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CADTH COMMON DRUG REVIEW

Clinical Review Report

Buprenorphine extended-release injection (Sublocade)

(Indivior Canada, Ltd.)

Indication: For the management of moderate-to-severe opioid use disorder in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product.

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Table of Contents

Tables

Figures

Abbreviations

AE	adverse event
AIC	Akaike information criterion
ALT	alanine transaminase
ARCI-WOWS	Addiction Research Centre Inventory – Weak Opiate Withdrawal Scale
AST	aspartate aminotransferase
BDI-II	Beck's Depression Inventory-II
BUP-ER	buprenorphine extended-release
BUP-IMP	buprenorphine implants
BUP-V	sublingual buprenorphine
CDF	cumulative distribution function
CDR	CADTH Common Drug Review
CGI	Clinical Global Impression
CGI-EI	Clinical Global Impression for Efficiency Index
CGI-I	Clinical Global Impression for Improvement
CGI-S	Clinical Global Impression for Severity
CI	confidence interval
CINA	Clinical Institute Narcotic Assessment
CNS	central nervous system
COWS	clinical opiate withdrawal scale
CrI	credible interval
DIC	deviance information criterion
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
HR	hazard ratio
ICC	intra-class correlation coefficients
IDC	individual drug counselling
ITC	indirect treatment comparison
K6	Kessler-6
LFT	liver function tests
MAT	medication-assisted treatment
MCID	minimal clinically important difference
MET-V	variable-dose methadone
mITT	modified intention-to-treat
MMRM	mixed model for repeated measure
NMA	network meta-analysis
NMP	N-methyl-2-pyrrolidone
OR	odds ratio
OUD	opioid use disorder
RCT	randomized controlled trial
SD	standard deviation
SE	standard error
SF-12	Short Form 12
SOWS	subjective opiate withdrawal scale
TLFB	timeline follow-back
UDS	urine drug screen
VAS	Visual Analog Scale

Drug	Buprenorphine extended-release injection (Sublocade)
Indication	For the management of moderate-to-severe opioid use disorder in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product. Sublocade should be used as part of a complete treatment plan that includes counselling and psychosocial support. Sublocade must only be administered subcutaneously in the abdominal region by a health care provider.
Reimbursement Request	As per indication. Sublocade should be used as part of a complete treatment plan that includes counselling and psychosocial support. Sublocade must only be administered subcutaneously in the abdominal region by a health care provider.
Dosage Form(s)	Solution for subcutaneous Injection, 100 mg/0.5 mL and 300 mg/1.5 mL
NOC Date	November 21, 2018
Manufacturer	Indivior Canada Inc.

Executive Summary

Introduction

Opioid use disorder (OUD) is a chronic relapsing illness associated with an 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 stakeholders across the country to respond to calls for action. In the first half of 2018, more than 2,000 Canadians lost their lives, meaning more than 9,000 lives have been lost in Canada between January 2016 and June 2018 to apparent opioid-related overdose.[2] Recent findings from the Public Health Agency in Canada suggest that life expectancy in Canada has slowed its progress, partly due to the dramatic rise in substance-related deaths (including opioid-related deaths).[2,3] Although the prevalence of OUD in Canada is not known, it is estimated to affect approximately 2.1% of the US population.[4]

The product under review is a non-aqueous solution dissolved in a polymeric (non-gelatin containing) delivery system (Atrigel) in a pre-filled syringe containing 100 mg (0.5 mL) or 300 mg (1.5 mL) of buprenorphine hydrochloride, a partial mu-opioid receptor agonist.[5] This product is administered through abdominal subcutaneous injections and forms a solid mass upon contact with bodily fluids to facilitate an extended release. The approved indication of buprenorphine extended-release injection (BUP-ER) is for the management of moderate-to-severe OUD in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product in combination with counselling and psychosocial support.[5] The recommended starting dose is 300 mg monthly for two months followed by a maintenance dose of 100 mg monthly. The maintenance dose can be increased to 300 mg monthly in the case of unsatisfactory clinical response and demonstrated ability to tolerate the 100 mg dose. Administration should be performed by a health care provider.[5] There is no suggested treatment duration provided for this product.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of BUP-ER 100 mg and 300 mg for the management of moderate-to-severe OUD in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product.

Results and Interpretation

Included Studies

One randomized controlled trial met the inclusion criteria for the review. In addition, an extension study of the included trial, one network meta-analysis (NMA) and one long-term observational study were covered in this review (see Appendices).

Study 13-0001 (N = 504),[6] was a double-blind, multi-centre, 24-week, placebo-controlled randomized controlled trial designed to investigate the efficacy and safety of BUP-ER in adult patients with moderate-to-severe OUD currently or in the past three months who were seeking medication-assisted therapy. Patients entered an open-label induction phase and received buprenorphine/ naloxone sublingual film for three days, followed by a dose-adjustment period of four to 11 days to achieve a daily dose between 8 mg and 24 mg buprenorphine. Patients were then randomized 4:4:1:1 to receive either BUP-ER 300 mg subcutaneously every four weeks for six doses (300 mg/300 mg), BUP-ER 300 mg subcutaneously every four weeks for two doses followed by BUP-ER 100 mg subcutaneously every four weeks for four doses (300 mg/100 mg), placebo volume-matched to the 300 mg/300 mg regimen, or placebo volume-matched to the 300 mg/100 mg regimen. Randomized patients in this study received once weekly individualized behavioural counselling as well as individualized drug counselling to accompany pharmacotherapy. The primary efficacy outcome was percentage abstinence, defined as the cumulative distribution function of the percentage urine samples negative for opioids combined with negative self-reports for illicit opioids from week 5 to week 24 of double-blind treatment.

There were a number of limitations noted for this trial. First, that there was a significant difference in the proportion of patients who completed the week 24 visit (either urine drug sample or self-reported use) between BUP-ER treatment groups (61.3% in the 300 mg/100 mg group and 64.3% in the 300 mg/300 mg group) and placebo (33.3%) ($P < 0.0001$). Missing urine drug samples and/or self-reports of illicit opioid use (including missing data from patients who dropped out of the study) were imputed as positive. Sensitivity analyses conducted by FDA investigators were supportive of the superiority claim of BUP-ER treatment regimens compared with placebo in regards to the primary outcome of the trial.[7] Second, outcomes of interest for this review related to withdrawal symptoms were subjective in nature, and therefore potentially impacted by recall bias and truthfulness of responses. Furthermore, these outcomes were not appropriately adjusted for multiplicity and therefore should be interpreted with consideration of the risk of Type I errors. Last, any patients with concurrent substance use disorders, and/or moderate or severe cocaine, alcohol, or cannabis use disorders and uncontrolled psychiatric comorbidities were to be excluded from this trial, potentially limiting the generalizability of trial results.

Efficacy

Pivotal Trial (Study 13-0001)

The primary outcome in Study 13-0001 was the percentage abstinence, for which both 300 mg/100 mg and 300 mg/300 mg treatment regimen arms of BUP-ER were found to be superior to placebo from week 5 to week 24, with a mean percentage abstinence of 42.7% and 41.3% in the 300 mg/100 mg and 300 mg/300 mg arms, respectively, compared with 5.0% in the placebo arm ($P < 0.0001$ for each regimen compared with placebo). In each of the BUP treatment groups, 12% to 13% of patients had no positive or missing urine drug samples or self-reports of illicit opioid use over this period of time, compared with 1% in the placebo group. Treatment success (defined as any patient with 80% or more of urine samples negative for opioids combined with negative self-reports) was statistically significantly higher in the 300 mg/100 mg (28%) and 300 mg/300 mg (29%) arms, compared with 2% in placebo ($P < 0.0001$). Also, the percentage of patients abstinent at any week from week 5 to week 24 was numerically higher in both the 300 mg/100 mg and 300 mg/300 mg groups compared with the placebo group in the full analysis set, ranging from 35.1% to 48.5% in the 300 mg/300 mg group and 38.5% to 45.4% in the 300 mg/100 mg group versus 2.0% to 11.1% in the placebo group.

In Study 13-0001, the mean Clinical Opioid Withdrawal Scale (COWS) and Subjective Opioid Withdrawal Scale (SOWS) were numerically low at baseline and at week 24 in all treatment groups (mean COWS 1.9 or lower; SOWS 4.9 or lower). Regarding the desire- or need-to-use Visual Analog Scale (VAS) scores, mean scores in the placebo group were slightly higher at baseline (9.5) compared with active treatment groups (5.5 in the 300 mg/100 mg group and 7.1 in the 300 mg/100 mg group). There was an increase in the placebo group noted at week 2 (26.9), and values remained high until week 24, indicating a higher desire to use. Final mean scores in the placebo group for the desire- or need-to-use VAS scores at week 24 (17.1) were significantly higher than in the active treatment groups (6.8 in the 300 mg/100 mg group and 3.2 in the 300 mg/300 mg group). Analyses for these outcomes were not adjusted for multiplicity, and therefore should be interpreted with consideration of the risk of Type I errors.

Other Studies

The extension study, Study 13-0003 (N = 669), was an open-label study designed to evaluate the safety and tolerability of BUP-ER over 48 weeks, and included a combination of patients who had completed Study 13-0001 with six doses of BUP-ER treatment or placebo, as well as newly enrolled patients.[8] Roll-over patients received six additional doses of BUP-ER and de novo patients received 12 doses of BUP-ER. Using the same efficacy end point as in the pivotal trial, mean percentage abstinence after 48 weeks of BUP-ER treatment was found to be 46% in newly initiated patients (de novo patients) compared with 57% of roll-over patients from Study 13-0001. No formal statistical tests were outlined a priori for this analysis; therefore, interpretations of the results are limited. About 8% of de novo patients achieved 100% abstinence compared with 18% of roll-over patients. Mean COWS, SOWS, and desire- or need-to-use VAS scores were also recorded throughout this study; however, according to the statistical analysis plan, results were not compared between groups. Mean COWS and SOWS scores were generally low at baseline and remained low in both groups until week 48. Mean opioid craving VAS scores were generally low in both groups at baseline (5.9 in de novo patients and 4.4 in roll-over patients); however, mean opioid craving VAS scores at week 48 were numerically different

(4.2 in roll-over patients compared with 8.3 in de novo patients). Limitations of this trial include the inability to draw comparisons from the data due to its study design, and the assumption that missing data in patient withdrawal symptoms scores (i.e., COWS, SOWS, and VAS scores) were missing at random, as it is possible that patients who completed the trial and those who did not were from different populations. Also, BUP-ER doses administered subsequent to the initial BUP-ER 300 mg dose were able to be adjusted either down to 100 mg or maintained at 300 mg based on the medical judgment of the investigator. No comparisons were made to establish differences in tolerability or efficacy between patients maintained on 300 mg per month and 100 mg per month in this trial. Finally, due to the open-label nature of this study, all efficacy results COWS, SOWS, and opioid craving VAS scores are subject to bias.

The NMA was submitted by the manufacturer and summarized indirect evidence comparing BUP-ER with other drugs currently used to treat OUD in their effect on treatment retention and opioid test positivity.[9] Interventions included BUP-ER 300 mg/100 mg, BUP-ER 300 mg/300 mg, methadone (variable dose), sublingual buprenorphine (variable dose), buprenorphine implants, and a different buprenorphine depot injection (CAM2038) for the outcomes of opioid test positivity and treatment retention. BUP-ER 300 mg/100 mg was associated with a significantly decreased likelihood of opioid test positivity compared with placebo (odds ratio [OR], 0.12; 95% credible interval [CrI], 0.06 to 0.24), sublingual buprenorphine (OR, 0.34; 95% CrI, 0.12 to 0.90), and buprenorphine implants (OR, 0.32; 95% CrI, 0.12 to 0.78). Similar results were observed in the BUP-ER 300 mg/300 mg arm. Neither BUP-ER dosage arm was significantly different than sublingual buprenorphine, buprenorphine implants, and CAM2038 with respect to study dropout. Using the same model, treatment with methadone was associated with a significantly lower rate of study dropout than both the BUP-ER 300 mg/100 mg and BUP-ER 300 mg/300 mg arms. Key limitations include the lack of transparency in systematic review methods, limited heterogeneity analyses performed, and the inclusion of studies with sparse baseline data, further limiting the generalizability of this study's findings.

The observational study, RECOVER (N = 826), was a longitudinal, observational study that included patients who had participated in studies 13-0001 and 13-0003 and received at least one study injection.[10] Data were collected up to 12 months before patients were treated with BUP-ER and up to 24 months after treatment initiation, to examine differences in criminal activity, opioid abstinence and withdrawal, depression and psychological stress, work attendance, and performance over time. Changes in criminal activity from the 12 months leading up to study enrolment until up to 12 months after initiation of BUP-ER treatment found a numerically lower number of total arrests; however, the proportion of patients receiving felony charges remained the same. Patients receiving placebo as well as those receiving BUP-ER treatment for 13 months or longer had a lower proportion of missed work days compared with patients receiving BUP-ER treatment for one to two months, three to eight months, and nine to 12 months. Also, patients with the longest recorded treatment duration with BUP-ER were associated with numerically lower mean scores on the K6 psychological distress scale (7.8 among patients in the one-to-two month group compared with 4.0 in the 13 to 18 month group), as well as a numerically lower proportion of patients with severe depression (Beck's depression inventory score 29 or greater). Results from this study should be interpreted with caution as these data were largely self-reported, and therefore limited by recall bias and truthfulness of responses. Results were also subject to bias in the differential length of follow-up between treatment groups, and losses to follow-up. Criminal data were obtained from public records, for which only 65% of patient records were found.

Harms

Adverse events (AEs) were reported by most patients treated with BUP-ER and frequency varied between studies, ranging from 66.7% to 76.4% in Study 13-0001 and from 57% to 73% in Study 13-0003.[6,8] Among patients who received BUP-ER in Study 13-0001, approximately 3% experienced a serious AE. The proportion of patients who stopped treatment due to AEs was generally low and was found to be 4% in both BUP-ER treatment groups. In Study 13-0003, 3.7% experienced a serious AE. One death was reported during this trial, in a patient belonging to the BUP-ER 300 mg/300 mg group. The death was considered unrelated to treatment.

No overdoses (fatal or non-fatal) were reported in either of the active treatment groups, compared with one non-fatal overdose reported in the placebo arm. No patients in the trial reported any AEs potentially related to respiratory depression. There appeared to be numerically similar proportions of patients with a shift from normal (at baseline) to low levels of testosterone between the active and placebo groups at any time during the trial.

