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CADTH COMMON DRUG REVIEW

Clinical Review Report

BUPRENORPHINE SUBDERMAL IMPLANT (PROBUPHINE)

(Knight Therapeutics Inc.)

Indication: Opioid use disorder

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Abbreviations

BPN	buprenorphine
CGI	Clinical Global Impressions scale
CI	confidence interval
COWS	Clinical Opioid Withdrawal Scale
FDA	US Food and Drug Administration
ITT	intention-to-treat population
MCID	minimum clinically important difference
mITT	modified intention-to-treat population
RCT	randomized controlled trial
SL	sublingual
SOWS	Subjective Opioid Withdrawal Scale
VAS	visual analogue scale

Drug	Buprenorphine hydrochloride subdermal implant (Probuphine)
Indication	The management of opioid dependence in patients clinically stabilized on no more than 8 mg of sublingual buprenorphine in combination with counselling and psychosocial support.
Reimbursement Request	As per indication
Dosage Form(s)	80 mg subdermal implants
NOC Date	April 18, 2018
Manufacturer	Knight Therapeutics Inc.

Executive Summary

Introduction

Opioid use disorder is a chronic relapsing illness associated with elevated risk of mortality and morbidity that has been described as one of the most challenging forms of addictions facing the Canadian health care system.[1] Rising rates of opioid poisonings and deaths have prompted the declaration of a public health emergency in British Columbia and prompted actions by stakeholders across the country in response to this crisis. In 2016, there were 2,946 apparent opioid-related deaths in Canada (8.1 deaths per 100,000), with the highest rates observed in Western Canada.[2] From January to September 2017, a total of 2,923 apparent opioid-related deaths were reported (10.6 per 100,000), which represents a 45% increase in deaths compared with the same period the previous year.[2] Most of the apparent opioid-related deaths in 2017 were accidental (92%) and an increasing proportion were associated with fentanyl (72% in 2017 versus 55% in 2016).[2] Although the prevalence of opioid use disorder in Canada is not known, it is estimated to affect approximately 2.1% of the US population.[3]

The product under review is a rod-shaped implant (26 mm by 2.5 mm) that contains 80 mg of buprenorphine hydrochloride (a partial mu-opioid receptor agonist) embedded in ethylene vinyl acetate. The approved indication of buprenorphine implants is for the management of opioid dependence in patients clinically stabilized on no more than 8 mg of sublingual (SL) buprenorphine, in combination with counselling and psychosocial support. The recommended dose is four implants (320 mg) inserted subdermally in the upper arm by a trained health care professional, with a suggested treatment duration of one year (initial set of implants removed after six months and a new set inserted into the opposite arm for an additional six months).

The objective of this report was to perform a systematic review of the beneficial and harmful effects of buprenorphine hydrochloride 80 mg subdermal implant for the treatment of patients with opioid drug dependence stabilized on SL buprenorphine (≤ 8 mg per day).

Of note: this review was initiated prior to the product receiving a Notice of Compliance (NOC) from Health Canada and the protocol was developed based on the proposed indication (adults with opioid drug dependence after initiation with a product containing transmucosal buprenorphine). Three randomized controlled trials (RCTs) met the inclusion

criteria; however, only one of the trials (Study 814) enrolled a population that is consistent with the approved indication. Thus, this report will focus on the findings of Study 814, although two other placebo-controlled trials (studies 805 and 806) have been summarized in this report.

Results and Interpretation

Included Studies

Study 814, the pivotal trial, enrolled clinically stable adult patients with opioid dependence who had received treatment with SL buprenorphine for at least six months and were on a dose of 8 mg or less per day for the past 90 days, with no positive urine toxicology for illicit opioids in that time and minimal symptoms of withdrawal at screening. Patients were randomized to receive 24 weeks of treatment with buprenorphine implants (four implants) plus placebo SL tablets, or SL buprenorphine/naloxone (at the buprenorphine dose they were on prior to study entry; ≤ 8 mg/day) plus four placebo implants (double-dummy).

The trial enrolled a total of 177 patients with a mean age of 39 years, of which 95% were white and 59% were male. Most patients were employed, either full-time (55%) or part-time (10%). The primary opioid of abuse was prescription opioids (74%). The median duration of buprenorphine treatment prior to enrolment was 3.0 years in the implant group and 2.5 years in the SL buprenorphine group.

Key limitations of Study 814 include the limited sample size (fewer than 90 patients per treatment group), short duration of treatment (six months) and uncertainty in the noninferiority margin selected.

The other included trials (studies 805 and 806) enrolled adults with opioid dependence who had not received treatment for their substance use disorder in the past 90 days. Patients underwent induction therapy with SL buprenorphine/naloxone and those whose withdrawal symptoms and cravings were controlled on 12 mg to 16 mg of buprenorphine daily were eligible for randomization (Study 806, N = 287; Study 805, N = 163). Patients were randomized to receive four buprenorphine or placebo implants (blinded). Study 806 also randomized patients to open-label SL buprenorphine/naloxone at a dose of 12 mg to 16 mg buprenorphine daily. Both studies were 24 weeks in duration.

The patients enrolled in studies 805 and 806 were similar, with a mean age per treatment group ranging from 35.2 to 39.3 years; 73% to 83% were white and 57% to 73% were male. The primary opioid of abuse was heroin for 52% to 67% of patients. In these trials, 32% to 45% of patients had received no prior treatment for opioid dependence. The trials had a differential frequency of withdrawal: in the active treatment groups, 34% to 39% of patients withdrew and, in the placebo treatment groups, 69% to 74% withdrew from the study. Other limitations include the lack of blinding for the SL buprenorphine treatment group in Study 806, the limited sample size (54 to 119 patients per group) and short treatment duration (six months).

Efficacy

Pivotal Trial (Study 814)

The primary outcome in Study 814 was the proportion of responders, which was defined as patients with no more than two of six months showing evidence of illicit opioid use (urine toxicology or self-reported use). More patients in the buprenorphine implant group met the

criteria for a responder (96.4%) than in the SL buprenorphine group (87.6%), with a between-group difference in proportions of 0.088; 95% confidence interval (CI), 0.009 to 0.167 (modified intention-to-treat [mITT] population). The buprenorphine implant was noninferior to SL buprenorphine, as the lower bound of the 95% CI was greater than the −0.20 noninferiority margin. Buprenorphine implant also demonstrated superiority to SL buprenorphine (P = 0.034) in the primary analysis, where missing urine tests were imputed with a 20% relative penalty to the buprenorphine implant group. This meant that missing values in the buprenorphine implant group were imputed based on 1.2 times the maximum mean proportion of within-patient positive tests from the two treatment groups. Noninferiority was met in the analysis based on the per-protocol population (proportion difference 0.053; 95% CI, −0.022 to 0.129), but not superiority (P = 0.18). Noninferiority was consistently met, based on the other sensitivity analyses conducted by the manufacturer as well as on the more conservative post hoc analyses reported by the FDA that used the intention-to-treat (ITT) population and assumed all missing urine samples were positive. Most sensitivity analyses, however, did not support a superiority claim, and superiority testing was not pre-specified in the study's protocol. Of note, there is considerable uncertainty with regard to the −0.20 noninferiority margin, as limited data are available to support this value, although even the analyses with the most conservative imputation assumptions were above the −0.20 noninferiority margin (minimum value −0.138).

The percentage of patients with no illicit opioid use per month (based on urine tests and self-reported use) ranged from 85% to 94% in the SL buprenorphine group and from 91% to 99% in the buprenorphine implant group, and the time to first illicit opioid use showed differences favouring the implant group. These outcomes, however, were not part of the fixed statistical testing procedure and thus should be interpreted as inconclusive. Moreover, the clinical relevance of the time-to-event analysis is unclear, given that occasional illicit opioid use is not unexpected, even among stable patients, and may not negatively affect the patients' overall treatment success.

Overall, the proportion of patients who remained in the study was high (94%) and was similar between groups. Fifteen patients (18%) in the buprenorphine implant group and 13 patients (15%) in the SL buprenorphine group were dispensed supplemental SL buprenorphine on one or more occasions, although it is not clear what doses were administered on how many days, and when they were received (e.g., at the beginning of treatment, throughout, or near the end of the trial). The average total dose of supplemental SL buprenorphine received per patient was higher in the implant group (85.8 mg) than the SL buprenorphine group (49.8 mg), although the clinical expert consulted for the review considered these quantities to be low when expressed in terms of milligrams per day.

In Study 814, the mean Clinical Opioid Withdrawal Scale (COWS), Subjective Opioid Withdrawal Scale (SOWS), and desire- or need-to-use visual analogue scale (VAS) scores in both treatment groups were generally low at baseline as well as at week 24 (mean COWS ≤ 1.0; SOWS ≤ 2.7; desire- or need-to-use VAS ≤ 6.8), and no statistically significant differences were detected between groups in the change from baseline to week 24 for any of these outcome measures, which were outside the fixed statistical testing procedure.

Other Studies (805 and 806)

Over the 24 weeks in Study 806, the mean percentage of negative urine samples was 36%, 35%, and 14% in the buprenorphine implant, SL buprenorphine, and placebo implant groups respectively. Statistically significant differences were detected between the

buprenorphine implant versus placebo (difference 21%; 95% CI, 13% to 31%). Buprenorphine implant was noninferior to SL buprenorphine based on the proportion of negative urine tests, as the lower bound of the 95% CI for the between-group difference (−10.7%) was higher than the −15% noninferiority margin. The cumulative distribution function of the percentage of urine samples that were negative for illicit opioids was statistically significant ($P < 0.0001$) for the buprenorphine implant versus placebo implant groups for both primary analyses (based on urine test data only or based on urine tests and self-reported illicit opioid use). No comparisons between the SL buprenorphine and implant groups were conducted based on the cumulative distribution function analysis.

In Study 805 from week 1 to 16, the mean percentage of negative urine samples was 40% in the buprenorphine implant group and 29% in the placebo group (difference 11%; 95% CI, 1 to 21%), and was 28% and 10%, respectively from week 17 to 24 (difference 18%; 95% CI, 8% to 28%). The cumulative distribution function of the percentage of urine samples that were negative for illicit opioids was analyzed for weeks 1 to 16 (primary outcome) and for weeks 17 to 24 (key secondary outcome). Statistically significant differences were detected between groups for both analyses (week 1 to 16: $P = 0.036$; week 17 to 24: $P = 0.0004$).

In studies 806 and 805, 22% and 20% of patients in the buprenorphine implant groups and 39% and 58% in the placebo implant groups, respectively, received one additional implant, whereas three patients (3%) in the SL buprenorphine group of Study 806 met the criteria for a dose increase. In the buprenorphine implant groups, 40% of patients in Study 806 and 62% in Study 805 received supplemental SL buprenorphine as rescue therapy, with a median total dose of 68 mg and 72 mg, respectively. In comparison, 6% of patients in the SL buprenorphine group received rescue therapy with a median total dose of 24 mg. The majority of patients in the placebo implant groups (Study 806: 67%; Study 805: 91%) received supplemental SL buprenorphine with a median total dose per patient of 100 mg (Study 806) and 188 mg (Study 805).

Although statistically significant differences were detected between buprenorphine implants and placebo in studies 805 and 806, the interpretation of these differences should take into consideration the appropriateness of the placebo control group and the substantial and differential withdrawal rates in these studies, which could potentially bias the results in favour of buprenorphine. Furthermore, the dosing used and the population enrolled (patients initiated on moderate to higher doses of buprenorphine) were not consistent with the indication approved by Health Canada. Thus, the data from these trials should be considered as supplementary evidence only.

Harms

Adverse events were reported by most patients and the frequency varied between studies, ranging from 56% to 58% in Study 814, from 67% to 72% in Study 806, and from 82% to 86% in Study 805. Among patients who received buprenorphine implants, 2% to 5% experienced a serious adverse event, compared with 6% and 7% of those in the placebo implant group and 3% to 6% in the SL buprenorphine groups. The proportion of patients who stopped treatment due to adverse events was generally low and ranged from 0% to 4%.

The frequency of implant-site adverse events was high in Study 805 and its extension study and, consequently, the manufacturer modified the applicator, the insertion and removal procedures, and the training materials for studies 806 and 814. Implant-site adverse events were reported in 14% to 27% of patients in these two trials, and no patients stopped

treatment or had a serious adverse event related to the implant site. An implant was expelled from one patient in Study 814 (placebo implant) and one patient in Study 805 (buprenorphine implant). There was one patient per group in Study 806 who experienced an overdose, and one incident of accidental pediatric overdose in the SL buprenorphine group in Study 814.

No new safety signals were identified in two open-label extension studies that enrolled 147 patients who had completed either Study 805 or 806. Of these patients, 107 (73%) had previously received buprenorphine implants; thus, their total duration of exposure to implants was up to one year. The suggested treatment duration for buprenorphine implants is one year (one set of implants per arm for six months each), as the monograph states there is no experience with inserting additional implants into other sites in the upper arm, sites other than the upper arm, or with reinserting into previously used sites.[4] The product monograph states that dosing beyond 24 months cannot be recommended at this time. [4]

Place in Therapy[1]

This six-monthly depot formulation of buprenorphine is suited for people with an opioid use disorder, especially secondary to prescription opioid use, who have been stable for at least 90 days on SL buprenorphine/naloxone 8 mg or less per day. Currently, patients who are stabilized and employed still have to interact more frequently with health care providers to obtain prescription refills and make visits to the pharmacy weekly. In some cases, this interaction has minimal therapeutic value if the patient is in remission, but serves mainly to minimize the risk of diversion to SL buprenorphine/naloxone.[5-7] That time could be better spent by the patient to address other issues, such as concurrent post-traumatic stress disorder (PTSD) or depression,[6] for example. Therefore, this population is likely to be better served by this formulation because they could exercise the option of having a bi-annual procedure for a year. In addition, it will reduce the stigma associated with treatment, especially the weekly visit to the pharmacy and the need for frequent urine drug testing. It could also fill the gap by providing access to those who live in remote areas where there is limited access to prescribers for the SL medication, and for those who have to travel for extended periods for work, especially to areas where there is restricted or no access to SL buprenorphine/naloxone. It also provides a choice to those patients who do not wish to take tablets every day, although at least 18% — based on Study 814 — might require some SL supplementation. Therefore, this implantable formulation of buprenorphine reduces the risk of diversion, but does not eliminate it completely.[8]

It will be easy to identify patients who are appropriate to receive buprenorphine implants based on the duration and response to SL buprenorphine/naloxone, and no special tests are required. Physicians will likely need training and certification to be able to place the implant. This might limit the availability of this treatment. One advantage is that in a medical emergency, the implants can be removed, unlike injectable formulations.[8]

It is not known whether there is any benefit to implanting more than two sets (i.e., one-year exposure) of buprenorphine implants. Thereafter, if the person still requires buprenorphine after one year, they will have to revert back to SL formulations, or be assessed to determine if the potential benefits of continuing buprenorphine implants outweigh the risks of additional insertion and removal procedures. Given the implants are inserted subdermally in the upper arms and reinsertion in the same site is not recommended, the effectiveness of

[1] This information is based on information provided in draft form by the clinical expert consulted by the CADTH Common Drug Review (CDR) reviewers for the purpose of this review.

the implant if inserted in other subdermal areas is unknown. A major concern is whether plasma levels of buprenorphine are high enough to act as an antagonist should the person relapse to highly potent opioids, such as fentanyl and/or hydromorphone, especially toward the end of the dosing interval.[5] Lastly, the risk of double-doctoring or of having access to diverted buprenorphine or additional SL buprenorphine/naloxone will still remain and will not be detectable in urine drug testing. The former could be detected by a prescription-monitoring program, but the latter will rely on self-reporting.

Conclusions

In adults with clinically stable opioid dependence adequately managed on low doses of SL buprenorphine, buprenorphine implants (320 mg total dose) were noninferior to SL buprenorphine at doses of 8 mg or less per day based on the proportion of responders, defined as those with no evidence of illicit opioid use for at least four out of six months. The proportion of patients remaining on treatment was high in both groups. Although data were reported on symptoms of withdrawal and cravings to use opioids, the trial was not powered to detect differences between groups for these outcomes. No data were available on health-related quality of life or social functioning.

The evidence available for the Health Canada–approved population was limited to a single RCT that included fewer than 90 patients per treatment group. Considering the sample sizes and duration of exposure in the pivotal and other placebo-controlled trials, it is not possible to determine the risks of infrequent but clinically important implant-related adverse events, or longer-term efficacy and safety.

Table 1: Summary of Efficacy Results

	Study 814			
Population/Analysis Method	**BPN Implant**	**BPN SL**	**BPN Implant Minus BPN SL**	
Proportion of responders (≥ 4 out of 6 months with no evidence of illicit opioid use)	**Responder, n (%)**	**Responder, n (%)**	**Proportion difference (95% CI)**	***P* value**
mITT	**N = 84**	**N = 89**		
Primary analysis 20% relative penalty imputation method for missing urine test data[a]	81 (96.4)	78 (87.6)	0.088 (0.009 to 0.167) NI met[b, c]	0.034[d]
PP	**N = 67**	**N = 72**		
20% relative penalty imputation method for missing urine test data	65 (97.0)	66 (91.7)	0.053 (−0.022 to 0.129)	0.176[d]
ITT (post hoc)[e]	**N = 87**	**N = 89**		
Missing urine samples imputed as positive	78 (89.7)	76 (85.4)	0.043 (−0.055 to 0.140)	0.39

Population/Outcome	Study 806					Study 805		
	BPN Implant	SL BPN	Placebo Implant	Treatment Difference		BPN Implant	Placebo Implant	Treatment Difference
				BPN implant Versus SL BPN (95% CI), *P* Value	BPN Implant Versus Placebo Implant (95% CI), *P* Value			BPN Implant Versus Placebo Implant (95% CI), *P* Value
ITT	**N = 114**	**N = 119**	**N = 54**			**N = 108**	**N = 55**	
Proportion of negative urine tests								
Cumulative probability, week 1 to 24	31.2	33.5	NR	(−10.7 to 6.2) NI met[f]	NR	NR	NR	NR
Mean % of negative urine samples								
Week 1 to 24, LS mean (SE)	36.0 (2.8)	35.1 (2.8)	14.4 (3.8)	0.9 (−6.4 to 8.2), *P* = 0.81[g, h]	21.6 (12.5 to 30.8) *P* < 0.0001[g, h]	NR	NR	NR

Population/Outcome	Study 806					Study 805		
	BPN Implant	SL BPN	Placebo Implant	Treatment Difference		BPN Implant	Placebo Implant	Treatment Difference
				BPN implant Versus SL BPN (95% CI), *P* Value	BPN Implant Versus Placebo Implant (95% CI), *P* Value			BPN Implant Versus Placebo Implant (95% CI), *P* Value
Week 1 to 16, LS mean (SE)						40.3 (3.2)	28.9 (4.3)	11.4 (1.4 to 21.4), *P* = 0.025[g]
Week 17 to 24, LS mean (SE)						27.9 (3.3)	9.8 (4.4)	18.1 (7.8 to 28.3), *P* = 0.0006[g]

ANCOVA = analysis of covariance; ANOVA = analysis of variance; BPN = buprenorphine; CI = confidence interval; CSR = Clinical Study Report; ITT = intention-to-treat; LS = least squares; mITT = modified intention-to-treat; NI = noninferiority; NR = not reported; PP = per-protocol; SE = standard error; SL = sublingual.

[a] The primary analysis placed a 20% penalty on the buprenorphine implant group. This meant that missing values in the BPN implant group were imputed based on 1.2 times the maximum mean proportion of within-patient positive tests from the two treatment groups.

[b] Noninferiority was met for buprenorphine implant relative to SL buprenorphine as the lower bound of the 95% CI was greater than −0.2.

[c] *P* value for noninferiority < 0.001.

[d] Based on chi-square test for superiority claim.

[e] This analysis was reported by the FDA, as a more conservative imputation method for missing data, and using the randomized and treated population, rather than the mITT that was used by the manufacturer.

[f] Noninferiority was met for BPN implant relative to SL BPN as the lower bound of the 95% CI was greater than −15.0 (*P* value NR).

[g] Study 806: ANOVA model, including treatment, pooled site, and gender. Study 805: ANCOVA model, including treatment, pooled centre, gender, and treatment by gender interaction.

[h] Outside the statistical testing hierarchy and thus should be considered inclusive.

Source: CSR,[9-11] Rosenthal et al., 2016.[12]

Table 2: Summary of Other Outcomes and Harms

	Study 814		Study 806			Study 805	
	BPN Implant N = 87	BPN SL N = 89	BPN Implant N = 114	BPN SL N = 119	Placebo Implant N = 54	BPN Implant N = 108	Placebo Implant N = 55
Required supplemental SL BPN, n (%)	15 (18)[a]	13 (15)	45 (40)	7 (6)	36 (67)	67 (62)	50 (91)
Received a dose increase, n (%)	NA	NA	25 (22)	3 (3)	21 (39)	22 (20)	32 (58)
Discontinued study, n (%)	6 (7)	5 (6)	41 (36)[b]	43 (36)	40 (74)	37 (34)[c]	38 (69)
Stopped treatment due to adverse events, n (%)	1 (1)	0	2 (2)	5 (4)	2 (4)	4 (4)	0
SAEs, n (%)	2 (2)	3 (3)	6 (5)	7 (6)	3 (6)	2 (2)	4 (7)
Implant-site adverse events, n (%)	20 (23)	12 (14)	31 (27)	NA	14 (26)	62 (57)	25 (46)

BPN = buprenorphine; CSR = Clinical Study Report; NA = not applicable; SAE = serious adverse event; SL = sublingual.

[a] Total N = 84.

[b] Difference in the proportion of completers for buprenorphine implant versus placebo implant, $P = 0.0002$.

[c] Difference in the proportion of completers for buprenorphine implant versus placebo implant, $P < 0.0001$ (outside the statistical testing hierarchy).

Source: CSRs.[9-11]

Introduction

Disease Prevalence and Incidence

Opioid use disorder is a chronic relapsing illness associated with elevated risk of mortality and morbidity that has been described as one of the most challenging forms of addictions facing the Canadian health care system.[1] Rising rates of opioid poisonings and deaths have prompted the declaration of a public health emergency in British Columbia, and prompted actions by stakeholders across the country in response to this crisis. In 2016, there were 2,946 apparent opioid-related deaths in Canada (8.1 deaths per 100,000), with the highest rates observed in Western Canada.[2] From January to September 2017, a total of 2,923 apparent opioid-related deaths were reported (10.6 per 100,000), which represents a 45% increase in deaths compared with the same period the previous year.[2] Most of the apparent opioid-related deaths in 2017 were accidental (92%) and an increasing proportion were associated with fentanyl (72% in 2017 versus 55% in 2016).[2] Although the prevalence of opioid use disorder in Canada is not known, it is estimated to affect approximately 2.1% of the US population.[3]

Standards of Therapy

For the treatment of opioid use disorder, opioid agonist therapy has been shown to be superior to withdrawal management in terms of retention in treatment, abstinence from opioid use, morbidity, and mortality.[3] Canadian guidelines recommend the use of buprenorphine/naloxone as the first-line treatment of adults with opioid use disorder, as it has been shown to be safer than methadone in terms of overdose risk, has fewer prescribing restrictions, and may be administered at home in suitable patients.[1] Methadone is recommended in patients responding poorly to buprenorphine/naloxone, or when buprenorphine/naloxone is not the preferred agent.[1] Existing evidence suggests buprenorphine/naloxone and methadone, at moderate to high doses, are equally effective in terms of treatment retention and reducing illicit opioid use.[3] Other opioid treatment options include slow-release oral morphine, although this is not an approved indication in Canada. Slow-release morphine was recommended only in patients in whom first- and second-line agents are ineffective or contraindicated and is to be prescribed by or in consultation with addiction specialists.[1] Oral naltrexone, an opioid antagonist, can also be considered as an adjunct medication if cessation of opioid use is achieved.[1] Canadian guidelines recommend against opioid-withdrawal management alone (i.e., detoxification without immediate transition to long-term addiction treatment), as this has been associated with increased rates of relapse, morbidity (e.g., HIV and hepatitis C), and death from overdose.[1,3] The guidelines state that all patients should have information on and referrals to harm-reduction services, including take-home naloxone, as well as psychosocial interventions and supports.[1] The guidelines endorse a stepped and integrated approach in which treatment is adjusted to accommodate patients' needs and preferences and allows patients to transition between treatments over time.[1] Other off-label opioid-replacement therapies that were not addressed by the Canadian guidelines include injectable hydromorphone or diacetylmorphine (pharmaceutical-grade heroin).[1]

Prescribing restrictions have been in place for methadone, which required an exemption from the Minister of Health Canada (Table 3). However, the Government of Canada recently announced that these restrictions will be lifted in order to facilitate greater access to methadone treatment.[13] In addition, amendments to the restrictions on diacetylmorphine

will provide flexibility by allowing patients to receive the product outside a hospital setting, such as at substance use–disorder clinics.[13]

Drug

Buprenorphine is a partial mu-opioid receptor agonist which has high receptor affinity, thereby reducing the binding of other opioids to the mu-receptors. The product under review is a rod-shaped implant (26 mm by 2.5 mm) that contains 80 mg of buprenorphine hydrochloride embedded in ethylene vinyl acetate, and the recommended dose is four implants (320 mg) inserted subdermally in the upper arm for up to six months.[4] The approved indication of buprenorphine implants is for the management of opioid dependence in patients clinically stabilized on no more than 8 mg of sublingual buprenorphine in combination with counselling and psychosocial support.[4] All health care professionals who wish to perform implant insertions or removals are required to complete a live training program to become certified. The product monograph suggests a treatment duration of one year (initial set of implants removed after six months and a new set inserted into the opposite arm for an additional six months), and any patient who requires treatment after one year may be transitioned back to their previous sublingual (SL) buprenorphine dose.[4] Use beyond 24 months is not recommended.[4]

Table 3: Pharmacotherapies for Opioid Use Disorder

	Buprenorphine Subdermal Implant	Buprenorphine/ Naloxone	Methadone	Naltrexone
Mechanism of Action	Partial mu-opioid agonist.	Buprenorphine: partial mu-opioid agonist. Naloxone (opioid antagonist): to deter injection and intranasal misuse and abuse.	Opioid agonist with activity at mu receptor.	Opioid antagonist.
Indication[a]	The management of opioid dependence in patients clinically stabilized on no more than 8 mg of sublingual buprenorphine in combination with counselling and psychosocial support.	For substitution treatment in adults with problematic opioid drug dependence.	For the detoxification treatment of opioid addiction (heroin or other morphine-like drugs), as well as the maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.	To block the pharmacologic effects of exogenously administered opioids as an adjunct to the maintenance of the opioid-free state in detoxified, formerly opioid-dependent individuals.
Route of Administration	Subdermal	Sublingual[b]	Oral	Oral
Recommended Dose	Four 80 mg implants inserted subdermally for up to six months. If continued treatment is desired, another six months of treatment is an option by replacing implants.	Maintenance dose of 12 mg to 16 mg of buprenorphine once daily is clinically effective for most patients. Maximum single daily dose of 24 mg. Available as 2 mg buprenorphine/0.5 mg	Maintenance therapy starting dose of 10 mg to 40 mg daily, titrated based on patient response up to 80 mg per day. Maximum daily dose is 120 mg.	50 mg daily or alternate-day dosage regimens (e.g., 100 mg Monday and Wednesday, 150 mg Friday).

