RESULTS OF A SIX-MONTH, RANDOMIZED, CONTROLLED, PHASE 3 TRIAL COMPARING THE EFFICACY AND SAFETY OF BUPRENORPHINE IMPLANTS TO PLACEBO IMPLANTS, AND SUBLINGUAL BUPRENORPHINE/NALOXONE FOR OPIOID ADDICTION

Katherine L. Beebe, PhD;[1] Richard N. Rosenthal, MD;[2] Walter Ling, MD;[3] Paul Casadonte, MD;[4] Frank Vocci, PhD;[5] Genie L. Bailey, MD;[6] Kyle Kampman, MD;[7] Ashwin Patkar, MD;[8] Steven Chavoustie, MD[9]

[1]Titan Pharmaceuticals, Inc., South San Francisco, CA; [2]Department of Psychiatry, Columbia University College of Physicians & Surgeons and St. Luke's Roosevelt Hospital Center New York, NY; [3]Department of Psychiatry and Bio-Behavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA; [4]Department of Psychiatry, New York University School of Medicine; [5]Friends Research Institute, Inc., Baltimore, MD; [6]Department of Psychiatry and Human Behavior Warren Alpert Medical School of Brown University, Providence, RI; [7]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [8]Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham NC; [9]Segal Clinical Research Institute, and University of Miami, Miami, FL

ABSTRACT

Subcutaneous buprenorphine implants (Probuphine™) deliver constant, low levels of buprenorphine for up to six months with minimal fluctuations in steady-state plasma concentration, and offer potential treatment advantages over sublingual buprenorphine by ensuring patient compliance and limiting diversion. In previous studies, treatment with buprenorphine implants has been shown to be well-tolerated and efficacious in significantly reducing illicit opioid use, retaining patients in treatment, controlling withdrawal symptoms and opioid cravings, and improving global disease severity.

In this six-month confirmatory efficacy and safety study, 287 opioid-dependent patients were enrolled at 20 US sites. Following brief induction with sublingual buprenorphine/naloxone tablets (12-16mg/day), patients were randomized to receive double-blind buprenorphine implants, placebo implants, or open-label sublingual buprenorphine tablets. Urine samples were collected thrice weekly, and routine assessments of other clinical symptoms of opioid dependence and safety were conducted. Patients also received regular counseling, and study completers were given the option of enrolling in a 6-month, open-label, re-treatment safety study. Greater than 80% of eligible completers requested re-treatment.

Over the initial 24-week study, the buprenorphine group was clinically and statistically superior to the placebo group on the percentages of opioid-negative urines (p<.0001); trial retention (64% for buprenorphine implants, 26% placebo, p<.0002), and was shown to be non-inferior to sublingual buprenorphine in regard to reductions in the use of illicit opioids using a pre-specified non-inferiority margin of -15%. The rates of adverse events were low and similar between treatment groups. Procedures to administer and remove the buprenorphine and placebo implants were also well-tolerated. Safety and efficacy data in the re-treatment study were also consistent with earlier findings.

BACKGROUND

- Following induction with sublingual buprenorphine, buprenorphine implants (Probuphine™) are inserted subdermally into the inner side of the upper arm in a 10-15 minute in-office procedure under local anesthetic, and provide sustained release of buprenorphine for 6 months.
- At the end of treatment, the implants are removed in a brief, in-office procedure, and completers were given the option to enroll in a 6-month, open label re-treatment safety study.
- In a previously conducted 24-week, randomized, placebo-controlled trial (Ling et. al., 2010), treatment with buprenorphine implants was associated with:
  - A higher percentage of urines negative for illicit opioids: 40.4% vs. 28.3% (p<.05).
  - A higher retention rate: 65.7% vs. 30.9% (p<.001).
  - A lower incidence of clinician-rated (p<.001) and patient-rated (p=.004) withdrawal symptoms.
  - A lower patient ratings of craving (p<.001).
- The main study was designed to confirm the efficacy of buprenorphine implants during 24 weeks of outpatient treatment.

Study Objectives:

Primary

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

Secondary

- To confirm the efficacy of buprenorphine implants vs. placebo implants in opioid dependence over weeks 1-16, and 17-24 of outpatient treatment.
- To demonstrate the non-inferiority of buprenorphine implants vs. sublingual buprenorphine in opioid dependence over weeks 1-24 of outpatient treatment.
- To examine the safety of buprenorphine implants over the course of 24 weeks of double-blind treatment and an additional 24 weeks of on-label re-treatment.

METHODS

Main Study Design and Treatment

- Brief induction with sublingual buprenorphine/naloxone tablets (12-16mg/day).
- Patients 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.
- All patients also received regular drug counseling.
- Urine samples were collected thrice weekly, and routine assessments of other clinical symptoms of opioid dependence and safety were conducted.
- At the end of 24 weeks, study completers given option of enrolling in a six-month, open-label buprenorphine implant re-treatment safety study.