The frequency of injection site AES was high in Study 13-0001 and Study 13-0003.[6,8] Most were reported as mild or moderate, resulting in pain, tenderness, and induration. Three patients stopped treatment citing an injection site reaction (pain, swelling, and ulcer). No patients in either of the two clinical trials required depot removal throughout the 48 week period, and there were no reports of attempted removals of the depot.

In Study 13-0001, the frequency of AEs associated with liver disorders was found to be 7.1% in the BUP-ER arms compared with 1% in the placebo arm. Three patients in the 300 mg/300 mg arm withdrew due to AEs related to liver injury. Similar results were observed in Study 13-0003, where the frequency of AEs associated with liver disorders in all patients receiving BUP-ER was 8.2%. Two patients withdrew from the trial due to liver-related events. A total of 15 patients (2.2%) had to have their BUP-ER dose reduced due to liver-related AEs or liver-related enzyme issues (i.e., increased aspartate aminotransferase or alanine aminotransferease). It is presumed that these patients were reduced from the BUP-ER 300 mg dose to the 100 mg dose.

BUP-ER contains a solvent that is a known teratogenic compound that causes developmental toxicity in animals, with a paucity of human data.[11] High exposure of this solvent has also been linked to abnormal sperm parameters in animals. As a result, both trials in this review required that women of childbearing potential provide a negative pregnancy test prior to enrolment, and that all men and women of childbearing potential agreed to contraceptive use throughout treatment.[6,8] Currently, the product monograph recommends that the use of BUP-ER in women of childbearing potential who are not using effective contraception be avoided.[5]

Potential Place in Therapy[1]

Subcutaneous monthly injections of a non-divertible formulation of 300 mg or 100 mg of buprenorphine after a minimum seven-day induction on a transmucosal buprenorphine-containing product for the management of moderate-to-severe OUD in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product is another option to address the current opioid epidemic. Most people with moderate-to-severe OUD do not access treatment due to systemic, clinical, and individual barriers. In addition, the treatment requirements paradoxically lead to disengagement from care with significant morbidity and mortality. Monthly injections might help address some of these gaps, including access for those in remote areas of the country who have difficulty with daily or weekly visits to pharmacies to be medicated.

Existing oral methadone or sublingual buprenorphine require regular observation and risk of diversion necessitating more urine testing for medication adherence. The potential benefits of buprenorphine monthly injection include an indication for induction of remission regardless of the dose of sublingual buprenorphine required, and more exposure to treatment, especially given that the risk of dropout is high in the early induction phase of buprenorphine. This is very important in the rapid access clinics where they will be able to provide an injection after one week of transmucosal buprenorphine while they arrange for a transfer to a treatment program. Given the blocking effects observed after one injection, the monthly injection will potentially provide protection to those at highest risk of death from overdose (e.g., those who are using multiple substances, including alcohol, prescribed or street-obtained opioids, and who have comorbid mental health conditions).

An injection is likely to be associated with less stigma because there is no requirement to attend a pharmacy for weekly doses, and there will be a reduced need for urine toxicological drug testing, allowing for more meaningful counselling and engagement in recovery-oriented treatment. The expectation with such a treatment is that patients will re-integrate more easily into the workforce, be able to travel, and engage in normal activities, which are key outcomes assessed in practice. In addition, it is expected that this formulation may allow care delivery to be better integrated in primary care settings, with minimal burden on the practice. Collectively, this could expand treatment and address the unmet need of patients.

There are no special tests required to identify these patients other than insurance coverage and willingness to attend monthly for injections. Caution will be needed in prescribing buprenorphine monthly injection to those 65 years and older, and in those using sedative hypnotics or other depressants (such as alcohol) to prevent mixed drug overdose. Patients younger than 18 years of age are a growing population of those with OUD and who often go without treatment.[12,13] Although buprenorphine monthly injection is currently not indicated for use in this patient group because of a lack of data,[5] it is possible that physicians would consider using the drug for these patients. Another important subpopulation of patients is pregnant women with OUD, for whom buprenorphine is a preferred treatment.[12] However, the black box warning might limit the use of this product for these patients. Physicians will have to balance these risks against the continued exposure to buprenorphine/naloxone combinations that are currently marketed in Canada.

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

Conclusions

In adults with moderate or severe OUD inducted and clinically stabilized on 8 mg to 24 mg of sublingual buprenorphine/naloxone, BUP-ER injections (at either 300 mg every four weeks for six doses, or 300 mg every four weeks for two doses, followed by 100 mg every four weeks for four doses) administered subcutaneously was superior to volume-matched placebo injections based on the cumulative distribution function of percentage abstinence, defined as a combination of percentage urine samples negative for opioids and negative self-reports for illicit opioid use at the end of 24 weeks. The proportion of patients completing treatment was significantly higher in patients treated with BUP-ER compared with placebo. Results appear to be supported by improvements in symptoms of withdrawal and desire or cravings to use opioids in patients on BUP-ER compared with placebo; however, these outcomes should be interpreted with consideration of the risk of Type I error and it is unclear whether the degree of difference is clinically relevant. Identified harms were consistent with the safety profile of buprenorphine. There was a numerically higher frequency of injection site reactions with the use of BUP-ER, most of which were mild to moderate in nature. BUP-ER is not recommended to be used in women of childbearing potential who are not using an effective and reliable method of contraception.

There is limited evidence on the longer-term benefits and harms associated with BUP-ER and the comparative effects versus non-placebo comparators. Significant limitations exist with the extension study, observational study, and NMA summarized within this review. As a result, the comparative effectiveness of BUP-ER in adults with moderate or severe OUD is uncertain.

Table 1: Key Efficacy and Safety Outcomes for Buprenorphine Extended-Release Treatment Regimens and Placebo in Patients With Opioid Use Disorder in Study 13-0001

End Point	BUP-ER 300 mg/100 mg + IDC	BUP-ER 300 mg/300 mg + IDC	Placebo + IDC (N = 99)
Efficacy			
Percentage Abstinence (CDF of Percentage Urine Drug Samples Negative for Opioids Combined With Self-Reports Negative for Illicit Opioid Use) from Week 5 Through Week 24			
Full Analysis Set[a]	**N = 194**	**N = 196**	**N = 99**
≥ 50%	86 (44.3)	82 (41.8)	4 (4.0)
≥ 60%	78 (40.2)	70 (35.7)	4 (4.0)
≥ 70%	66 (34.0)	67 (34.2)	2 (2.0)
≥ 80%	55 (28.4)	57 (29.1)	2 (2.0)
≥ 90%	41 (21.1)	48 (24.5)	2 (2.0)
100%	25 (12.9)	23 (11.7)	1 (1.0)
P value[b] (comparison with placebo + IDC)	< 0.0001	< 0.0001	–
Mean (SD)	42.7% (38.50%)	41.3% (39.66%)	5.0% (16.98%)
Median (range)	32.5% (0% to 100%)	30.0% (0% to 100%)	0.0% (0% to 100%)
Harms			
Safety Analysis Set	**N = 203**	**N = 201**	**N = 100**
Patients with > 0 AEs, N (%)	155 (76.4)	134 (66.7)	56 (56.0)
Patients with > 0 SAEs, N (%)	4 (2.0)	7 (3.5)	5 (5.0)
Number of WDAEs	7 (3.4)	10 (5.0)	2 (2.0)
Number of deaths, N (%)	0	1 (0.5)	0
Notable Harms			
Overdoses (fatal/non-fatal)	0 (0.0)	0 (0.0)	1 (1.0)
Respiratory depression	0 (0.0)	0 (0.0)	0 (0.0)
Increased hepatic transaminases[c]	9 (4.5)	15 (7.5)	3 (3.0)
Low serum testosterone[d]	41/135 (30.4)	38/137 (27.7)	22/65 (33.8)
Injection Site Reactions			
Mild	120 (59.1)	132 (65.7)	62 (62.0)
Moderate	16 (7.9)	19 (9.5)	11 (11.0)
Severe	0	4 (2.0)	0
Potentially life-threatening	0	1 (0.5)	0

AE = adverse event; BUP-ER = buprenorphine extended-release; CDF = cumulative distribution function; IDC = behavioural counselling/individual drug counselling; SAE = serious adverse events; SD = standard deviation; WDAE = withdrawals due to adverse events.

[a] Patients from Site 20 were excluded from the analysis. All missing results for opioids were considered non-negative.

[b] The Wilcoxon rank sum test was used to compare treatment groups. Each dose regimen was compared with placebo with respect to the composite primary end point at a significance level of alpha equals 0.025.

[c] Patients with hepatic transaminases (alanine aminotransferase and aspartate aminotransferases) greater than three times the upper limit of normal at any time from week 1 to week 29.

[d] Patients with shifts in testosterone from normal at baseline to worst value at any time after the first study injection to week 25.

Source: Clinical study report for Study 13-0001.[6]

Introduction

Disease Prevalence and Incidence

Opioid use disorder (OUD) is a chronic relapsing illness associated with an 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 stakeholders across the country to respond. In the first half of 2018, more than 2,000 Canadians lost their lives, meaning more than 9,000 lives have been lost in Canada between January 2016 and June 2018 to apparent opioid-related overdose.[2] Of deaths reported from January to June of 2018, 94% were the result of accidental overdose, 72% of which involved fentanyl-related substances (compared with 55% in 2016). In addition to these deaths, there has been a 27% increase in hospitalizations due to opioid-related poisonings over the past five years, disproportionately affecting smaller communities with populations between 50,000 and 100,000. Recent findings from the Public Health Agency in Canada suggest that life expectancy in Canada has slowed its progress, partly due to the dramatic rise in substance-related deaths (including opioid-related deaths).[14] Although the prevalence of OUD in Canada is not known, it is estimated to affect approximately 2.1% of the US population.[4]

Standards of Therapy

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 for the treatment of OUD.[4] Canadian guidelines recommend the use of buprenorphine/naloxone as first-line treatment of adults with OUD, 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 drug.[1] Existing evidence suggests that buprenorphine/naloxone and methadone, at moderate-to-high doses, are equally effective in terms of treatment retention and reducing illicit opioid use (use of any opioids excluding opioid maintenance therapy).[4] Other opioid treatment options include slow-release oral morphine, although this is not an approved indication in Canada. Slow-release morphine was recommended in Canadian guidelines, but only in patients in whom first- and second-line drugs are ineffective or contraindicated, 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.[1,4] The guidelines state that all patients should have information 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 allow 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 2). However, the Government of Canada

recently announced that these restrictions will be lifted in order to facilitate greater access to methadone treatment.[15] In addition, amendments to the restrictions on diacetylmorphine will provide flexibility by allowing patients to receive the product outside a hospital setting, such as in substance use disorder clinics.[15]

Drug

Buprenorphine is a partial mu-opioid-receptor agonist that has a high receptor affinity, thereby reducing the binding of other opioids to the mu-receptors. The product under review is a non-aqueous solution dissolved in a polymeric (non-gelatin containing) delivery system (Atrigel) placed in a pre-filled syringe.[5,6] This product is administered through abdominal subcutaneous injection and forms a solid mass upon contact with bodily fluids. If administered intravenously, it can cause life-threatening pulmonary emboli. Sublocade (Buprenorphine extended-release [BUP-ER]) has a long half-life and should only be administered monthly.[5]

The approved indication of BUP-ER subcutaneous injection is for the management of moderate-to-severe OUD in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product.[5] It has also been stipulated to be used as part of a complete treatment plan that includes counselling and psychosocial support, and only administered subcutaneously in the abdominal region by a health care provider.[5] In order for treatment to be initiated, patients must be stabilized on a transmucosal dose of 8 mg to 24 mg of buprenorphine for at least seven days.[5] The recommended dose, following induction and stabilization, starts at 300 mg per month for two months, followed by a maintenance dose of 100 mg per month. The maintenance dose may be increased to 300 mg per month if the patients does not demonstrate satisfactory clinical response to the 100 mg dose, and can tolerate it.[5] Rationale for the dosage aligns with pharmacokinetic studies that indicate that a maximum serum concentration achieved with the 300 mg initial dose enabled the target of 70% mu-opioid-receptor occupancy, which could not be reached with the 100 mg or 200 mg dose after the first month.[16,17] Simulations also showed that repeated doses of 100 mg BUP-ER was able to maintain mu-opioid-receptor occupancy above 70% at a steady-state plasma level throughout a six-month treatment phase. [11,17]

A minimum of 26 days is required between consecutive doses.[5]

Table 2: Pharmacotherapies for Opioid Use Disorder

	Buprenorphine Extended-Release Subcutaneous Injection	Buprenorphine Subdermal Implant	Buprenorphine/Naloxone	Methadone	Naltrexone
Mechanism of Action	Partial mu-opioid agonist	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]	For the management of moderate-to-severe opioid use disorder in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product	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 provide blockade of 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	Subcutaneous	Subdermal	Sublingual[b]	Oral	Oral
Recommended Dose	300 mg/month for two months, followed by a maintenance dose of 100 mg/month Maintenance dose may be increased to 300 mg/month only if patient does not demonstrate satisfactory clinical response and can tolerate the 100 mg 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 naloxone, 8 mg buprenorphine/2 mg naloxone, 12 mg buprenorphine/3 mg naloxone, 16 mg buprenorphine/4 mg naloxone SL tablet	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 dose regimens (e.g., 100 mg Monday and Wednesday, 150 mg Friday)

	Buprenorphine Extended-Release Subcutaneous Injection	Buprenorphine Subdermal Implant	Buprenorphine/Naloxone	Methadone	Naltrexone
Serious Side Effects / Safety Issues	Contraindicated in patients with severe respiratory insufficiency; severe hepatic impairment; acute alcoholism or delirium tremens; known or suspected mechanical gastrointestinal obstruction or any conditions affecting bowel transit; suspected surgical abdomen; severe central nervous system depression; increased cerebrospinal or intracranial pressure; head injury; convulsive or seizure disorders; congenital long QT syndrome or QT prolongation at baseline; uncorrected hypokalemia, hypomagnesemia or hypocalcemia AE: Headache, constipation, nausea, injection site pruritis, vomiting, hepatic enzymes increase, injection site pain, fatigue, injection site erythema, somnolence, sedation, dizziness, upper abdominal pain	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 QT 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 gastrointestinal 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 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

	Buprenorphine Extended-Release Subcutaneous Injection	Buprenorphine Subdermal Implant	Buprenorphine/Naloxone	Methadone	Naltrexone
Other	Should be used as part of a complete treatment plan that includes counselling and psychosocial support Must only be administered subcutaneously in the abdominal region by a health care provider	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: i) experience in substitution treatment in opioid drug dependence, and ii) completion of a recognized buprenorphine and naloxone education program Daily dose 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 Patients should be carefully monitored within a framework of medical, social, and psychological support as part of a comprehensive opioid dependence treatment program	Available only through physicians who have received an exemption from the Minister of Health Canada to prescribe methadone pursuant to section 56 of the CDSA[c]	Patients must be opioid free for 7 to 10 days

AE = adverse event; CNS = central nervous system; CDSA = Controlled Drugs and Substances Act; 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,[5,18-26] guidelines.[4]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of BUP-ER subcutaneous injection 100 mg and 300 mg for the treatment of OUD in adult patients with moderate-to-severe OUD who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review (CDR) and to Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adults with opioid use disorder who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product. Subgroups: • Age • Opioid source of access (i.e., pure prescription pathway, illicit prescription opioid use, IVDU) • Potency of opioid used (i.e., fentanyl)
Intervention	Buprenorphine extended-release subcutaneous injection 100 mg and 300 mg monthly (minimum of 26 days required between consecutive doses)
Comparators	Buprenorphine-containing product with or without naloxone Methadone (oral) Naltrexone (oral) Placebo
Outcomes	**Efficacy outcomes:** • Opioid use (e.g., urine test, self-report of illicit opioid use, abstinence) • Retention in treatment • Social functioning (e.g., employment, criminality, HIV risk behaviour) • Health-related quality of life • Opioid withdrawal symptoms • Opioid cravings • Treatment diversion • Need for supplemental medication to manage opioid withdrawal or craving symptoms • Incidence of HIV and hepatitis C **Harms outcomes:** AEs, SAEs, WDAEs, mortality, overdose (fatal and non-fatal), injection site reactions, respiratory depression, low serum testosterone, hepatic toxicity
Study Design	Published and unpublished phase III and IV RCTs

AE = adverse event; IVDU = intravenous drug users; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

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 All (1946–) via Ovid; Embase (1974–) via Ovid; PsyINFO 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 "buprenorphine" AND an "extended-release" keyword string.