	Buprenorphine Subdermal Implant	Buprenorphine/ Naloxone	Methadone	Naltrexone
		naloxone or 8 mg buprenorphine/ 2 mg naloxone SL tablet.		
Serious Side Effects / Safety Issues	Contraindicated in patients with: severe respiratory or hepatic insufficiency; acute alcoholism or delirium tremens; convulsive or seizure disorders; severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury; GI obstruction; long QT syndrome or QTc prolongation; or uncorrected hypokalemia, hypomagnesemia, or hypocalcemia. Not recommended in patients with moderate hepatic insufficiency. Cautions: Risk of implant migration, protrusion, expulsion, and nerve damage resulting from the procedure. Use with caution in patients receiving other CNS depressants, including benzodiazepines and alcohol.	Contraindicated in patients with: severe respiratory insufficiency; hepatic impairment; acute alcoholism, delirium tremens, and convulsive disorders; known or suspected mechanical GI obstruction or any diseases/conditions that affect bowel transit, or suspected surgical abdomen; severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury; patients taking monoamine oxidase inhibitors. AE: dependence, interactions with CNS depressants, neonatal opioid-withdrawal syndrome.	Contraindicated in patients with respiratory depression, acute bronchial asthma, or hypercarbia; diarrhea due to antibiotic-related pseudomembranous colitis or poisoning. Use with caution in patients on other CNS depressant drugs or alcohol. Potential drug interactions with many common medications. AE: QT interval prolongation, altered mental states, sexual dysfunction, respiratory depression, neonatal opioid-withdrawal syndrome, hypotension, dependence.	Contraindicated in patients who are using opioids, have a positive urine test for opioids, or are showing withdrawal symptoms; acute hepatitis; or liver failure. Caution in those with severe or active liver or kidney problems. AE: hepatotoxicity, difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache.
Other	Inserted and removed only by health care professionals who have successfully completed a live training program. Patients should be carefully monitored within a framework of medical, social, and psychological support as part of a comprehensive opioid-dependence treatment program.	Prescribed by physicians who meet the following requirements: • experience in substitution treatment in opioid drug dependence and • completion of a recognized buprenorphine and naloxone education program Daily dosing supervised by a health care professional progressing to unsupervised administration as the patient's clinical stability permits and if the patient is able to safely store medication. Take-home doses should be assessed and reviewed on a regular basis.	Available only through physicians who have received an exemption from Canada's Minister of Health to prescribe methadone pursuant to section 56 of the CDSA.[c]	Patients must be opioid-free for 7 to 10 days.

	Buprenorphine Subdermal Implant	Buprenorphine/ Naloxone	Methadone	Naltrexone
		Patients should be carefully monitored within a framework of medical, social, and psychological support as part of a comprehensive opioid-dependence treatment program.		

AE: adverse event; CDSA = *Controlled Drugs and Substances Act*; CNS = central nervous system; GI = gastrointestinal; SL = sublingual.

[a] Health Canada indication.

[b] There are other formulations of buprenorphine available in Canada (such as the oral buccal film) that may be used off-label for opioid use disorder.[14]

[c] Regulatory amendments to remove the restrictions on prescribing methadone have been announced by Health Canada.[13]

Source: Product monographs[4,15-17] and guidelines.[3]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of buprenorphine hydrochloride 80 mg subdermal implants for the treatment of adults with opioid drug dependence stabilized on SL buprenorphine (≤ 8 mg per day).

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient Population	Adults with opioid drug dependence after initiation with a product containing transmucosal buprenorphine[a] Subgroups: • age • sex (including during pregnancy) • illicit opioid used (prescription opioids versus other) • comorbid psychiatric conditions (e.g., depression)
Intervention	Buprenorphine hydrochloride 80 mg subdermal implant (dose: four implants)
Comparators	Buprenorphine with or without naloxone (transmucosal) Methadone (oral) Naltrexone (oral) Placebo
Outcomes[b]	**Key efficacy outcomes:** • opioid use (e.g., positive urine test, self-report, abstinence) • retention in treatment • social functioning (e.g., employment, criminality, HIV risk behaviour) • health-related quality of life **Other efficacy outcomes:** • opioid withdrawal symptoms • opioid cravings • treatment diversion • need for supplemental medication to manage opioid withdrawal or craving symptoms **Harms outcomes:** AEs, SAEs, WDAEs, mortality, overdose, implant-site reaction or other implant complications, orthostatic hypotension, hepatic toxicity, respiratory depression
Study Design	Published and unpublished Phase III RCTs

AE = adverse event; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Based on the proposed indication in the draft product monograph.[18]

[b] No patient group input was submitted to CADTH to inform which outcomes are considered most important to patients.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Probuphine (buprenorphine hydrochloride subdermal implant).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on January 26, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on May 16, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies; Health Economics; Clinical Practice Guidelines; Drug and Device Regulatory Approvals; Advisories and Warnings; Drug Class Reviews; Clinical trials; and Databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5; excluded studies (with reasons) are presented in Appendix 3.

Of note: This review was initiated prior to the product receiving a Notice of Compliance (NOC) from Health Canada and the protocol was developed based on the proposed indication.[18] On March 14, CADTH was notified of a change in the indication to the following:

"Probuphine (buprenorphine hydrochloride subdermal implant) is indicated in the management of opioid dependence in patients clinically stabilized on no more than 8 mg of sublingual buprenorphine in combination with counselling and psychosocial support" (draft product monograph).[19]

This indication is consistent with the population enrolled in Study 814, and this pivotal trial is the focus of this review. Data from studies 805 and 806 have been included in this review, as per the protocol developed a priori; however, the population enrolled is not consistent with the approved Health Canada indication.

Results

Findings From the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

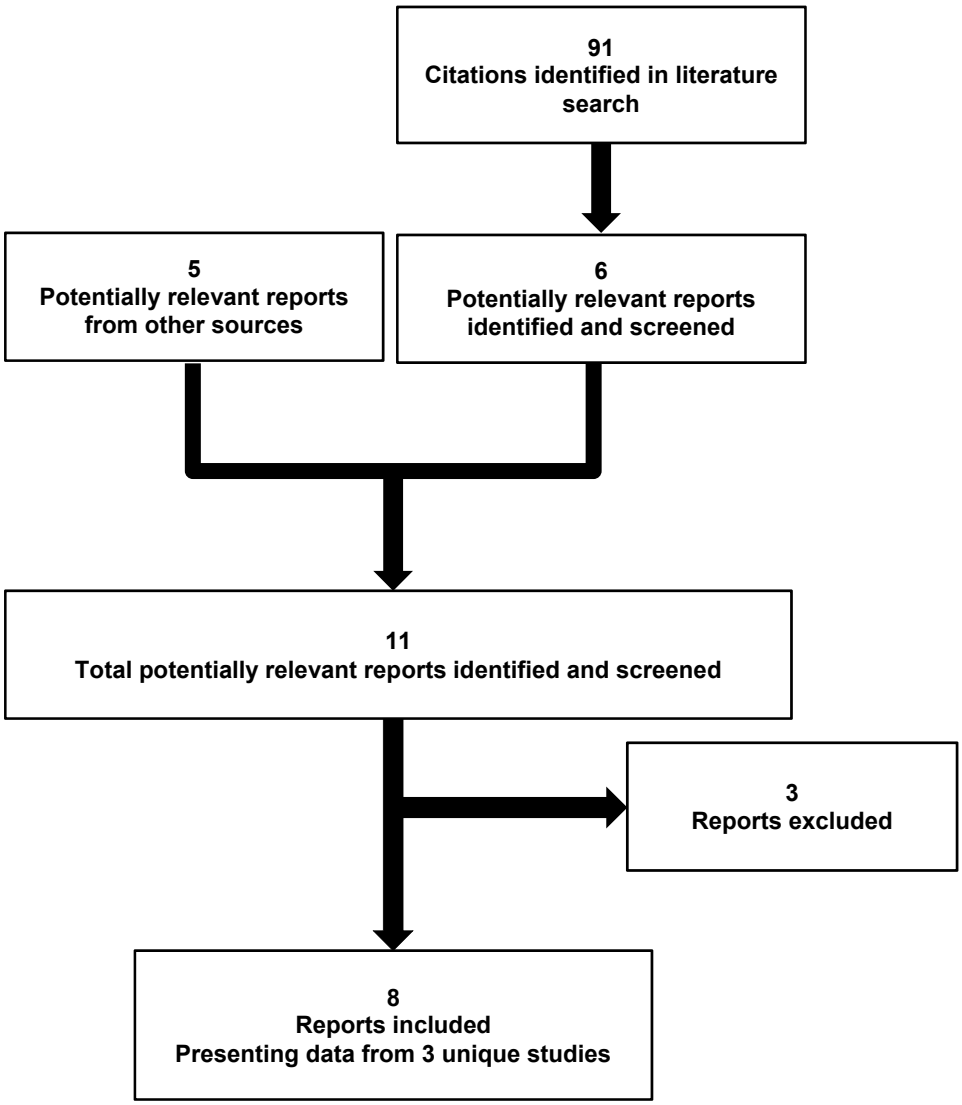


Table 5: Details of Included Studies

		Study-814 (Pivotal)	Study 806	Study 805
Designs & Populations	**Study Design**	DB RCT noninferiority	DB and open-label RCT, superiority/noninferiority	DB RCT superiority
	Locations	21 sites in US	21 sites in US	18 sites in the US
	Randomized (N)	177	287	163
	Inclusion Criteria	• Adult outpatients (18 to 65 years old) with opioid dependence (met DSM-IV-TR criteria) • Clinically stable defined as: on SL buprenorphine for 24 weeks; on ≤ 8 mg daily SL buprenorphine for at least the last 90 days; and no positive urine test for illicit opioids in past 90 days • Free from significant withdrawal symptoms (≤ 5 on COWS)	• Adult outpatients (18 to 65 years old) with opioid dependence (met DSM-IV-TR criteria) • Had successfully completed induction therapy with SL buprenorphine/naloxone and achieved daily buprenorphine dose of 12 mg to 16 mg for three consecutive days • No substantial withdrawal symptoms (≤ 12 on COWS) • No substantial cravings (≤ 20 mm on 100 mm VAS)	• Adult outpatients (18 to 65 years old) with opioid dependence (met DSM-IV-TR criteria) • Had successfully completed induction therapy with SL buprenorphine/naloxone and achieved daily buprenorphine dose of 12 mg to 16 mg for three consecutive days • No substantial withdrawal symptoms (≤ 12 on COWS) • No substantial cravings (≤ 20 mm on 100 mm VAS)
	Exclusion Criteria	• Acquired immune deficiency syndrome • Chronic pain syndrome or condition with acute flares that require opioid treatment • Recent scarring or tattoos on upper arm; keloid scarring • Treatment with drugs metabolized through CYP3A4 isoenzyme • Coagulopathy or current treatment with anticoagulants • Substance dependence disorder for psychoactive drugs other than opioids or nicotine • Abnormal liver function tests, elevated creatinine or bilirubin levels or clinically significantly low platelet count • Concurrent medical conditions that may prevent safe study participation • Symptoms, pending legal action, or other factors that could prohibit participation in the study • Pregnancy; not using a reliable means of contraception	• Received medication-assisted treatment for opioid dependence (methadone or buprenorphine) in last 90 days • Acquired immune deficiency syndrome • Chronic pain that requires opioid treatment • Treatment with drugs metabolized through CYP3A4 isoenzyme • Coagulopathy or current treatment with anticoagulants • Substance dependence disorder for psychoactive drugs other than opioids or nicotine • Abnormal liver function tests, elevated creatinine or bilirubin levels, or clinically significantly low platelet count • Concurrent medical conditions that may prevent safe study participation • Medical or psychiatric symptoms, cognitive impairment, or pending legal action that could prohibit participation in the study • Pregnancy; not using a reliable means of contraception	• Received medication-assisted treatment for opioid dependence (methadone or buprenorphine) in last 90 days • Acquired immune deficiency syndrome • Chronic pain that requires opioid treatment • Treatment with drugs metabolized through CYP3A4 isoenzyme • Current treatment with anticoagulants or INR > 1.2 • Substance dependence disorder for psychoactive drugs other than opioids or nicotine • Abnormal liver function tests, elevated creatinine or bilirubin levels • Concurrent medical conditions that may prevent safe study participation • Medical or psychiatric symptoms, cognitive impairment, or pending legal action that could prohibit participation in the study • Use of benzodiazepines for other than physician prescribed use • Pregnancy; not using a reliable means of contraception

		Study-814 (Pivotal)	Study 806	Study 805
Interventions	**Intervention**	Four buprenorphine 80 mg implants (total 320 mg) plus daily SL placebo	Four buprenorphine 80 mg implants (total 320 mg) (DB)	Four buprenorphine 80 mg implants (total 320 mg)
	Comparator(s)	≤ 8 mg daily buprenorphine/naloxone SL plus placebo implants	Placebo implants (DB) or 12 to 16 mg buprenorphine/naloxone SL daily (open-label)	Placebo implants
	Co-Interventions	Manual guided psychosocial counselling (monthly) Supplemental SL buprenorphine/naloxone (dosed at the investigator's discretion), if needed (open-label)	Manual guided drug counselling (twice weekly for 12 weeks then weekly) Supplemental SL buprenorphine/naloxone (2 mg increments), if needed (open-label)	Manual guided drug counselling (twice weekly for 12 weeks then weekly) Supplemental SL buprenorphine/naloxone (2 mg increments), if needed (open-label)
Duration	Induction	NA	3 to 16 days	3 to 10 days
	Double-blind	24 weeks	24 weeks	24 weeks
	Follow-up	2 weeks	2 weeks	2 weeks
Outcomes	**Primary End Point**	Responder rate (no evidence of illicit opioid use for more than 2 out of 6 months)	Proportion of urine samples negative for illicit opioids in buprenorphine implant versus placebo groups from week 1 to 24 (co-primary outcomes based on two different analysis methods)	Proportion of urine samples negative for illicit opioids from week 1 to 16
	Other End Points	• % with no illicit opioid use per month • Time to first illicit opioid use • Cumulative % of illicit opioid use by month • % with no self-reported use of any illicit drugs by month • Change from baseline in desire-to-use VAS and need-to-use VAS • Change from baseline in COWS and SOWS • Use of supplemental VAS buprenorphine • Additional treatments for opioid dependence • Urine toxicology for other drugs of abuse • Treatment discontinuation	• % urine samples negative for illicit opioids in buprenorphine implant versus placebo groups from week 1 to 16, and week 17 to 24 • Noninferiority of buprenorphine implant versus SL buprenorphine group based on % urine samples negative for illicit opioids • % study completers • Mean % urine samples negative for illicit opioids • COWS, SOWS • Craving VAS • CGI-self, CGI-observer • Weeks of abstinence	• Proportion of urine samples negative for illicit opioids from week 17 to 24 • Proportion of study completers • Mean weeks of abstinence and continuous abstinence • COWS, SOWS • Cravings VAS • CGI-self, CGI-observer • Plasma buprenorphine levels
Notes	**Publications**	Rosenthal et al., 2016[12]	Rosenthal et al., 2013[20]	Ling et al., 2010[21]

CDR = CADTH Common Drug Review; CGI-observer = Clinical Global Impressions scale, observer-reported; CGI-self = Clinical Global Impressions scale, self-reported; CYP3A4 = cytochrome 3A4; COWS = Clinical Opiate Withdrawal Scale; CSR = Clinical Study Report; DB = double-blind; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; INR = international normalized ratio; NA = not applicable; RCT = randomized controlled trial; SL = sublingual; SOWS = Subjective Opiate Withdrawal Scale; VAS = visual analogue scale.

Note: Two additional reports were included (FDA Advisory Committee Report,[22] CDR submission[23]).

Source: CSRs,[9-11] Rosenthal et al., 2016;[12] Rosenthal et al., 2013.[20]

Included Studies

Description of Studies

Pivotal Trial (Study 814)

Study 814 was a randomized double-blind study that was designed to assess the noninferiority of buprenorphine implants versus daily SL buprenorphine in adult outpatients with opioid dependence who were clinically stable on SL buprenorphine at doses of 8 mg or less per day. Patients in Study 814 were randomized 1:1 via a central interactive voice or Web response system managed by the sponsor (block size of four with no stratification) to 24 weeks of treatment with four 80 mg buprenorphine implants plus placebo SL tablets, or 8 mg or less per day of SL buprenorphine plus placebo implants. The primary outcome was the proportion of responders, which was defined as those patients with no more than two of six months showing evidence of illicit opioid use, based on positive urine toxicology or self-reported use.

Other Studies (805 and 806)

Also included were two 24-week randomized double-blind placebo-controlled trials in patients who were not currently receiving treatment for their opioid dependence (studies 806 and 805). These trials used an enrichment design, where patients had to successfully complete induction with SL buprenorphine/naloxone (over three to 16 days) and reach a target dose of 12 mg to 16 mg of buprenorphine daily for three consecutive days to be eligible for randomization.

In Study 806, patients were randomized 2:1:2 to three groups: buprenorphine implant; placebo implant; or SL buprenorphine. Randomization was via a central interactive voice or Web response system in blocks stratified by gender. Patients and investigators were blinded to the treatment received by patients who were randomized to buprenorphine or placebo implants. Patients randomized to SL buprenorphine received open-label study drug.

In Study 805, patients were randomized 2:1 to buprenorphine implant or placebo implant. Randomization was via a central interactive voice or Web response system in blocks stratified by gender and site. Patients and investigators were blinded to treatment allocation.

The primary outcome in the placebo-controlled trials was the proportion of urine samples that were negative for illicit opioids in the buprenorphine implant versus the placebo implant groups. Study 806 also tested the noninferiority of the buprenorphine implant versus SL buprenorphine for the percentage of urine samples that were negative for illicit opioids. Patients in the placebo or buprenorphine implant group, and select patients from the SL buprenorphine group who completed the 24-week study, were eligible to enter into the extension studies (Appendix 6).

Populations

Inclusion and Exclusion Criteria

All three trials enrolled adults 18 to 65 years of age who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) criteria for current opioid dependence (Table 5).

Study 814 enrolled patients who had received treatment with SL buprenorphine for at least six months and were on doses of 8 mg or less per day for the past 90 days, with no positive urine toxicology for illicit opioids during that time and minimal symptoms of withdrawal at screening (Clinical Opioid Withdrawal Scale [COWS] ≤ 5).

Studies 805 and 806 enrolled patients who had not received treatment for their substance use disorder in the past 90 days. Patients underwent induction therapy with SL buprenorphine/naloxone and those whose withdrawal symptoms and cravings were controlled on 12 mg to 16 mg of buprenorphine daily (COWS ≤ 12; cravings visual analogue scale [VAS] ≤ 20 mm), were eligible for randomization.

All three trials had similar exclusion criteria and excluded patients with chronic pain that required opioids, with substance dependence disorder for other psychoactive substances besides opioids and nicotine, or with other cognitive, medical, or other factors that could affect patient safety or adherence to the study protocol.

Baseline Characteristics

Study 814 enrolled a total of 177 patients with a mean age of 39 years, of which 95% were white and 59% were male. Most patients were employed full-time (55%) or part-time (10%), and 18% were unemployed (Table 6). The primary opioid of abuse was prescription opioids (74%) versus heroin (22%). The majority of patients had previously entered buprenorphine treatment once (70%) or twice (23%), and the median duration of previous treatment was 3.0 years in the implant group and 2.5 years in the SL buprenorphine group. Patient characteristics were similar between groups, although the median years since first diagnosis of opioid dependence was higher in the buprenorphine implant group (5.4 years) than in the SL buprenorphine group (3.9 years), and there were more patients with major depressive disorder in the SL versus implant group.

In studies 805 and 806, the mean age per treatment group ranged from 35.2 to 39.3 years, 73% to 83% were white, and 57% to 73% were male. The primary opioid of abuse in the placebo-controlled trials was heroin for 52% to 67% of patients. In Study 806, 44% of patients had received no prior therapies for opioid dependence and, in Study 805, it was 33%. The patient characteristics appeared to be similar between groups within the two studies.

Table 6: Summary of Baseline Characteristics

	Study 814		Study 806			Study 805	
	BPN Implant N = 87	BPN SL N = 89	BPN Implant N = 114	BPN SL N = 119	Placebo Implant N = 54	BPN Implant N = 108	Placebo Implant N = 55
Age, years, mean (SD)	38 (11.2)	39 (10.8)	36.4 (11.0)	35.3 (10.9)	35.2 (10.3)	35.8 (11.0)	39.3 (11.7)
Male, n (%)	52 (60)	52 (58)	72 (63)	72 (61)	31 (57)	72 (67)	40 (73)
Race, n (%)							
White	82 (94)	85 (96)	95 (83)	97 (82)	45 (83)	82 (76)	40 (73)
Black	3 (3)	2 (2)	14 (12)	16 (13)	7 (13)	14 (13)	6 (11)
Other	2 (2)	2 (2)	5 (4)	6 (5)	2 (4)	12 (11)	9 (16)
Primary opioid of abuse, n (%)							
Prescription opioid	66 (76)	65 (73)	38 (33)	43 (36)	26 (48)	39 (36)	21 (38)
Heroin	15 (17)	22 (25)	76 (67)	75 (63)	28 (52)	69 (64)	34 (62)

	Study 814		Study 806			Study 805	
	BPN Implant N = 87	BPN SL N = 89	BPN Implant N = 114	BPN SL N = 119	Placebo Implant N = 54	BPN Implant N = 108	Placebo Implant N = 55
Other	5 (6)	2 (2)	0	1 (1)	0	0	0
Years since first opioid abuse, median (range)	10.1 (1.4 to 36.6)	10.7 (1.6 to 45.6)	NR	NR	NR	NR	NR
Years since first diagnosis of opioid dependence							
Median (range)	5.4 (0.5 to 34.6)	3.9 (0.6 to 43.6)	NR	NR	NR	NR	NR
Within 5 years, n (%)			85 (75)	82 (69)	42 (78)	78 (72)	40 (73)
> 5 years, n (%)			27 (24)	37 (31)	12 (22)	30 (28)	15 (27)
Previously treated for opioid abuse, n (%)	87 (100)	89 (100)	63 (55)	68 (57)	31 (57)	73 (68)	36 (65)
Prior buprenorphine treatment duration (years) median (range)	3.0 (0.5 to 10.0)	2.5 (0.4 to 10.0)	NA	NA	NA	NA	NA
Major depressive disorder, n (%)							
Current (2 weeks)	1 (1)	2 (2)	5 (4)	1 (1)	6 (11)	13 (16)[a]	8 (18)[a]
Past	19 (22)	30 (34)	5 (4)	7 (6)	6 (11)	–	–
Recurrent	4 (5)	11 (12)	3 (3)	4 (3)	3 (6)	8 (10)[a]	6 (14)[a]
Suicidality (past month), n (%)	6 (7)	9 (10)	33 (29)	19 (16)	15 (28)	15 (18)	7 (16)
Employment, n (%)			NR	NR	NR	NR	NR
Full-time	52 (60)	45 (51)	–	–	–	–	–
Part-time	5 (6)	12 (14)	–	–	–	–	–
Student	4 (5)	4 (5)	–	–	–	–	–
Unemployed	15 (17)	17 (19)	–	–	–	–	–
Retired / has a disability / homemaker	11 (13)	11 (12)	–	–	–	–	–

BPN = buprenorphine; CSR = Clinical Study Report; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; SL = sublingual.

[a] Major depressive episode.

Source: CSRs,[9-11] Rosenthal et al.,[20] Ling et al.[21]

Interventions

Pivotal Trial (Study 814)

Patients in Study 814 were randomized to receive buprenorphine implant (four implants) plus placebo SL tablets, or SL buprenorphine plus naloxone (at the buprenorphine dose they were on prior to study entry; ≤ 8 mg/day) plus four placebo implants (Table 7). Buprenorphine or placebo implants were inserted on day 1 and patients received monthly supplies of SL buprenorphine/naloxone or placebo tablets. All patients received manual guided psychosocial counselling every four weeks. The investigator was instructed to treat additional symptoms of opioid dependence as they normally would (e.g., additional counselling, SL buprenorphine, or other drugs). Any additional patient- or investigator-requested visits or treatments were recorded with the reason for supplemental visit or therapy. Patients received a stipend for attending study visits that was, on average, $40 per visit, for a total ranging from $350 to $725.[12]

The patient, investigational site personnel, and sponsor were not aware of the treatment administered. The SL buprenorphine/naloxone had a near matching placebo, and both had

an appearance different from commercially available SL buprenorphine and from the product that was used for open-label supplemental buprenorphine doses. Investigators were aware of the results of urine toxicology results from the central lab. Pill counts were used to assess adherence to SL buprenorphine or placebo. Patients who attempted to remove the implants were withdrawn from the study.

Patients requiring pain control for emergency treatments or surgery were to be treated with non-opioid drugs, if possible. If opioids were used, caution was warranted, as higher doses may be required for analgesia, with the increased risk of toxicity. Any use of opioids for longer than seven days was documented. Use of other narcotic anesthetics, benzodiazepines, phenothiazines, tranquilizers, or other central nervous system depressants, including alcohol, were to be avoided.

Table 7: Buprenorphine Dose — Study 814

	Study 814	
Buprenorphine Dose at Study Entry (mg/Day)	**BPN Implant (N = 87) n (%)**	**BPN SL (N = 89) n (%)**
2	6 (7)	3 (3)
4	12 (14)	15 (17)
6	8 (9)	4 (5)
8	61 (70)	67 (75)

BPN = buprenorphine; CSR = Clinical Study Report; SL = sublingual.

Source: CSRs.[11]

In all three trials, implants were inserted and removed by health care professionals that had undergone training and certification by the manufacturer. All implants were inserted subdermally in the inside of the non-dominant upper arm on study day 1 and removed at the end of the study. Implants were inserted within 12 to 24 hours after the patient's last SL buprenorphine dose. Since the placebo implants were slightly different in appearance than the buprenorphine implants, the implanting physician was not involved in study evaluations and patients were shielded from seeing the implants. Of note: the implantation procedure and applicator device were changed after Study 805, and new procedures were in place for Study 806 and 814. Four buprenorphine 80 mg implants were expected to yield buprenorphine plasma levels that were similar to the average plasma levels for daily doses of 8 mg or less of SL buprenorphine (0.5 ng/mL to 1.0 ng/mL).

Other Studies (805 and 806)

In studies 805 and 806, all patients underwent induction therapy with SL buprenorphine/naloxone and were eligible for randomization if they achieved a target dose of 12 mg to 16 mg per day for at least three consecutive days immediately prior to randomization, and within 10 days (Study 805) or 16 days (Study 806) of the start of induction.

Eligible patients in Study 806 were randomized to receive buprenorphine implant (four implants), placebo implant (four implants) or SL buprenorphine plus naloxone at a dose of 12 mg to 16 mg buprenorphine daily. SL buprenorphine was open-label, whereas patients and investigators were blinded to the implant received (except for those who performed surgery to insert or remove implants). Patients in the SL buprenorphine group received up to seven days' supply of the study drug at a time.