Primary Efficacy Endpoints

- Percent of urine samples negative for illicit opioids in Weeks 1-24 analyzed as a cumulative distribution function (CDF) for buprenorphine implants vs. placebo implants.
- Percent of urine samples negative for illicit opioids, Weeks 1-24, incorporating patient self-reported opioid use and analyzed as a CDF for buprenorphine implants vs. placebo implants.

Secondary Efficacy Endpoints

1. Percent of urine samples negative for illicit opioids in Weeks 1-16 and separately Weeks 17 to 24, analyzed as CDFs for buprenorphine implants vs. placebo implants.
2. Non-inferiority of buprenorphine implants vs. sublingual buprenorphine in regard to percent of urine samples negative for illicit opioids in Weeks 1 to 24.
3. Proportion of study completers (retention) for buprenorphine implants vs. placebo implants.
4. Mean % negative urines (Weeks 1-24, 1-16, 17-24) for buprenorphine implants vs. placebo implants.
5. Clinician-rated Opioid Withdrawal Scale (COWS) and Subject-rated Opioid Withdrawal Scale (SOWS) for buprenorphine implants vs. placebo implants.
6. Opioid craving VAS for buprenorphine implants vs. placebo implants.
7. Clinician-rated Global Impression, Severity & Improvement (CGI-S; CGI-I) for buprenorphine implants vs. placebo implants.

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RESULTS

Figure 1. Main Study Design and Patient Disposition

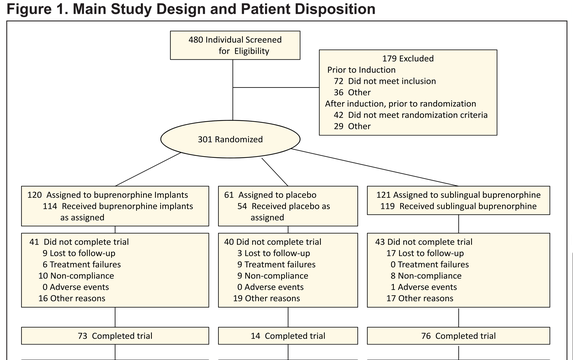
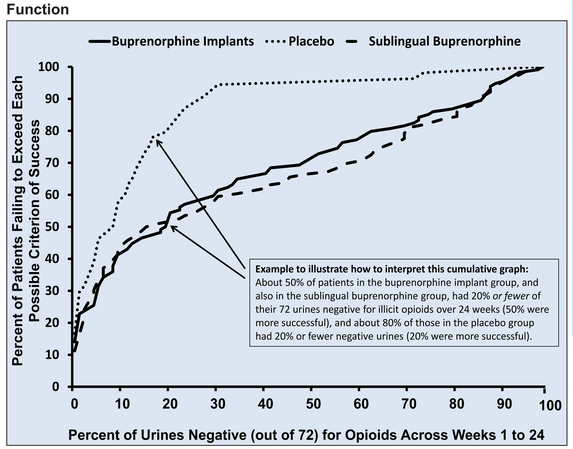


Table 1. Baseline Demographic and Clinical Characteristics

	Buprenorphine Implants (n=114)	Placebo Implants (n=54)	Sublingual Buprenorphine (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	67%	52%	63%
Prescription Opioid analgesics	33%	48%	36%
Opioid dependence for >5 years	25%	22%	31%
Prior Tx for Opioid Abuse, % *	55%	57%	57%

* Includes psychosocial and pharmacotherapy

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



Non-Inferiority Comparison (-15% Margin):

- Buprenorphine implants: 31%; Sublingual buprenorphine: 33%.
- 95%-CI of the difference score: (-10.7, 6.2). Non-inferiority demonstrated because the lower bound of the confidence interval does not contain -15%.

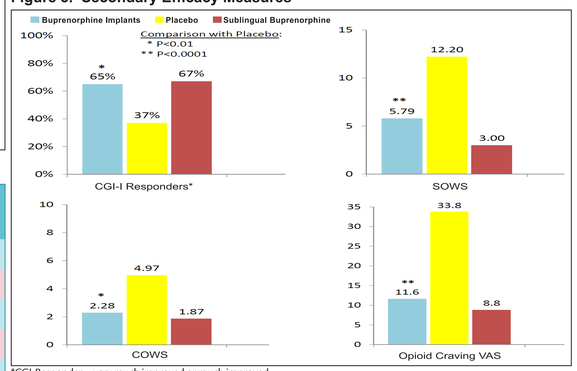
Least-Squared Means (SE) Comparisons:

- Buprenorphine implants (36%) vs. placebo implants (14%): Weeks 1 to 24: p < .0001 (also significant [p < .0001] for Weeks 1 to 16 and Weeks 17-24).
- Buprenorphine implants (36%) vs. sublingual buprenorphine (35%): not significantly different.