No methodological filters were applied to limit retrieval. 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 15, 2019. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on May 15, 2019. 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 trial registries
- databases (free)
- health statistics
- Internet search
- open access journals.

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 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.

Results

Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

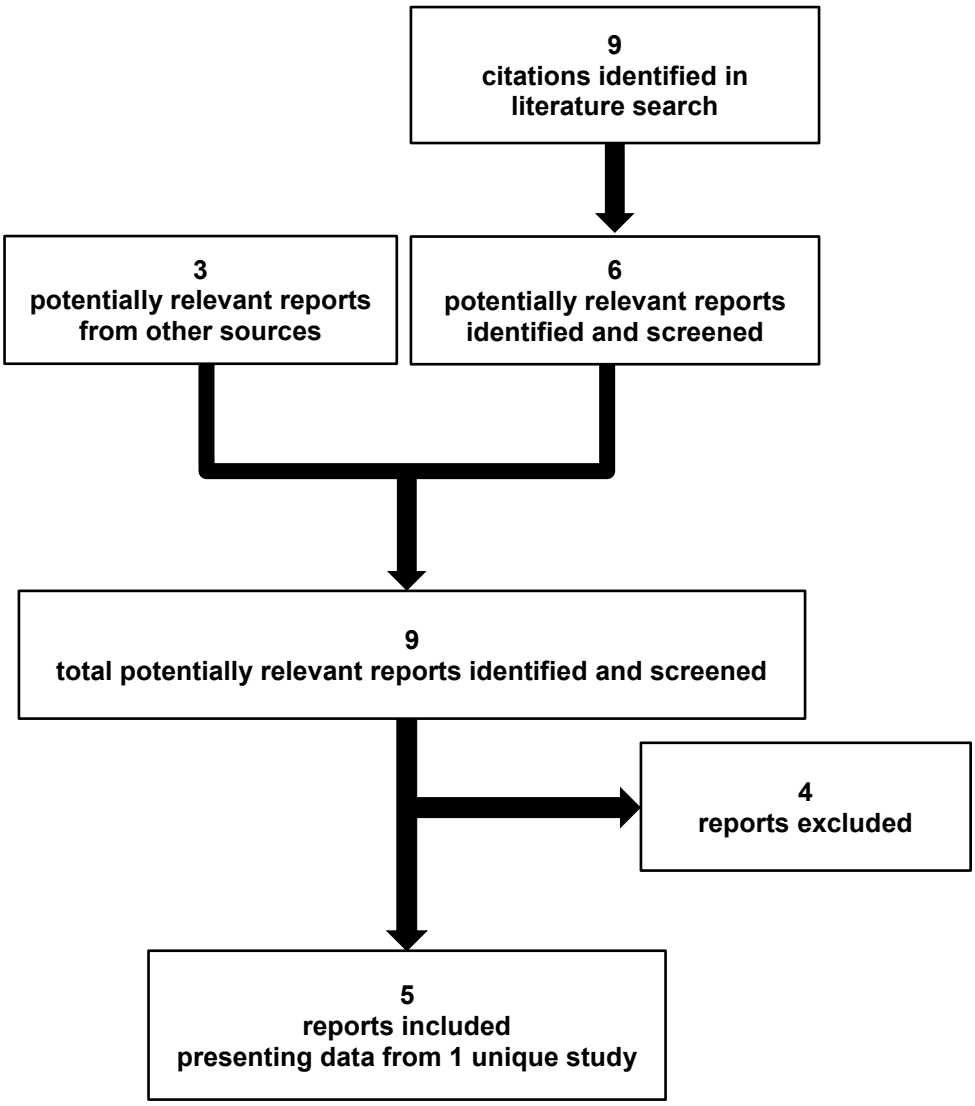


Table 4: Details of Pivotal Study 13-0001

		13-0001
Designs and Populations	**Study Design**	Multi-centre, multi-dose, double-blind, placebo-controlled RCT
	Locations	US
	Randomized (N)	504
	Inclusion Criteria	• Moderate or severe OUD[a] currently or in past three months • Seeking MAT for opioid use disorder • Age ≥ 18 to ≤ 65 years and BMI ≥ 18.0 to ≤ 35.0 kg/m^2 • Women of childbearing potential to have a negative pregnancy test prior to enrolment • All men and women of childbearing potential agreed to contraception use
	Exclusion Criteria	• Current diagnosis, other than OUD, requiring chronic opioid treatment • Current substance use disorder,[a] other than opioids, cocaine, cannabis, tobacco, or alcohol • Positive UDS results for cocaine and cannabis at screening and either moderate or severe cocaine use disorder or cannabis use disorder[a] • Moderate or severe alcohol use disorder[a] • Receiving MAT for OUD in the 90 days prior to providing written informed consent • Treatment for OUD by court order • Pregnant or lactating female • Current incarceration or pending incarceration/legal action • Use of medications that were clinically relevant CYP 3A4 or CYP 2C8 inducers or inhibitors, with the exception of marijuana (see excluded medications list [link]) • History of suicidal ideation within 30 days • Chest pain, palpitations with either exertion or drug use, peripheral or generalized edema, or major cardiovascular event (including IE) within 6 months • Significantly abnormal BP in opinion of investigator • Previous receipt of buprenorphine extended-release injection (BUP-ER) • Diagnosis of acquired immunodeficiency syndrome • Use of barbiturates, benzodiazepines methadone, or buprenorphine or a positive UDS result at screening (1-time retest within 48 hours permitted if suspected false-positive)
Drugs	**Intervention**	Buprenorphine extended-release injection 300 mg every 4 weeks SC x 6 doses Buprenorphine extended-release injection 300 mg every 4 weeks x 2 doses, followed by 100 mg every 4 weeks x 4 doses
	Comparator	Placebo (volume-matched) injection SC every 4 weeks SC x 6 doses
Duration	**Phase**	
	Induction	2 weeks
	Double-blind	24 weeks
	Follow-up	4 weeks
Outcomes	**Primary End Point**	CDF of percentage urine samples negative for opioids combined with negative self-reports for illicit opioid use from weeks 5 through 24
	Other End Points	Treatment success (any patient with ≥ 80% of urine samples negative for opioids) combined with negative self-reports for illicit opioid use from week 5 through week 24 CDF of percentage of urine samples negative for opioids from week 5 through week 24 CDF of percentage of self-reports negative for illicit opioid use collected from week 5 through week 24 Change from baseline in opioid craving VAS, CGI-I, CGI-S, COWS, SOWS score from week 5 through week 24 Percentage of completers Percentage of patients abstinent

		13-0001
Notes	**Publications**	Haight (2019)[27]

BMI= body mass index; BP = blood pressure; BUP-ER = buprenorphine extended-release injection; CDF = cumulative distribution function; CGI-I= Clinical Global Impression for Improvement; CGI-S = Clinical Global Impression for Severity; COWS = clinical opiate withdrawal scale; *DSM-5= Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; IE= infective endocarditis; MAT= medication-assisted treatment; OUD= opioid use disorder; RCT = randomized controlled trial; SC = subcutaneous; SOWS = subjective opiate withdrawal scale; UDS = urine drug screen; VAS = Visual Analog Scale.

Note: Three additional reports were included (FDA Medical and Statistical Review Reports,[7,28] HC reviewer's reports,[11] articles).

[a] Based on *DSM-5* criteria.

Source: Clinical study report for Study 13-0001,[6] Haight 2019.[27]

Included Studies

Description of Studies

Pivotal Trial (Study 13-0001)

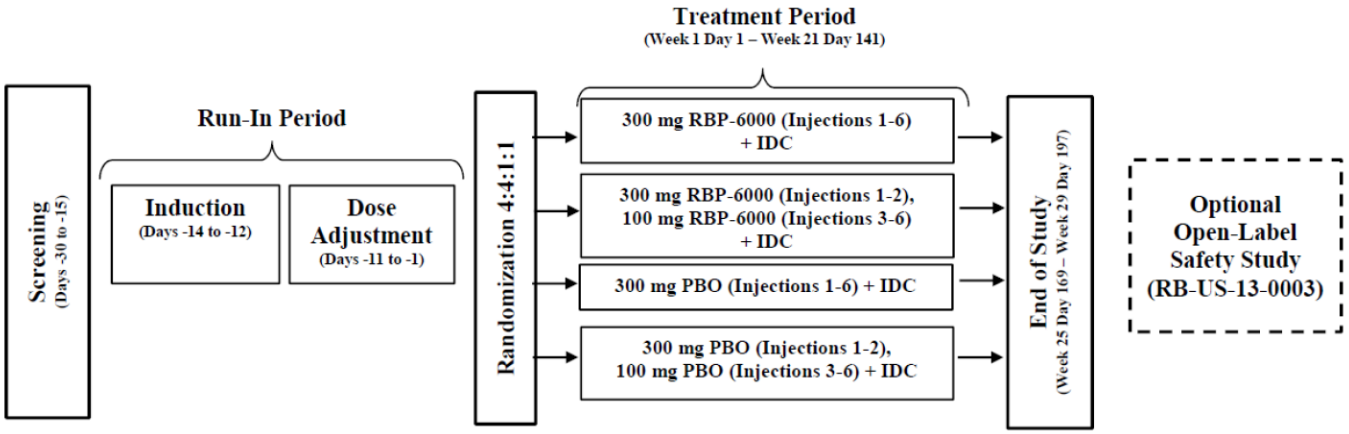
Study 13-0001 was a randomized, double-blind, placebo-controlled trial that was designed to assess efficacy, safety, and tolerability of BUP-ER subcutaneous injection (100 mg and 300 mg) over 24 weeks in treatment-seeking patients with OUD. This study design consisted of a screening phase for up to two weeks, an open-label run-in induction phase for up to two weeks to achieve a buprenorphine dose of 8 mg to 24 mg with sublingual buprenorphine, a randomized, double-blind treatment phase lasting 24 weeks, and a follow-up period of up to four weeks. Subsequently, patients completing this study were able to enter a long-term safety extension study (Study 13-0003).

Eligible patients aged 18 to 65 years were randomized in a 4:4:1:1 ratio to receive one of the following regimens:

- Regimen 1: BUP-ER 300 mg subcutaneous every four weeks for six doses
- Regimen 2: BUP-ER 300 mg subcutaneous every four weeks for two doses followed by BUP-ER 100 mg subcutaneous every four weeks for four doses
- Regimen 3: Placebo volume-matched to regimen 1
- Regimen 4: Placebo volume-matched to regimen 2

All regimens were administered with manual-guided behaviour counselling and individual drug counselling. Further details on study design are depicted in Figure 2.

Figure 2: Study Design of Study 13-0001



IDC=individual drug counselling

Note: Subjects received IDC during the double-blind treatment period. A total of 163 of the 504 subjects enrolled (32.3%) received a 5-day SUBOXONE taper as follows: Day 1 (6 mg), Day 2 (4 mg), Day 3 (4 mg), Day 4 (2 mg) and Day 5 (2 mg), according to Amendment 2.

Source: Clinical study report for Study 13-0001.

After initiating the study, the protocol was amended to include a five-day taper with buprenorphine / naloxone sublingual film after randomization in order to reduce early dropout by mitigating potential withdrawal signs in patients in the placebo arms of the study. This was administered following the first injection of study treatment for five days, and then discontinued. Therefore, after study treatment, patients in placebo groups were not permitted supplemental buprenorphine / naloxone sublingual film except for the five-day taper beginning on day 1. Patients requiring additional supplemental buprenorphine/naloxone sublingual film or other sublingual buprenorphine pharmacotherapy after day 1 were withdrawn for lack of efficacy and referred for appropriate treatment.

Populations

Inclusion and Exclusion Criteria

This trial enrolled adults meeting the *Diagnostic and Statistical Manual of Mental Disorders V (DSM-5)* criteria for current opioid dependence (Table 4) between 18 and 65 years of age who could tolerate buprenorphine, reach a stable buprenorphine dose within about two weeks of sublingual buprenorphine, and comply with returning to the study site through the induction period. At the end of the induction period, patients had to be on a daily buprenorphine dose between 8 mg and 24 mg, have a clinical opiate withdrawal scale (COWS) score 12 or less as well as an opioid craving Visual Analog Scale (VAS) of 20 mm or less in order to meet criteria for randomization. Exclusion criteria in this study included an existing diagnosis requiring chronic opioid treatment, those meeting *DSM-5* criteria for moderate or severe cocaine, alcohol or cannabis use disorder, receiving medication-assisted treatment (MAT) for OUD in the past 90 days, and patients who had use of barbiturates, benzodiazepines, methadone, or buprenorphine within the past 30 days.