Patients in Study 805 were randomized to receive buprenorphine implant (four implants) or placebo implant (four implants) and all participants were blinded to the implant received (except for those who performed surgery to insert or remove implants).

All patients in studies 805 and 806 underwent manual guided drug counselling twice weekly for the first 12 weeks and then weekly for the remainder of the study. Patients could receive additional SL buprenorphine if they met all the following conditions in Study 806, or one of the following conditions in Study 805:

- withdrawal symptoms with COWS score > 12 points
- cravings with a score > 20 mm on VAS
- request for supplemental dosing deemed appropriate by the investigator.

Supplemental SL buprenorphine was administered in 2 mg increments as clinically indicated and based on patient's response. In studies 805 and 806, patients were eligible to receive one dose increase if they required supplemental SL buprenorphine on three or more days per week for two consecutive weeks, or on eight days over four consecutive weeks. For patients randomized to placebo or buprenorphine implants, a fifth implant could be inserted for patients meeting these criteria. Patients in the SL buprenorphine group of Study 806 were eligible for one dose increase of 2 mg or 4 mg per day, up to a maximum of 16 mg per day, at the investigator's discretion. In response to an adverse event, one dose reduction was also allowed but the dose could not fall lower than the study's minimum daily dose of 12 mg buprenorphine. Patients in the SL buprenorphine group who could not tolerate 12 mg buprenorphine daily were withdrawn from the study. Pill counts were used to assess adherence in the SL buprenorphine group in Study 806.

In studies 805 and 806, any patient who met the criteria for treatment failure was withdrawn from the study. This included any patient in the SL buprenorphine group of Study 806 who was receiving 16 mg per day at baseline and then met the criteria for a dose increase. Any patient who met the criteria for a second dose increase (i.e., required additional SL buprenorphine on three or more days for two consecutive weeks or on eight or more days over four consecutive weeks) or those who required more than one additional day of counselling for four consecutive weeks was considered a treatment failure. Patients who missed nine consecutive urine collections or six consecutive counselling sessions or otherwise refused or were unable to follow the study protocol were considered non-compliant and were withdrawn from the trial. Those who attempted to remove the implants, used other treatments for opioid dependence, were pregnant, required continual use of opioid analgesics for more than seven days or general anesthesia, were also withdrawn.

Outcomes

Pivotal Trial (Study 814)

In Study 814 the primary outcome was the proportion of responders, defined as patients with no more than two of six months with any evidence of illicit opioid use. Evidence of illicit opioid use was defined as a positive opioid urine toxicology result or self-reported illicit opioid use.

Secondary outcomes included the following: the percentage of patients with no illicit opioid use by month; time to first evidence of illicit opioid use; cumulative percentage of illicit opioid use by month for all scheduled visits between week four and week 24; percentage of patient with no self-reported use of any illicit drug by month; change from baseline in desire-

to use or need-to-use VAS; change from baseline in COWS and Subjective Opioid Withdrawal Scale (SOWS) scores. Other exploratory outcomes included the percentage of patients who: required supplemental SL buprenorphine, counselling, or other drug treatments for opioid dependence; had positive urine toxicology for other drugs of abuse; or discontinued treatment.

Study visits were scheduled for one week and four weeks after implants were inserted, and every four weeks after that. Urine samples for toxicology tests were collected at screening and every four weeks, plus four random samples were taken over the 24-week study duration (total of 10 samples). Samples were tested for opioids (quantitative analysis) and other drugs of abuse (qualitative analysis, i.e., positive or negative). The opioids tested for included codeine, morphine, hydrocodone, oxymorphone, hydromorphone, oxycodone, methadone, dihydrocodeine, and fentanyl, plus an opioid metabolite for methadone and norfentanyl.[22] Self-reported illicit drug-use data were collected monthly, including use of illicit or prescription opioids or other drugs of abuse using the timeline follow-back interview method. Other data collected monthly included: the desire to use and need to use (each based on a 100 mm VAS), SOWS, and COWS.

Other Studies (805 and 806)

Study 806 compared the buprenorphine implant group with the placebo implant group for the cumulative distribution function of the percentage of urine samples that were negative for illicit opioids from week 1 to 24, with two different analyses as co-primary outcomes. The first analysis used no imputation and was based on the results of urine tests only. The second analysis imputed data based on self-reported illicit opioid use data and was added at the request of the FDA, which used this analysis as the primary outcome when making its assessment.

The key secondary outcomes in Study 806 were the cumulative distribution function of the percentage of urine samples that were negative for illicit opioids from week 1 to 16, and from week 17 to 24 (buprenorphine and placebo implant), and the noninferiority of buprenorphine implant versus SL buprenorphine based on the difference in proportions of urine samples that were negative for illicit opioids over 24 weeks. Numerous other secondary and exploratory outcomes were performed comparing buprenorphine implant with placebo implant or with SL buprenorphine, and for various time points (e.g., week 1 to 24, week 1 to 16, week 17 to 24). The outcomes tested included: the proportion of study completers; the mean percentage of urine samples that were negative for illicit opioids; mean total score on the COWS, SOWS, and opioid cravings scale (based on 100 mm VAS); Clinical Global Impressions (CGI) self-reported and observer-reported scores; and mean total weeks of abstinence or of continuous abstinence.

In Study 805, the primary outcome compared the buprenorphine implant group with the placebo implant group for the cumulative distribution function of the percentage of urine samples that were negative for illicit opioids from week 1 to 16, with the key secondary outcome examining the difference between groups for weeks 17 to 24. Other secondary outcomes included the proportion of study completers, the mean weeks of abstinence and mean weeks of continuous abstinence, the mean total COWS and SOWS scores, mean opioid cravings VAS scores, CGI self-reported and CGI observer-reported ratings, and improvement since baseline. Data were analyzed separately for weeks 1 to 16 and for weeks 17 to 24. Exploratory outcomes included self-reported use of illicit opioids and other drugs, supplemental SL buprenorphine use, mean Addiction Severity Index scores and treatment failures.

In Study 806, urine samples were collected three days a week throughout the 24-week study (59 visits), and patients had another 17 or 18 assessment or treatment visits for a total of 76 or 77 study visits. In Study 805, there were approximately 88 scheduled visits: 16 study visits and 72 urine collection visits. Patients and investigators were blind to the results of urine toxicology tests. Self-reported illicit drug use was recorded by asking patients about any drug used, number of days used, amount used per day, and whether they "got high."

The patient-reported outcome data collected during the three trials included measures of withdrawal, cravings, and addiction severity. The SOWS (self-reported) and COWS (clinician-reported) instruments rate the intensity of withdrawal. The SOWS includes 16 questions for subjective symptoms of withdrawal, with each item scored from 0 (not at all) to 4 (extremely) for a total ranging from 0 to 64.[24] Higher scores indicate more intense withdrawal symptoms.[24] The COWS includes 11 objective signs and symptoms of opiate withdrawal that are rated on a numeric scale (0 to 4 or 5 points, with higher numbers indicating worse withdrawal symptoms) and based on a timed period of observation of the patient by the rater (total score 47).[25] Based on the COWS score, withdrawal symptoms have been classified as mild (5 to 12 points), moderate (13 to 24), moderately severe (25 to 36), or severe (> 36), although these groupings have not been validated.[26] No data on the minimum clinically important difference (MCID) was found in the literature for either instrument.

For the assessment of cravings, need-to-use or desire-to-use VAS, patients were asked to mark the degree of craving, need, or desire to use since the last visit on a 100 mm VAS, where 0 represents no cravings, desire, or need to use, and 100 represents the strongest craving, desire, or need.[9-11] No MCID was identified.

Patients rated the severity of their current opioid-related problems on a seven-point Likert scale for the CGI self-reported outcome, and investigators rated patients' global severity of opioid dependence on a seven-point Likert scale (CGI observer-reported) over the past week.[9,10] Patients and investigators also rated the degree of improvement since baseline on a seven-point scale ranging from 1 (very much improved) to 7 (very much worse).[9,10] The MCID is not known.

The Addiction Severity Index is a multidimensional interview-based instrument that provides a patient problem severity profile to assist with the diagnosis and management of patients with substance abuse. It has seven domains, including medical status, employment and support, alcohol use, drug use, legal status, family and social status, and psychiatric status.[27] The domains include 11 to 38 objective and subjective items per domain, which have dichotomous, Likert scale, and other numerical responses. A composite score is calculated for each domain (range 0 to 1) with higher scores indicating greater problem severity.[27] No MCID was identified in the literature.

In all three studies, an adverse event was defined as any untoward medical occurrence in a patient administered a pharmaceutical product that did not necessarily have a causal relationship with this treatment. A serious adverse event was defined as any adverse drug experience occurring at any dose that: resulted in death; was life-threatening (at the time of the event); required in-patient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect (in an offspring); or may have jeopardized the patients or required medical or surgical intervention to prevent one of these outcomes. Hospitalizations that occurred more than 14 days after the end-of-treatment visit were not considered serious adverse events.

Statistical Analysis

Pivotal Trial (Study 814)

In Study 814 the primary hypothesis tested was the noninferiority of buprenorphine implant versus SL buprenorphine for the responder rate in the modified intention-to-treat (mITT) population based on a one-sided test with a significance threshold of $P < 0.025$. Noninferiority was established if the lower bound of the 95% confidence interval (CI) for the difference in proportions was greater than −0.20 (i.e., 20% noninferiority margin). If noninferiority was met, then superiority was tested.

Urine toxicology samples that were missing or unanalyzable or due to patient's early discontinuation of the study were imputed based on several methods. The primary analysis placed a 20% penalty on the buprenorphine implant group. This meant that missing values in the buprenorphine implant group were imputed based on 1.2 times the maximum mean proportion of within-patient positive tests from the two treatment groups. For example, if the proportion of opioid-positive urine samples was 14% for the buprenorphine implant group and 15% of the SL buprenorphine group, then imputation was based on 18% (15% x 1.2) for the buprenorphine implant group and 15% for the SL buprenorphine group. For the primary analysis, the monthly visit window was defined as the time from the previous scheduled visit to the current window date. Therefore, the number of days in each window could vary for a given patient or between patients. Four a priori sensitivity analyses were conducted for the responder outcome including using a 10% relative penalty for missing urine test data the buprenorphine implant group, based on a different method to define the monthly window (fixed number of days per month that was consistent for all patients), for a subset of patients who provided all required samples (completer analysis), and based on the per-protocol population with the primary imputation method for missing data.

The 20% noninferiority margin specified in the protocol was selected based on several sources including studies in patients on longer-term buprenorphine or methadone therapy who were tapered off treatment or abruptly withdrawn. These data suggest 15% to 31% would remain abstinent. The manufacturer also conducted a survey of 18 addiction treatment specialists and estimated that 25% of patients on stable doses of 8 mg per day or less of buprenorphine would remain abstinent if they were abruptly taken off treatment. Based on this, a 20% noninferiority margin would preserve more than 70% of the treatment effect (assuming 100% abstinence while on treatment and 25% when off therapy).

Secondary outcomes and their analysis methods are included in Table 8.

Table 8: Analysis of Secondary Outcomes — Study 814

Secondary Outcome	Analysis Method
Percentage of patients with no illicit opioid use by month	Chi-square test Same definition of monthly window, evidence of illicit opioid use (i.e., self-reported or positive urine test) and imputation method for missing urine test data as per primary outcome
Time to first evidence of opioid use	Log-rank test, Kaplan–Meier method for survival curve Same definition of evidence of illicit opioid use (i.e., self-reported or positive urine test) and imputation method for missing urine test data as per primary outcome Patients with no opioid-positive tests during the entire trial or prior to discontinuation were censored on the day when the last sample was collected
Change from baseline in desire-to-use or need-to-use VAS, COWS and SOWS scores	ANCOVA model with treatment and baseline values as covariates; missing values imputed using last observation carried forward as primary analysis, and mixed-model repeated-measures method as supporting analysis; No time point was specified as primary

ANCOVA = analysis of covariance; COWS = Clinical Opiate Withdrawal Scale; SOWS = Subjective Opiate Withdrawal Scale; VAS = visual analogue scale.

Exploratory outcomes of interest to this review included supplemental SL buprenorphine use and treatment discontinuation. There was no imputation for missing data for these outcomes and data were reported descriptively.

There was one primary outcome (responder rate) and no adjustment was made for multiplicity among the secondary outcomes. No subgroup data analyses were planned, although a post hoc analysis of the responder rate was conducted by gender. A sample size of 180 was selected to achieve 87.3% power to determine noninferiority, assuming both groups had a 75% response rate. No data were presented to support the 75% response rate used in the sample size calculations.

Other Studies (805 and 806)

In Study 806, the analysis of the primary outcome compared the cumulative distribution function of the percentage of urine samples that were negative for illicit opioids (week 1 through week 24) for the buprenorphine implant group versus the placebo implant group based on a stratified Wilcoxon rank sum test (two-sided alpha of 0.05, stratified on gender and pooled site, intention-to-treat [ITT] population). Based on 150 patients enrolled in the two implant groups (buprenorphine or placebo), the study had 80% power to detect a 20% shift between groups, taking into account the 2:1 randomization and normal distributions without stratification with a common standard deviation of 30% and assuming a 40% attrition rate.

Missing urine samples were considered positive, including all samples for a patient who withdrew from the study for the study visits after the withdrawal date, any non-authentic samples, or samples missing for other reasons. An exception was made for samples that were collected but not analyzed (e.g., lost in transit). These samples were treated as missing and not analyzed, but were not considered positive tests.

There were two analyses of the primary outcome:

- the cumulative distribution function of the percentage of urine samples negative for illicit opioids (week 1 through week 24) for buprenorphine implant versus placebo implant based on urine testing data only
- the cumulative distribution function of the percentage of urine samples that were negative for illicit opioids (week 1 through week 24) for buprenorphine implant versus

placebo implant with imputation based on self-reported illicit drug use. For each interval covered by a self-reported drug-use form, the urine toxicology results must have had at least one positive test for each self-reported day of drug use. If there were more self-reported days of drug use than there were urine tests, all urine tests in that interval were changed to positive. Missing self-reported drug-use data were not imputed.

The key secondary outcomes (the cumulative distribution function of the percentage of urine samples negative for illicit opioids for buprenorphine implant versus placebo implant week 1 through week 16, and week 17 through 24) were analyzed using the same methods as primary outcome number one.

Noninferiority of buprenorphine implant versus SL buprenorphine was tested based on the difference in the proportions of urine samples that were negative for illicit opioids over 24 weeks. This outcome was analyzed using the normal approximation to the binomial, and noninferiority was met if the lower bound of the 95% CI was greater than −0.15. The noninferiority margin was based on placebo-controlled studies with SL buprenorphine that showed 30% to 40% of urine samples were negative versus 5% for placebo.

The proportion of patients who completed the 24-week study was analyzed using a Mantel–Haenszel exact test stratified by gender and pooled site. The mean percentage of urine tests that were negative for illicit opioids were analyzed using analysis of covariance (ANCOVA) model, adjusted for gender and site. Treatment by gender interaction was tested and if the *P* value for the interaction term was 0.10 or lower, then analyses were conducted separately for each gender. SOWS and COWS scores were analyzed using a repeated-measures model that included gender, site, treatment, week, week-by-treatment interaction, baseline scores, and patient (as a random variable). If there were three missing items on the COWS and four missing items on the SOWS for a given visit, that score was set to missing for that patient visit. Visits with missing scores were imputed using last observation carried forward (LOCF). CGI scores were analyzed using a Cochran–Mantel–Haenszel test with modified ridit scores and stratified by gender and site. No subgroup analyses were reported for the efficacy outcomes in Study 806.

A fixed sequential testing procedure was performed with each primary and secondary outcome tested at a 5% significance level, and testing was stopped at the first non-significant finding. A total of 35 analyses were included in the testing sequence (Appendix 4, Table 17).

In Study 805, the primary and key secondary outcome (the cumulative distribution function of the percentage of urine samples that were negative for illicit opioids week 1 through week 16 and week 17 to 24) was analyzed using a stratified Wilcoxon rank sum (van Elteren) test (two-sided alpha of 0.05, stratified on gender and pooled site, ITT population). Based on 150 patients enrolled, the study had 80% power to detect a 20% shift between groups, taking into account the 2:1 randomization and normal distributions without stratification, with a common standard deviation of 30% and assuming a 40% attrition rate. Data to support the values used in the power calculations were taken from prior studies with SL buprenorphine. Missing urine samples were considered positive and the same rules for missing samples were applied in Study 805 as in Study 806.

The mean percentage of negative illicit opioid tests and mean weeks of abstinence were analyzed using an ANCOVA model that was adjusted for gender and site. Treatment by gender interaction terms was tested and, if significant ($P \leq 0.10$), then subgroup analyses were conducted by gender.

The mean COWS, SOWS, and cravings VAS scores were analyzed using a mixed-model repeated-measures method that included gender, site, week, and treatment as fixed effects, patient as a random effect, baseline values, and week-by-treatment interaction term. Missing values were imputed using LOCF. Exploratory outcomes (SL buprenorphine use, treatment failures, Addiction Severity Index) were reported descriptively with no imputation for missing data. Subgroup analyses by gender were conducted for the primary and secondary outcomes.

A fixed sequential testing procedure was performed with each primary and secondary outcome tested at a 5% significance level, and testing was stopped at the first non-significant finding in the order listed in Appendix 4, Table 17.

Analysis Populations

In Study 814, efficacy was analyzed using an mITT population, which was defined as all randomized patients who received study medication and provided some efficacy data.

In studies 805 and 806, efficacy analyses were based on an ITT population that included all randomized patients who received the study drug. Although the population described (i.e., randomized and treated) is, in fact, an mITT population, all randomized patients in studies 805 and 806 were treated and analyzed, which is consistent with an ITT population.

The per-protocol population included all patients in the ITT (studies 805 and 806) or mITT (Study 814) analysis that had no major protocol violation. The safety population included all patients who received study medication and was analyzed according to the treatment received, regardless of the randomized treatment group.

Patient Disposition

In Study 814, a total of 211 patients were assessed for eligibility and 177 (84%) were randomized (Table 9). One patient randomized to placebo implants received buprenorphine implants and was reassigned to the active implant group. Five per cent and 6% of patients in the SL buprenorphine and implant group, respectively, discontinued the study. Three patients in the buprenorphine implant group received treatment but did not supply any efficacy outcome data and were excluded from the mITT analysis.

In Study 806 and 805, 78% and 72% of patients screened met the inclusion criteria and entered induction therapy, and 60% and 47% successfully completed induction and were randomized to the study drug (Table 9). Withdrawal rates were higher among patients randomized to placebo implants (74% and 69%) than among those who received buprenorphine implants (36% and 34%) or SL buprenorphine (36%). Treatment failure, patient request, and non-compliance were the most common reasons for withdrawal among those who received placebo. Among those who receive active treatment, loss to follow-up, non-compliance, and patient request were the most common reasons for withdrawal.

Table 9: Patient Disposition

	Study 814		Study 806			Study 805	
	BPN Implant	BPN SL	BPN Implant	BPN SL	Placebo Implant	BPN Implant	Placebo Implant
Screened, N	211		480			348	
Entered induction, N (%)	NA		372 (78)[a]			250 (72)[b]	
Randomized, N (%)	177 (84)[c]		287 (60)[d]			163 (47)[d]	
	87	90	114	119	54	108	55
Discontinued study, N (%)	6 (7)	5 (6)	41 (36)	43 (36)	40 (74)	37 (34)	38 (69)
Adverse event	1 (1)	0	0	1 (1)	0	4 (4)	0
Lost to follow-up	4 (5)	2 (2)	9 (8)	17 (14)	3 (6)	10 (9)	4 (7)
Patient request	0	2 (2)	5 (4)	4 (3)	9 (17)	8 (7)	9 (16)
Non-compliance			10 (9)	8 (7)	9 (17)	12 (11)	7 (13)
Treatment failure			6 (5)	0	9 (17)	0	17 (31)
Request of sponsor or regulatory agency	0	1 (1)	0	0	0	0	0
Attempted implant removal	0	0	0	0	0	1 (1)	0
Other	1 (1)	0	11 (10)[e]	13 (11)[e]	10 (19)[e]	2 (2)	1 (2)
ITT, N	–	–	114	119	54	108	55
mITT, N	84[f]	89	–	–	–	–	–
PP, N	67	72	105	115	47	101	51
Safety, N	87	89	114	119	54	108	55

BPN = buprenorphine; CSR = Clinical Study Report; ITT = intention-to-treat; mITT = modified intention-to-treat; PP = per-protocol; SL = sublingual.

[a] Of the patients screened, 108 (23%) were excluded prior to induction (72 did not meet inclusion criteria, 36 were excluded for other reasons). After induction, another 71 patients (15%) were excluded (42 did not meet randomization criteria, 29 were excluded for other reasons).

[b] Ninety-seven patients were excluded prior to induction (63 did not meet inclusion criteria, 11 were lost to follow-up, 9 had blood draw problems, 8 withdrew consent, 7 were excluded for other reasons). After or during induction, another 87 withdrew (23 lost to follow-up, 22 withdrew consent, 15 failed induction criteria, 9 did not meet inclusion criteria, 6 were non-adherent, 12 were excluded for other reasons).

[c] Reasons for exclusion included: did not meet eligibility requirement (n = 23); withdrew consent (n = 6); did not return for randomization (n = 4); outside of three-week screening window (n = 1).

[d] Percentage calculated based on patients screened.

[e] Most common other reason for discontinuation was incarceration in five, four, and two patients in the SL BPN, BPN implant, and placebo implant groups, respectively.

[f] Three patients did not submit any post-baseline efficacy data and were excluded from the ITT population.

Source: CSRs,[9-11] Rosenthal et al., 2016;[12] Rosenthal et al., 2013;[20] Ling et al.[9]

Exposure to Study Treatments

In Study 814, the median duration of exposure was 169 days in both treatment groups (Table 10). There was no evidence that any patient attempted to remove the implants; however, one spontaneous implant expulsion was reported (placebo implant). Two patients reported that the SL buprenorphine/placebo tablets were stolen. In two patients, only three implants could be located for removal at the end of the study.

In the placebo-controlled trials, the dose of SL buprenorphine received during induction was similar among the three groups in Study 806, with a median total dose of 140 mg, 132 mg, and 124 mg in the SL buprenorphine, buprenorphine implant, and placebo implant groups, respectively. In Study 805, the median total dose of buprenorphine received during induction was 104 mg for both study groups. The median duration of exposure was higher in the buprenorphine implant or SL buprenorphine groups (24 to 25 weeks) in Study 806 and 805 than in the placebo groups (15.5 to 16.6 weeks) (Table 10). In Study 806, there

was no evidence that any patient had attempted to remove the implants. Median adherence for those in the SL buprenorphine group was 95% (range 7% to 122%) and was 80% or above for 82% of patients, based on pill counts. The average daily buprenorphine dose was 12.8 mg (median: 13.8 mg; range: 1 mg to 19 mg) in the SL buprenorphine group. One patient in Study 805 attempted to remove the buprenorphine implant.

Table 10: Exposure to Study Drug

	Study 814		Study 806			Study 805	
	BPN Implant N = 87	BPN SL N = 89	BPN Implant N = 114	BPN SL N = 119	Placebo Implant N = 54	BPN Implant N = 108	Placebo Implant N = 55
Duration of exposure, median (range)	169 days[a] (1 to 191)	169 days[a] (35 to 190)	25 weeks (4 to 60)	25 weeks (1 to 65)	15.5 weeks (1 to 56)	24 weeks (0 to 43)	16.6 weeks (3 to 34)
Proportion of patients with at least: n (%)							
12 weeks of exposure	82 (94)	88 (99)					
18 weeks of exposure	81 (93)	87 (98)					
24 weeks exposure	57 (66)	61 (69)					

BPN = buprenorphine; CSR = Clinical Study Report; SL = sublingual.

[a] Duration: 169 days is 24.1 weeks.

Source: CSRs.[9-11]

Critical Appraisal

Internal Validity

Pivotal Trial (Study 814)

Allocation concealment and randomization procedures appear to be adequate for Study 814 and the trial used a double-dummy design to maintain blinding. The clinician who performed the implant insertion and removal was not involved in the assessment of the patient, as the active and placebo implants had differences in appearance and could be identified. However, some unblinding may have occurred, as those experiencing withdrawal symptoms would note the response, or lack of response, after taking their daily SL buprenorphine or placebo tablets. Although the providers who performed the insertion of the implants (and who would be able to distinguish between the two treatments) were cautioned not to release any information on treatment allocation, it is possible that some unblinding occurred. No assessment of the extent of unblinding was reported in the Clinical Study Report, and although the primary outcome was unlikely to be biased by knowledge of the treatment allocation, it is possible that other measures, such as the SOWS or desire-to-use VAS and receipt of co-interventions, could have been affected.

The characteristics of patients at baseline appeared to be generally balanced between treatment groups, although some differences were noted in the frequency of depression and years since first diagnosis of opioid dependence. Withdrawal rates were low in Study 814 and were similar in the implant and SL buprenorphine groups (6% and 7%).

In Study 814, the primary hypothesis tested was the noninferiority of buprenorphine implants versus SL buprenorphine in the difference in the proportion of responders (defined as a patient showing evidence of illicit opioid use in no more than two of the six months, based on self-reported opioid use or positive urine toxicology tests). A 20% noninferiority margin was defined a priori, which was based on expert opinion and available literature.

The calculation of the manufacturer assumed 100% abstinence among patients on SL buprenorphine treatment, with 25% remaining abstinent after treatment was stopped; thus, the 20% margin preserved approximately 70% of the treatment effect versus placebo. There is uncertainty in these assumptions, as 100% response rate may be unrealistic and was not achieved in the SL buprenorphine group of Study 814, which was a selective subset of patients with opioid dependence who would be expected to have good treatment response. In addition, the response rate among patients on placebo is unclear, as the estimates varied among the studies reported in the literature. There were differences in the populations enrolled and in the conduct of these historical studies; thus, their applicability is uncertain.[22] Furthermore, it is unclear what proportion of the treatment effect should be preserved in this context. Despite these questions regarding the noninferiority margin selected, the lower bounds of the 95% CI for the primary and sensitivity analyses were well above the margin (minimum value −0.138), including those for the most conservative estimates calculated post hoc by the FDA.[22] Subsequent to noninferiority being achieved, the data were tested for superiority of buprenorphine implants versus SL tablets, without adjustment for multiplicity. Although this is allowed according to the guidance from the FDA on noninferiority trials,[28] the testing of superiority was not specified a priori in the study's protocol.

Efficacy analyses were not based on a true ITT approach, but instead used an mITT analysis that excluded patients randomized but not treated and those who did not provide any post-baseline efficacy data. This may compromise the randomization process, which aims to balance known and unknown confounders between groups. However, the ITT analysis may not be the most conservative estimate in a noninferiority trial.[28] A sensitivity analysis was conducted based on the per-protocol population, which also demonstrated noninferiority.

