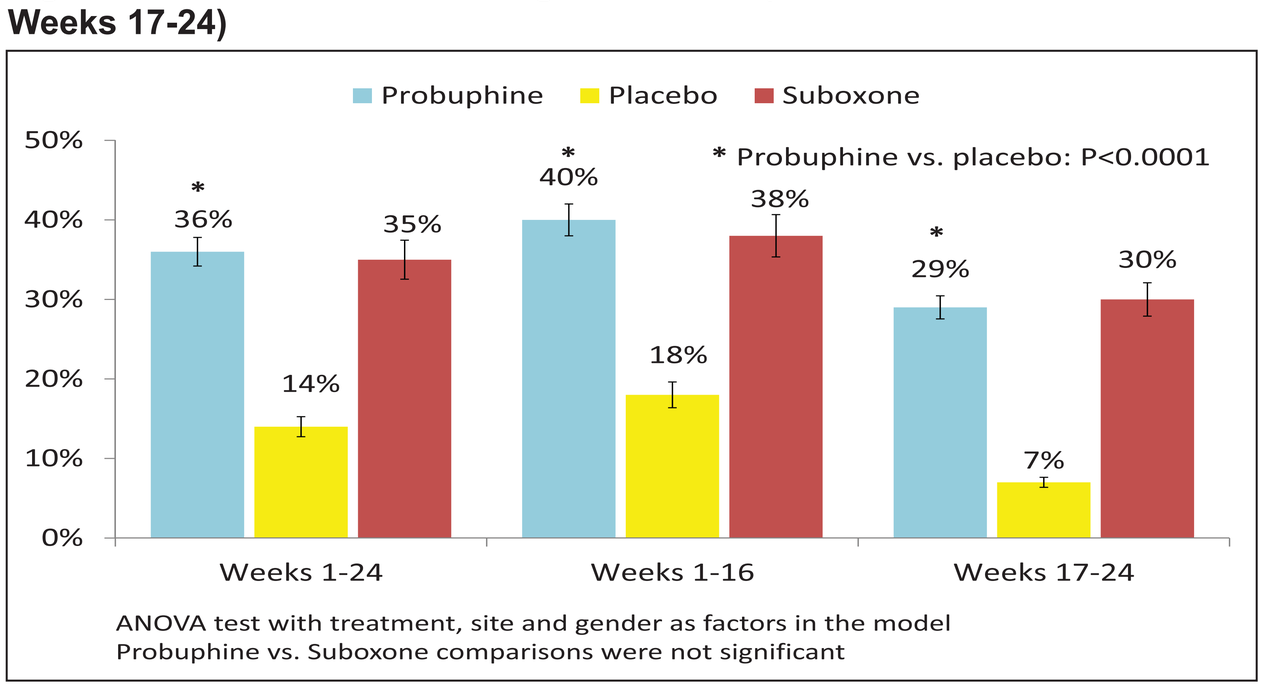


Figure 4. Additional Secondary Efficacy Measures

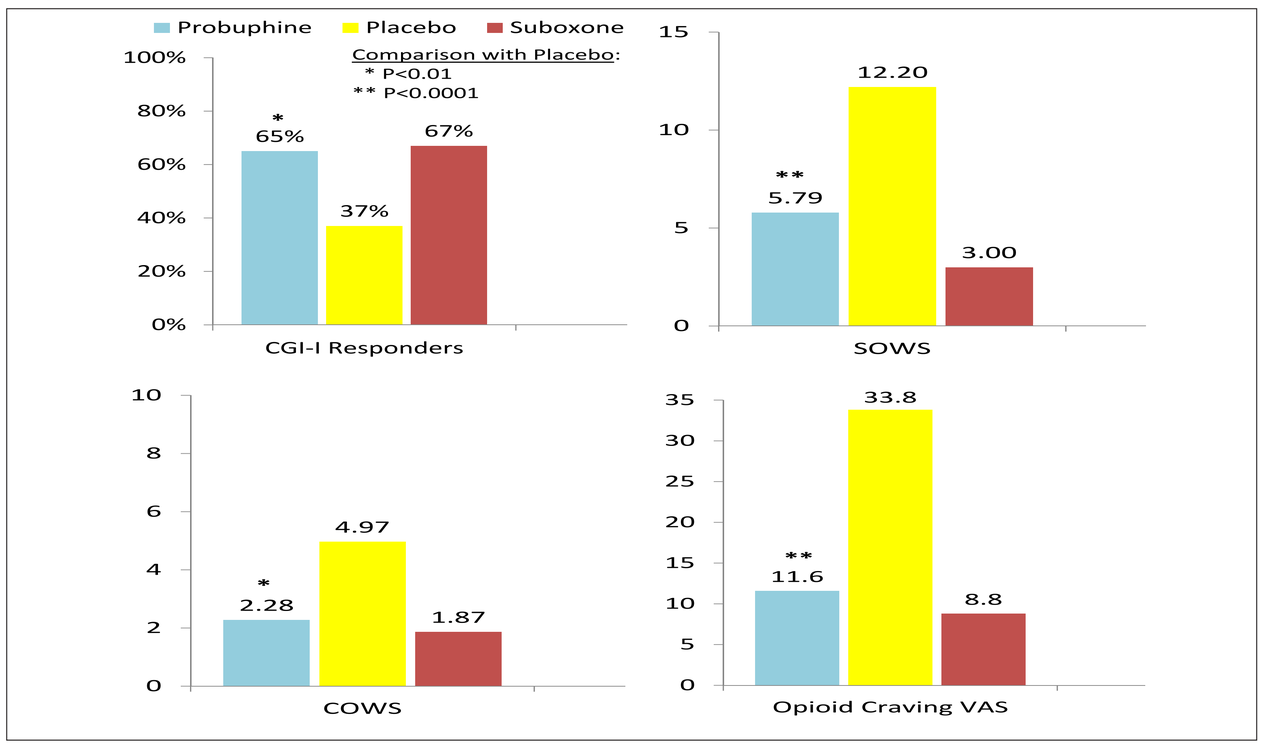


Table 2. Incidence of Adverse Events (≥5% for Probuphine)

Event	Probuphine (n=114)	Placebo (n=54)	Suboxone (n=119)
Any adverse event	67.5%	61.1%	71.4%
Headache	13.2%	9.3%	16.0%
Upper respir. infection	8.8%	7.4%	9.2%
Depression*	8.8%	3.7%	2.5%
Oropharyngeal pain	7.0%	1.9%	3.4%
Nausea	6.1%	1.9%	6.7%
Vomitting	6.1%	1.9%	4.2%
Nasopharyngitis	5.3%	5.6%	10.1%
Back pain	5.3%	5.6%	5.9%
Any "severe" event	7.9%‡	5.6%	11.8%
Any "serious" event	5.3%	5.6%	8.9%

‡ Umbilical hernia, pneumonia (n=2), breast cancer, hypotension, tooth abscess * $P<0.05$

• No serious events were judged by investigators to be related to study drug; there was one death (accidental overdose) in the Suboxone group

CONCLUSIONS

- The efficacy of Probuphine for the treatment of opioid dependence was confirmed
- Significant efficacy was demonstrated on the primary endpoint (CDF of the % urine samples negative for illicit opioids at Weeks 1-24)
- Significant efficacy was also demonstrated on multiple secondary endpoints, including measures of opioid withdrawal, drug craving, and treatment retention
- Treatment with Probuphine was found to be non-inferior in efficacy to Suboxone
- Treatment with Probuphine for 24 weeks was found to be safe and generally well-tolerated