Baseline Characteristics

Study 13-0001 enrolled a total of 504 patients, 100 to placebo, 203 to the BUP-ER 100 mg group, and 201 to BUP-ER 300 mg group. Although 504 patients were randomized in this study, 15 patients (nine patients receiving 300 mg/100 mg, five patients receiving 300 mg/300 mg, and one patient receiving placebo) were ultimately excluded from the trial due to compliance issues identified at Site 20, resulting in site closure by the sponsor.

The demographic and baseline characteristics appeared to be comparable between groups (Table 5). The mean age in all treatment groups was approximately 40 years. Overall, 44% of participants fell between the 30 and 44 year range. About 3% of patients across all groups were 60 years of age or older. The majority of patients in Study 13-0001 were white (72%) and male (67%). Baseline body mass index and weight appeared to be similar across treatment groups. Overall, about 44% of patients had a history of injectable opioid use.

Between 46% and 53% of patients across treatment groups were suspected to have used illicit opioids in addition to buprenorphine/naloxone sublingual film in the run-in period, as indicated by a positive urine drug sample (UDS) on day 1 of the double-blind period. All prior medications, including over the counter medication, dietary supplements, and herbal preparations, taken within the 30 days prior to screening were recorded.

Table 5: Summary of Baseline Characteristics — Safety Analysis Set

		Study 13-0001		
		BUP-ER 300 mg/100 mg + IDC N = 203	**BUP-ER 300 mg/300 mg + IDC N = 201**	**Placebo + IDC N = 100**
Age (years)	Mean (SD)	39.9 (11.32)	39.2 (10.99)	39.1 (10.92)
	Median (range)	38.0 (19 to 64)	38.0 (19 to 64)	37.5 (20 to 63)
Male, n (%)		136 (67.0)	135 (67.2)	65 (65.0)
Race, n (%)				
White		140 (69.0)	144 (71.6)	78 (78.0)
Black[a]		57 (28.1)	55 (27.4)	20 (20.0)
Other		6 (3.0)	2 (1.0)	2 (2.0)
Mean weight, kg (SD)		77.0 (15.8)	79.8 (16.5)	75.6 (16.1)
Mean BMI, kg/m^2 (SD)		25.3 (4.2)	26.4 (4.5)	25.3 (4.2)
Substance Use at Screening, n (%)				
Tobacco		187 (92.1)	186 (92.5)	93 (93.0)
Alcohol		160 (78.8)	160 (79.6)	81 (81.0)
Full Analysis Set (mITT)[b]		**N = 194**	**N = 196**	**N = 99**
Opioid Users at Screening				
Non-injectable opioid users		138 (71.1)	136 (69.4)	57 (57.6)
Injectable opioid users		84 (43.3)	80 (40.8)	50 (50.5)
Positive UDS on day 1[c]		91 (46.9)	104 (53.1)	45 (45.5)
Negative UDS on day 1[d]		103 (53.1)	92 (46.9)	54 (54.5)

	Study 13-0001		
Relevant Medical History			
Drug abuse	161 (83.0)	163 (83.2)	83 (83.8)
Drug dependence	30 (15.5)	33 (16.8)	15 (15.2)
Depression	28 (14.4)	22 (11.2)	13 (13.1)
Anxiety	18 (9.3)	19 (9.7)	10 (10.1)
Hepatitis C	31 (16.0)	24 (12.2)	10 (10.1)
HIV infection	1 (0.5)	0 (0.0)	0 (0.0)
At least one concomitant medication	118 (60.8)	115 (58.7)	59 (59.6)
Ibuprofen	38 (19.6)	32 (16.3)	13 (13.1)
Hydroxyzine	30(15.5)	14 (7.1)	12 (12.1)
Acetaminophen	13 (6.7)	19 (9.7)	8 (8.1)
Amoxicillin	15 (7.7)	5 (2.6)	1 (1.0)
Natural opium alkaloids	9 (4.6)	7 (3.6)	1 (1.0)
Morphine	1 (0.5)	1 (0.5)	0 (0.0)
Oxycodone/ acetaminophen	1 (0.5)	1 (0.5)	0 (0.0)
Oxycodone	1 (0.5)	3 (1.5)	0 (0.0)
Hydromorphone	0 (0.0)	1 (0.5)	0 (0.0)
Hydrocodone/ acetaminophen	6 (3.1)	3 (1.5)	1 (1.0)
SSRIs	9 (4.6)	4 (2.0)	5 (5.0)
Citalopram	3 (1.5)	1 (0.5)	3 (3.0)
Sertraline	5 (2.4)	1 (0.5)	3 (3.0)
Other antidepressants	14 (7.2)	4 (2.0)	4 (4.0)
Buproprion	4 (2.1)	0 (0.0)	0 (0.0)
Trazodone	6 (3.1)	1 (0.5)	2 (2.0)
Venlafaxine	2 (1.0)	3 (1.5)	1 (1.0)
Desvenlafaxine	1 (0.5)	1 (0.5)	1 (1.0)
Vortioxetine	2 (1.0)	0 (0.0)	0 (0.0)

BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling; mITT = modified intention-to-treat analysis; SD= standard deviation; SSRI = selective serotonin reuptake inhibitors; UDS= urine drug screen.

[a] Black or African-American.

[b] Patients from Site 20 (n = 15) were excluded from the analysis set.

[c] Indicative of illicit opioid use in addition to run-in medication up until day 1.

[d] Indicative of no illicit opioid use in addition to run-in medication up until day 1.

Source: Clinical study report for Study 13-0001.[6]

Table 6 depicts the drug use history in the safety analysis set of patients within Study 13-0001. Apart from opioids, there were 113 (55.7%) of patients in the 300 mg/100 mg group using cannabis compared with 95 (47.3%) in the 300 mg/300 mg group and 53 (53.0%) in the placebo group. A total of 94 (46.3%) patients in the 300 mg/100 mg group had previously used cocaine compared with 80 (39.8%) in the 300 mg/300 mg group and 42 (42.0%) in the placebo group. There were 53 (26.1%) patients recorded in the 300 mg/100 mg group compared with 29 (14.4%) in the 300 mg/300 mg group and 19 (19.0%) in the

placebo group who had previously used amphetamines/methamphetamines. There were 25 (12.3%) patients in the 300 mg/100 mg group documented to have used methadone, compared with 14 (7.0%) patients in the 300 mg/300 mg group and five (5.0%) in the placebo group. Drug use history was similar for the full analysis set and per-protocol set compared with the safety analysis set.

Table 6: Drug Use History — Safety Analysis Set

	Study 13-0001, N (%)		
	BUP-ER 300 mg/100 mg + IDC (N = 203)	**BUP-ER 300 mg/300 mg + IDC (N = 201)**	**Placebo + IDC (N = 100)**
Opioids	203 (100.0)	201 (100.0)	100 (100.0)
Cannabinoids	113 (55.7)	95 (47.3)	53 (53.0)
Cocaine	94 (46.3)	80 (39.8)	42 (42.0)
Amphetamines/ Methamphetamine	53 (26.1)	29 (14.4)	19 (19.0)
Methadone	25 (12.3)	14 (7.0)	5 (5.0)
Benzodiazepines	25 (12.3)	20 (10.0)	13 (13.0)
Buprenorphine	20 (9.9)	16 (8.0)	6 (6.0)
Barbiturates	3 (1.5)	1 (0.5)	0 (0.0)
Phencyclidine	0 (0.0)	2 (1.0)	1 (1.0)
Other	2 (1.0)	6 (3.0)	1 (1.0)

BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling.

Source: Clinical study report for Study13-0001.[6]

Interventions

Patients enrolled in this trial were administered buprenorphine/naloxone sublingual film, buprenorphine long-acting depot (BUP-ER), and placebo. For a detailed account of treatments administered throughout the induction, randomization, and double-blind phases of the trial, please refer to Table 7.

Table 7: Treatments Administered Throughout Induction, Randomization, and Double-Blind Treatment Phases of Study 13-0001

Run-In Period		Randomization	Double-Blind Treatment (Includes IDC)		
Induction (3 days)	**Dose Adjustment (4-11 days)**		**Buprenorphine/ Naloxone SL[a] Taper (Week 1/ Day 1 to Week 1 Day 5)**	**300 mg Dose Injections 1 to 2 (Week 1/ Day 1 to Week 5/ Day 29)**	**Randomized Dose Injections 3 to 6 (Week 9/Day 57 to Week 21/Day 141)**
Initially 2 mg/0.5 mg or 4 mg/ 1 mg (titrated upwards in 2 mg or 4 mg increments of buprenorphine at approximately 2 hour intervals on day 1, followed by previous day doses on days 2 and 3) In accordance with COWS > 12 and withdrawal symptoms	Buprenorphine daily dosages ranging from 8 mg to 24 mg (adjusted at approximately 3 to 4 day intervals) In accordance with opioid craving VAS, COWS and SOWS To meet randomization criteria (Day 1), patients had COWS ≤ 12 and opioid craving VAS ≤ 20 mm[b]	BUP-ER dose regimen #1 or dose regimen #2	All randomized patients received the following taper doses: Day 1: 6 mg/1.5 mg Day 2: 4 mg/1 mg Day 3: 4 mg/1 mg Day 4: 2 mg/0.5 mg Day 5: 2 mg/0.5 mg	BUP-ER containing 300 mg buprenorphine (376 patients randomized to receive BUP-ER)	188 patients receiving BUP-ER 300 mg
					188 patients receiving BUP-ER 100 mg
		Placebo[c]		94 patients volume-matched for 300 mg BUP-ER	47 patients receiving volume-matched BUP-ER 300 mg
					47 patients receiving BUP-ER 100 mg

BUP-ER = buprenorphine extended-release; COWS = clinical opiate withdrawal scale; IDC = behavioural counselling/individual drug counselling; SL= sublingual; SOWS = subjective opiate withdrawal scale; VAS = Visual Analog Scale.

[a] Buprenorphine/naloxone sublingual film was administered as Suboxone.

[b] Patients who did not meet randomization criteria.

[c] 94 patients were to be randomized to placebo at an equivalent volume of BUP-ER with 300 mg buprenorphine for the first two injections. Half of the placebo group was then to be randomized to placebo at an equivalent volume of BUP-ER containing 100 mg buprenorphine and the other half was to continue on with placebo at equivalent volumes of BUP-ER containing 300 mg buprenorphine.

Source: Clinical study report for Study 13-0001.[6]

Buprenorphine/Naloxone Sublingual Film

Buprenorphine/naloxone sublingual film (Suboxone) was supplied as an orange, rectangular sublingual film with a white, printed logo. This product was manufactured by Indivior. Each sublingual film contained buprenorphine hydrochloride and naloxone hydrochloride dehydrate at a 4:1 ratio expressed as the free bases. In this trial, films were available in four dosage strengths, which were 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, and 12 mg/3 mg buprenorphine/naloxone.

Patients in all treatment groups used buprenorphine/naloxone sublingual film during the open-label run-in induction and dose-adjustment phases of the study. In order to preserve blinding within the study, a five-day taper of buprenorphine/naloxone sublingual film was suggested by the FDA and later adopted as a protocol amendment, with the taper beginning on day 1, following the first injection of study treatment (BUP-ER or placebo). A total of 163 randomized patients received the five-day taper, which was administered on days 1 and 2 during clinic visits. Additional doses for days 3, 4, and 5 were dispensed at the day 2 visit for at-home administration. The dosage schedule for the taper is detailed in Table 8.

Table 8: Buprenorphine/Naloxone Sublingual Film Taper

Day	Day 1	Day 2	Day 3	Day 4	Day 5
Buprenorphine/ naloxone sublingual film dose[a]	6 mg	4 mg	4 mg	2 mg	2 mg
Dose location	Clinic	Clinic	Home	Home	Home

[a] Dose applied to buprenorphine amount.

Source: Clinical study report for Study 13-0001.[6]

Buprenorphine Extended-Release

BUP-ER was supplied as buprenorphine in an Atrigel delivery system. The entire contents of this single-syringe system were administered with each dose. BUP-ER contains buprenorphine in two dose strengths, 300 mg and 100 mg. The approximate volume delivered is 0.5 mL for 100 mg injection and 1.5 mL for the 300 mg injection.

Placebo

Placebo was administered in the form of single-syringes, identical (including containing Atrigel) to those used to deliver active drug, and packaged in matching containers. The approximate volume delivered was 0.5 mL for the 100 mg placebo injection and 1.5 mL for the 300 mg placebo injection.

Behavioural Counselling / Individual Drug Counselling

Randomized patients in this study received once weekly individualized behavioural counselling as well as individualized drug counselling (IDC) to accompany pharmacotherapy. Therapy was administered by appropriately qualified and trained staff members on-site who were blinded to patient's UDS results. Behavioural counselling and IDC were to continue once weekly until an early termination or end-of-study visit.

Outcomes

Primary Outcome

In Study 13-0001, the primary outcome was a combination of the cumulative distribution function of the percentage of urine samples negative for opioids combined with negative self-reports of illicit opioid use collected from weeks 5 to 24 in the full analysis set of the patient population. This outcome was referred to in the trial as "percentage abstinence." The first four weeks were intended as a grace period for patients to achieve better treatment stabilization as well as adequate plasma levels of buprenorphine.

The UDS was used to detect the presence of codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. There were three different immunoassays used for this analysis.

Self-reports were conducted via a timeline follow-back (TLFB) interview. The TLFB interview was conducted in this trial to assess recent drug use, including opioids, methadone, buprenorphine, cocaine, barbiturates, ethanol, benzodiazepines, amphetamines/methamphetamines, and phencyclidine. The interview instrument was administered electronically by an interviewer and asked patients to estimate their own drug use in the 30 days prior to screening at the screening visit and since the last visit at all subsequent visits. Patients were to only report whether there was use or no use, not the frequency or amount used.

The UDS samples and TLFB interviews were carried out and collected every week between weeks 5 and 24. Missing UDS samples and/or self-reports were considered to be non-negative and were imputed as such. Derivation of the composite primary efficacy end point is detailed in Table 9.

Table 9: Composite Primary Efficacy Outcome Derivation

UDS Result[a]	Self-Report of Illicit Opioid Use Result	Primary Efficacy Outcome
Non-negative	Non-negative	Non-negative
Non-negative	Negative	Non-negative
Negative	Non-negative	Non-negative
Negative	Non-negative	Non-negative
Negative	Negative	Negative

UDS= urine drug screen.

[a] Missing urine drug screen samples and/or self-reports were counted as non-negative.

[b] The self-reports of illicit opioid use were obtained from timeline follow-back interviews.