For the primary analysis, any missing urine sample data were imputed using a method that applied a 20% relative penalty to the buprenorphine implant group. This imputation method assumes that the likelihood of samples being missing is unrelated to the patients' illicit opioid use, which may not be true. Although four additional sensitivity analyses were planned, none of these a priori analyses applied the most conservative approach to missing data that is used in many other studies, which assumes that all missing samples are positive. Additional analyses were conducted post hoc to explore missing data assumptions, the impact of supplemental SL buprenorphine use, and exclusions after randomization. These and other post hoc analyses were reported in Table 2 in Rosenthal et al.[12] and by the FDA,[22] and showed noninferiority but not superiority of buprenorphine implants versus SL buprenorphine. Of note, the number of patients with missing urine samples was the same in both groups (11 patients [13%] per group had one or more missing urine samples).

No subgroup analyses were specified in the protocol; however, descriptive data for subgroups based on gender were reported in the Clinical Study Report. Gender was not a stratification factor in randomization, thus these should be interpreted with caution as confounders may not be balanced between treatment groups within the subgroups.

The trial specified one primary efficacy variable, and adjustment for multiplicity was not performed for the secondary outcomes. Thus, all secondary outcomes should be interpreted as inconclusive with respect to statistical significance. This included the analysis of the time to first use of illicit opioids, which was used to inform the pharmacoeconomic analysis. Withdrawal symptoms were measured using the COWS and SOWS scales, which

have been validated in this patient population, although the MCID is unknown. The validity and reliability of the need-to-use and desire-to-use VAS are uncertain. Although measures of illicit opioid use are accepted outcomes in substance abuse treatment trials, these are surrogates for patients' social, medical, and psychological well-being, which are the goals of treatment.

Generally, the number of patients enrolled per treatment group was small (≤ 90) and the trial duration was limited to six months, which may be considered the minimum duration to show a treatment effect in patients with substance abuse disorder. The trial had insufficient numbers to evaluate infrequent device-related adverse events, such as migration of the implant or nerve damage, that have been observed with other similar contraceptive implant devices.[22]

Other Studies (805 and 806)

Allocation concealment and randomization procedures appear to be appropriate in studies 805 and 806, and blinding to the implant device was maintained as described for Study 814. The SL buprenorphine group was unblinded in Study 806, which may have had an impact on the reporting of subjective outcomes (e.g., SOWS, cravings VAS, CGI), adverse events, and requests for co-interventions. Patient characteristics appeared to be balanced at baseline; however, the withdrawal rate was high in these trials, with substantive differences between active and placebo groups. Between 34% and 39% of patients in the buprenorphine implant or SL groups withdrew early, compared with 69% to 74% of those who received placebo implants. This meant that data were imputed for the two-thirds of patients in the placebo group and the one-third of patients in the active treatment groups. Missing urine samples were imputed as positive, which is the most conservative assumption. No other imputation methods were tested. Considering the differential withdrawal rate and the conservative imputation method, this could potentially bias the results in favour of buprenorphine.

The appropriateness of the placebo control group may be questioned, as patients were inducted on SL buprenorphine and then had access only to rescue therapy. This is not consistent with current treatment guidelines for opioid use disorders.[1] Study 806 included an active comparator arm, however, most comparisons between the two active treatment groups were outside the statistical testing hierarchy. The exception was the noninferiority of buprenorphine implants versus SL buprenorphine on the percentage of negative urine samples, which was included as a secondary outcome. Noninferiority was based on a 15% noninferiority margin, but limited evidence was presented to support this value.

External Validity

Patients in all trials met the DSM-IV-TR criteria for opioid dependence while, currently, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) is in use. The patients enrolled may be comparable to those with moderate to severe opioid use disorder (i.e., patients with four or more diagnostic criteria within a 12-month period) based on the DSM-V.[29]

The pivotal trial enrolled adults who were controlled on low doses of buprenorphine and had been receiving opioid agonist therapy for 3.5 years, on average. The majority of patients enrolled were white (95%), employed (64%), and had at least a high school diploma (79%). These patients represent a small subset of patients with opioid use disorder, who are likely to have the most positive outcomes. Generalizability is uncertain for patients who have

initiated treatment more recently and thus may have greater clinical instability, as well as those populations who may be marginalized, are dependent on other substances, or have chronic pain. All the trials were conducted in the US, where the management of opioid dependence may be different than in Canada, according to the clinical expert consulted for this review. In addition, patients in Study 814 were paid a stipend for attending study visits, which may have had an impact on their willingness to continue in treatment.

Studies 805 and 806 enrolled patients who were being initiated on opioid agonist therapy, which does not reflect the approved indication in Canada. The generalizability of these trials may be affected by the enrichment design (which selected patients who received successful induction with SL buprenorphine), and key exclusion criteria, such as patients dependent on other substances. Moreover, the trial used a strict dosing protocol during induction and for the SL buprenorphine rescue therapy, with limited flexibility to adjust doses to patients' needs, as may be done in clinical practice. Dosing of buprenorphine implants allowed for insertion of a fifth implant, which is not consistent with the product monograph. Patients also had frequent contact with health care professionals throughout the trials (three or more times per week).

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. See Appendix 4 for detailed efficacy data. There was no information in any of the included studies on health-related quality of life or social functioning, two outcomes that had been identified in the protocol.

Response Rate

Pivotal Trial (Study 814)

Based on the primary analysis in Study 814, 87.6% in the SL buprenorphine group and 96.4% in the buprenorphine implant group met the criteria for a responder (no positive urine tests or self-reported illicit opioid use for at least four out of six months), with a between-group difference in proportions of 0.088; 95% CI, 0.009 to 0.167 (Table 11). The buprenorphine implant was noninferior to SL buprenorphine, as the lower bound of the 95% CI was greater than −0.20. Buprenorphine implant also demonstrated superiority to SL buprenorphine ($P = 0.034$). Noninferiority was met in the analysis, based on the per-protocol population (proportion difference 0.053; 95% CI, −0.022 to 0.129), but not superiority ($P = 0.18$). Noninferiority was consistently met based on the other sensitivity analyses conducted by the manufacturer. The FDA Advisory Committee Report listed a number of other post hoc analyses that assumed all missing samples were positive and patients who did not provide any post-baseline efficacy data were nonresponders, and buprenorphine implant was noninferior to SL buprenorphine in these analyses as well.[22] Most sensitivity analyses, however, did not support a superiority claim.

In the post hoc subgroup analyses, 100% and 97% of females and 94% and 81% of males in the buprenorphine implant and SL groups, respectively, met the criteria for responder (Table 11).

Table 11: Responder Rate — Study 814

	Study 814			
	BPN Implant	BPN SL	BPN Implant Minus BPN SL	
Population / Analysis Method	**Responder, n (%)**	**Responder, n (%)**	**Proportion Difference (95% CI)**	***P* Value[a]**
mITT	**N = 84**	**N = 89**		
Primary analysis 20% relative penalty imputation method for missing urine test data[b]	81 (96.4)	78 (87.6)	0.088 (0.009 to 0.167)[c]	0.034
10% relative penalty imputation method for missing urine test data	81 (96.4)	78 (87.6)	0.088 (0.009 to 0.167)	0.034
Adjusted monthly window, treatment-based imputation method for missing urine test data	81 (96.4)	78 (87.6)	0.088 (0.009 to 0.167)	0.034
Completer[d]	**N = 76**	**N = 79**		
20% relative penalty imputation method for missing urine test data[b]	73 (96.1)	70 (88.6)	0.074 (−0.008 to 0.157)	0.083
PP	**N = 67**	**N = 72**		
20% relative penalty imputation method for missing urine test data[b]	65 (97.0)	66 (91.7)	0.053 (−0.022 to 0.129)	0.176
ITT (post hoc FDA analyses)	**N = 87**	**N = 89**		
Includes three patients in the BPN implant group who were excluded from the mITT population (analyzed as nonresponders)	81 (93.1)	78 (87.6)	0.055 (−0.032 to 0.141)	0.22
Missing urine samples imputed as positive[e]	78 (89.7)	76 (85.4)	0.043 (−0.055 to 0.140)	0.39
Missing urine samples imputed as positive and patients with supplemental SL BPN use counted as nonresponders[e]	63 (72.4)	65 (73.0)	−0.006 (−0.138 to 0.125)	0.93
Missing urine panels imputed as positive[f]	73 (83.9)	70 (78.7)	0.053 (−0.062 to 0.167)	0.37
Missing urine panels imputed as positive and patients with supplemental SL BPN use counted as nonresponders[f]	58 (66.7)	59 (66.3)	0.004 (−0.136 to 0.143)	0.96
Post hoc subgroup analyses				
Males	47/50 (94)	42/52 (81)	NR	NR
Females	34/34 (100)	36/37 (97)	NR	NR

BPN = buprenorphine; CI = confidence interval; CSR = Clinical Study Report; ITT = intention-to-treat; mITT = modified intention-to-treat population; NR = not reported; PP = per-protocol; SL = sublingual.

[a] Based on chi-square test for superiority claim.

[b] The primary analysis placed a 20% penalty on the buprenorphine implant group. This meant that missing values in the buprenorphine implant group were imputed based on 1.2 times the maximum mean proportion of within-patient positive tests from the two treatment groups.

[c] *P* value for noninferiority: < 0.001.

[d] Completer analysis included patients who supplied all requested urine samples.

[e] Eleven patients in each group (13%) had one or more missing urine samples. Six per cent of urine toxicology samples were missing in the buprenorphine implant group compared with 3% of samples in the SL buprenorphine group in the safety population of Study 814.[22]

[f] Incomplete panels were urine samples that could not be tested for all opioids of interest. In the BPN implant group, 22 patients (25%) had an incomplete panel compared with 16 patients (18%) in the SL BPN group. Seven per cent and 4% of samples in the implant and SL buprenorphine groups, respectively, had samples collected, but they could not be analyzed for all 17 of the illicit substances that were planned.[22]

Source: CSR,[11] Rosenthal et al., 2016;[12] FDA Advisory Committee Report.[22]

Other Studies (805 and 806)

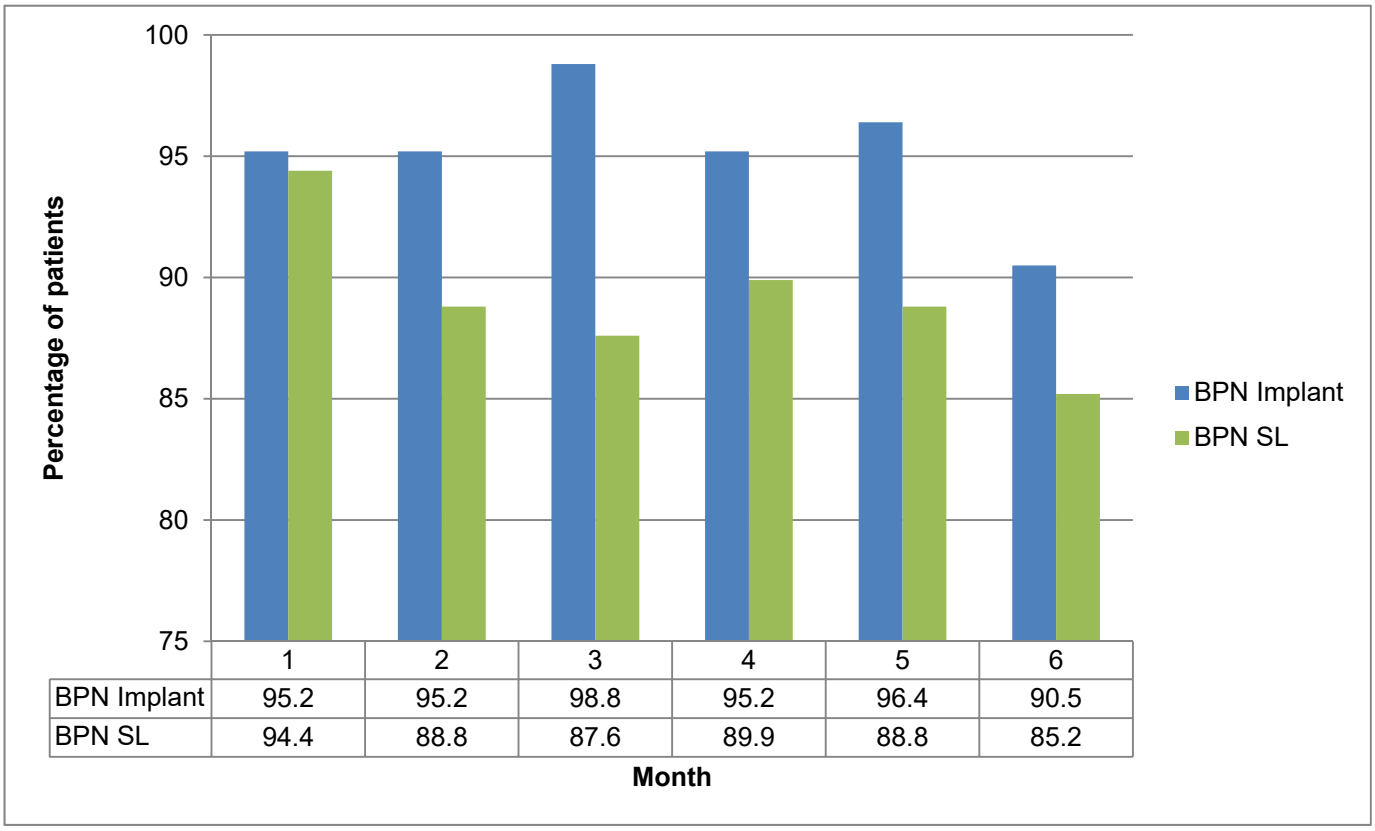
Study 806 and 805 reported the proportion of patients who met the criteria for treatment failure, which was defined based on the need for supplemental SL buprenorphine for three or more days per week for two consecutive weeks or for eight or more days over four consecutive weeks at any time after a dose increase or based on the need for additional counselling. In Study 806, six buprenorphine implant patients (15%) and nine (23%) placebo implant patients were reported as a treatment failure. No patients in the SL buprenorphine group failed treatment. In Study 805, 17 patients (45%) in the placebo group and no patients in the buprenorphine group met the criteria for treatment failure. No patients were defined as experiencing treatment failure based on the need for additional counselling in either study.

Opioid Use

Pivotal Trial (Study 814)

In Study 814, the percentage of patients with no illicit opioid use per month (based on urine tests and self-reported use) ranged from 85% to 94% in the SL buprenorphine group and from 91% to 99% in the buprenorphine implant groups (Figure 2). The Kaplan–Meier curve for the time to first illicit opioid use in Study 814 is presented in Figure 3. The log-rank test showed a *P* value of 0.037; however, this outcome was not part of the fixed statistical testing procedure and should be interpreted as inconclusive. An additional analysis of the time to first positive illicit opioid urine test, self-reported opioid use, or supplemental SL buprenorphine treatment was reported in FDA documents (Appendix 4, Figure 4).[22] In this analysis, most of the first-time rescue therapy or illicit opioid use in the buprenorphine group occurred in the first two months of therapy. The median time to illicit opioid use could not be calculated, as less than half of the patients had evidence of illicit use.

Figure 2: Percentage of Patients With No Illicit Opioid Use by Month (mITT) — Study 814

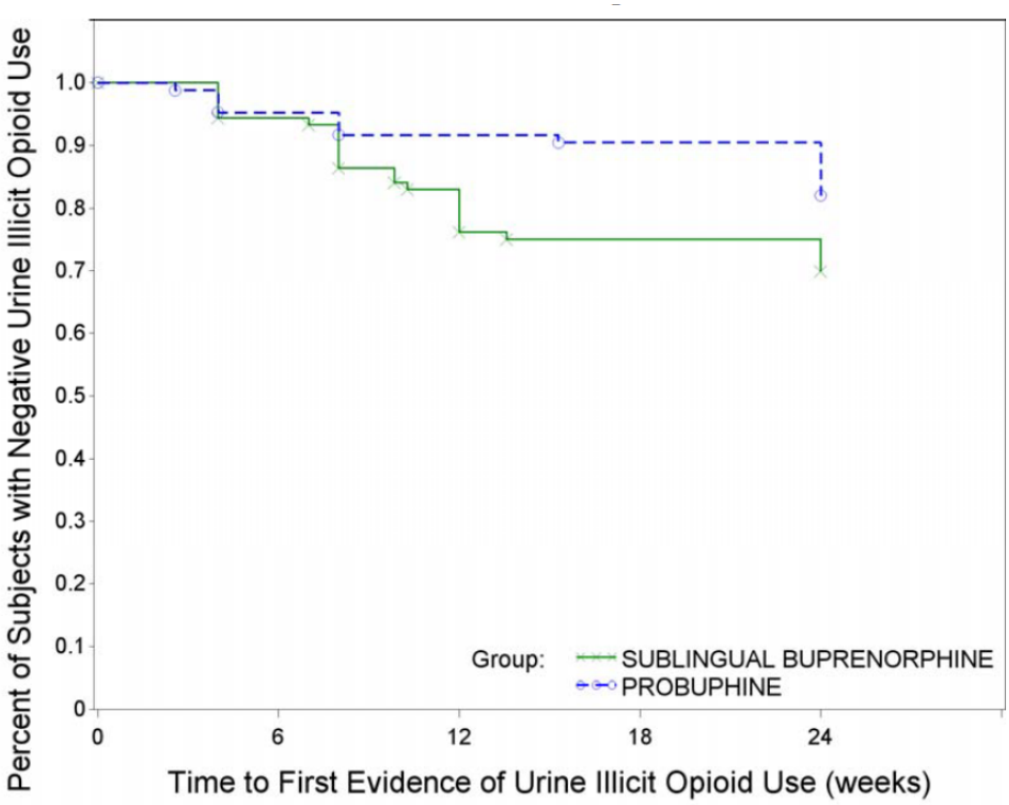


	1	2	3	4	5	6
BPN Implant	95.2	95.2	98.8	95.2	96.4	90.5
BPN SL	94.4	88.8	87.6	89.9	88.8	85.2

BPN = buprenorphine; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; mITT = modified intention-to-treat population; SL = sublingual

Source: Generated by CDR based on data from the CSR.[11]

Figure 3: Time to First Evidence of Illicit Opioid Use (mITT) — Study 814



BPN = buprenorphine; CSR = Clinical Study Report; mITT = modified intention-to-treat population; SL = sublingual.
Note: Number of patients included in the analysis in the BPN implant and SL BPN groups, respectively: week 0: 84, 89; week 12: 76, 73; week 24: 43, 44.[12]
Source: CSR,[11] Rosenthal et al., 2016.[12]

Other Studies (805 and 806)

Data on the proportion of urine samples that were negative for illicit opioids were reported and analyzed in a number of different ways in studies 805 and 806. Appendix 4, Figure 5 shows the mean percentage of urine samples that were negative each week, with 95% CI, for Study 806. This graph shows a separation between placebo and active treatment groups starting in week 6; however, interpretation of these data should take into with consideration the differential withdrawal rate between placebo and buprenorphine groups. Similar data for Study 805 are shown in Figure 6 and, like Study 806, this trial had a substantial and differential withdrawal rates from the two treatment groups.

Over the 24 weeks in Study 806, the mean percentage of negative urine samples was 36%, 35%, and 14% in the buprenorphine implant, SL buprenorphine, and placebo implant groups respectively. Statistically significant differences were detected between buprenorphine implant versus placebo (difference: 21%; 95% CI, 13% to 31%) (Appendix 4, Table 18). The buprenorphine implant was noninferior to SL buprenorphine based on the proportion of negative urine tests, as the lower bound of the 95% CI for the between-group difference (−10.7%) was higher than the −15% noninferiority margin.

In Study 805 from week 1 to 16, the mean percentage of negative urine samples was 40% in the buprenorphine implant group and 29% in the placebo group (difference: 11%; 95% CI, 1% to 21%), and was 28% and 10%, respectively from week 17 to week 24 (difference: 18%; 95% CI, 8% to 28%) (Appendix 4, Table 18).

From Study 806, data on the cumulative distribution function of the percentage of urine samples that were negative for illicit opioids from week 1 to 24 are presented in Figure 7 (primary analysis number one; based on urine test data only) and Figure 8 (primary analysis number two; imputed illicit opioid use based on self-reported data). Both analyses showed statistically significant differences between the buprenorphine implant and placebo implant groups ($P < 0.0001$) (Table 19). In these analyses, the data were presented as the probability of having a given percentage of urine samples, or less, that were negative. So, for example, 50% of patients in the buprenorphine groups had 20% or less of the negative urine samples compared with 80% of patients in the placebo group who had 20% or less of the negative urine samples. This means that 50% of patients in the buprenorphine implant group and 20% in the placebo group were more successful (i.e., 20% or more urine samples from those patients were negative for illicit opioids). No comparisons between the SL buprenorphine and implant groups were conducted based on the cumulative distribution function analysis.

For Study 805, the cumulative distribution function of the percentage of urine samples that were negative for illicit opioids for weeks 1 to 16 is presented in Figure 9, and for weeks 17 to 24 in Figure 10. Statistically significant differences were detected between groups for both analyses (week 1 to 16: $P = 0.036$; week 17 to 24: $P = 0.0004$) (Appendix 4, Table 19).

In Study 806, the mean weeks of abstinence were higher among those who received buprenorphine implants or SL tablets (5.3 weeks and 5.0 weeks) than placebo (1.7 weeks), as was the mean maximal period of abstinence (buprenorphine implant: 2.5 weeks; buprenorphine SL: 2.4 weeks) versus placebo implant (0.9 weeks) (Appendix 4, Table 18). In Study 805, the mean weeks of abstinence were 2.9 and 2.6 weeks in the buprenorphine and placebo implant groups, respectively, for weeks 1 to 16, and 1.1 weeks and 0.3 weeks, respectively, for weeks 17 to 24. The mean maximal period of continuous abstinence was 1.6 weeks and 1.5 weeks (study weeks 1 to 16), and 0.7 weeks and 0.2 weeks (study weeks 17 to 24), in the buprenorphine and placebo implant groups, respectively. These outcomes were outside the statistical testing hierarchy and considered inconclusive in both trials.

Completing Treatment

In Study 814, the percentage of patients who completed the study was 93% in the implant group and 94% in the SL buprenorphine group.

In Study 806, 64% of patients in the SL or buprenorphine implant groups completed 24 weeks of the study, compared with 26% of patients in the placebo implant group, with the difference between the implant groups showing statistical significance ($P = 0.0002$) ($P = 0.62$ for buprenorphine implant versus SL) (Table 20). The percentage of patients completing treatment in Study 805 showed similar results as Study 806, with 66% and 31% in the buprenorphine and placebo implant groups completing 24 weeks. The Kaplan–Meier plot of the days to discontinuation for Study 806 is shown in Figure 11.

Need for Supplemental Therapy

In Study 814, 15 patients (18%) in the buprenorphine implant group and 13 patients (15%) in the SL buprenorphine group received supplemental SL buprenorphine (Table 12). Supplemental buprenorphine was dispensed one to 21 times per patient; however, the details on actual doses received and dates doses were taken were not reported. The average total number of buprenorphine 2 mg tablets per patient was 42.9 in the buprenorphine implant group compared with 24.9 in the SL buprenorphine group.[22] The manufacturer noted that 21 of 28 patients who received supplemental doses were seen at two study sites. These patients included 12 of 13 (92%) in the SL buprenorphine group and 9 of 15 (60%) in the buprenorphine implant group who required one or more days of SL buprenorphine therapy. None of the patients who required supplemental therapy had required supplemental doses in the six months prior to enrolment in the trial. In total, 25 patients received supplemental counselling during the study, including 12 patients (15%) in the buprenorphine implant group and 13 patients (15%) in the SL buprenorphine group.

In the placebo-controlled studies, 22% and 20% of patients in the buprenorphine implant groups and 39% and 58% in the placebo implant groups in studies 806 and 805, respectively, received one additional implant (Table 12). Three patients (3%) in the SL buprenorphine group of Study 806 met the criteria for a dose increase. In the buprenorphine implant groups, 40% of patients in Study 806 and 62% in Study 805 received supplemental SL buprenorphine as rescue therapy, with a median total dose of 68 mg and 72 mg, respectively. In comparison, 6% of patients in the SL buprenorphine group received rescue therapy, with a median total dose of 24 mg. The majority of patients in the placebo implant groups (Study 806: 67%; Study 805: 91%) received supplemental SL buprenorphine, with a median total dose per patient of 100 mg (Study 806) and 188 mg (Study 805).

Table 12: Need for Supplemental Sublingual Buprenorphine or Implant

	Study 814		Study 806			Study 805	
Weeks 1 to 24	**BPN Implant N = 84**	**BPN SL N = 89**	**BPN Implant N = 114**	**BPN SL N = 119**	**Placebo Implant N = 54**	**BPN Implant N = 108**	**Placebo Implant N = 55**
Number of patients who received additional implant or a dose increase for daily SL BPN, n (%)	NA	NA	25 (22)	3 (3)	21 (39)	22 (20)	32 (58)
Number of patients requiring supplemental SL BPN, n (%)	15 (18)	13 (15)	45 (40)	7 (6)	36 (67)	67 (62)	50 (91)
Total number of days of SL BPN							
Median (range)	NR	NR	NR	NR	NR	8.0 (1 to 39)	21.5 (1 to 122)
Total dose (mg)							
Median (range)	NR	NR	68 (8 to 876)	24 (16 to 36)	100 (8 to 560)	72 (2 to 440)	188 (8 to 1152)
Average daily dose (mg)							
Median (range)	NR	NR	NR	NR	NR	0.5 (0 to 13)	1.6 (0 to 13)
Total number of dispensing episodes			NR	NR	NR	NR	NR
1	5 (6)	0					
2	2 (2)	3 (3)					

	Study 814		Study 806			Study 805	
Weeks 1 to 24	**BPN Implant N = 84**	**BPN SL N = 89**	**BPN Implant N = 114**	**BPN SL N = 119**	**Placebo Implant N = 54**	**BPN Implant N = 108**	**Placebo Implant N = 55**
3	0	2 (2)					
4	1 (1)	4 (5)					
5	2 (2)	2 (2)					
6	3 (4)	1 (1)					
7	1 (1)	1 (1)					
21	1 (1)	0					
Average number of 2 mg tablets dispensed and not returned per patient	42.9	24.9					

BPN = buprenorphine; CSR = Clinical Study Report; NR = not reported; SL = sublingual.

Source: CSRs,[9-11] FDA Advisory Committee Report.[22]

Withdrawal and Cravings

Pivotal Trial (Study 814)

In Study 814, the mean COWS, SOWS, and desire- or need-to-use VAS scores in both treatment groups were generally low at baseline as well as at week 24 (mean COWS ≤ 1.0; SOWS ≤ 2.7; desire- or need-to-use ≤ 6.8) (Table 21). No statistically significant differences were detected between groups in the change from baseline to week 24 for any of these outcome measures. Of note, all four outcomes were outside the fixed statistical testing procedure.

Other Studies (805 and 806)

Data from the COWS, SOWS, and cravings VAS scores for studies 805 and 806 are presented in Appendix 4, Table 22. Statistically significant differences in the mean end-of-treatment SOWS, COWS, and VAS scores were detected between the buprenorphine and placebo implant groups in Study 806; however, the clinical significance of the differences observed is unclear, as there is no MCID known for these instruments. Differences were detected between the buprenorphine implant and SL buprenorphine in Study 806 and between buprenorphine and placebo implants in Study 805, but these comparisons were outside the statistical testing hierarchy and are considered inconclusive.