Completion of 6 Months of Treatment:

- Buprenorphine implanted subjects had a higher completion rate relative to placebo (64% vs. 26%, p<.0002).

Figure 3. Secondary Efficacy Measures



*CGI-Responder = very much improved or much improved

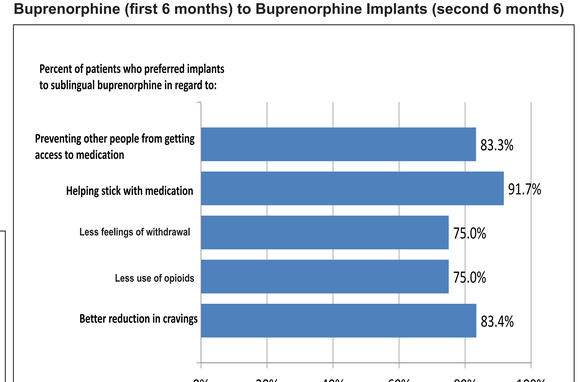
Table 2. Incidence of Adverse Events (≥5% for buprenorphine implants)

	Randomized Phase (First 6 Months)			Re-Treatment Phase (Second 6 Months)
Event	Buprenorphine Implants (n=114)	Placebo Implants (n=54)	Sublingual Buprenorphine (n=119)	Buprenorphine Implants (n=85)
Any adverse event	67.5%	61.1%	71.4%	67.1%
Headache	13.2%	9.3%	16.0%	11.8%
Upper resp. infection	8.8%	7.4%	9.2%	8.2%
Mood symptoms	8.8%	5.6%	3.4%	7.0%
Insomnia	7.9%	14.8%	13.4%	2.4%
Sore throat	7.0%	1.9%	3.4%	1.2%
Nausea	6.1%	1.9%	6.7%	3.5%
Vomitting	6.1%	1.9%	4.2%	2.4%
Nasopharyngitis	5.3%	5.6%	10.1%	2.4%
Back pain	5.3%	5.6%	5.9%	5.9%
Any "severe" event	7.9%	5.6%	11.8%	7.1%
Any "serious" event	5.3%[†]	5.6%	5.9%	2.4%

† Umbilical hernia, pneumonia (n=2), breast cancer, hypotension, tooth abscess . No serious events were judged by investigators to be related to study drug. There was one death (accidental OD) in the sublingual buprenorphine group.

- There were no serious events judged by investigators to be related to study drug; there was one death (accidental OD) in the sublingual buprenorphine group.
- No significant differences between the 3 groups on any adverse events.
- Minor implant site reactions were comparable in the buprenorphine implant (27.2%) and placebo groups (25.9%).

Figure 4. Treatment Satisfaction for Patients Switched from Sublingual Buprenorphine (first 6 months) to Buprenorphine Implants (second 6 months)



- Greater than 80% of eligible completers from the main study requested re-treatment.
- Treatment satisfaction was high during the re-treatment phase (Figure 4); craving and withdrawal symptoms remained low.
- Overall, 57 of 85 subjects (67.1%) who entered the re-treatment phase experienced treatment-emergent adverse events. No new safety concerns were identified following an additional 24 weeks of treatment with buprenorphine implants.
- 14% of those who participated in the re-treatment experienced implant site adverse events; none of these were considered serious adverse events, led to study drug discontinuation, or were considered related to study drug.
- Patients treated with placebo or sublingual buprenorphine during the initial 6-month treatment phase decreased their self-reported drug use by 25% and 20%, respectively, during the 6-month re-treatment phase when switched to buprenorphine implants.

CONCLUSIONS

- In the treatment of opioid dependence, the efficacy of buprenorphine implants relative to placebo implants was confirmed.
- Efficacy demonstrated on primary endpoint (% urine samples negative for illicit opioids at Weeks 1-24, examined as a CDF).
- Efficacy also demonstrated on multiple secondary endpoints, including measures of opioid withdrawal, drug craving, and treatment retention.
- Treatment with buprenorphine implants was non-inferior and comparable to sublingual buprenorphine.
- Buprenorphine implants were found to be generally safe and well-tolerated during the 24 week double-blind phase and the 24 week re-treatment phase.
- Patients treated with sublingual buprenorphine during the initial 24 week period and then switched to buprenorphine implants during the 24 week re-treatment phase reported high levels of satisfaction with the implants in comparison to sublingual buprenorphine.

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.

DISCLOSURES

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