Source: Clinical study report for Study 13-0001.[6]

Secondary Outcome

The key secondary end point was treatment success, which was defined as any patient with 80% or more of urine samples negative for opioids combined with self-reports negative for illicit opioid use (from the TLFB interview) from week 5 to week 24. Treatment success was evaluated in the full analysis set population to assess statistically significant differences between active treatment and placebo groups and was pre-specified in the statistical analysis plan.

Additional secondary efficacy end points included percentage of UDS negative for opioids from week 5 to week 24, percentage of self-reports negative for illicit opioid use from week 5 to week 24, change from baseline in opioid craving VAS from week 5 to week 24, opioid withdrawal, change from baseline in Clinical Global Impression scale based on severity and improvement from week 5 to week 24, participants who completed their last visit (completers, either the UDS or TLFB assessment), participants who were abstinent (defined as having urine samples negative for opioids as well as self-reports negative for illicit opioid use by TLFB interview) at week 24, change from baseline in total score on the COWS from week 5 through week 24, and change from baseline in total score on the subjective opiate withdrawal scale (SOWS) from week 5 to week 24.

More detailed information about the validity of these outcomes are provided in Appendix 5.

Exploratory Outcomes

The exploratory outcomes for this study were the per cent of urine toxicology results positive for substance other than opioids, and time to first urine sample negative for illicit opioids combined with self-reports negative for illicit opioid use collected from week 5 through week 24.

Statistical Analysis

In Study 13-0001, the primary efficacy end point, the cumulative distribution function (CDF) of the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use, was analyzed using the Wilcoxon rank sum test used for comparisons between treatment groups in the full analysis set population.

According to the protocol, a 20% margin between placebo and active treatment was selected in determining a clinically meaningful difference. The protocol cited two placebo-controlled, double-dummy randomized controlled trials (RCTs) as the rationale for employing this margin, which were conducted on patients with OUD to determine the effectiveness of buprenorphine implants, in which a 20% non-inferiority margin was chosen.[29,30] For the sample size estimate in this study, a smaller treatment difference was used in order to avoid under-powering the study, according to the protocol, and a difference of 15% was assumed. In order to achieve at least 90% power using a two-sided Wilcoxon rank sum test with alpha equal to 5%, 92 patients per group were needed in each treatment group. In order to obtain at least 150 patients per treatment group in the extension study, Study 13-0003, at least 150 patients per treatment group were targeted for inclusion, and assuming a 20% patient dropout rate, the minimum planned sample size was increased to 188 patients per active treatment group and 94 patients in placebo. A final number of 588 patients were to be enrolled, assuming a 20% dropout rate, with a 4:4:1:1 randomization to BUP-ER 300 mg/100 mg, BUP-ER 300 mg/300 mg, and volume-matched placebo.

A preplanned nonparametric test was used as the primary end point was expected to be not normally distributed. The two placebo groups were combined and analyzed as one placebo group.

The primary null hypothesis was that neither of the two dose regimens of BUP-ER (regimen #1: 6 x 300 mg or regimen #2: 2 x 300 mg + 4 x 100 mg) is superior to placebo at week 24 with respect to the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use from week 5 through week 24, examined as CDF. The alternate hypothesis was that at least one of the two dose regimens of BUP-ER (regimen #1: 6 x 300 mg or regimen #2: 2 x 300 mg + 4 x 100 mg) is superior to placebo at week 24

with respect to the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use collected from week 5 through week 24, examined as CDF.

The key secondary null hypothesis was that neither of the two dose regimens of BUP-ER (regimen #1: 6 x 300 mg or regimen #2: 2 x 300 mg + 4 x 100 mg) is superior to placebo with respect to treatment success (defined as any patient with 80% or more of urine samples negative for opioids combined with negative self-reports for illicit opioid use) from week 5 through week 24. The alternate hypothesis was that at least one of the two dose regimens of BUP-ER (regimen #1: 6 x 300 mg or regimen #2: 2 x 300 mg + 4 x 100 mg) is superior to placebo with respect to treatment success from week 5 to week 24.

There were a total of four hypotheses that were adjusted for multiplicity: two primary efficacy comparisons and two key secondary efficacy comparisons. A parallel Bonferroni gatekeeping approach was used throughout these hypotheses to achieve control on the family-wise error rate at alpha equal to 0.05. Each of the two primary hypotheses were tested individually at alpha equal to 0.025. The two key secondary end points were tested using a step-up Hochberg procedure outlined as follows. Initially, the primary hypotheses were tested under a truncated Hochberg procedure with a truncation parameter of 0, which reduced to Bonferroni. If at least one of the primary hypotheses tests were found to be significant, both of the key secondary hypotheses were tested. Adjustments to multiplicity for the key secondary end points were carried out using the Hochberg step-up procedure. The Hochberg step-up procedure was applied as follows for the two key secondary endpoints: *P* values were ranked from largest to smallest, the largest *P* value was compared with 0.025, and if the result was deemed significant, the procedure was to be stopped and both BUP-ER doses would be considered superior to placebo with respect to the key secondary end point. If the result was not deemed significant, the smallest value was to be compared with 0.0125.

A sensitivity analysis was conducted on the primary efficacy end point using the per-protocol population.

Relevant secondary outcomes and their analysis methods are included in Table 10. For additional statistical testing data, refer to Table 31.

Table 10: Summary of Secondary End Points and Analysis Strategy

	Statistical Method	Analysis Set	Approach to Missing Data
CDF of the percentage of urine samples negative for opioids from week 5 through week 24	Wilcoxon rank sum test	FAS	All missing data considered non-negative for opioids
CDF of the percentage of self-reports negative for illicit opioids from week 5 through week 24	Wilcoxon rank sum test	FAS	All missing data considered non-negative for opioids
Change from baseline in opioid craving VAS (week 5 through week 24)	MMRM	FAS	Model-based; no imputation
Percentage of completers	CMH test	FAS	No imputation
Percentage of patients abstinent	CMH test	FAS	No imputation
Change from baseline in CGI-S (week 5 through week 24)	MMRM	FAS	Model-based; no imputation

	Statistical Method	Analysis Set	Approach to Missing Data
Change from baseline in total score on the COWS (week 5 through week 24)	MMRM	FAS	Model-based; no imputation
Change from baseline in total score on the SOWS (week 5 through week 24)	MMRM	FAS	Model-based; no imputation
Percentage of urine toxicology results positive for substance other than opioids	Wilcoxon rank sum test	FAS	All missing data were considered non-negative for opioids

CDF = cumulative distribution function; CGI-S = Clinical Global Impression for Severity; CMH = Cochran-Mantel-Haenszel; COWS = clinical opiate withdrawal scale; FAS = full analysis set; MMRM = mixed model for repeated measure; SOWS = subjective opiate withdrawal scale; VAS = Visual Analog Scale.

Source: Clinical study report for Study 13-0001.[6]

Missing Data

For dichotomous outcomes (i.e., UDS results and self-reports for illicit opioid use), all missing observations were considered to be non-negative. For all continuous outcomes (i.e., COWS, SOWS, and opioid craving VAS), missing data were assumed to be missing at random. The missing data were not imputed for mixed model for repeated measure (MMRM) analyses. Sensitivity analyses were done for MMRM with imputation of worst case of the score for patients discontinuing due to adverse events (AEs). For time-to-event variables, if the event of interest was not observed before withdrawal or end of treatment, observations were censored at the time of withdrawal or at the end of treatment.

Subgroups

The count and frequencies of patients in the following pre-specified subgroups were presented in the full analysis set: non-injectable opioid users (including oral, nasal, and smoking) at screening, injectable opioid users at screening, patients using illicit opioids in addition to run-in medication as indicated by positive UDS during the run-in phase, patients not using illicit opioids in addition to run-in medication as indicated by positive UDS during the run-in phase, patients with behavioural counselling/IDC attendance of 50% or less, patients with an IDC attendance greater than 50% and less than 70%, patients with IDC attendance of 70% or greater, patients aged 18 and older but younger than 30, patients age 30 and older but younger than 45, patients aged 60 and older, male patients, female patients, white patients, and non-white patients.

It did not appear that treatment groups could be compared between subgroups, and no appropriate tests of interactions were conducted for the subgroups. Furthermore, multiplicity did not appear to be considered in the presentation of its findings.

Analysis Populations

The populations used for data analysis are defined in Table 11.

While Study 13-0001 was being conducted in August 2015, compliance issues were identified at Site 20 that resulted in site closure by the sponsor. As a result, the safety analysis set included all 504 patients; however, the efficacy analyses was a modified intention-to-treat (mITT) population due to the exclusion of these 15 patients.

Table 11: Analysis Populations From Study 13-0001

Analysis Set	Description
FAS	All randomized patients, defined as any patient, randomized (not necessarily according to the treatment received) and allocated study treatment in the interactive voice response system.
PP set	All randomized patients who received at least one dose of study medication and did not have important protocol deviations during the course of the trial. This population was used for supportive efficacy analyses.
Run-in safety set	All enrolled patients who received at least one dose of buprenorphine/naloxone SL film during the run-in phase. An enrolled patients was defined as any patient who signed the informed consent form and received buprenorphine/naloxone SL film. This population was used when analyzing adverse event reported during the run-in phase.
Safety analysis set	All enrolled patients who received at least one dose of randomized study treatment. This population was used for all safety analyses. Unlike FAS, patients in this set were analyzed according to the actual treatment received.

FAS= full analysis set; PP = per-protocol; SL= sublingual.

Source: Clinical study report for Study 13-0001;[6] Health Canada Reviewer's Report.[11]

Patient Disposition

After the study was initiated, the protocol was amended to incorporate a taper at the end of the sublingual film run-in to mitigate the potential effects of abrupt discontinuation on patients blindly switching to placebo injections. A total of 163 (32%) patients received a five-day buprenorphine/naloxone sublingual film taper following the first injection of study treatment.

A total of 1,187 patients were screened, 682 of which were considered screen failures. A total of 665 patients subsequently entered the open-label run-in phase and 161 were considered run-in failures. A total of 504 patients were later randomized into this study, and ultimately included in the full analysis set as well as the safety analysis set, consisting of 201 patients in the BUP-ER 300 mg/300 mg group, 203 patients in the 300 mg/100 mg group, and 100 patients in the placebo group.

In the BUP-ER groups, 60% of the patients completed the study compared with 34% of patients in the placebo group. The most common reasons for discontinuation were similar between both active treatment groups, and were being lost to follow-up and withdrawal of consent. The most common reasons for discontinuation in the placebo group were withdrawal of consent (18%) and perceived lack of efficacy (18%). There were more patients in the placebo group who withdrew for perceived lack of efficacy (18%) than in either of the BUP-ER groups (1.5% and 2.5%), as well as more patients withdrawing consent in the placebo group (18%) compared with the BUP-ER groups (10% in each). Across both active treatment groups and placebo, rates of discontinuation due to AEs were about 5%.

The majority of patients in all treatment arms did not have a major protocol violation and were included in the per-protocol set (91% of patients in active treatment and 89% of patients assigned to placebo).

During the course of this trial, compliance issues were identified at Site 20, which resulted in the closure of the site by the study sponsor. As a result, a total of 15 patients were excluded from all efficacy analyses but remained included in the safety analyses.

Table 12: Patient Disposition

	BUP-ER 300 mg/ 100 mg + IDC	BUP-ER 300 mg/ 300 mg + IDC	Placebo + IDC
Screened, N (%)	1,187		
Screen failures	682		
Screen failures and entered run-in phase[a]	160		
Screen failures and not in run-in phase	522		
Run-in phase,[b] N (%)	665		
Run-in failures[c]	161		
Randomized, N (%)	203	201	100
Randomized but not treated	0 (0.0)	0 (0.0)	0 (0.0)
Randomized and treated[d]	203 (100.0)	201 (100.0)	100 (100.0)
Completed, N (%)	125 (61.6)	129 (64.2)	34 (34.0)
Discontinued, N (%)	78 (38%)	72 (36%)	66 (66%)
Reason for discontinuation			
Adverse event	6 (3%)	10 (5%)	2 (2%)
Death[e]	0	0	0
Withdrawal symptoms	1 (0.5%)	1 (0.5%)	3 (3%)
Lost to follow-up	26 (13%)	23 (11%)	12 (12%)
Noncompliance with study drug	2 (1%)	0	2 (2%)
Physician decision	0	1 (0.5%)	1 (1%)
Patient withdrew consent	20 (10%)	21 (10%)	18 (18%)
Patient withdrawn by investigator	1 (0.5%)	0	3 (3%)
Lack of efficacy	3 (1.5%)	5 (2.5%)	18 (18%)
Protocol deviation	2 (1%)	5 (2.5%)	0
Other[f]	17 (8%)	6 (3%)	7 (7%)
ITT (full analysis set), N	203	201	100
mITT (full analysis set)[g]	194	196	99
PP, N	185	183	89
Safety, N	203	201	100

BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling; ITT = intention-to-treat; mITT = modified intention-to-treat; PP = per-protocol.

[a] These patients were in the clinical database as screen failures, however they also received at least one dose of buprenorphine/naloxone sublingual film.

[b] Includes patients who received at least one dose of buprenorphine/naloxone sublingual film during the run-in phase.

[c] An additional 34 patients were identified as run-in failures in the datasets but did not enter the run-in phase. These 34 patients were not included in the count of run-in failures, as they did not take any run-in medication and were therefore included in the 522 patients who were "screen failures and not in run-in phase."

[d] One patient was randomized, but did not receive any study treatment during the double-blind phase, included the buprenorphine/naloxone sublingual film taper.

[e] One patient in the BUP-ER 300 mg/300 mg group discontinued due to adverse event that later led to death.

[f] Discontinuation due to "other" includes site closed by sponsor (n = 9), incarceration (n = 7), relocation (n=4), noncompliance with study visits/lost to follow-up type reasons (n = 4).

[g] Due to compliance issues found at one of the study sites leading to site closure, patients from Site 20 (n = 15) were excluded from all efficacy analyses but remained included in the safety analyses.

Source: Clinical study report for Study 13-0001.[6]

Exposure to Study Treatments

During the run-in phase of this study, patients were intended to have attained a daily dosage of between 8 mg and 24 mg buprenorphine by the third induction day. They were intended to have continued on that dosage through the remainder of buprenorphine/naloxone sublingual film treatment; however, further dose adjustments may have been necessary during the dose-adjustment period.

The most common dose of buprenorphine/naloxone sublingual film administered during induction day 1 was 8 mg/2 mg (60.2% of patients) and 4 mg/1 mg (30.7% of patients); during induction day 2 was 12 mg/3 mg (32.5% of patients) and 8 mg/2 mg (26.0% of patients); during induction day 3 was 8 mg/2 mg (28.4% of patients) and 12 mg/3 mg (25.1% of patients). The actual dose-adjustment period that followed ranged from 4 to 22 days, which was higher than the planned 4 to 11 days.