Other Outcomes

Other Studies (805 and 806)

CGI self-reported and CGI observer-reported data prior to induction and end of treatment from Study 806 and 805 are presented in Figure 12 and Figure 14 (Appendix 4). A shift was observed during the trial, with most patients in these trials rated has having marked, severe, or most extreme problems or symptoms prior to induction; whereas, at the end of treatment, the majority of patients in the buprenorphine groups had mild to no problems or symptoms. The self- and investigator-reported CGI improvement ratings were statistically significantly different for the buprenorphine implant versus placebo implant, but not between the two buprenorphine groups (Appendix 4, Figure 13) in Study 806. Differences were detected between the buprenorphine implant and placebo implant in the CGI improvement ratings in Study 805 (Appendix 4, Figure 15); however, it should be noted that CGI data were missing

for approximately 18% of patients, and these analyses were outside the statistical testing hierarchy and should be interpreted as inconclusive.

The Addiction Severity Index was reported as an exploratory outcome in Study 805 (Appendix 4, Table 23). The mean domain scores were similar at baseline and at the end of treatment within groups, and no between-group comparisons were reported.

Harms

Only those harms identified in the review protocol are reported subsequently (see 2.2.1, Protocol).

Adverse Events

The proportion of patients reporting adverse events was similar between the two treatment groups in Study 814 (56% to 58%) (Table 13). Nasopharyngitis, headache, and depression were reported most frequently (7% to 8%) by patients in the buprenorphine implant group.

Adverse events were reported by 67% to 72% of patients in Study 806 and 82% to 86% in Study 805 (Table 13). Headache and insomnia were reported more frequently in Study 805 than in the other two trials.

Serious Adverse Events

Among patients who received buprenorphine implants, 2% to 5% experienced a serious adverse event, compared with 6% to 7% of those in the placebo implant group and 3% to 6% in the SL buprenorphine groups (Table 14). Specific serious adverse events were reported in one patient per group, except for pneumonia, which was reported in two buprenorphine implant group patients in Study 806. One patient in the placebo group of Study 805 had implant-site cellulitis that was considered a serious adverse event.

Withdrawals Due to Adverse Events

The proportion of patients who stopped treatment due to adverse events ranged from 1% to 4% in the buprenorphine implant groups, 0% to 4% in the placebo implant groups, and was 4% in the SL buprenorphine group (Table 14). In Study 805, three patients in the buprenorphine group discontinued due to implant-site adverse events of cellulitis and pain.

Mortality

No deaths were reported in Study 814 or Study 805 but one patient died in Study 806 (Table 14). This patient was randomized to SL buprenorphine and was receiving 16 mg per day. The patient requested to be withdrawn from the study on November 15 (no reason specified) and received her last dose of study drug on that day. The investigator-assessed CGI results showed marked symptoms of opioid dependence with no change from baseline. On November 18, the patient experienced a fatal heroin overdose.

Notable Harms

Implant-site adverse events were reported more frequently in Study 805 (46% and 57%) than in Study 806 (26% and 27%) and Study 814 (14% and 23%) (Table 15). After Study 805, the manufacturer made changes to the implantation and removal procedures, which were implemented for the other two trials.

The most frequently reported implant-site adverse events were hematoma (7% to 11%), pain (5% to 9%), and pruritus (1% to 5%) in Study 814 or 806, and the frequency was generally similar among those who received buprenorphine and placebo implants. In Study 805, pain was reported in 22% and pruritus in 25% of patients who received buprenorphine implants compared with 11% and 15% who received placebo. In Study 805, erythema was reported in 25% and 22% of patients with buprenorphine and placebo implants, respectively, but ranged from 0% to 4% per group in the other two trials.

No patients in Study 806 or 814 stopped treatment or had an implant-site adverse event that was considered serious. In Study 806, one patient in the buprenorphine implant group experienced light-headedness and faintness following the implant removal procedure. In Study 814, one patient reported paresthesia (buprenorphine implant) and one reported peripheral sensory neuropathy (placebo implant).

Implant expulsion was reported in one patient in the buprenorphine group of Study 805, and one patient in Study 814. The patient in Study 814 had moderate cellulitis of the implant site and, at week 4, had a single placebo implant protrude from their arm. All four implants were removed from the arm and new implants were inserted in the other arm.

Other notable adverse events specified in the review protocol were reported infrequently. There was one patient per group who experienced an overdose in Study 806, and one accidental pediatric overdose from a patient who received SL buprenorphine in Study 814.

Table 13: Harms

	Study 814		Study 806			Study 805	
	BPN Implant N = 87	**BPN SL N = 89**	**BPN Implant N = 114**	**BPN SL N = 119**	**Placebo Implant N = 54**	**BPN Implant N = 108**	**Placebo Implant N = 55**
Patients with ≥ 1 AEs, n (%)	50 (58)	50 (56)	82 (72)	85 (71)	36 (67)	93 (86)	45 (82)
Most common AEs[a]							
Nasopharyngitis	7 (8)	4 (5)	6 (5)	12 (10)	3 (6)	15 (14)	3 (6)
Gastroenteritis, viral	4 (5)	3 (3)	3 (3)	2 (2)	1 (2)	0	3 (6)
Urinary tract infection	4 (5)	3 (3)	1 (1)	2 (2)	0	2 (2)	0
Depression	6 (7)	2 (2)	10 (9)	3 (3)	2 (4)	5 (5)	3 (6)
Constipation	4 (5)	0	5 (4)	5 (4)	1 (2)	15 (14)	3 (6)
Headache	6 (7)	3 (3)	15 (13)	19 (16)	5 (9)	27 (25)	10 (18)
Contusion	0	4 (5)	3 (3)	2 (2)	1 (2)	3 (3)	2 (4)
Insomnia	0	2 (2)	9 (8)	16 (13)	8 (15)	23 (21)	12 (22)
Anxiety	3 (3)	4 (5)	2 (2)	6 (5)	3 (6)	11 (10)	5 (9)
Upper respiratory tract infection	1 (1)	3 (3)	10 (9)	11 (9)	4 (7)	14 (13)	6 (11)
Abscess limb	NR	NR	3 (3)	5 (4)	4 (7)	2 (2)	1 (2)
Nausea	1 (1)	2 (2)	7 (6)	8 (7)	1 (2)	15 (14)	7 (13)
Vomiting	2 (2)	1 (1)	7 (6)	5 (4)	1 (2)	8 (7)	4 (7)
Diarrhea	2 (2)	1 (1)	2 (2)	2 (2)	3 (6)	6 (6)	7 (13)
Abdominal pain upper	NR	NR	2 (2)	5 (4)	1 (2)	10 (9)	1 (2)
Stomach discomfort	NR	NR	NR	NR	NR	2 (2)	3 (6)
Toothache	0	3 (3)	4 (4)	5 (4)	1 (2)	12 (11)	3 (6)
Oropharyngeal pain	1 (1)	2 (2)	8 (7)	4 (3)	1 (2)	NR	NR
Back pain	1 (1)	3 (3)	6 (5)	7 (6)	3 (6)	13 (12)	3 (6)
Hyperhidrosis	NR	NR	3 (3)	2 (2)	3 (6)	1 (1)	0

	Study 814		Study 806			Study 805	
	BPN Implant N = 87	BPN SL N = 89	BPN Implant N = 114	BPN SL N = 119	Placebo Implant N = 54	BPN Implant N = 108	Placebo Implant N = 55
Fatigue	0	2 (2)	4 (4)	0	1 (2)	6 (6)	2 (4)
Pain	2 (2)	1 (1)	5 (4)	3 (3)	2 (4)	5 (5)	3 (6)
Cough	1 (1)	0	4 (4)	3 (3)	0	6 (6)	2 (4)
Pharyngolaryngeal pain	NR	NR	NR	NR	NR	7 (7)	3 (6)
Dizziness	0	1 (1)	5 (4)	1 (1)	1 (2)	7 (7)	5 (9)
ALT increased	1 (1)	0	0	2 (2)	0	4 (4)	3 (6)
GGT increased	1 (1)	0	0	1 (1)	0	3 (3)	4 (7)

AE = adverse event; ALT = alanine aminotransferase; BPN = buprenorphine; CSR = Clinical Study Report; GGT = gamma-glutamyltransferase; NR = not reported; SL = sublingual.

[a] Frequency ≥ 5% in a treatment group per study. Any implant-site AEs occurring with a frequency of ≥ 5% are listed in the notable harms section.

Source: CSRs.[9-11]

Table 14: Serious Adverse Events, Withdrawals Due to Adverse Events, and Deaths

	Study 814		Study 806			Study 805	
	BPN Implant N = 87	BPN SL N = 89	BPN Implant N = 114	BPN SL N = 119	Placebo Implant N = 54	BPN Implant N = 108	Placebo Implant N = 55
Subjects with ≥ 1 SAEs, n (%)	2 (2)	3 (3)	6 (5)	7 (6)	3 (6)	2 (2)	4 (7)
Description of SAEs	Convulsion, bipolar disorder	Biliary colic, chronic cholecystitis, bronchitis	Hernia, pneumonia (2), tooth abscess, breast cancer, hypotension	Angina, pyrexia, overdose, rib fracture, spontaneous abortion, depression, pulmonary embolism	Abscess limb, gastroenteritis, overdose	Burns, COPD and pulmonary embolism	Pneumonia, drug dependence, suicidal ideation, respiratory failure, implant-site cellulitis
Stopped treatment due to AEs, n (%)	1 (1)	0	2 (2)	5 (4)	2 (4)	4 (4)	0
Description	Muscle spasms		Breast cancer, abnormal liver function test	ALT increased, AST increased, drug dependence, weight decrease	Overdose, hepatitis C	Hepatic enzyme increased, implant-site pain, implant-site infection	
Number of deaths, n (%)	0	0	0	1 (1)	0	0	0

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPN = buprenorphine; COPD = chronic obstructive pulmonary disease; SAE = serious adverse event; SL = sublingual.

Source: CSRs.[9-11]

Table 15: Notable Harms

	Study 814		Study 806			Study 805	
	BPN Implant N = 87	BPN SL N = 89	BPN Implant N = 114	BPN SL N = 119	Placebo Implant N = 54	BPN Implant N = 108	Placebo Implant N = 55
Notable harms, n (%)							
Implant-site TEAE	20 (23)	12 (14)	31 (27)	NA	14 (26)	62 (57)	25 (46)
Implant-site pain	4 (5)	4 (5)	6 (5)	NA	5 (9)	24 (22)	6 (11)
Implant-site pruritus	4 (5)	1 (1)	5 (4)	NA	2 (4)	27 (25)	8 (15)
Implant-site hematoma	–	–	8 (7)	NA	6 (11)	2 (2)	1 (2)
Implant-site erythema	1 (1)	1 (1)	4 (4)	NA	0	27 (25)	12 (22)
Implant-site hemorrhage	1 (1)	0	2 (2)	NA	2 (4)	13 (12)	7 (13)
Implant-site edema	1 (1) (peripheral edema)	0	2 (2)	NA	0	14 (13)	5 (9)
Implant expulsion	0	1 (1)	–	NA	–	1 (1)	0
Infection or infestation (SOC)	3 (3) cellulitis, wound infection, purulent discharge	3 (3) cellulitis, wound infection, incision infection	1 (1)	NA	2 (4)	NR	NR
Nervous system disorders (SOC)	1 (1) paresthesia	1 (1) peripheral sensory neuropathy	–	NA	–	NR	NR
Overdose	–	–	1 (1)	0	1 (2)	–	–
Accidental overdose	–	–	0	1 (1)	0	–	–
Accidental pediatric overdose	0	1 (1)	–	–	–	–	–
Orthostatic hypotension	–	–	–	–	–	–	–
Respiratory depression	–	–	–	–	–	1 (1)	0
Hepatic toxicity	–	–	–	–	–	–	–
Abnormal hepatic enzyme of severe intensity	0	1 (1)	–	–	–	–	–

BPN = buprenorphine; CSR = Clinical Study Report; NA = not applicable; NR = not reported; SL = sublingual; SOC = system organ class; TEAE = treatment-emergent adverse event.

Source: CSRs.[9-11]

Discussion

Summary of Available Evidence

Although three RCTs were included in this review, which was initiated prior to the NOC being granted; only Study 814 is considered pivotal and is consistent with the approved Health Canada indication.

Study 814 enrolled 177 clinically stable patients with opioid dependence who had received treatment with SL buprenorphine for at least six months and were on doses of 8 mg or less per day for the past 90 days. Patients were randomized to receive buprenorphine implants or SL buprenorphine/naloxone (at the buprenorphine dose they were on prior to study entry; ≤ 8 mg/day) for 24 weeks (double-dummy design). The primary outcome was the proportion of responders, which was defined as showing evidence of illicit opioid use in no more than two of the six months.

The other included trials (studies 805 and 806) enrolled adults with opioid dependence who had not received treatment for their substance use disorder in the past 90 days. Patients underwent induction therapy with SL buprenorphine/naloxone and those whose withdrawal symptoms and cravings were controlled on 12 mg to 16 mg of buprenorphine daily were eligible for randomization (Study 806, N = 287; Study 805, N = 163). Patients were randomized to receive four buprenorphine or placebo implants (blinded). Study 806 also randomized patients to open-label SL buprenorphine plus naloxone at a dose of 12 mg to 16 mg buprenorphine daily. The primary outcome was the cumulative distribution function of the percentage of urine samples that were negative for illicit opioids in the buprenorphine implant versus placebo groups.

Interpretation of Results

Efficacy

Pivotal Trial (Study 814)

In Study 814, buprenorphine implants were noninferior to SL buprenorphine for the proportion of responders, based on a −0.20 noninferiority margin (primary analysis: 0.088; 95% CI, 0.009 to 0.167). Noninferiority was met for the per-protocol population (0.053; 95% CI, −0.022 to 0.129) and across pre-planned and post hoc sensitivity analyses. The superiority of implants versus SL buprenorphine, however, was met for the primary analysis but not for other sensitivity analyses that tested key assumptions. For example, the results did not favour buprenorphine implants in the analyses that included all randomized and treated patients (0.055; 95% CI, −0.032 to 0.141) or that assumed all missing urine samples were positive (0.043; 95% CI, −0.055 to 0.14). The former analysis included three patients in the buprenorphine group who were excluded from the ITT population, and the latter used a more conservative imputation for missing data.

The percentage of patients with no illicit opioid use per month (based on urine tests and self-reported use) ranged from 85% to 94% in the SL buprenorphine group, and from 91% to 99% in the buprenorphine implant group, and the time to first illicit opioid use showed differences favouring the buprenorphine implant group. These outcomes, however, were not part of the fixed statistical testing procedure and thus should be interpreted as inconclusive. Moreover, the clinical relevance of the time-to-event analysis is unclear, given

that occasional illicit opioid use (a lapse) is not unexpected, even among stable patients and, within a harm-reduction treatment paradigm, complete abstinence from drug use is not required. A more clinically important question is whether patients can recover from a lapse, or if the lapse leads to a relapse, which may include ongoing illicit opioid use, discontinuation of treatment, or worsening so that the patient once again meets the diagnostic criteria for opioid use disorder. However, the Kaplan–Meier curves of the time to first illicit opioid use (or need for SL buprenorphine) do provide some data of interest that showed that most lapses occurred in the first two months of buprenorphine implant therapy and there were few late lapses. Late lapses may suggest the efficacy of the implants was waning near the end of the six months.

Overall, the proportion of patients who remained in the study was high (94%) and was similar between groups. Fifteen patients (18%) in the buprenorphine implant group and 13 patients (15%) in the SL buprenorphine group were dispensed supplemental SL buprenorphine on one or more occasions, although it is not clear what doses were administered on how many days and when they were received (e.g., at the beginning of treatment, throughout, or near the end of the trial). The average total dose received per patient was higher in the implant group (85.8 mg) than in the SL buprenorphine group (49.8 mg), although the clinical expert consulted for the review considered these quantities to be low when expressed in terms of milligrams per day. Administration of supplemental buprenorphine was at the investigator's discretion, and 75% of patients who receive rescue therapy were from two study sites; therefore, supplemental dosing may be related to site-specific practices in Study 814. However, the need for supplemental SL buprenorphine in approximately one-fifth of patients potentially negates some of the proposed advantages of the implant in terms of reduced risk of accidental pediatric exposure or treatment diversion, and the product monograph states that the use of buprenorphine implants should be reconsidered if patients require ongoing SL buprenorphine.[4]

Based on data from the COWS, SOWS and desire- or need-to-use VAS scores, it appears that patients' withdrawal symptoms and cravings were controlled in both treatment groups, as the mean scores were generally low at baseline and at week 24, with no statistically significant differences detected between groups for any of these outcome measures. The trial, however, was not powered to detect differences between groups for these outcomes, and the patient-reported outcomes were outside the fixed statistical testing procedure. There was no data on social functioning or health-related quality of life. Although no submissions were received in the call for patient input, patients interviewed regarding their opioid-maintenance therapy emphasized the importance of making positive changes in their lives, such as obtaining housing and returning to work or volunteering, over the results of urine testing as key measures of treatment success.[30]

Of note, the insertion and removal of implants must be performed by health care professionals who have successfully completed a live training program.[4] Moreover, as a prerequisite for participating in the training program, health care professionals must have performed at least one qualifying surgical procedure in the last three months (e.g., making skin incisions, or placing sutures under local anesthesia using aseptic technique).[4] This may impact the accessibility of the implants if a certified health care professional is not available near the patient's place of residence.

Other Studies (805 and 806)

Studies 805 and 806 found statistically significant differences between buprenorphine and placebo implants on the frequency of illicit opioid use, measured based on urine toxicology

tests and self-reported use. Interpretation of these differences, however, should take into consideration the appropriateness of the placebo control group and the substantial and differential withdrawal rates in these studies. Furthermore, the studies allowed for a fifth buprenorphine implant to be inserted, and the population enrolled (patients initiated on moderate to higher doses of buprenorphine) were not consistent with the indication approved by Health Canada. Thus, the data from these trials should be considered as supplementary evidence only.

Harms

Adverse events were reported by most patients and the frequency varied between studies, ranging from 56% to 58% in Study 814, from 67% to 72% in Study 806, and from 82% to 86% in Study 805. Among patients who received buprenorphine implants, 2% to 5% experienced a serious adverse event compared with 6% and 7% of those in the placebo implant group and 3% to 6% in the SL buprenorphine groups. The proportion of patients who stopped treatment due to adverse events was generally low and ranged from 0% to 4%.

The frequency of implant-site adverse events was high in Study 805 and its extension study (Appendix 6), and consequently the manufacturer modified the applicator, the insertion and removal procedures, and the training materials for studies 806 and 814. Implant-site adverse events were reported in 14% to 27% of patients in these two trials and no patients stopped treatment or had a serious adverse event related to the implant site. An implant was expelled from the arm of one patient in Study 814 (placebo implant) and one patient in Study 805 (buprenorphine implant). There was one patient per group who experienced an overdose in Study 806, and one incident of accidental pediatric overdose was reported in the SL buprenorphine group in Study 814.

No new safety signals were identified in two open-label extension studies that enrolled 147 patients who had completed Study 805 or 806. Of these patients, 107 (73%) had previously received buprenorphine implants and, thus, their total duration of exposure to implants was up to one year. The suggested treatment duration for buprenorphine implants is limited to one year (one set of implants per arm for six months each), as the monograph states there is no experience with inserting additional implants into other sites of the arm, sites other than the upper arm, or reinsertion into previously used sites.[4] Patients who require longer-term therapy should be transitioned back to their previous dose of SL buprenorphine; however, if the potential benefits of continuing buprenorphine implants outweigh the potential risk of additional insertion and removal procedures, the product monograph provides guidance for the insertion of two additional sets of implants in alternate sites in the upper arm.[4] The product monograph states that dosing beyond 24 months cannot be recommended at this time.[4] The risks to patients lost to follow-up, who may have implants in situ for longer than six months, is not known.

Although buprenorphine has been available for a number of years and its risk profile is generally known, there are some adverse effects which may be specific to this product. The monograph states that in an overdose situation, higher than normal doses of naloxone may be required, as the implants will continue to release buprenorphine, and the high affinity of this drug for opioid mu-receptors will reduce the binding ability of naloxone on these receptors.[4] Breakage of the implant is not expected to alter the pharmacokinetics of the device. Given the sample sizes and duration of exposure of the available evidence, it is not possible to determine the longer-term risks of the implants or the infrequent but clinically important adverse events that have been observed with other similar contraceptive implant

devices.[22] In the US, a Risk Evaluation and Mitigation Strategy was required by the FDA to mitigate the risk of complications of migration, protrusion, expulsion, and nerve damage associated with the insertion and removal of the implants, and the risks of accidental overdose, misuse, and abuse.[31,32]

Potential Place in Therapy[2]

This six-monthly depot formulation of buprenorphine is suited for those people with an opioid use disorder, especially secondary to prescription opioids, who are stable for at least 90 days on SL buprenorphine/naloxone 8 mg or less per day. Currently, patients who are stabilized and employed still have to interact more frequently with health care providers to obtain prescription refills and make visits to the pharmacy weekly. In some cases, this has minimal therapeutic value if the patient is in remission, but serves mainly to minimize the risk of diversion to SL buprenorphine/naloxone.[5-7] That time could be better spent by the patient to address other issues such as concurrent post-traumatic stress disorder (PTSD) or depression,[6] for example. Therefore, this population is likely to be better served by this formulation because they could exercise the option of having a bi-annual procedure for a year. In addition, it will reduce the stigma associated with treatment, especially the weekly visit to the pharmacy and the need for frequent urine drug testing. It could also fill the gap by providing access to those who live in remote areas where there is limited access to prescribers for the sublingual medication and for those who have to travel for extended periods for work, especially to areas where there is restricted or no access to SL buprenorphine/naloxone. It also provides a choice to those patients who do not wish to take tablets every day, although at least 18% — based on Study 814 — might require some sublingual supplementation. Therefore, this implantable formulation of buprenorphine reduces the risk of diversion, but does not eliminate it completely.[8]

It will be easy to identify patients who are appropriate to receive buprenorphine implants based on the duration and response to SL buprenorphine/naloxone, and no special tests are required. Physicians will likely need training and certification to be able to place the implant. This might limit the availability of this treatment. One advantage is that in a medical emergency, the implants can be removed, unlike injectable formulations.[8]

It is not known whether there is any benefit to implanting more than two sets (i.e., one-year exposure) of buprenorphine implants. Thereafter, if the person still requires buprenorphine after one year, they will have to revert back to SL formulations, or be assessed to determine if the potential benefits of continuing buprenorphine implants outweigh the risks of additional insertion and removal procedures. Given the implants are inserted subdermally in the upper arms and reinsertion in the same site is not recommended, the effectiveness of the implant if inserted in other subdermal areas is unknown. A major concern is whether plasma levels of buprenorphine are high enough to act as an antagonist should the person relapse to highly potent opioids, such as fentanyl and/or hydromorphone, especially toward the end of the dosing interval.[5] Lastly, the risk of double-doctoring or of having access to diverted buprenorphine or additional SL buprenorphine/naloxone will still remain and will not be detectable in urine drug testing. The former could be detected by a prescription-monitoring program, but the latter will rely on self-reporting.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

In adults with clinically stable opioid dependence adequately managed on low doses of SL buprenorphine, buprenorphine implants (320 mg total dose) were noninferior to SL buprenorphine at doses of 8 mg or less per day based on the proportion of responders, defined as those with no evidence of illicit opioid use for at least four out of six months. The proportion of patients remaining on treatment was high in both groups. Although data were reported on symptoms of withdrawal and cravings to use opioids, the trial was not powered to detect differences between groups for these outcomes. No data were available on health-related quality of life or social functioning.

The evidence available for the Health Canada–approved population was limited to a single RCT that included fewer than 90 patients per treatment group. Considering the sample sizes and duration of exposure in the pivotal and other placebo-controlled trials, it is not possible to determine the risks of infrequent but clinically important implant-related adverse events, or longer-term efficacy and safety.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

No submissions were received from patient groups.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-process and other non-indexed citations Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of search:	January 26, 2018
Alerts:	Bi-weekly search updates until May 16, 2018
Study types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(probuphine* or probuphenine*).ti,ab,ot,kf,hw,rn,nm.
2	buprenorphine/
3	(buprenorphine* or buprenorfina* or buprenorphinum*).ti,ab,ot,kf,hw,rn,nm.
4	(belbuca* or buprenex* or buprex* or buprenorphine* or buprenorfina* or buprenorphinum* or butrans* or finibron* or prefin* or sublocade* or subutex* or temgesic* or MR 56 or CAM2038 or RBP-6000 or EINECS 257-950-6 or 6029-M).ti,ab,ot,kf,hw,rn,nm.
5	(56W8MW3EN1 or 40D3SCR4GZ or 53152-21-9 or 52485-79-7).rn,nm.
6	2 or 3 or 4 or 5
7	drug implants/
8	(implant* or subdermal*).ti,ab,ot,kf,hw.

MULTI-DATABASE STRATEGY
9 (under* adj2 skin).ti,ab,ot,kf,hw.
10 (below adj2 skin).ti,ab,ot,kf,hw.
11 7 or 8 or 9 or 10
12 6 and 11
13 1 or 12
14 13 use medall
15 (probuphine* or probuphenine*).ti,ab,ot,kw.
16 *buprenorphine/
17 (buprenorphine* or buprenorfina* or buprenorphinum*).ti,ab,ot,kw.
18 (belbuca* or buprenex* or buprex* or buprenorphine* or buprenorfina* or buprenorphinum* or butrans* or finibron* or prefin* or sublocade* or subutex* or temgesic* or MR 56 or CAM2038 or RBP-6000 or EINECS 257-950-6 or 6029-M).ti,ab,ot,kw.
19 16 or 17 or 18
20 drug implants/
21 (implant* or subdermal*).ti,ab,ot,kw.
22 (under* adj2 skin).ti,ab,ot,kw.
23 (below adj2 skin).ti,ab,ot,kw.
24 20 or 21 or 22 or 23
25 19 and 24
26 15 or 25
27 26 use oemezd
28 conference abstract.pt.
29 27 not 28
30 14 or 29
31 remove duplicates from 30
32 exp animals/
33 exp animal experimentation/ or exp animal experiment/
34 exp models animal/
35 nonhuman/
36 exp vertebrate/ or exp vertebrates/
37 or/32-36
38 exp humans/
39 exp human experimentation/ or exp human experiment/
40 or/38-39
41 37 not 40
42 31 not 41

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for search:	January 18 to 23, 2018
Keywords:	Probuphine (buprenorphine hydrochloride), opioid drug dependence
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Table 16: Excluded Studies

Reference	Reason for Exclusion
Dammerman R, Bailey GL, Beebe KL, Chen M, Rosenthal RN, Sigmon SC, et al. Long-term buprenorphine implants for treatment of opioid dependence: safety outcomes from two open-label extension trials. J Addict Behav Ther Rehabil. 2017;6(1). Tetrault JM, Fiellin DA. Adding buprenorphine implants to counselling reduces opioid use over 6 months in opioid-dependent adults. Evid Based Ment Health. 2011 Feb;14(1):30. Comment on: JAMA. 2010 Oct 13;304(14):1576-83.	Not a randomized controlled trial
Beebe KL, Chavoustie S, Ling W, Sigmon S, Leiderman D, Bailey G. Buprenorphine implants for the treatment of opioid dependence: six and 12 month outcomes. Neuropsychopharmacology [Internet]. 2012 [cited 2018 Feb 6];38:S266-S267. Available from: https://www.nature.com/npp/journal/v38/n1s/index.html (Presented at American College of Neuropsychopharmacology 51st Annual Meeting; 2012 Dec 2-6; Hollywood, FL).	Abstract for Study 806[20] and extension study[33]

Appendix 4: Detailed Outcome Data

Table 17: Statistical Testing Hierarchy — Study 806 and 805

Study 806	Study 805
1. CDF of the percentage of urine samples that are negative for illicit opioids over weeks 1−24 of treatment for groups A vs. B (primary outcome 1) 2. CDF of the percentage of urine samples that are negative for illicit opioids with imputation based on illicit drug self-report data over weeks 1−24 of treatment for groups A vs. B (primary outcome 2) 3. CDF of the percentage of urine samples that are negative for illicit opioids over weeks 1–16 of treatment for groups A vs. B 4. CDF of the percentage of urine samples that are negative for illicit opioids over weeks 17–24 of treatment for groups A vs. B 5. Difference of proportions of urine samples negative for illicit opioids over 24 weeks of treatment for groups A vs. C (noninferiority) 6. Proportion (percentage) of study completers, groups A vs. B 7. Mean percentage of urine samples negative for illicit opioids, groups A vs. B, weeks 1–24 8. Mean percentage of urine samples negative for illicit opioids, groups A vs. B, weeks 1–16 9. Mean percentage of urine samples negative for illicit opioids, groups A vs. B, weeks 17–24 10. Mean total score on the COWS, groups A vs. B, weeks 1–24 11. Mean total score on the SOWS, groups A vs. B, weeks 1–24 12. Mean subjective opioid craving assessment (VAS), groups A vs. B, weeks 1–24 13. Self-assessed global improvement scores (CGI), groups A vs. B, weeks 1–24 14. Observer-assessed global improvement scores (CGI), groups A vs. B, weeks 1–24 15. Proportion (per cent) of study completers, groups A vs. C[a] 16. Mean percentage of urine samples negative for illicit opioids, groups A vs. C, weeks 1–24 17. Mean percentage of urine samples negative for illicit opioids, groups A vs. C, weeks 1–16 18. Mean percentage of urine samples negative for illicit opioids, groups A vs. C, weeks 17–24 19. Mean total score on the SOWS, groups A vs. C, weeks 1–24 20. Mean total score on the COWS, groups A vs. C, weeks 1–24 21. Mean subjective opioid craving assessment (VAS), groups A vs. C, weeks 1–24 22. Self-assessed global improvement scores (CGI), groups A vs. C, weeks 1–24 23. Observer-assessed global improvement scores (CGI), groups A vs. C, weeks 1–24 24. Mean total number of weeks of abstinence, groups A vs. B, weeks 1–24	1. CDF of the percentage of urine samples that were negative for illicit opioids for weeks 1 through 16 (primary). 2. CDF of the percentage of urine samples that were negative for illicit opioids over weeks 17–24 of treatment 3. Mean percentage of urine samples negative for illicit opioids (weeks 1–16 and weeks 17–24) 4. Proportion (percentage) of study completers (weeks 1–16 and weeks 17–24) 5. Mean total number of weeks of abstinence (weeks 1–16 and weeks 17–24)[a] 6. Mean maximal period of continuous abstinence (weeks 1–16 and weeks 17–24) 7. Mean total score on the SOWS (weeks 1–16 and weeks 17–24) 8. Mean total score on the COWS (weeks 1–16 and weeks 17–24) 9. Mean subjective opioid craving assessment (VAS) (weeks 1–16 and weeks 17–24) 10. Subject-rated current severity of opioid dependence and improvement since baseline (weeks 1–16 and weeks 17–24) 11. Physician-rated severity of opioid dependence over past week and improvement since baseline (weeks 1–16 and weeks 17–24) 12. Pharmacokinetics

Study 806	Study 805
25. Mean total number of weeks of abstinence, groups A vs. B, weeks 1–16	
26. Mean total number of weeks of abstinence, groups A vs. B, weeks 17–24	
27. Mean maximum period of continuous abstinence, groups A vs. B, weeks 1–24	
28. Mean maximum period of continuous abstinence, groups A vs. B, weeks 1–16	
29. Mean maximum period of continuous abstinence, groups A vs. B, weeks 17–24	
30. Mean total number of weeks of abstinence, groups A vs. C, weeks 1–24	
31. Mean total number of weeks of abstinence, groups A vs. C, weeks 1–16	
32. Mean total number of weeks of abstinence, groups A vs. C, weeks 17–24	
33. Mean maximum period of continuous abstinence, groups A vs. C, weeks 1–24	
34. Mean maximum period of continuous abstinence, groups A vs. C, weeks 1–16	
35. Mean maximum period of continuous abstinence, groups A vs. C, weeks 17–24	

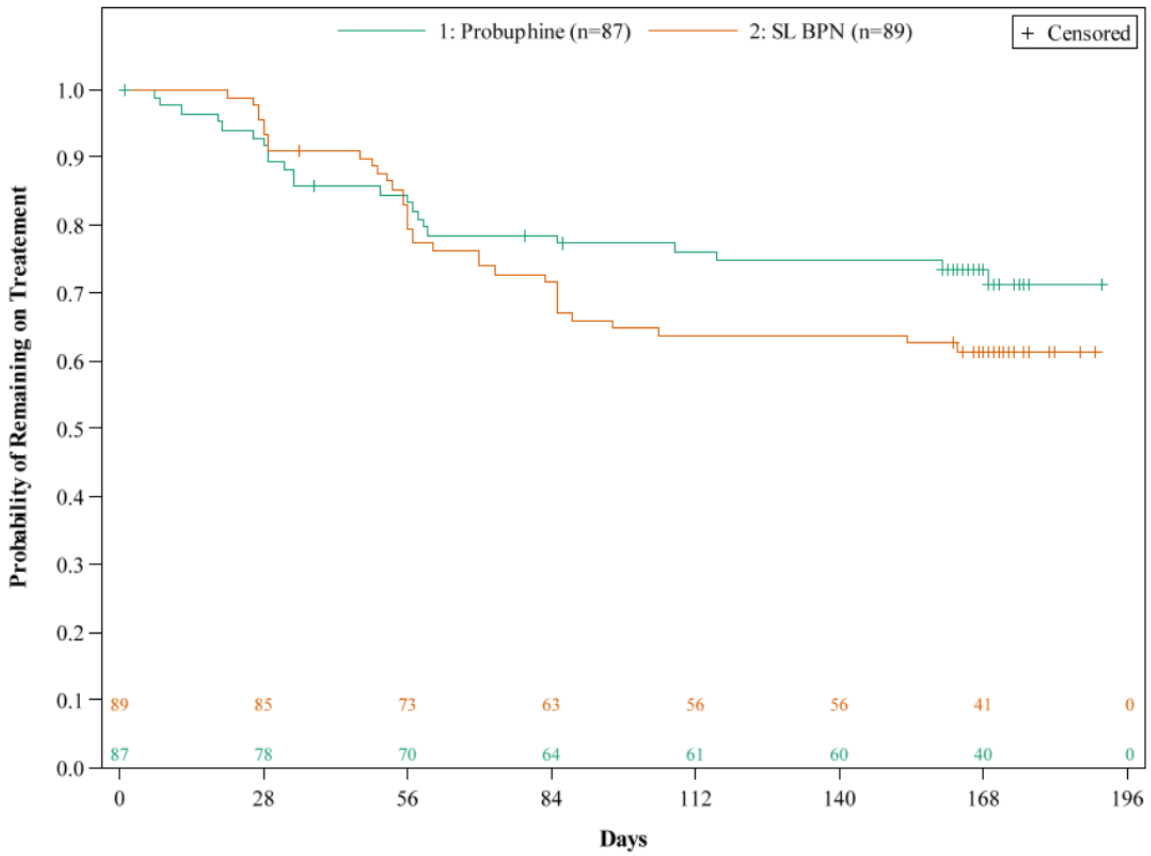
CDF = cumulative distribution function; CGI = Clinical Global Impressions scale; COWS = Clinical Opiate Withdrawal Scale; CSR = Clinical Study Report; SL = sublingual; SOWS = Subjective Opiate Withdrawal Scale; VAS = visual analogue scale; vs. = versus.

Note: Group A = buprenorphine implant; Group B = placebo implant; Group C = open-label SL buprenorphine.

[a] Statistical significance was not achieved for this outcome; thus, all subsequent outcomes should be considered inconclusive.

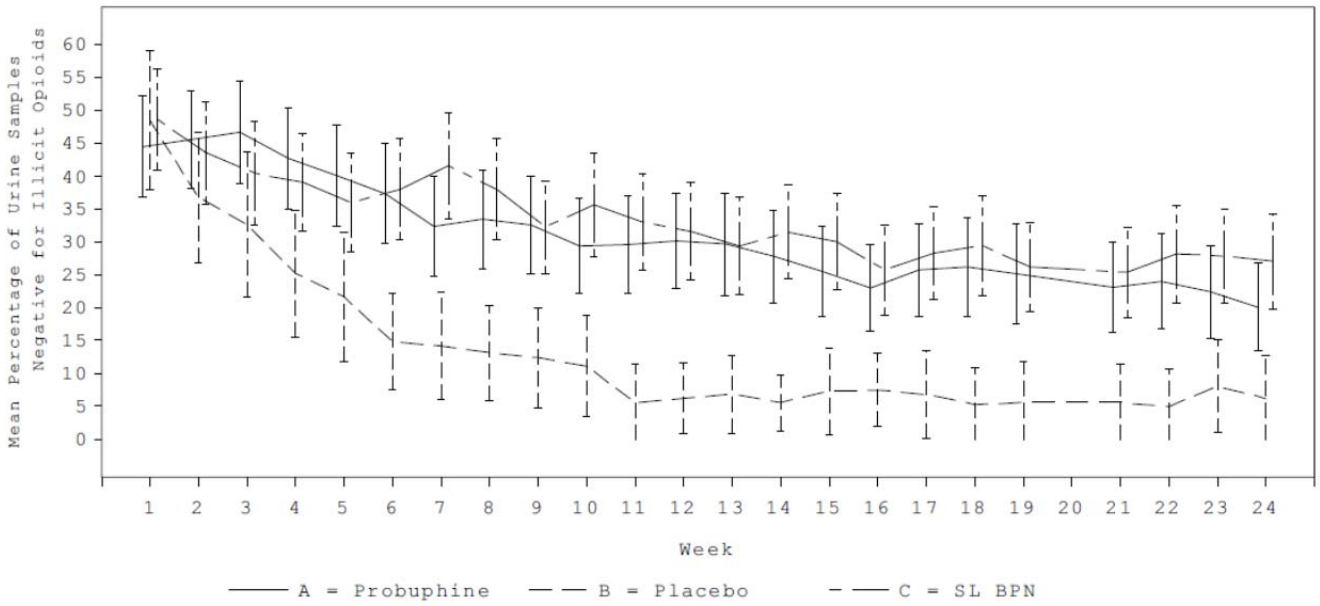
Source: CSR.[9,10]

Figure 4: Time to First Illicit Opioid Use or Supplemental Medication Dispensing (ITT) — Study 814



BPN = buprenorphine; ITT = intention-to-treat; SL = sublingual.
Source: FDA Advisor Committee Report,[22] page 33.

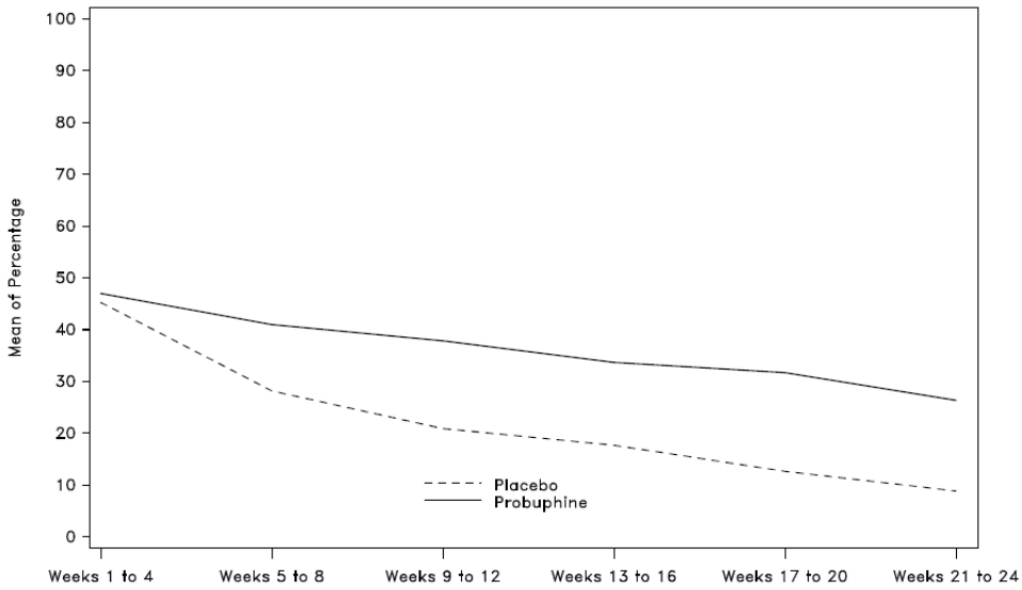
Figure 5: Mean Percentage of Urine Samples Negative for Illicit Opioid Use by Week (With 95% CI, ITT) — Study 806



BPN = buprenorphine; CI = confidence interval; SL = sublingual.

Source: Clinical Study Report.[10]

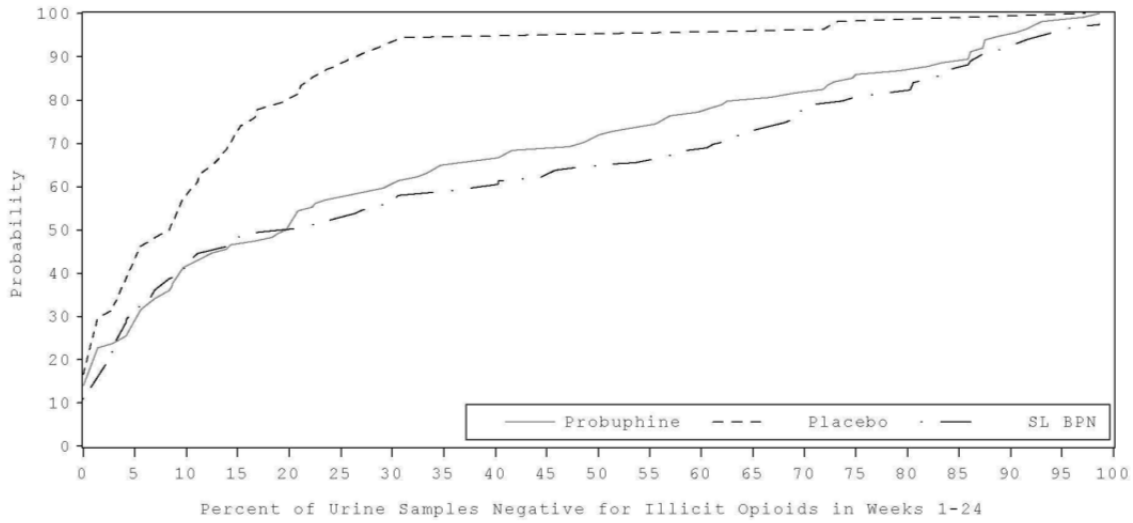
Figure 6: Mean Percentage of Urine Samples Negative for Illicit Opioid Use by Week (ITT) — Study 805



ITT = intention-to-treat.

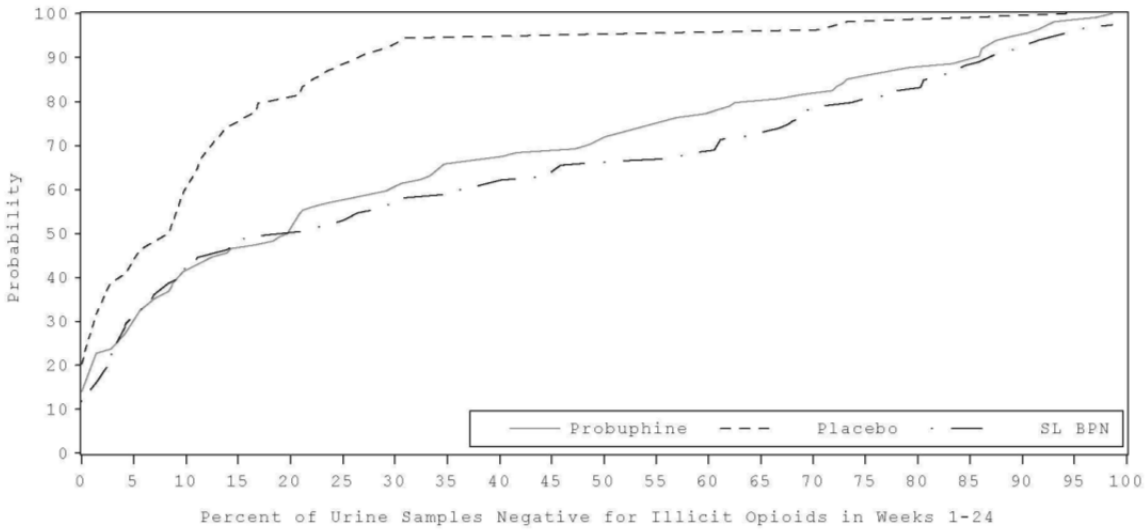
Source: Clinical Study Report.[9]

Figure 7: Cumulative Distribution Function of the Percentage of Urine Samples Negative for Illicit Opioid Use (Weeks 1 to 24, ITT, No Imputation) — Study 806



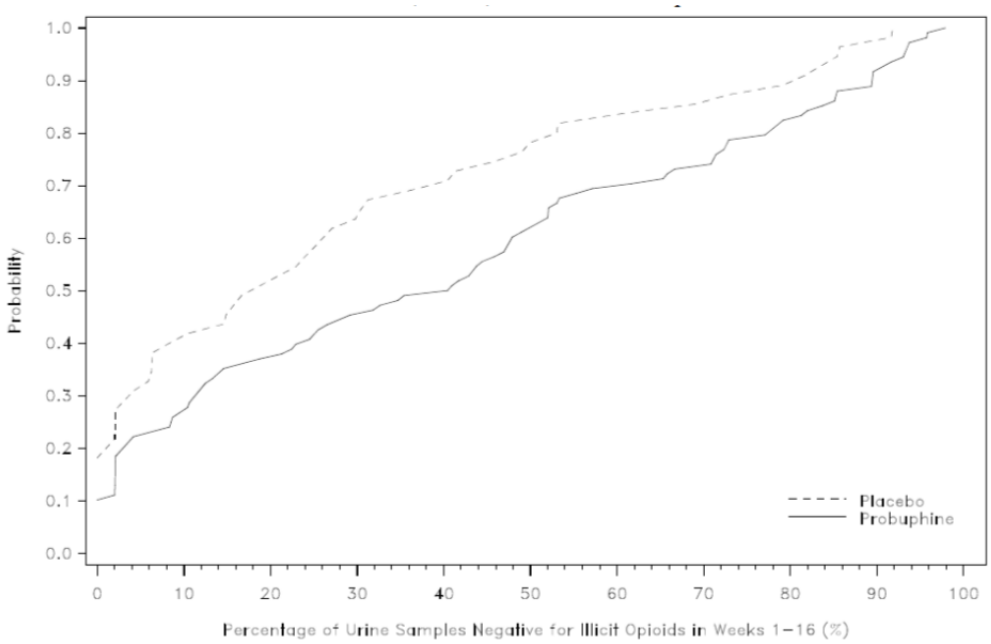
BPN = buprenorphine; CSR = Clinical Study Report; ITT = intention-to-treat; SL = sublingual.
Source: CSR.[10]

Figure 8: Cumulative Distribution Function of the Percentage of Urine Samples Negative for Illicit Opioid Use (Weeks 1 to 24, ITT, Self-Reported Use Imputation) — Study 806



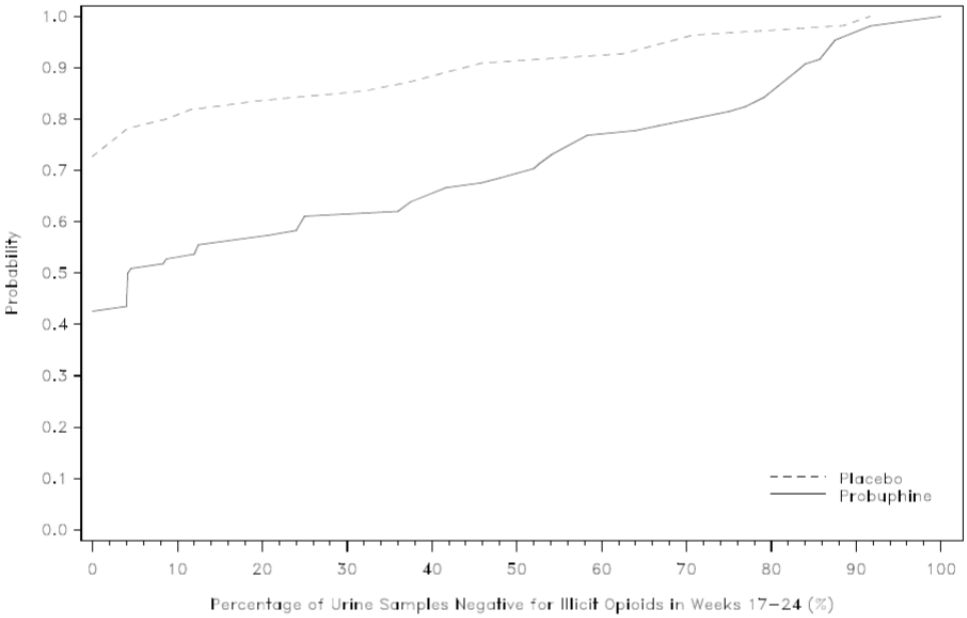
BPN = buprenorphine; CSR = Clinical Study Report; ITT = intention-to-treat; SL = sublingual.
Source: CSR.[10]

Figure 9: Cumulative Distribution Function of the Percentage of Urine Samples Negative for Illicit Opioid Use (Weeks 1 to 16, ITT) — Study 805



CSR = Clinical Study Report; ITT = intention-to-treat.
Source: CSR.[9]

Figure 10: Cumulative Distribution Function of the Percentage of Urine Samples Negative for Illicit Opioid Use (Weeks 17 to 24, ITT) — Study 805



CSR = Clinical Study Report; ITT = intention-to-treat.
Source: CSR.[9]

Table 18: Other Efficacy Outcomes — Studies 805 and 806

	Study 806					Study 805		
	BPN Implant	SL BPN	Placebo Implant	Treatment Difference		BPN Implant	Placebo Implant	Treatment Difference
				BPN Implant Versus SL BPN (95% CI), *P* Value	BPN Implant Versus Placebo Implant (95% CI), *P* Value			BPN Implant Versus Placebo Implant (95% CI), *P* Value
ITT	**N = 114**	**N = 119**	**N = 54**			**N = 108**	**N = 55**	
Proportion of negative urine tests								
Cumulative probability, week 1 to 24	31.2	33.5	NR	(−10.7 to 6.2) NI met[a] *P* = NR	NR	NR	NR	NR
Mean % of negative urine samples[b]								
Week 1 to 24, LS mean (SE)	36.0 (2.8)	35.1 (2.8)	14.4 (3.8)	0.9 (−6.4 to 8.2), *P* = 0.81[c]	21.6 (12.5 to 30.8) *P* < 0.0001[c]	NR	NR	NR
Week 1 to 16, LS mean (SE)						40.3 (3.2)	28.9 (4.3)	11.4 (1.4 to 21.4), *P* = 0.025
Week 17 to 24, LS mean (SE)						27.9 (3.3)	9.8 (4.4)	18.1 (7.8 to 28.3), *P* = 0.0006
Mean number of weeks of abstinence[d]								
Week 1 to 24, LS mean (SE)	5.3 (0.6)	5.0 (0.5)	1.7 (0.7)	0.3 (−1.2 to 1.7), *P* = 0.72[c]	3.6 (1.8 to 5.4), *P* = 0.0001[c]	NR	NR	NR
Week 1 to 16, LS mean (SE)						2.9 (0.4)	2.6 (0.5)	0.3 (−0.9 to 1.6), *P* = 0.62[e]
Week 17 to 24, LS mean (SE)						1.1 (0.2)	0.3 (0.2)	0.8 (0.3 to 1.3), *P* = 0.0018[c]
Mean maximal period of continuous abstinence[f]								
Week 1 to 24, LS mean (SE)	2.5 (0.3)	2.4 (0.3)	0.9 (0.4)	0.06 (−0.6 to 0.8), *P* = 0.87[c]	1.6 (0.7 to 2.4), *P* = 0.0005[c]	NR	NR	NR
Week 1 to 16, LS mean (SE)						1.6 (0.2)	1.5 (0.3)	0.1 (−0.6 to 0.8), *P* = 0.78[c]

	Study 806					Study 805		
	BPN Implant	SL BPN	Placebo Implant	Treatment Difference		BPN Implant	Placebo Implant	Treatment Difference
				BPN Implant Versus SL BPN (95% CI), *P* Value	BPN Implant Versus Placebo Implant (95% CI), *P* Value			BPN Implant Versus Placebo Implant (95% CI), *P* Value
Week 17 to 24, LS mean (SE)						0.7 (0.1)	0.2 (0.2)	0.6 (0.2 to 0.9), *P* = 0.0039[c]

ANCOVA = analysis of covariance; ANOVA = analysis of variance; BPN = buprenorphine; CI = confidence interval; CSR = Clinical Study Report; ITT = intention-to-treat; LS = least squares; NI = noninferiority; NR = not reported; SE = standard error; SL = sublingual.

[a] Noninferiority was met for buprenorphine implant relative to SL buprenorphine, as the lower bound of the 95% CI was greater than −15.0.

[b] Study 806: ANOVA model, including treatment, pooled site, and gender. Study 805: ANCOVA model, including treatment, pooled centre, gender, and treatment by gender interaction.

[c] Outside the statistical testing hierarchy; therefore, should be interpreted as inconclusive.

[d] Study 806: ANOVA model, including treatment, pooled site, and gender. Study 805 ANCOVA model, including treatment, pooled centre, gender, and treatment by gender interaction. Treatment by gender interaction term was significant in the week 1 to 16 model and thus was included in the final model.

[e] First outcome in the statistical testing hierarchy that failed to achieve statistical significance; thus, all further outcomes should be interpreted as inconclusive.

[f] Study 806: ANCOVA model, including treatment, pooled site, and gender. Study 805 ANCOVA model, including treatment, pooled centre, gender, and treatment by gender interaction. Treatment by gender interaction term was significant in the week 1 to 16 model and thus was included in the final model.