As noted earlier in this report, a total of 163 patients who were randomized subsequently received a buprenorphine/naloxone sublingual film taper after the protocol was amended. The taper schedule is displayed in Table 8. On day 1 of the taper, similar proportions of patients in the 300 mg/100 mg and 300 mg/300 mg groups (31.4% and 29.1%, respectively) were administered their doses compared with the placebo group (29.3%). Day 2 of the taper was also administered to similar proportions of patients (33.5% in the 300 mg/100 mg group, 26.5% in the 300 mg/100 mg group, and 30.3% in the placebo group). Dosages for the final three days of the taper were intended for at-home administration; however, one patient in the 300 mg/300 mg group received a buprenorphine/naloxone 4 mg/1 mg in the clinic on day 3.

The exposure of patients to study treatment in the injection phase in Study 13-0001 is summarized in Table 13.

Table 13: Summary of Exposure in the Injection Phase — Safety Analysis Set

	BUP-ER 300 mg/100 mg + IDC (N = 203)	BUP-ER 300 mg/300 mg + IDC (N = 201)	Placebo + IDC (N = 100)
Number of Actual Doses			
Mean (SD)	4.7 (1.90)	4.7 (1.90)	3.3 (2.24)
Median (range)	6.0 (1 to 6)	6.0 (1 to 6)	2.5 (1 to 6)
Total Number of Actual Doses, n (%)			
1	27 (13.3)	26 (12.9)	40 (40.0)
2	15 (7.4)	15 (7.5)	10 (10.0)
3	11 (5.4)	12 (6.0)	7 (7.0)
4	9 (4.4)	14 (7.0)	4 (4.0)
5	13 (6.4)	5 (2.5)	4 (4.0)
6	128 (63.1)	129 (64.2)	35 (35.0)
Cumulative Number of Injections Received, n (%)			
At least 1 actual dose	203 (100.0)	201 (100.0)	100 (100.0)
At least 2 actual doses	176 (86.7)	175 (87.1)	60 (60.0)
At least 3 actual doses	161 (79.1)	160 (79.1)	50 (50.0)

		BUP-ER 300 mg/100 mg + IDC (N = 203)	BUP-ER 300 mg/300 mg + IDC (N = 201)	Placebo + IDC (N = 100)
At least 4 actual doses		150 (73.9)	148 (73.6)	43 (43.0)
At least 5 actual doses		141 (69.5)	134 (66.7)	39 (39.0)
With 6 actual doses		128 (63.1)	129 (64.2)	35 (35.0)
Total Number of Doses Received in Injection Phase				
0 to < 6 weeks	N (%)	203 (100%)	201 (100%)	100 (100%)
	Mean (SD)	1.9 (0.35)	1.9 (0.34)	1.6 (0.49)
6 to < 12 weeks	N (%)	161 (79.3%)	159 (79.1%)	50 (50.0%)
	Mean (SD)	1.0 (0.20)	1.0 (0.11)	1.0 (0.14)
12 to < 18 weeks	N (%)	150 (73.9%)	148 (73.6%)	43 (43.0%)
	Mean (SD)	1.9 (0.33)	1.9 (0.33)	1.9 (0.32)
≥ 18 weeks	N (%)	130 (64.0%)	130 (64.7%)	35 (35.0%)
	Mean (SD)	1.0 (0.09)	1.0 (0.12)	1.0 (0.00)

BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling; SD = standard deviation.

Note: Buprenorphine/naloxone sublingual film taper phase was not included.

Source: Clinical study report for Study 13-0001.[6]

Table 14 summarizes the percentage of attendance at weekly behavioural counselling/IDC by treatment group over the course of treatment from week 1 to week 24. Among patients who completed their week 24 visit by either undergoing UDS or TLFB assessment, all attended at least 70% of their weekly IDC sessions.

Table 14: Summary of Weekly Behavioural Counselling/Individual Drug Counselling Attendance by Percentage (%) — Full Analysis Set (mITT)[a]

	BUP-ER 300 mg/100 mg + IDC (N = 194)	BUP-ER 300 mg/300 mg + IDC (N = 196)	Placebo + IDC (N = 99)
Mean Percentage Attendance (SD)	76.0 (33.51)	76.1 (33.09)	50.4 (39.37)
Median Percentage Attendance (Range)	100 (4 to 100)	100 (4 to 100)	36.0 (4 to 100)

BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling; mITT = modified intention-to-treat; SD = standard deviation.

Note: Buprenorphine/naloxone sublingual film taper phase was not included.

[a] Patients from Site 20 (n = 15) were excluded from the analysis set.

Source: Clinical study report for Study 13-0001.[6]

Critical Appraisal

Internal Validity

- The characteristics of patients at baseline appeared to be generally balanced between treatment groups, although there was a slightly higher proportion of non-injectable opioid users in the BUP-ER groups (71.1% in the 300 mg/100 mg group and 69.4% in the 300 mg/300 mg group) compared with the placebo group (57.6%). Randomization procedures appeared to be adequate for Study 13-0001, and the trial employed a volume-matched placebo to maintain blinding. According to the product monograph,

BUP-ER is injected as a solution, after which a mass containing buprenorphine forms at the injection site, which delivers buprenorphine in extended-release form.[5] The placebo formulation contained the same Atrigel system as the BUP-ER formulations, thereby minimizing the potential for unblinding among randomized patients or study site personnel based on differences in the appearance and chemical characteristics of each study treatment.

- While Study 13-0001 was being conducted in August 2015, compliance issues were identified at Site 20 that resulted in site closure by the sponsor. A total 15 patients from Site 20 were subsequently excluded from all efficacy analyses but were included in the safety analyses. A sensitivity analysis was conducted by the FDA statistical reviewer, which did not change the conclusion of the primary analysis, as there was a statistically significant treatment effect noted for both doses of BUP-ER.[7]
- Due to the closure of Site 20, 15 patients were excluded from all supportive efficacy analyses as well as the primary and key secondary outcomes. As a result, supportive efficacy analyses of interest (i.e., COWS, SOWS, opioid craving VAS, Clinical Global Impression for Improvement [CGI-I], Clinical Global Impression for Severity [CGI-S] scores, and so forth) were not able to be conducted on the full analysis set that was defined a priori. Instead, it was conducted on a modified cohort of patients who had been randomized and allocated study treatment by the interactive voice response system, with the exclusion of patients who received study treatment at Site 20.
- After completion of the original protocol in October 2014, an amendment was filed in August 2015 in response to FDA feedback. This amendment required that all randomized patients receive a five-day buprenorphine/naloxone sublingual film taper beginning on day 1 (Table 8) in order to reduce unblinding and minimize abrupt discontinuation of MAT in patients randomized to placebo (most withdrawals in the placebo group occurred in the first six weeks of Study 13-0001). A total of 163 (32%) patients in this study were able to taper buprenorphine/naloxone. The effect of adding a taper was analyzed in the FDA statistical review by comparing the CDFs of percentage of negative drug use by tapering status, and no differences were found between the active groups and placebo.[7] In addition, there was no obvious difference found in treatment retention or response between patients in placebo groups who were administered a taper and those in placebo groups who were not. Due to the high rate of premature withdrawal in patients in the placebo group (66%), and the proportion of those citing lack of efficacy as the reason for discontinuation (18%), it is still difficult to rule out whether unblinding in this group may have occurred.
- As mentioned, there was a higher rate of premature withdrawals found in the placebo group (66%) compared with the BUP-ER groups (38% in the 300 mg/100 mg group and 36% in the 300 mg/300 mg group), with 50% of patients in the placebo group dropping out within the first six weeks compared with 21% in both BUP-ER groups. Reasons for premature withdrawal in the placebo group were mainly due to lack of efficacy, patients withdrawing consent, and loss to follow-up. There is no indication that patients randomized to receive placebo received opioid maintenance therapy upon discontinuation, or that they were adequately followed. A longitudinal observational study, RECOVER, was submitted by manufacturer, which followed patients after discontinuation from Study 13-0001.[10] Only 33 (33%) patients randomized to placebo in Study 13-0001 were included in RECOVER, and it is unclear what proportion of these patients prematurely withdrew from the study.[10]
- There was a high number of patients with missing data for opioid craving and withdrawal symptom scores (i.e., COWS, SOWS, and opioid craving VAS).

- For the UDS results and self-reports for illicit opioid use outcomes that were dichotomous, missing data caused by early dropout was imputed as non-negative. The clinical expert involved in this review believed this to be a reasonable assumption to make in this patient population. The FDA statistical reviewer conducted a sensitivity analysis based on the impact of early dropouts on the primary outcome and concluded that these analyses agreed with the main analysis.[7] Missing data for other continuous outcomes (i.e., COWS, SOWS, and opioid craving VAS) were assumed to be missing at random, and missing data were not imputed for their analysis; however, there is a possibility that patients who prematurely withdrew from this study and those who did not were different patient populations (data were missing not at random). This may have biased the results of the MMRM analysis as well, as it would have violated the assumption that patients were missing at random. Sensitivity analyses for continuous outcomes imputing the worst case of score for patients discontinuing due to AEs appeared to support the secondary end point conclusions; however, missing data in these outcomes could underestimate the variability in the results, potentially overestimating treatment effects in these results.
- The primary hypothesis in Study 13-0001 was at least one of the two dose regimens of BUP-ER was superior to placebo at week 24 with respect to the CDF of percentage abstinence (defined as percentage urine samples negative for opioids and self-reports negative for illicit opioid use) from week 5 through week 24. The assumed clinically meaningful difference was 15%, cited from previous placebo-controlled, double-dummy RCTs in this patient population where a 20% non-inferiority margin used,[29,31] and reduced to avoid under-powering the study. The RCTs in which this 20% margin was used were covered in a previous CDR review on Probuphine.[32] Clinical reviewers involved in that report questioned the certainty of the assumptions leading to the choice of the 20% margin, which included that there would be a 100% abstinence rate among patients on sublingual buprenorphine treatment, and that 25% of patients would remain abstinent after treatment with sublingual buprenorphine was stopped. Furthermore, there was an assumption in the calculation that 20% of patients randomized to active treatment would drop out of the trial. It was unclear what this assumption was based on, and the actual proportion of patients in the active treatment group (37%) who ultimately dropped out of this trial was higher than what was assumed.
- The choice of primary outcome was deemed appropriate by both the FDA and Health Canada reviewers, as well as the clinical expert consulted for this review.[11,28] However, it was noted in the Health Canada reviewer's report that given that results collected at any time during the course of the study would be integrated into a resulting level of abstinence (i.e., 80% or less, 90% or less), there is potential for a higher overall result for the primary outcome.[11] Results for this outcome were also presented on a weekly basis, which was considered to be a more robust set of values per treatment arm (Table 16). The Health Canada reviewer appeared to consider the secondary outcome, treatment success, defined as the proportions of patients with 80% or more of urine samples negative for opioids combined with self-reports negative for illicit opioid use from weeks 5 to 24 and above (Table 15), a more clinically relevant outcome.
- Study 13-0001 specified both a primary and key secondary efficacy outcome, and any adjustments to multiplicity were not performed for other outcomes. As a result, all other secondary and exploratory outcomes should be interpreted with consideration of the risk of Type I errors. This included analysis of withdrawal symptoms, such as change from baseline in COWS, SOWS, opioid craving VAS, as well as change in CGI-I and CGI-S. The COWS and SOWS scales used throughout this trial have been validated in this

patient population; however, minimal clinically important difference (MCID) is unknown. The clinical expert involved in this review added that these scales are typically only employed in practice to decide on what dosage to induct patients on opioid maintenance therapy. The validity and reliability of the need-to-use or desire-to-use VAS remains uncertain. CGI scales have historically been criticized for lacking in consistency, reliability, validity, scoring anchors, and responsiveness.[33-35] Further information on the validity of these outcomes is provided in Appendix 5.

- Self-reports of illicit opioid use was collected in the format of a timeline follow-back interview, which was administered electronically by an interviewer. The interview instrument required patients to retrospectively estimate their drug use in the 30 days prior to screening, as well as the last visit at all subsequent visits, by answering with use or no use. The drugs also assessed the illicit use of opioids, cocaine, barbiturates, benzodiazepines, amphetamines/methamphetamine, phencyclidine, and ethanol. As a result, this interview format may have been impacted by the truthfulness of responses and recall bias, as well as non-response bias. In addition, since there were significantly higher dropout rates in the placebo group, it is difficult to rule out whether this self-reported end point were impacted by patients becoming aware of their treatment assignments due to the nature of the intervention of the onset of symptoms of opioid-related withdrawal.
- Study 13-0001 demonstrated superiority of both the 300 mg/300 mg regimen and 300 mg/100 mg regimen over placebo in the patient population; however, the study design did not allow direct comparisons to be made between BUP-ER dosage arms, the 300 mg/100 mg regimen arm being most consistent with the recommended dosage in the Health Canada monograph.[5] The manufacturer provided comments on a draft of the CDR review report and noted that the use of a placebo control group was discussed with the FDA, and that the FDA agreed to a placebo-controlled trial plus IDC as there was no consensus regarding a standard treatment for OUD at the time Study 13-0001 was designed. The FDA also agreed to use of a placebo group in order to assess the safety of the BUP-ER injections relative to injections without the drug.The manufacturer also suggested that a comparison with, for example, daily buprenorphine would have created bias. Patients receiving daily treatment with buprenorphine would have had a higher behavioural burden because they would have to come for doses more frequently, and might have been more likely to withdraw, which could have biased the outcome of the study.
- There was no assessment of balance undertaken and no formal test of interaction performed for subgroups of interest, such as patients with a history of injectable opioid use. Due to this, results for subgroups should be interpreted with caution.

External Validity

- The appropriateness of a placebo control group is questionable, as the original protocol design had patients in the placebo group inducted on sublingual buprenorphine/ naloxone and then issued placebo injections over a period of 24 weeks, with no access to any form of opioid maintenance or rescue therapy for withdrawal. This protocol was amended about one year later at the request of the FDA to include a five-day taper in order to preserve blinding in the placebo group of the trial; however, this was only administered to 32% of the study population. Though this amendment mitigated some concerns, treatment in the placebo arm of the trial is inconsistent with current guidelines for treating opioid use disorders.[1] As a result, the choice of comparator risks

overestimating the treatment effect of the BUP-ER arms among patients with OUD in Canada, given their access to current opioid maintenance therapy interventions.