Source: CSRs.[9,10]

Table 19: Primary Efficacy Outcomes — Studies 805 and 806

	Study 806		Study 805
Analysis	**BPN Implant Versus SL BPN**	**BPN Implant Versus Placebo**	**BPN Implant Versus Placebo**
Cumulative Distribution Function of % Negative Urine Tests (mITT)	***P* Value**	***P* Value**	***P* Value**
Week 1 to 24 Based on results of urine tests only	NR	< 0.0001[a]	NR
Week 1 to 24 Imputation based on self-reported opioid use	NR	< 0.0001[a]	NR
Week 1 to 16 Based on results of urine tests only	NR	< 0.0001	0.036[b]
Week 17 to 24 Based on results of urine tests only	NR	0.0002	0.0004

BPN = buprenorphine; CSR = Clinical Study Report; mITT = modified intention-to-treat; NR = not reported; SL = sublingual.

[a] Co-primary outcomes in Study 806.

[b] Primary outcome in Study 805.

Source: CSRs.[9,10]

Table 20: Proportion of Patients Completing Trial — Study 806 and 805

	Study 806					Study 805		
	BPN Implant	**SL BPN**	**Placebo Implant**	**Treatment Difference**		**BPN Implant**	**Placebo Implant**	**Treatment Difference**
				BPN Implant Versus SL BPN (95% CI), *P* Value	**BPN Implant Versus Placebo Implant (95% CI), *P* Value**			**BPN Implant Versus Placebo Implant (95% CI), *P* Value**
ITT	**N = 114**	**N = 119**	**N = 54**			**N = 108**	**N = 55**	
Proportion of patients completing 24 weeks[a]								
n (%)	73 (64)	76 (64)	14 (26)	(NR) *P* = 0.62[b]	(NR) *P* = 0.0002	71 (66)	17 (31)	(NR) *P* < 0.0001[b]

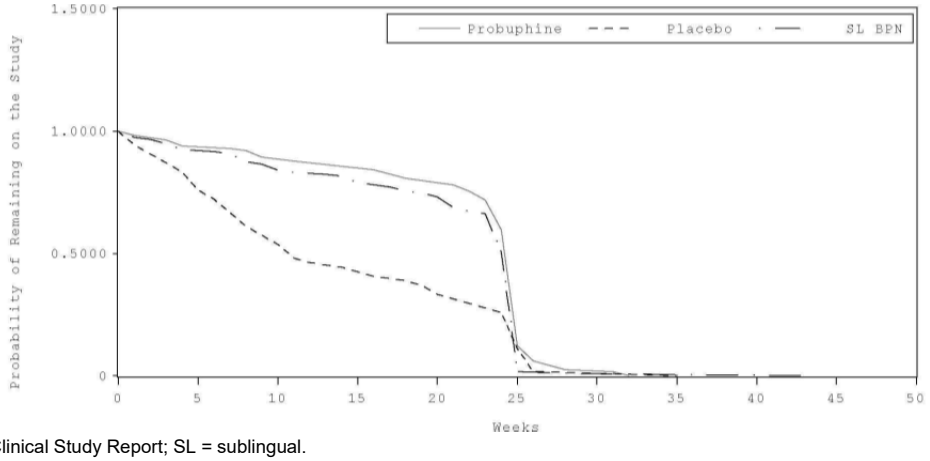
BPN = buprenorphine; CI = confidence interval; CSR = Clinical Study Report; ITT = intention-to-treat; NR = not reported; SL = sublingual.

[a] Cochran–Mantel–Haenszel stratified on gender and pooled site.

[b] Outside the statistical testing hierarchy; therefore, should be interpreted as inconclusive.

Source: CSRs.[9,10]

Figure 11: Kaplan–Meier Plot of Days to Discontinuation (Intention-to-Treat) — Study 806



BPN = buprenorphine; CSR = Clinical Study Report; SL = sublingual.
Source: CSR.[10]

Table 21: Withdrawal Symptom Scales and Cravings Visual Analogue Scale — Study 814

Outcome	Study 814			
	BPN Implant	Placebo Implant	Treatment Difference	
			BPN Implant Versus Placebo Implant (95% CI)	*P* Value
mITT	**N = 84**	**N = 89**		
COWS				
Baseline, N	84	89		
mean total score (SD)	1.0 (1.3)	1.0 (1.1)		
Week 24/EOT, N	84	89		
LS mean change from baseline (SE)[a]	−0.1 (0.2)	−0.1 (0.2)	−0.0 (−0.5 to 0.4)	0.92[b]
SOWS				
Baseline, N	84	89		
mean total score (SD)	2.7 (3.8)	2.2 (3.2)		
Week 24/EOT, N	84	89		
LS mean change from baseline (SE)[a]	−0.6 (0.5)	0.0 (0.5)	−0.6 (−2.1 to 0.9)	0.43[b]
Desire-to-Use VAS				
Baseline, N	84	88		
mean score (SD)	5.4 (14.0)	6.8 (16.0)		
Week 24/EOT, N	84	88		
LS mean change from baseline (SE)[a]	−2.8 (1.4)	−2.4 (1.3)	−0.4 (−4.2 to 3.4)	0.83[b]
Need-to-Use VAS				
Baseline, N	83	89		
mean score (SD)	5.4 (15.2)	6.0 (13.0)		
Week 24/EOT, N	83	89		
LS mean change from baseline (SE)[a]	−3.0 (1.4)	−1.7 (1.3)	−1.3 (−5.0 to 2.5)	0.51[b]

ANCOVA = analysis of covariance; BPN = buprenorphine; CI = confidence interval; COWS = Clinical Opioid Withdrawal Scale; CSR = Clinical Study Report; EOT = end of treatment; LS = least squares; mITT = modified intention-to-treat; SD = standard deviation; SE = standard error; SOWS = Subjective Opioid Withdrawal Scale; VAS = visual analogue scale.

[a] Based on ANCOVA model, including treatment and baseline as covariates.

[b] Outside the fixed statistical testing procedure; thus, should be interpreted as inconclusive.

Source: CSR.[11]

Table 22: Withdrawal Symptom Scales and Cravings Visual Analogue Scale — Studies 805 and 806

	Study 806					Study 805		
	BPN Implant	SL BPN	Placebo Implant	Treatment Difference		BPN Implant	Placebo Implant	Treatment Difference
				BPN Implant Versus SL BPN *P* Value	BPN Implant Versus Placebo Implant *P* Value			BPN Implant Versus Placebo Implant *P* Value
ITT	**N = 114**	**N = 119**	**N = 54**			**N = 108**	**N = 55**	
COWS				***Max score 44***				
Pre-induction, N						108	55	
Mean total score (SE)	NR	NR	NR			5.3 (0.5)	5.6 (0.8)	
Baseline, N	114	119	54			108	55	
Mean total score (SE)	2.9 (0.3)	2.6 (0.2)	2.6 (0.4)			3.0 (0.3)	2.4 (0.3)	
EOT, N	112	116	52			106	55	
LS mean total score (SE)[a]	2.6 (0.2)	1.7 (0.2)	5.0 (0.3)	*P* = 0.0005[b]	*P* < 0.0001	2.3 (0.2)	3.4 (0.3)	*P* = 0.0004[b]
SOWS				***Max score 64***				
Pre-induction, N						108	55	
Mean total score (SE)	NR	NR	NR			16.9 (1.6)	16.2 (2.0)	
Baseline, N	114	119	54			108	55	
Mean total score (SE)	5.3 (0.6)	5.6 (0.6)	4.4 (1.0)			6.5 (0.8)	3.9 (0.5)	
EOT, N	112	116	52			106	55	
LS mean total score (SE)[a]	5.6 (0.6)	2.9 (0.6)	10.3 (1.0)	*P* = 0.0006[b]	*P* < 0.0001	4.1 (0.5)	6.5 (0.7)	*P* = 0.0039[b]
Cravings VAS				***Max score 100***				
Screening; pre-induction, N	113	119	53			108	55	
Mean score (SE)	62.4 (2.8)	63.8 (2.5)	65.8 (3.1)			57.8 (2.6)	54.9 (3.9)	
Baseline, N	114	119	54			108	55	
Mean score (SE)	7.7 (0.9)	8.0 (0.9)	7.0 (1.3)			10.4 (1.2)	8.7 (1.2)	
Week 24/EOT, N	112	116	52			106	55	
LS mean total score (SE)[a]	11.2 (1.4)	7.6 (1.4)	28.8 (2.3)	*P* = 0.054[b]	*P* < 0.0001	9.9 (1.1)	15.8 (1.6)	*P* = 0.0009[b]

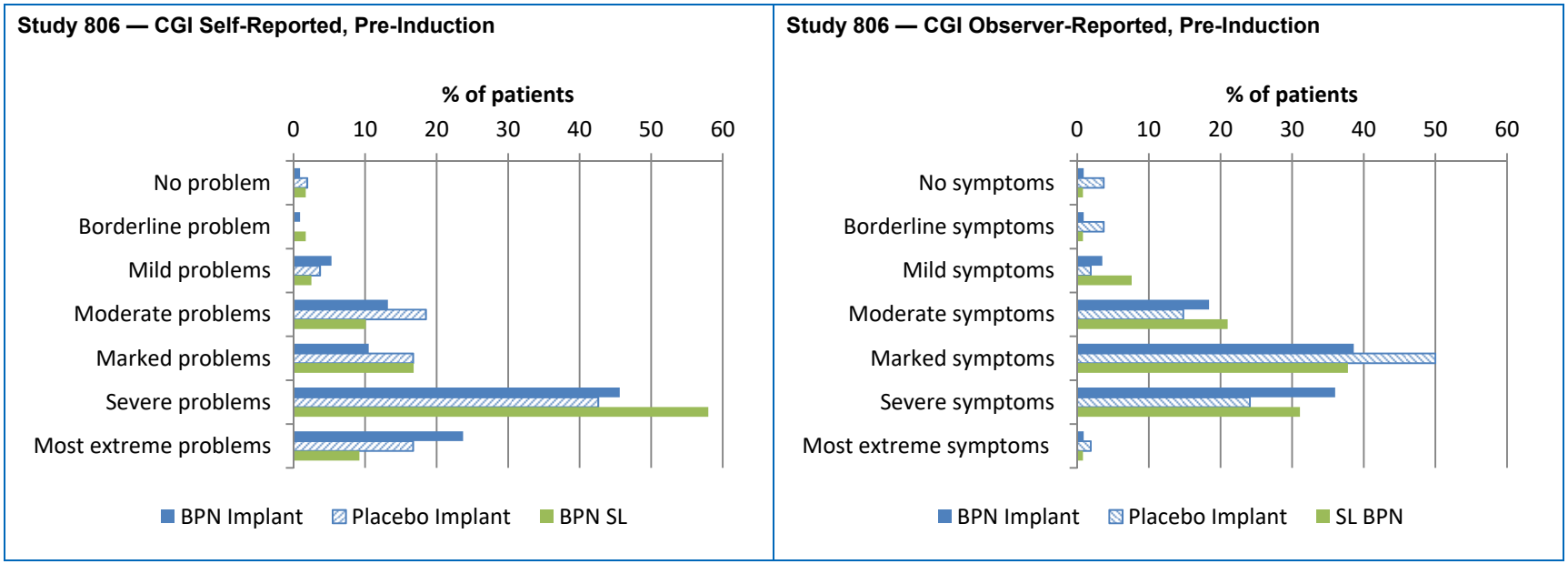
ANCOVA = analysis of covariance; BPN = buprenorphine; COWS = Clinical Opioid Withdrawal Scale; CSR = Clinical Study Report; EOT = end of treatment; ITT = intention-to-treat; LS = least squares; SE = standard error; SL = sublingual; SOWS = Subjective Opioid Withdrawal Scale; VAS = visual analogue scale.

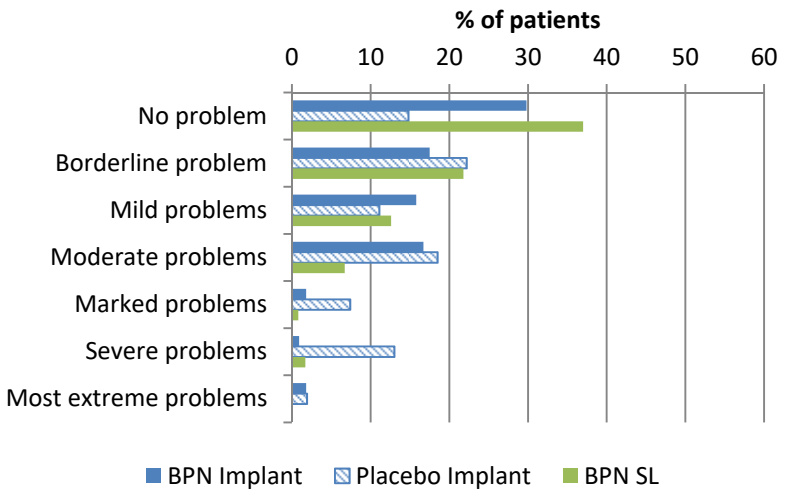
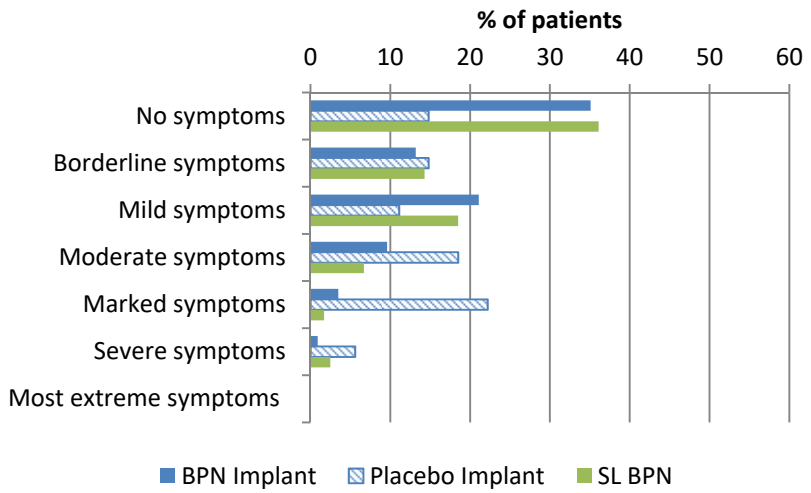
[a] Repeated-measures ANCOVA model with treatment, week, treatment by week, gender, and site as categorical factors, baseline as a covariate, and patient as a random effect. If treatment by week interaction term was not significant at the 0.10 level, it was dropped from the analysis.

[b] Outside the statistical testing hierarchy; therefore, should be interpreted as inconclusive.

Source: CSRs.[9,10]

Figure 12: CGI — Self- and Observer-Reported — Study 806

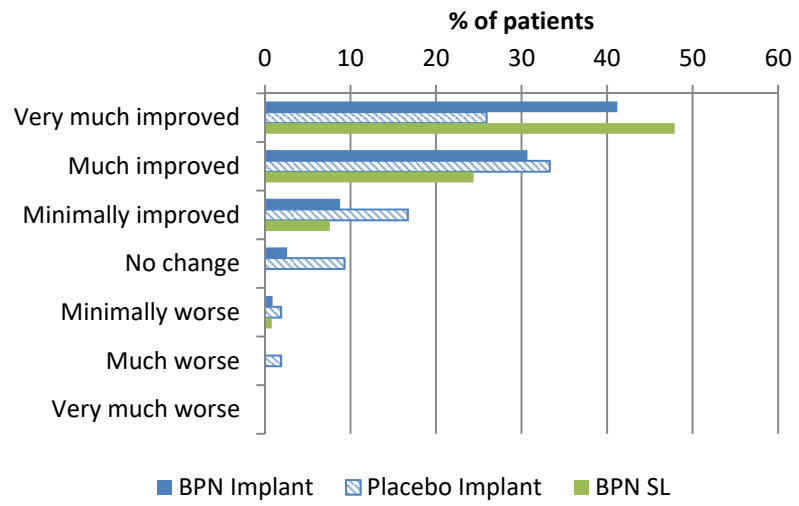
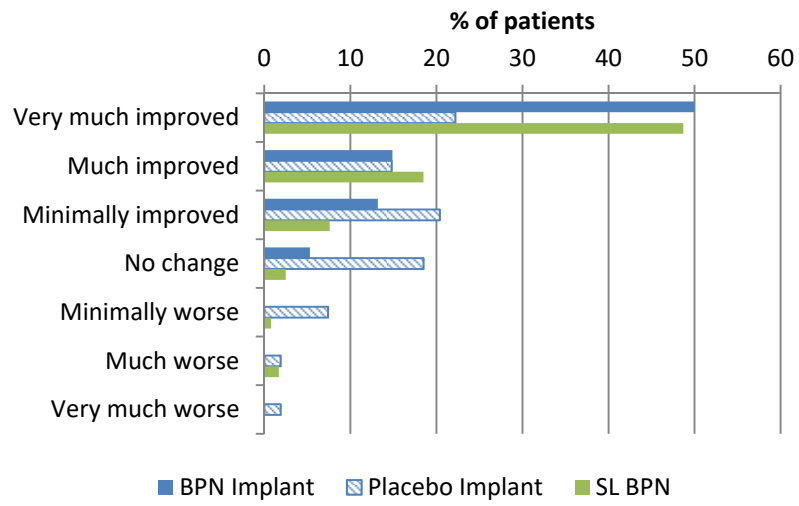


Study 806 — CGI Self-Reported, EOT	Study 806 — CGI Observer-Reported, EOT
	

BPN = buprenorphine; CDR = CADTH Common Drug Review; CGI = Clinical Global Impressions scale; CSR = Clinical Study Report; EOT = end of treatment; SL = sublingual.

Source: Generated by CDR based on data from the CSR.[10]

Figure 13: CGI Improvement — Self- and Observer-Reported — Study 806

Study 806 — CGI Self-Reported End-of-Treatment Change	Study 806 — CGI Observer-Reported End-of-Treatment Change
	
BPN implant versus SL BPN, *P* = 0.30; BPN implant versus placebo implant, *P* = 0.031[a]	BPN implant versus SL BPN, *P* = 0.99; BPN implant versus placebo implant, *P* = 0.0002[a]

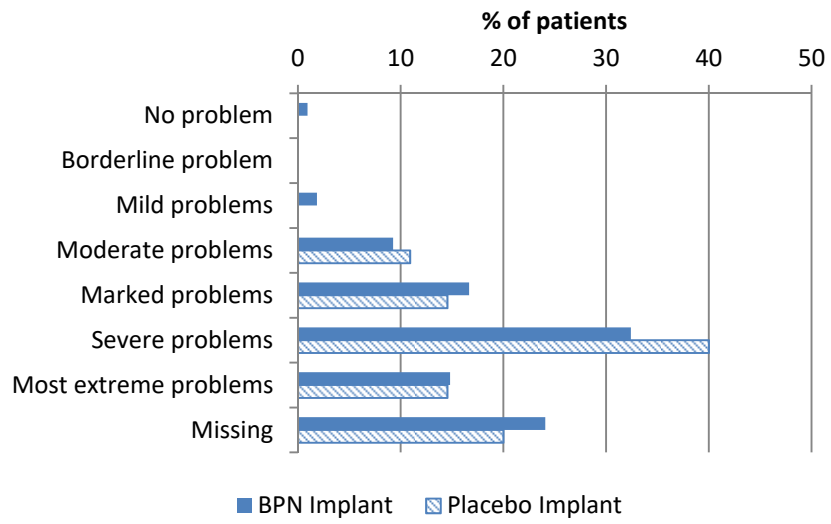
BPN = buprenorphine; CDR = CADTH Common Drug Review; CGI = Clinical Global Impressions scale; CSR = Clinical Study Report; SL = sublingual.

[a] Cochran–Mantel–Haenszel with modified ridits as category scores and stratified by gender and pooled site. Comparison between BPN implant and BPN SL group was outside the statistical testing hierarchy and thus interpreted as inconclusive.

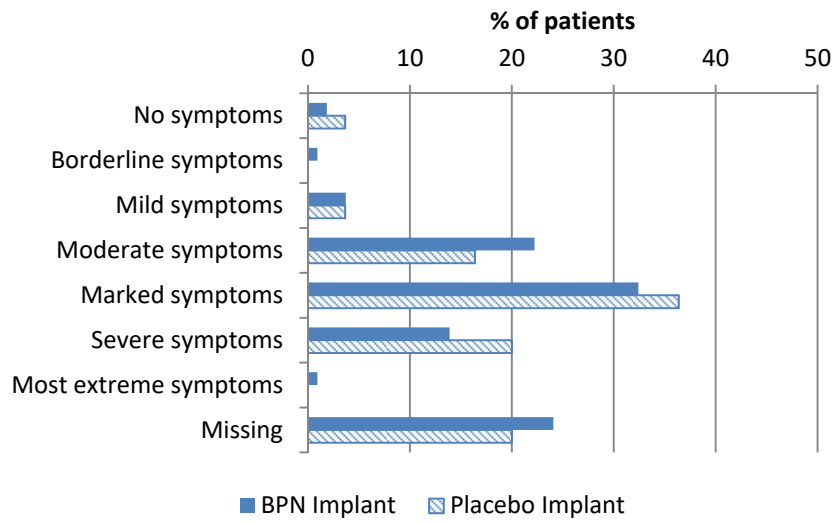
Source: Generated by CDR based on data from the CSR.[10]

Figure 14: CGI Self- and Observer-Reported — Study 805

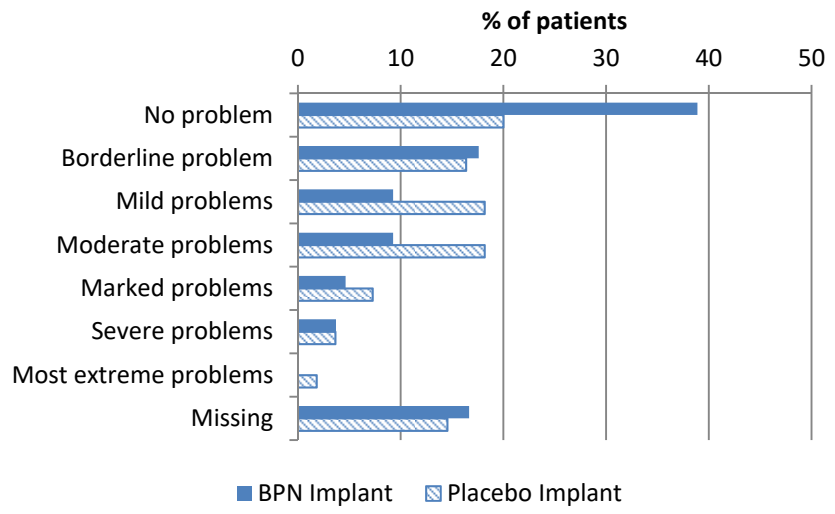
Study 805 CGI Self-Reported — Pre-Induction



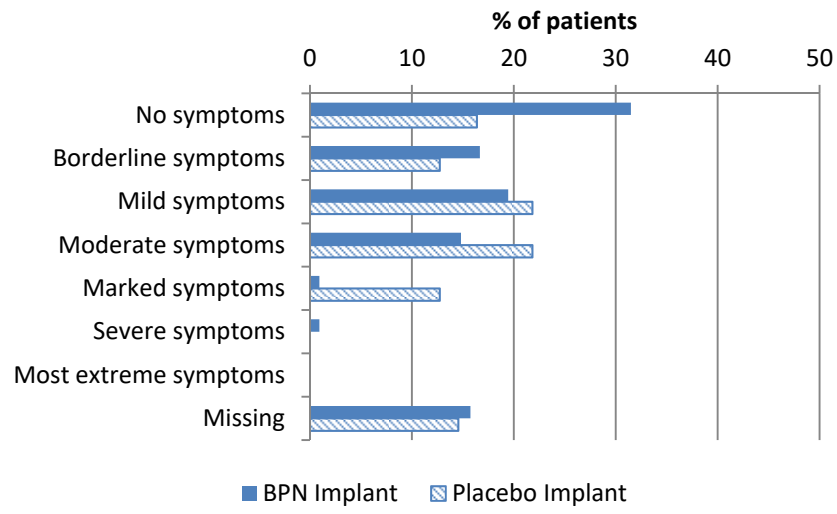
Study 805 CGI-Observer — Pre-Induction



Study 805 CGI Self-Reported — EOT



Study 805 CGI Observer-Reported — EOT

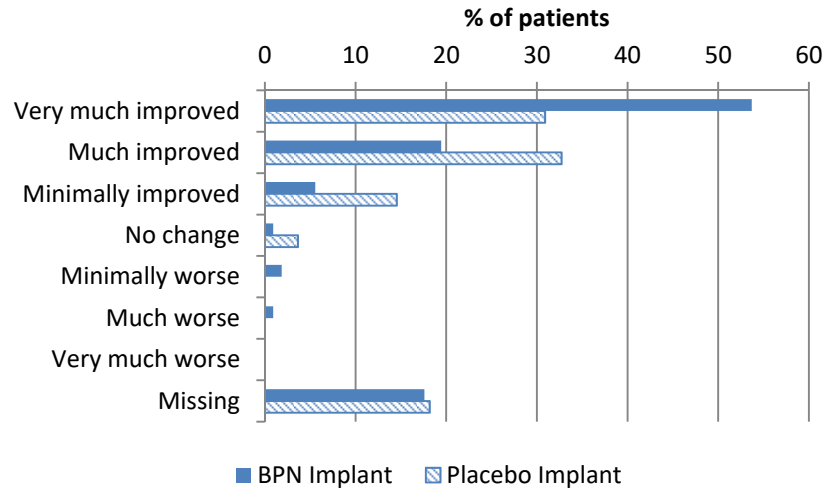


BPN = buprenorphine; CDR = CADTH Common Drug Review; CGI = Clinical Global Impressions scale; CSR = Clinical Study Report; EOT = end of treatment; ITT = intention-to-treat; SL = sublingual.

Source: Generated by CDR based on data from the CSR.[9]

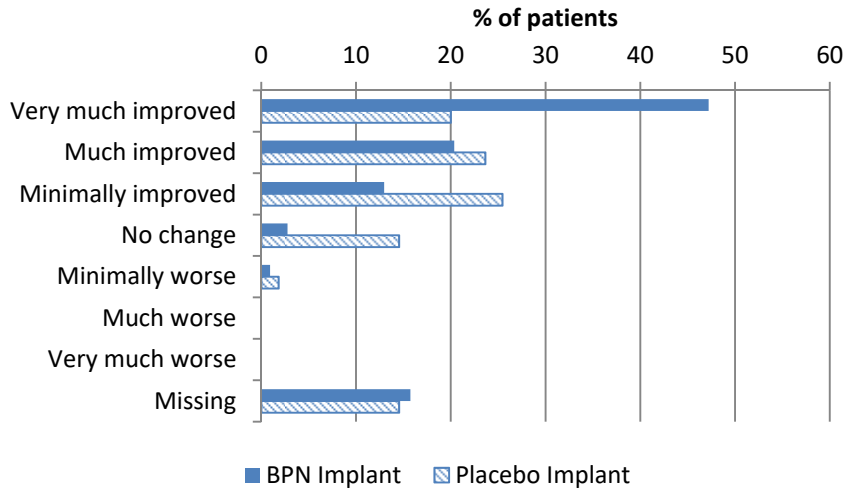
Figure 15: CGI Improvement — Self- and Observer-Reported — Study 805

Study 805 CGI Self-Reported End-of-Treatment Change



BPN implant versus placebo implant, $P = 0.0009$[a]

Study 805 — CGI Observer-Reported End-of-Treatment Change



BPN implant versus placebo implant, $P < 0.0001$[a]

BPN = buprenorphine; CDR = CADTH Common Drug Review; CGI = Clinical Global Impressions scale.