- In Study 13-0001, 1,187 patients were screened for inclusion, of which only 504 patients were randomized to begin the 24-week double-blind treatment phase of this study. Of those, 682 (57.5%) were recorded as screen failures. In addition, about one-quarter of the patients who entered the run-in period (161 out of 665) were not randomized. The exclusion criteria in Study 13-0001 was extended to patients with any concurrent substance use disorder (excluding cocaine, cannabis, tobacco, and alcohol), as well as those meeting *DSM-5* criteria for either moderate or severe cocaine, alcohol, or cannabis use disorder. According to the clinical expert involved in this review, concurrent substance use disorders are very common in this patient population, and cannabis use is especially prevalent. However, it should be noted that 47% (BUP-ER 300 mg/300 mg), 55% (BUP-ER 300 mg/100 mg), and 53% (placebo) reported concomitant cannabis use; 40% (BUP-ER 300 mg/300 mg), 47% (BUP-ER 300 mg/ 100 mg), and 42% (placebo) reported cocaine use; and approximately 90% reported alcohol and tobacco use at screening.[27] No additional information was reported describing the nature or degree of use of these substances. Similarly, patients with uncontrolled psychiatric comorbidities (i.e., depression, post-traumatic stress disorder, anxiety) were also to be excluded from this trial, which are well-known to occur among patients with OUD.[1,36,37] However, 11% to 14% of patients reported depression and approximately 10% of patients across groups reported anxiety at baseline.[27] Also, patients with infective endocarditis were excluded from this study. Stringent inclusion and exclusion criteria can potentially lead to the inclusion of a select group of patients, which may not be representative of population of patients with moderate-to-severe OUD in Canada who are seeking MAT and can potentially limit the generalizability of the trial results. Moreover, lack of details regarding those with relevant concurrent substance use and comorbid conditions makes it difficult to assess the characteristics of the patient population.
- The majority of patients who were enrolled in Study 13-0001 were white (72%) and male (66.4%), with a mean age of 39.5 years. A breakdown of social characteristics (i.e., housing, employment, past criminality) of the study population was not provided. Regarding concurrent medical history, 13.3% of patients in the study had hepatitis C and 0.1% had HIV, and regarding concurrent psychiatric history, 12.9% had depression and 9.6% had anxiety documented. These rates are much lower than what is found in the general population,[1,36-38] and therefore may be more likely to have positive outcomes. Generalizability is also uncertain for patients who belong to marginalized or socially disadvantaged populations (i.e., homeless or jobless patients) as well as specific high-risk population of interest, such as youth or Indigenous peoples, and those with chronic pain, who have not been represented in this study.[37] Lastly, this trial was conducted in the US, where the management of opioid dependence may be different to Canada, according to the clinical expert consulted for this review.
- The clinical expert involved in this review deemed the length of induction of sublingual buprenorphine/ naloxone and dosage adjustment period, as well as the length and respective dosages of the five-day taper with sublingual buprenorphine/naloxone and dose regimen to be reasonable due to the long half-life of buprenorphine itself.
- The included study focused on short-term outcomes and does not provide evidence of observed reductions or patient control of drug use that are of clinical and social benefit. In addition, questions around the impact of BUP-ER on patient-important outcomes,

such as health-related quality of life, work productivity, and incarceration rates, were not available for this trial.

- The clinical expert involved in this review raised the issue of the increased sensitivity to pain in this patient population, and whether this could impact a patient's willingness to receive an injectable medication to treat OUD. When applying the utility of BUP-ER subcutaneous injections to a larger population of patients with OUD, previous studies have shown that patients receiving opioid treatment report a higher pain intensity and unpleasantness score in response to needle insertion for subcutaneous injection compared with patients receiving non-opioid treatment.[39] The clinical expert also stressed the importance of considering the impact of health care professionals injecting certain patients who may have previously been injecting themselves.
- All randomized patients in this trial received manual-guided individual behavioural counselling as well as IDC once weekly in addition to pharmacotherapy, administered by an appropriately qualified and trained staff member at the site. The focus of this counselling program was around a 12-step approach, which differs from current Canadian programs that come from a harm-reduction approach. The clinical expert involved in this study added that most prescribers in Canada provide brief behavioural intervention during visits, which are provided on a weekly bases in the early part of treatment and can increase in duration depending on negative urine tests. Intense counselling by a separate provider is usually unlikely to happen in the Canadian patient population. Furthermore, weekly individual counselling in this trial was voluntary and study treatments were administered monthly, limiting the requirement for patients to engage in or attend weekly sessions.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Table 3.

Primary Efficacy End Point

The primary end point in this trial was the CDF of percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use, referred to as "percentage abstinence." Table 15 presents the CDF values at different percentages of negative drug use in 10% increments. Both arms of BUP-ER regimens were found to be statistically significantly better than placebo from week 5 to week 24 (P value < 0.0001 for each BUP-ER regimen compared with placebo, based on the Wilcoxon rank sum test). The placebo-subtracted mean per cent abstinence values were 38% for the BUP-ER 300 mg/100 mg regimen and 36% for the BUP-ER 300 mg/300 mg regimen. Missing UDS samples and self-reports were imputed as positive in the primary analysis; however, only about 12 to 13% of patients in each of the two active groups had no positive or missing samples or self-reports of illicit use from week 5 to week 24 compared with 1% of patients in the placebo arm. The total proportion of patients with missing urine drug samples that needed to be positively imputed from week 5 to week 24 was 33%, and the total proportion of patients with missing self-reports of illicit opioid use needing to be positively imputed was 34%.

The secondary outcome, treatment success, was defined as any patient with 80% or more of urine samples negative for opioids combined with self-reports negative for illicit opioid use between week 5 and week 24 (Table 15). The results for this outcome were statistically significantly higher in both the BUP-ER 300 mg/100 mg (28.4%) and the 300 mg/300 mg

(29.1%) groups compared with placebo (2.0%) in the full analysis set ($P < 0.0001$ for both active treatment arms compared with placebo).

Table 15: Cumulative Distribution Function of the Percentage Urine Drug Samples Negative for Opioids Combined With Self-Reports Negative for Illicit Opioid Use (Percentage Abstinence) From Week 5 Through Week 24 — Full Analysis Set (mITT)[a]

Percentage Abstinence	Number (%) of Patients		
	BUP-ER 300 mg/100 mg + IDC (N = 194)	BUP-ER 300 mg/300 mg + IDC (N = 196)	Placebo + IDC (N = 99)
≥ 0%	194 (100.0)	196 (100.0)	99 (100.0)
≥ 10%	139 (71.6)	126 (64.3)	11 (11.1)
≥ 20%	115 (59.3)	111 (56.6)	7 (7.1)
≥ 30%	101 (52.1)	101 (51.5)	6 (6.1)
≥ 40%	90 (46.4)	90 (45.9)	6 (6.1)
≥ 50%	86 (44.3)	82 (41.8)	4 (4.0)
≥ 60%	78 (40.2)	70 (35.7)	4 (4.0)
≥ 70%	66 (34.0)	67 (34.2)	2 (2.0)
≥ 80%	55 (28.4)	57 (29.1)	2 (2.0)
≥ 90%	41 (21.1)	48 (24.5)	2 (2.0)
100%	25 (12.9)	23 (11.7)	1 (1.0)
P value[b] (comparison with placebo + IDC)	< 0.0001	< 0.0001	–
Mean (SD)	42.7% (38.50%)	41.3% (39.66%)	5.0% (16.98%)
Median	32.5%	30.0%	0.0%
Minimum, maximum	0% to 100%	0% to 100%	0% to 100%

BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling; mITT = modified intention-to-treat; SD = standard deviation.

[a] Patients from Site 20 (n = 15) were excluded from the analysis. All missing results for opioids were considered non-negative.

[b] Wilcoxon rank sum test was used to compare treatment groups. Each dose regimen was compared with placebo with respect to the composite primary end point at a significance level of alpha equals 0.025.

Source: Clinical study report for Study 13-0001.[6]

Table 16 represents the breakdown of the proportion of patients by treatment group considered abstinent (with a UDS sample negative for opioids combined with self-reports negative for illicit opioids) collected at different time points from week 5 to week 24. Patients in the 300 mg/100 mg group and 300 mg/300 mg group were found to have similar rates of abstinence throughout week 5 and week 24 (35.1% to 47.4% in the 300 mg/100 mg group and 38.8% to 45.4% in the 300 mg/300 mg group). The rates of abstinence were lower over these time points in the placebo group (2.0% to 11.1%). At week 24, the difference between the two dose regimens and placebo in percentage abstinence was statistically significant with *P* value < 0.0001 for each active treatment group based on the Cochran-Mantel-Haenszel test. It is also noted that there was a significantly higher proportion of patients who completed the study in the active treatment groups (61.3% in the 300 mg/100 mg group and 64.3%% in the 300 mg/300 mg group) compared with the placebo group (33.3%), and all missing data were considered non-negative for opioids.

Table 16: Weekly Percentage Abstinence From Week 5 Through Week 24 — Full Analysis Set (mITT)[a]

Week	Number (%) of Patients		
	BUP-ER 300 mg/100 mg + IDC (N = 194)	BUP-ER 300 mg/300 mg + IDC (N = 196)	Placebo + IDC (N = 99)
Week 5	92 (47.4)	78 (39.8)	11 (11.1)
Week 6	92 (47.4)	89 (45.4)	9 (9.1)
Week 7	94 (48.5)	88 (44.9)	7 (7.1)
Week 8	92 (47.4)	89 (45.4)	6 (6.1)
Week 9	87 (44.8)	83 (42.3)	5 (5.1)
Week 10	88 (45.4)	82 (41.8)	6 (6.1)
Week 11	88 (45.4)	76 (38.8)	6 (6.1)
Week 12	87 (44.8)	80 (40.8)	4 (4.0)
Week 13	82 (42.3)	79 (40.3)	5 (5.1)
Week 14	79 (40.7)	82 (41.8)	4 (4.0)
Week 15	81 (41.8)	81 (41.3)	6 (6.1)
Week 16	75 (38.7)	81 (41.3)	4 (4.0)
Week 17	86 (44.3)	77 (39.3)	4 (4.0)
Week 18	82 (42.3)	79 (40.3)	4 (4.0)
Week 19	73 (37.6)	79 (40.3)	5 (5.1)
Week 20	82 (42.3)	78 (39.8)	4 (4.0)
Week 21	79 (40.7)	77 (39.3)	3 (3.0)
Week 22	79 (40.7)	77 (39.3)	2 (2.0)
Week 23	68 (35.1)	79 (40.3)	2 (2.0)
Week 24	71 (36.6)	87 (44.4)	2 (2.0)
P value (vs. Placebo + IDC)	< 0.0001	< 0.0001	–
Patients considered completers[b] at week 24	119 (61.3)	126 (64.3)	33 (33.3)
P value (vs. Placebo + IDC)	< 0.0001	< 0.0001	–

BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling; mITT = modified intention-to-treat; SD = standard deviation; vs. = versus.

Note: All missing data were considered non-negative for opioids.

[a] Patients from Site 20 (n = 15) were excluded from the analysis. All missing results for opioids were considered non-negative.

[b] A completer was defined as a patient who completed the week 24 visit (either urine drug screen or timeline follow-back assessment).

Source: Clinical study report for Study 13-0001.[6]

Table 17 summarizes the CDF of the percentage of urine drug samples negative for opioid use alone in 10% increments, without combining with results from the TLFB assessment of self-reports negative for opioid use. Results for this outcome appear to be similar to composite primary end point.

Table 17: Cumulative Distribution Function of the Percentage Urine Drug Samples Negative for Opioid Use From Week 5 Through Week 24 — Full Analysis Set (mITT)[a]

Percentage UDS Negative for Opioid Use	Number (%) of Patients		
	BUP-ER 300 mg/100 mg + IDC (N = 194)	BUP-ER 300 mg/300 mg + IDC (N = 196)	Placebo + IDC (N = 99)
≥ 0%	194 (100.0)	196 (100.0)	99 (100.0)
≥ 10%	140 (72.2)	129 (65.8)	17 (17.2)
≥ 20%	120 (61.9)	114 (58.2)	9 (9.1)
≥ 30%	106 (54.6)	109 (55.6)	8 (8.1)
≥ 40%	97 (50.0)	98 (50.0)	7 (7.1)
≥ 50%	91 (46.9)	88 (44.9)	6 (6.1)
≥ 60%	82 (42.3)	74 (37.8)	5 (5.1)
≥ 70%	73 (37.6)	69 (35.2)	4 (4.0)
≥ 80%	64 (33.0)	61 (31.1)	4 (4.0)
≥ 90%	47 (24.2)	51 (26.0)	2 (2.0)
P value[b] (comparison with placebo + IDC)	< 0.0001	< 0.0001	–
Mean (SD)	46.0% (39.58%)	43.8% (40.24%)	7.0% (19.34%)
Median	37.5%	37.5%	0.0%
Minimum, maximum	0% to 100%	0% to 100%	0% to 100%

BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling; mITT = modified intention-to-treat; UDS = urine drug screen; SD = standard deviation.

[a] Patients from Site 20 (n = 15) were excluded from the analysis. All missing results for opioids were considered non-negative.

[b] Wilcoxon rank sum test was used to compare treatment groups. Each dose regimen was compared with placebo with respect to the composite primary end point at a significance level of alpha equals 0.025.

Source: Clinical study report for Study 13-0001.[6]

Table 18 summarizes the CDF of the percentage of self-reports negative for opioid use alone in 10% increments, without combining with urine drug screens. Mean overall values appear to be slightly higher than those associated with the composite primary end point.

Table 18: Cumulative Distribution Function of the Percentage of Self-Reports Negative from Week 5 Through Week 24 — Full Analysis Set (mITT)[a]

Percentage UDS Negative for Opioid Use	Number (%) of Patients		
	BUP-ER 300 mg/100 mg + IDC (N = 194)	BUP-ER 300 mg/300 mg + IDC (N = 196)	Placebo + IDC (N = 99)
≥ 0%	194 (100.0)	196 (100.0)	99 (100.0)
≥ 10%	163 (84.0)	162 (82.7)	37 (37.4)
≥ 20%	155 (79.9)	152 (77.6)	29 (29.3)
≥ 30%	139 (71.6)	139 (70.9)	24 (24.2)
≥ 40%	132 (68.0)	132 (70.9)	20 (20.2)
≥ 50%	125 (64.4)	125 (63.8)	18 (18.2)
≥ 60%	120 (61.9)	117 (59.7)	17 (17.2)
≥ 70%	108 (55.7)	112 (57.1)	14 (14.1)

Percentage UDS Negative for Opioid Use	Number (%) of Patients		
≥ 80%	102 (52.6)	101 (51.5)	9 (9.1)
≥ 90%	92 (47.4)	91 (46.4)	7 (7.1)
P value[b] (comparison with placebo + IDC)	< 0.0001	< 0.0001	–
Mean (SD)	63.0% (38.59)	62.1% (39.56%)	19.1% (31.41%)
Median	85.0%	85.0%	0.0%
Minimum, Maximum	0% to 100%	0% to 100%	0% to 100%

BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling; mITT = modified intention-to-treat; UDS = urine drug screen; SD = standard deviation.