[a] Cochran–Mantel–Haenszel with modified ridits as category scores and stratified by gender and pooled site. Outside the statistical testing hierarchy and thus should be interpreted as inconclusive.

Source: Generated by CDR based on data from the CSR.[9]

Table 23: Addiction Severity Index — Study 805

Addiction Severity Index Domain	Study 808			
	Baseline		End of Treatment	
	BPN Implant	Placebo Implant	BPN Implant	Placebo Implant
ITT	**N = 108**	**N = 55**		
Composite score, mean (SE)	N = 106	N = 54	N = 94	N = 50
Medical status	0.2 (0.03)	0.1 (0.03)	0.2 (0.03)	0.1 (0.03)
Employment and support	0.2 (0.32)	0.4 (0.05)	20.8 (20.3)[a]	0.5 (0.05)
Alcohol use	0.0 (0.02)	0.0 (0.01)	0.0 (0.01)	0.0 (0.01)
Drug use	0.4 (0.05)	0.3 (0.01)	0.2 (0.06)	0.1 (0.02)
Legal status	0.1 (0.02)	0.1 (0.03)	0.1 (0.01)	0.1 (0.02)
Family/social status	0.2 (0.02)	0.2 (0.03)	0.1 (0.02)	0.1 (0.03)
Psychiatric status	0.3 (0.07)	0.2 (0.05)	0.2 (0.05)	0.3 (0.08)

BPN = buprenorphine; CSR = Clinical Study Report; ITT = intention-to-treat; SE = standard error.

[a] Abnormally high value due to discrepancy in one patient.

Source: CSR.[9]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Addiction Severity Index (ASI)
- Clinical Global Impressions scale (CGI), self-reported and observer-reported
- Clinical Opiate Withdrawal Scale (COWS)
- Subjective Opiate Withdrawal Scale (SOWS)
- visual analogue scale (VAS) for cravings.

Findings

Table 24: Summary of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
ASI	Interview-based instrument that includes both objective and subjective items that cover seven areas of concern for patients with substance abuse; including: • alcohol use • drug use • medical • psychological/psychiatric • legal • family/social • emotional/support Higher ratings indicate greater impairment	Yes	Not identified	Kosten 1983[34] McLellan 1980[35] McLellan 1992[27]
CGI	CGI-observer • The physician assesses the patient's global severity of opioid dependence over the previous week (7-point Likert-type scale) and the degree of the patient's global improvement from baseline (7-point bipolar scale) CGI-self • Used to rate the current severity of problems related to opioid dependence (7-point Likert-type scale) and the improvement in opioid-dependence symptoms from baseline (7-point bipolar scale)	No evidence of validation in patients with substance abuse	Not identified	Study 806 Clinical Study Report[10]
COWS	Clinician-administered, 11-item instrument used to assess the signs and symptoms associated with opioid withdrawal. A higher score indicates more severe withdrawal.	Yes	Not identified	Tompkins 2009[26]
SOWS	16-item self-administered instrument used to rate the intensity and presence of opiate withdrawal symptoms.	Yes	Not identified	Handelsman 1987[24]
VAS for cravings	An instrument used to quantify the state of craving a patient experienced in the previous 24 hours. The scale is 13.5 cm long and is anchored on the left by "no craving at all" and anchored on the right by "strongest craving ever."	No	Not identified	McMillan 1996[36]

ASI = Addiction Severity Index; CGI-observer = Clinical Global Impressions scale, observer-reported; CGI-self = Clinical Global Impressions scale, self-reported; COWS = Clinical Opiate Withdrawal Scale; MCID = minimal clinically important difference; SOWS = Subjective Opiate Withdrawal Scale; VAS = visual analogue scale.

Addiction Severity Index

The ASI is a multidimensional interview-based research instrument that was developed to help produce a patient problem severity profile that is used to aid in the diagnosis of addiction and help guide subsequent treatment.[35] It can be used to assess patients suffering from either alcohol or drug abuse. The ASI covers six general areas of a patient's functioning, including chemical abuse (which was later separated into alcohol use and drug use in the fifth version),[27] medical, psychological/psychiatric, legal, family/social, and emotional/support.[35] Both objective and subjective information is collected in all seven areas during a semi-structured interview and are used to produce the patient's severity profile. The collected objective data, including the intensity, number, and duration of the problematic symptoms within each of the areas, is combined with subjective patient ratings in these areas.[34] The patient's judgment of the severity of their problems in the seven areas is measured using a five-point scale (0 = not at all; 1 = slightly; 2 = moderately; 3 = considerably; 4 = extremely). Responses also include the extent to which the patient feels that treatment for their problems would be important. In order to produce the overall severity ratings, the ASI interviewer integrates both the objective and subjective data using an unanchored 10-point scale in order to achieve the estimates of severity for each area, with higher ratings indicating greater severity.[34,35] The general guidance with regard to these severity ratings includes the following: 0 to 1, no real problem and treatment is not indicated; 2 to 3, slight problems and treatment is probably not necessary; 4 to 5, moderate problem for which some treatment is indicated; 6 to 7, considerable problem for which treatment is necessary; 8 to 9, extreme problem for which treatment is absolutely necessary.[37] There is a two-step method for estimating the severity ratings: the interviewer selects a rating based on the objective measures and then, after interviewing the patient, adjusts this ratings based on their answers. However, it should be noted that these are only estimates of the severity and the patient's potential for benefiting from treatment; they are simply ratings used as recommendations to guide initial treatment planning and referral[27] and are not the actual outcome measures.[37] The ASI instrument focuses on how the patient was in the 30 days prior to the interview and usually takes an average of 50 to 60 minutes to administer.[27,35,37]

By 1992 (a decade after its development), the original authors of the ASI determined that updates to the ASI were required due to changes in the substances being abused, alternate routes of administration, and increased knowledge about substance abuse and its treatment. The fifth edition of the ASI (which can be used only in an adult population, not adolescent, and now includes seven areas) was updated to include the following (which was determined to be important in the assessment of a patient with substance abuse):

- route of administration was added to the alcohol and drug use problem area (formally termed chemical abuse)
- criminal charges were added to the legal problem area
- four areas were addressed in the family/social area including family history of alcohol/drug psychiatric problems, abusive relationships, safety and support of living situations, and antisocial personality disorder.[27]

Composite scores were developed by combining the items in each of the individual seven areas that are able to show change, with the new items not being included in the composite score calculation.[27] The composite scores are factor scores that vary from 0 to 1, with indications of greater severity shown by higher scores.[27]

The ASI has been validated and found reliable in many different contexts and for use in many different languages.[27] Preliminary validity for each of the problem severity scales was assessed by calculating correlations between the scale scores and other independent scales that were expected to be related (e.g., such as the Beck Depression Inventory [BDI] when comparing it with the psychological area composite scale score). Correlation coefficients ranged between midrange (0.43) and higher (top of range: 0.72), indicating construct validity.[35] Concurrent validity of the ASI with other measures used to assess the same problem areas was later examined in a cohort of 204 patients suffering from addictions. A correlation coefficient of 0.51 was observed between the psychological scale of the ASI and the Beck Depression Inventory, while a correlation coefficient of 0.46 was observed between the social functioning scale of the ASI and the Social Adjustment Scale self-report.[34] In addition, both the ASI and BDI were able to differentiate between depressed and non-depressed patients with addiction (with a cut-off of > 3 for the ASI and a cut-off of > 8 for the BDI, which were suggested previously).[34]

Inter-rater reliability (reliability coefficients obtained using the Spearman–Brown formula) was assessed in male (n = 16) veteran substance abuse patients who were interviewed by four separate baccalaureate-level researchers. Strong, but statistically non-significant correlations were observed (average range between 0.885 to 0.915), even when examining the patients at different time points (months in between assessments) and in different subgroups (e.g., alcohol versus drug abuse).[35] In another study by Hodgins et al. that examined patients with substance abuse disorder and comorbid psychiatric problems (primarily major affective disorder, anxiety disorder, and schizophrenia),[38] the authors noted moderate Pearson correlations between the composite scores and interviewer severity ratings in most areas; however, this was not observed in the legal and employment areas.[38] Internal consistency of the composite scores was acceptable (intra-class correlation coefficients [ICCs] greater than 0.7,[39] with the exception of the legal area); however, the authors did note issues (in their particular population with psychiatric comorbidities) with the low intra-class correlation coefficient for the family/social area interviewer severity ratings. The authors advised (based on their results) that perhaps separate scales were needed for men and women, in addition to separating the social and family functioning scales, in order to obtain adequate reliability in their population.[38]

No minimal clinically important difference (MCID) for the ASI was identified in patients being treated for substance abuse.

Clinical Global Impressions Scale

The CGI (observer-reported and self-reported) performed in the clinical trials was used to ascertain the patient's level of severity of opioid-related problems and dependence, and the global improvement in symptoms of opioid dependence from baseline.[10] Patients rated the severity of their current opioid-related problems on a seven-point Likert scale for the CGI self-reported outcome, based on the following response options: no problem, borderline problems, mild problems, moderate problems, marked problems, severe problems, and most extreme problems possible.[10]

Investigators rated each patient's global severity of opioid dependence on a seven-point Likert scale (CGI observer-reported) over the past week (normal, no symptoms, borderline symptoms, mild symptoms, moderate symptoms, marked symptoms, severe symptoms, most severe symptoms).[9,10] Patients and investigators also rated the degree of improvement since baseline on a seven-point bipolar scale ranging from 1 (very much improved) to 7 (very much worse).[9,10] As the CGI is quick to administer, it is suited to

clinical settings; however, no information regarding its reliability or validity for patients with any indication was identified in the literature search, particularly in the patient population suffering from opioid dependence. No evidence of an MCID for the CGI was identified in patients with any indication, including in patients being treated for substance abuse.

Clinical Opiate Withdrawal Scale

The COWS is an instrument used by the clinician to assess the signs and symptoms associated with opioid withdrawal in the patient presenting with substance abuse disorder.[25] It can be administered in an office, clinic, or hospital setting, and is quick to administer (generally within a few minutes).[25,26] It was originally published in a buprenorphine treatment training manual.[25,26] The COWS can also be used to track opioid withdrawal and differentiate it from opioid toxicity through serial measurements.[26] It is comprised of and rates 11 common signs and symptoms of opioid withdrawal, including resting pulse rate (beats/minutes), sweating (during the past 30 minutes and not accounted for by room temperature or activity), restlessness (during assessment), pupil size (during assessment), aching bones or joints (only additional component attributed to withdrawal is scored), runny nose or tearing (not accounted for by cold or allergies), gastrointestinal upset (during the past 30 minutes), tremor (observing outstretched hands), yawning (during assessment), anxiety or irritability (during assessment), and gooseflesh skin (during assessment).[25] Each symptom is scored on a scale ranging from 0 to 4 or 0 to 5, with higher scores indicating more severe symptoms. The total score is created by summing the scores on the 11 items, and ranges from 0 to 47. Overall scores can be interpreted as follows: 5 to 12 = mild; 13 to 24 = moderate; 25 to 36 = moderately severe; more than 36 = severe withdrawal, although these groupings have not been validated.[25,26] The overall score may be used to assess the physical level of opioid dependence.[25]

Tompkins et al.[26] obtained measurements with the COWS, the previously validated Clinical Institute Narcotic Assessment (CINA) scale, and VAS self-report items (e.g., bad drug effect, feeling sick) in order to examine the validity and reliability of the COWS in a sample of 46 out-of-treatment people who were opioid-dependent and had been randomized to complete naloxone and placebo challenges. In the naloxone challenge, COWS and CINA scores were similar in terms of magnitude and the time course when they occurred). A positive correlation between the peak COWS and CINA was evident ($r = 0.66$; $P < 0.0001$) in addition to a strong positive correlation between the peak scores ($r = 0.85$; $P < 0.001$) in the naloxone challenges. The aforementioned provides evidence of concurrent validity between the two instruments.[26]

When analyzing the internal consistency of the COWS, an overall Cronbach's alpha of 0.78 indicated good reliability.[26] In addition, content validity was evident, as there was only a small amount of inter-item correlation observed between most of the individual COWS items. The only significant correlation that was observed was between the anxiety/irritability and restlessness items (0.67), and yawning and runny nose/tearing items (0.54).[26] The COWS differentiates between mild opiate withdrawal and its absence.[26] The COWS has also been validated and found reliable when translated into other languages.[40]

No evidence of an MCID for the COWS was identified in patients being treated for substance abuse.

Subjective Opiate Withdrawal Scale

The SOWS is a patient-completed instrument that is used to rate the intensity and presence of opiate withdrawal symptoms.[24] It comprises 16 items that reflect common symptoms associated with opiate withdrawal, namely, psychic, musculoskeletal, gastrointestinal, motor, and autonomic issues. Each symptom is rated on a scale of 0 to 4, with 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, and 4 = extremely. The total SOWS score is the sum of the individual item scores and ranges from 0 to 64, with a higher score indicating greater withdrawal severity.[24]

In order to assess the SOWS validity and reliability, Handelsman et al.[24] examined male patients in or entering treatment for substance abuse who were abusing only opioids or opioids and another substance. In addition to the SOWS, the investigators also administered the previously validated Addiction Research Centre Inventory Weak Opiate Withdrawal Scale (ARCI-WOWS) to the same cohort. Validity was assessed by administering the two instruments before-and-after pharmacological interventions (methadone and naloxone) that were likely to significantly alter the opiate withdrawal level. Statistically significant decreases in the before-and-after total SOWS and the ARCI-WOWS scores were observed; however, those patients with concomitant opioid and another substance abuse had more variability in their SOWS scores.[24] SOWS scores significantly increased after receiving a naloxone challenge; however, this change was not significant in the ARCI-WOWS.

In order to examine the test–retest reliability of the SOWS, Handelsman et al.[24] administered the SOWS and the ARCI-WOWS on two occasions (one week separating the administration of the tests) in patients that were expected to maintain stable levels of opiate withdrawal symptoms. The ICCs were moderate for the SOWS (ICC = 0.60) and strong for the ACRI-WOWS (ICC = 0.85); however, the ARCI-WOW displayed a higher degree of test–retest reliability over one week.[24] All of the aforementioned results indicate that the SOWS (and the ARCI-WOW) is sensitive to changes in opiate withdrawal symptom severity that occur spontaneously and in response to naloxone.[24]

No evidence of an MCID for the SOWS was identified in patients being treated for substance abuse.

VAS for Cravings

In the only study identified that had used the VAS for cravings, McMillan and Gilmore-Thomas[36] examined cravings in 16 patients who suffered from hydromorphone addiction and were being treated at a methadone maintenance clinic. The VAS was used to measure cravings in the previous 24 hours for five days a week for four weeks, with patients indicating the time of day of their peak craving level. Variation both within and between patients on methadone was observed in terms of the 24-hour recall of peak cravings. In addition, the craving recall measure was not correlated to methadone-dosing change requests or time since dosing.[41] The test–retest reliability for the patients' mean weekly VAS for cravings score was 0.53 for week 1 versus week 4 and 0.87 for week 3 versus week 4. Thus, between week 3 and week 4, the test–retest reliability would be considered adequate based on a threshold of 0.70,[39] but would not be considered adequate over the longer interval from week 1 to week 4. However, due to the aforementioned variability, the authors suggested that the VAS not be used alone when assessing cravings in the patient with substance abuse who is undergoing methadone maintenance treatment.[41]

No evidence of an MCID for the VAS for cravings was identified in patients being treated for substance abuse.

Conclusion

The ASI is a valid and reliable multidimensional interview-based instrument (that produces a patient problem severity profile used to aid in the diagnosis of addiction and help guide subsequent treatment) for use in patients suffering from substance abuse. It shows concurrent validity with the BDI, a previously validated instrument in this patient population. No MCID has been identified with regard to the ASI for patients suffering from substance abuse.

The COWS is a clinician-assessment instrument used to assess the signs and symptoms associated with opioid withdrawal in the patient presenting with substance abuse. It is a valid and reliable instrument that can differentiate between patients suffering from mild opiate withdrawal and those without withdrawal. It has also been concurrently validated with the CINA scale, a previously validated scale in this patient population. No MCID was identified for the COWS in patients suffering from substance abuse.

The SOWS is a valid and reliable patient-completed instrument that is used to rate the intensity and presence of opiate withdrawal symptoms. The SOWS is sensitive to changes in opiate withdrawal symptom severity that occur spontaneously and in response to naloxone. No MCID has been identified for the SOWS in patients suffering from substance abuse.

Neither the CGI (used to assess the overall severity and response to treatment of mental disorders) nor the VAS for cravings have been validated or found to be reliable in patients with substance abuse, and an MCID has not been identified for either instrument. It has been suggested the VAS for cravings not be used alone to ascertain the peak levels of cravings; rather, it should be used alongside another validated instrument.

Appendix 6: Summary of Other Studies

Objective

To summarize the safety and efficacy results from two open-label extensions trials. The following summary is based on the published data.[33]

Trial Description

Patients who had completed 24 weeks of the original two phase III randomized placebo-controlled trials (studies 805 and 806 discussed in the main report) were eligible to enter one of two six-month open-label extension studies. Patients in the extension studies were treated with four 80 mg subdermal buprenorphine implants; patients were treated with a fifth implant or supplemental sublingual buprenorphine if they met the opioid craving criteria. Safety was evaluated in terms of adverse events and serious adverse events. Certain efficacy outcomes were also assessed (completion rate, supplemental buprenorphine and additional implants, plasma buprenorphine concentrations, Subjective Opiate Withdrawal Scale [SOWS] / Clinical Opiate Withdrawal Scale [COWS] results, cravings, self-report of illicit drug use, and patient satisfaction).

Results

Patient Disposition

Of the 62 enrolled (57% of the Study 805 population) in the open-label Study 1 extension, 46 patients (74%) completed the study. Early withdrawal from the six-month extension was primarily due to patient request (n = 5) or non-compliance (n = 5), with 16 patients in total discontinuing. Of the 85 patients (75% of the Study 806 population who were in the Probuphine arm) enrolled in the open-label Study 2 extension, 67 patients (79%) completed the study. Early withdrawal was primarily due to patient request (n = 7) and loss to follow-up (n = 5), with 18 patients in total discontinuing. Details of the patient disposition are presented in Table 25.

The mean age of the patients enrolled was 38.6 years and 37.5 years, 71% and 66% were male and 77% and 85% where white in Study 1 and Study 2, respectively. Fifty patients in Study 1 (81%) and 57 in Study 2 (67%) had previously received buprenorphine implants in Study 805 or 806.

Table 25: Patient Disposition in the Six-Month Open-Label Extension Trials

	Open-Label Extension Studies	
	Study 1[a]	**Study 2[a]**
Patients enrolled in extension studies	62	85
Previous treatment, n (%)		
BPN implant	50 (80.6)	57 (67.1)
Placebo implant	12 (19.4)	8 (9.4)
SL BPN	–	20 (23.5)
Patients completing studies, n (%)	46 (74.2)	67 (78.8)
Patients withdrawing, n (%)	16 (25.8)	18 (21.2)
Adverse events	2 (3.2)	2 (2.4)

	Open-Label Extension Studies	
	Study 1[a]	Study 2[a]
Patient request	5 (8.1)	7 (8.2)
Non-compliance	5 (8.1)	–
Lost to follow-up	4 (6.5)	5 (5.9)
Treatment failure	–	1 (1.2)
Pregnancy	–	1 (1.2)
Incarceration	–	1 (1.2)

BPN = buprenorphine; SL = sublingual.

[a] Patients who had completed 24 weeks of treatment were eligible for the open-label studies.

Source: Dammerman et al.[33]

Safety Results

Of the 62 patients who were enrolled in Study 2, 75.8% (n = 147) experienced adverse events. The most common adverse events were headache, insomnia, and constipation at 25.8% (n = 16), 16.1% (n = 10), and 14.5% (n = 9), respectively. Of the 85 patients who were enrolled in Study 2, 67.1% (n = 57) experienced adverse events. The most common adverse events were headache, subcutaneous abscess, and upper respiratory tract infection at 11.8% (n = 10), 11.8% (n = 10), and 8.2 % (n = 7), respectively (Table 26).

In terms of notable harms, 28 (45.2%) and 12 (14.1%) patients in Study 1 and 2, respectively, experienced implant-site adverse events. Of note, new procedures for the implantation and removal of the devices were implemented after Study 1, which may explain some of the differences in the frequency of implant-site adverse events between the two studies. In Study 1, a total of 103 implant site–associated adverse events occurred and were reported to be mild or moderate in intensity. Four patients in Study 1 experienced adverse events associated with either the insertion or removal of the implant. In Study 2, a total of19 implant site–associated adverse events occurred and were reported as mild to moderate in intensity, with the exception of the implant-site reaction that was experienced by a patient who had previously received placebo in the original phase III study (Table 26). The most frequently reported implant-site adverse events were erythema, pain, and pruritus (n = 16 to 20) in Study 1, and hemorrhage, rash, and hematoma (n = 2 or 3) in Study 2. There was no evidence in either study that patients removed or attempted to remove the implants; however, two patients reported implant expulsion in Study 1.

Three patients (4.8%) In Study 1 experienced at least one serious adverse event, with one patient experiencing five separate serious adverse events. Two patients (3.2%) withdrew from the trial due to implant-site adverse events. Six patients (7.1%) in Study 2 experienced serious adverse events, with four of the serious adverse events occurring in patients who had previously received buprenorphine implants in the randomized controlled portion of the phase III trial. Two patients in Study 2 withdrew due to adverse events. No deaths were reported in the patients included in Study 1 and 2 (Table 26).

Table 26: Harms in the Six-Month Open-Label Extension Trials

	Open-Label Extension Studies	
	Study 1 N = 62	**Study 2 N = 85**
AEs, n (%)		
Patients with ≥ 1 AE	47(75.8)	57 (67.1)
AEs occurring in ≥ 2% of patients		
Back pain	6 (9.7)	5 (5.9)
Constipation	9 (14.5)	2 (2.4)
Depression	–	4 (4.7)
Excoriation	3 (4.8)	–
Fatigue	3 (4.8)	4 (4.7)
Headache	16 (25.8)	10 (11.8)
Increased ALT	3 (4.8)	–
Increased GLT	3 (4.8)	–
Implant-site bruising/hematoma	3 (4.8)	2 (2.4)
Implant-site erythema	4 (6.5)	–
Implant-site pain	4 (6.5)	–
Implant-site pruritus	3 (4.8)	–
Insomnia	10 (16.1)	2 (2.4)
Pharyngolaryngeal pain	3 (4.8)	–
Rash	4 (6.5)	–
Stomach discomfort	4 (6.5)	–
Subcutaneous abscess	–	10 (11.8)
Toothache	4 (6.5)	–
Upper respiratory tract infection	3 (4.8)	7 (8.2)
Urinary tract infection	–	5 (5.9)
WDAEs, n (%)	2 (3.2)	2 (2.4)
SAEs, n (%)	3 (4.8)	6 (7.1)
Deaths	0	0
Notable harms, n (%)		
Implant site–associated AEs	28 (45.2)	12 (14.1)

AE = adverse event; ALT = alanine aminotransferase; GLT = gamma-glutamyl transferase; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: Dammerman et al.[33]

Efficacy Results

A fifth buprenorphine implant was received by 6 (9.7%) and 9 (10.6%) of the patients in Study 1 and 2, respectively, while 41% (n = 26) and 21.2% (n = 17) also received supplemental sublingual buprenorphine (Table 27).

The mean COWS and SOWS scores were similar or decreased from the start of the open-label extension to the end of treatment (week 48) in patients in Study 1 and 2 (Table 27).

The mean VAS of cravings scores decreased from the start of the open-label extension to the end of treatment (week 48) for patients in Study 1; however, these scores increased during the same time period for patients in Study 2 (Table 3). The proportion of patients who reported illicit drug use (opioids and other substances) was 42% and 55% at baseline and at the end of treatment in Study 1, and 34% and 39% in Study 2 (Table 27).

Table 27: Efficacy Results From the Six-Month Open-Label Extension Trials

	Open-Label Extension Studies	
	Study 1 N = 62	**Study 2 N = 85**
Additional Implants (fifth), n (%)	6 (9.7)	9 (10.6)
Supplemental SL BPN	26 (41.9)	17 (21.2)
Days, mean (SE)	10.5 (1.98)	9.6 (1.96)
Total dose (mg) per patient, mean (SE)	146 (31.0)	74.7 (20.7)
COWS, mean (SE)		
Baseline (week 24)	2.8 (0.49)	3.4 (0.86)
End of study (week 48)	1.9 (0.31)	3.7 (0.68)
SOWS, mean (SE)		
Baseline (week 24)	5.0 (1.00)	1.7 (0.23)
End of study (week 48)	2.6 (0.55)	1.6 (0.24)
VAS of cravings (mm), mean (SE)		
Baseline (week 24)	12.3 (2.75)	4.3 (1.18)
End of study (week 48)	7.5 (1.45)	6.8 (1.54)
Self-report of illicit drug use,[a] %		
Overall incidence at baseline	41.9	34.1
Overall incidence at week 48	54.8	38.8

BPN = buprenorphine; COWS = Clinical Opioid Withdrawal Scale; SE = standard error; SL = sublingual; SOWS = Subjective Opioid Withdrawal Scale; VAS = visual analogue scale.

[a] Self-reported illicit drug use included all substances and was not limited to opioids.

Source: Dammerman et al.[33]

Critical Appraisal

The main limitations of both extension periods were the open-label nature of the study (which can potentially bias the reporting of subjective outcome measures such as the SOWS, COWS, or VAS scores), the lack of a control group, and limited sample size (62 and 85 patients) of what is likely a highly selective population. More than 20% of patients discontinued the studies early. No data on illicit opioid use during the trials were reported. These limitations preclude the ability to draw meaningful conclusions with regard to the efficacy of the buprenorphine implants. However, the main purpose of the extension study was to assess treatment safety. There were no new safety signals identified in the extension trials.

Summary

Two open-label extension studies reported data from a total 147 patients who received four buprenorphine implants and were followed for 24 weeks. Ten per cent of patients in each study required a dose increase to five implants, and 42% and 21% in Study 1 and 2, respectively, required supplemental sublingual buprenorphine. At the end of the studies, 55% and 39% reported illicit drug use, of which marijuana and heroin were the most commonly used drugs. No new safety signals were apparent, with 76% and 67% of patients in Study 1 and 2, respectively, experiencing at least one adverse event (the most common of which were headache, constipation, insomnia, and subcutaneous abscess), and 5% and 7% of patients in Study 1 and Study 2 experiencing a serious adverse event. However, due to the limitations of the two extension periods, no definitive conclusions can be made regarding long-term treatment with buprenorphine implants.

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