[a] Patients from Site 20 (n = 15) were excluded from the analysis. All missing results for self-reports were considered positive.

[b] Wilcoxon rank sum test was used to compare treatment groups. Each dose regimen was compared with placebo with respect to the composite primary end point at a significance level of alpha equals 0.025.

Source: Clinical study report for Study 13-0001.[6]

Withdrawal and Cravings

In Study 13-0001, the mean SOWS, COWS, and desire- or need-to-use VAS scores in all three treatment groups were measured during the double-blind period of the study, from baseline to week 24.

The SOWS was completed weekly by patients in order to assess their perception of opiate withdrawal symptoms throughout the double-blind treatment period, in the form of a 16-item scale. Further information about this outcome is detailed in Appendix 5.

The total scores by week from baseline to week 24 in the full analysis set are provided in Table 19. The mean SOWS total score at baseline were similar between all groups (3.6 in the 300 mg/100 mg group, 4.4 in the 300 mg/300 mg group, and 4.5 in the placebo group). Beyond the baseline values, the mean total scores in both active treatment groups were numerically lower than those of the placebo group. The change from baseline in SOWS total scores were analyzed using MMRM and compared with placebo. The difference in least squares means for the active treatment groups at week 24 compared with placebo was statistically significant for the 300 mg/300 mg group (–2.6) and not for the 300 mg/100 mg group (–1.6). However, the clinical relevance of these results are uncertain, since there is no identified MCID for this scale.

Table 19: Mean Subjective Opiate Withdrawal Scale From Weeks 1 to 24 by Treatment Group — Full Analysis Set (mITT)[a]

Week		SOWS Score		
		BUP-ER 300 mg/100 mg + IDC (N = 194)	**BUP-ER 300 mg/300 mg + IDC (N = 196)**	**Placebo + IDC (N = 99)**
Week 1, day 1 (baseline)	N	192	196	99
	Mean (SD)	3.6 (5.42)	4.4 (6.12)	4.5 (5.64)
Week 1, day 2	N	192	195	96
	Mean (SD)	3.7 (5.49)	3.2 (4.65)	4.9 (6.96)
Week 2	N	183	193	84
	Mean (SD)	3.9 (7.14)	3.7 (5.76)	9.1 (11.24)
Week 3	N	174	185	76

Week		SOWS Score		
	Mean (SD)	3.6 (6.62)	3.3 (5.73)	7.4 (9.66)
Week 4	N	174	181	68
	Mean (SD)	3.1 (6.20)	3.1 (5.91)	5.9 (7.57)
Week 5, day 1	N	168	171	60
	Mean (SD)	2.9 (5.08)	3.1 (5.35)	6.3 (8.94)
Week 5, day 2	N	160	165	59
	Mean (SD)	1.7 (3.50)	1.6 (2.90)	3.7 (6.07)
Week 6	N	160	162	57
	Mean (SD)	2.2 (5.41)	1.3 (2.49)	4.8 (7.54)
Week 7	N	161	162	52
	Mean (SD)	1.9 (4.32)	1.6 (3.07)	5.1 (8.10)
Week 8	N	157	160	54
	Mean (SD)	1.7 (3.95)	1.5 (2.85)	4.2 (6.80)
Week 9, day 1	N	156	155	49
	Mean (SD)	2.5 (4.80)	2.1 (3.80)	6.0 (10.72)
Week 9, day 2	N	155	151	49
	Mean (SD)	1.5 (3.16)	1.2 (2.66)	4.3 (7.05)
Week 10	N	148	150	49
	Mean (SD)	1.8 (3.96)	1.6 (2.90)	4.8 (7.97)
Week 11	N	144	148	45
	Mean (SD)	2.0 (4.32)	1.5 (2.89)	5.2 (8.00)
Week 12	N	143	146	46
	Mean (SD)	2.1 (4.28)	1.7 (4.32)	5.2 (7.62)
Week 13, day 1	N	145	146	42
	Mean (SD)	2.4 (4.39)	2.2 (4.32)	4.4 (6.71)
Week 13, day 2	N	142	142	42
	Mean (SD)	1.4 (3.39)	1.2 (2.93)	3.9 (6.24)
Week 14	N	138	143	40
	Mean (SD)	1.6 (3.52)	1.5 (3.56)	5.0 (7.88)
Week 15	N	135	137	40
	Mean (SD)	2.1 (6.31)	1.8 (5.06)	5.1 (8.33)
Week 16	N	136	136	39
	Mean (SD)	1.7 (3.64)	1.6 (3.45)	4.7 (7.76)
Week 17, day 1	N	138	133	38
	Mean (SD)	2.2 (4.76)	2.1 (5.22)	4.8 (7.28)
Week 17, day 2	N	134	131	36
	Mean (SD)	1.2	1.5	3.8
Week 18	N	131	130	36
	Mean (SD)	1.5 (4.67)	1.5 (3.96)	5.8 (11.04)
Week 19	N	128	134	34
	Mean (SD)	1.8 (4.64)	1.5 (4.01)	3.4 (6.56)
Week 20	N	129	128	36
	Mean (SD)	2.2 (5.62)	1.5 (3.69)	3.3 (6.58)
Week 21, day 1	N	131	130	35

Week		SOWS Score		
	Mean (SD)	2.6 (5.50)	2.5 (5.48)	4.5 (7.18)
Week 21, day 2	N	126	125	35
	Mean (SD)	2.1 (5.10)	1.6 (3.60)	4.7 (7.60)
Week 22	N	126	125	34
	Mean (SD)	2.3 (5.33)	1.3 (3.11)	3.4 (6.78)
Week 23	N	121	122	34
	Mean (SD)	2.2 (4.98)	1.1 (2.65)	5.3 (8.51)
Week 24	N	119	125	33
	Mean (SD)	2.4 (5.31)	1.3 (3.25)	4.9 (8.67)
Mean change in SOWS score from week 5 to week 24 (SD) [95% CI]		–0.3 (4.83) [–1.2 to 0.6]	–1.5 (3.22) [–2.1 to –0.9]	–1.7 (5.21) [–3.6 to 0.1]
LS mean change treatment effects at week 24 from baseline (SE) [95% CI]		-0.9 (0.51) [–1.93 to 0.10]	–2.0 (0.51) [–2.96 to –0.94]	0.7 (0.80) [–0.91 to 2.23]
Pairwise comparisons at week 24 compared with placebo + IDC groups		–1.6 (0.87) [–3.29 to 0.14)	–2.6 (0.87) [–4.32 to –0.90]	–
P value		0.0726	0.0028	–

BUP-ER = buprenorphine extended-release; CI = confidence interval; IDC = behavioural counselling/individual drug counselling; mITT = modified intention-to-treat; SD = standard deviation; SE = standard error; SOWS = subjective opiate withdrawal scale.

[a] Patients from Site 20 (n = 15) were excluded from the analysis.

Source: Clinical study report for Study 13-0001.[6]

The COWS was recorded throughout this study by clinicians to assess signs and symptoms of opiate withdrawal. Randomization criteria stipulated that patients have a COWS score below 12 after at least seven days of buprenorphine/naloxone sublingual film therapy.

Table 20 displays the mean COWS total scores recorded by week from baseline to week 24 of the double-blind treatment period. Mean COWS scores at baseline were similar between all three groups. Beyond the baseline score, there was a slight increase in COWS mean score in the placebo group compared with active treatment; however, the mean score was similar between all groups by the end of the double-blind treatment phase.

Table 20: Mean Clinical Opiate Withdrawal Scale From Weeks 1 to 24 by Treatment Group — Full Analysis Set (mITT)[a]

Week		COWS Score		
		BUP-ER 300 mg/100 mg + IDC (N = 194)	**BUP-ER 300 mg/300 mg + IDC (N = 196)**	**Placebo + IDC (N = 99)**
Week 1, day 1 (baseline)	N	191	192	97
	Mean (SD)	2.1 (2.31)	2.2 (2.56)	2.3 (2.50)
Week 1, day 2	N	191	195	96
	Mean (SD)	2.2 (2.74)	1.9 (2.11)	2.8 (3.52)
Week 2	N	183	192	84
	Mean (SD)	2.2 (3.00)	1.9 (2.34)	4.4 (5.17)
Week 3	N	174	184	75
	Mean (SD)	1.9 (2.59)	1.5 (2.21)	3.5 (3.96)
Week 4	N	174	181	67

Week		COWS Score		
	Mean (SD)	1.5 (2.10)	1.7 (2.59)	2.5 (2.78)
Week 5, day 1	N	166	170	60
	Mean (SD)	1.7 (2.59)	1.7 (2.26)	3.1 (3.62)
Week 5, day 2	N	160	164	59
	Mean (SD)	1.3 (1.75)	1.1 (1.48)	1.9 (2.29)
Week 6	N	160	162	57
	Mean (SD)	1.4 (2.75)	1.0 (1.36)	2.3 (2.88)
Week 7	N	161	162	51
	Mean (SD)	1.1 (1.49)	1.1 (1.56)	1.9 (2.65)
Week 8	N	157	160	54
	Mean (SD)	1.1 (1.56)	1.1 (1.49)	2.1 (3.08)
Week 9, day 1	N	155	155	49
	Mean (SD)	1.6 (2.23)	1.5 (2.11)	2.8 (4.03)
Week 9, day 2	N	155	151	49
	Mean (SD)	1.2 (1.72)	1.1 (1.70)	1.9 (2.35)
Week 10	N	147	150	49
	Mean (SD)	1.3 (1.74)	1.0 (1.49)	2.1 (3.10)
Week 11	N	144	148	45
	Mean (SD)	1.4 (2.16)	1.1 (1.82)	2.1 (2.83)
Week 12	N	143	145	46
	Mean (SD)	1.3 (2.04)	1.2 (2.05)	2.6 (3.14)
Week 13, day 1	N	145	146	42
	Mean (SD)	1.6 (2.34)	1.4 (2.23)	2.0 (2.81)
Week 13, day 2	N	142	142	42
	Mean (SD)	1.6 (2.22)	0.9 (1.67)	1.6 (2.55)
Week 14	N	137	143	40
	Mean (SD)	1.1 (1.59)	1.1 (1.80)	2.3 (3.51)
Week 15	N	135	134	40
	Mean (SD)	1.1 (2.05)	1.2 (2.11)	2.3 (3.23)
Week 16	N	136	136	39
	Mean (SD)	1.0 (1.49)	0.9 (1.43)	1.8 (2.61)
Week 17, day 1	N	138	133	38
	Mean (SD)	1.4 (2.19)	1.3 (2.06)	1.8 (2.30)
Week 17, day 2	N	134	131	36
	Mean (SD)	1.1 (1.86)	0.9 (1.63)	1.9 (2.53)
Week 18	N	131	130	36
	Mean (SD)	1.0 (1.78)	0.8 (1.49)	2.3 (3.54)
Week 19	N	128	133	34
	Mean (SD)	1.1 (1.73)	1.0 (1.79)	1.4 (2.36)
Week 20	N	129	128	36
	Mean (SD)	1.1 (1.95)	0.8 (1.47)	1.7 (2.31)
Week 21, day 1	N	131	130	35
	Mean (SD)	1.5 (2.40)	1.3 (2.03)	1.7 (2.01)
Week 21, day 2	N	124	125	35
	Mean (SD)	1.2 (2.22)	1.1 (1.64)	2.0 (2.83)

Week		COWS Score		
Week 22	N	126	125	34
	Mean (SD)	1.0 (1.87)	0.9 (1.59)	1.4 (2.02)
Week 23	N	121	121	33
	Mean (SD)	1.1 (2.01)	0.9 (1.36)	1.5 (2.40)
Week 24	N	118	124	33
	Mean (SD)	1.5 (2.59)	0.8 (1.37)	1.9 (2.38)
Mean change in COWS score from week 5 to week 24 (SD) [95% CI]		–0.2 (2.74) [–0.7 to 0.3]	–0.8 (1.99) [–1.1 to –0.4]	–1.4 (2.72) [–2.4 to –0.5]
LS mean change treatment effects at week 24 from baseline (SE) [95% CI]		–0.5 (0.22) [–0.94 to –0.09]	–1.1 (0.21) [–1.53 to –0.69]	–0.1 (0.35) [–0.82 to 0.55]
Pairwise comparisons at week 24 compared with placebo + IDC groups		–0.4 (0.38) [–1.13 to 0.36]	–1.0 (0.38) [–1.72 to –0.23]	–
P value		0.3143	0.0101	–

BUP-ER = buprenorphine extended-release; CI = confidence interval; COWS = clinical opiate withdrawal scale; IDC = behavioural counselling/individual drug counselling; mITT = modified intention-to-treat; SD = standard deviation; SE = standard error.

Note: *P* values derived from mixed model for repeated measures for change from baseline in COWS score.

[a] Patients from Site 20 (n = 15) were excluded from the analysis.

Source: Clinical study report for Study 13-0001.[6]

Mean opioid craving VAS scores throughout the double-blind treatment phase of the study are summarized in Table 21. The mean opioid craving VAS scores were generally low at baseline (5.5 in the 300 mg/100 mg group, 7.1 in the 300 mg/300 mg group, and 9.5 in the placebo group) with a slightly higher score in the placebo group. There was, however, a drastic increase in these scores in the placebo group from week 2 and these remained relatively high at week 24 (mean score, 17.1; standard error [SE], 25.4). There was a significant difference from baseline to week 24, with a least squares mean change in VAS score of 11.5 (SE, 2.48; 95% confidence interval [CI], 6.64 to 16.38). Mean scores in the active treatment groups were maintained at a low score throughout the double-blind period, with no significant change from baseline to week 24 in either group.

Table 21: Mean Opioid Craving Visual Analog Scale From Weeks 1 to 24 by Treatment Group — Full Analysis Set (mITT)[a]

Week		Opioid Craving VAS Score		
		BUP-ER 300 mg/100 mg + IDC (N = 194)	**BUP-ER 300 mg/300 mg + IDC (N = 196)**	**Placebo + IDC (N = 99)**
Week 1, day 1 (baseline)	N	192	193	97
	Mean (SD)	5.5 (10.97)	7.1 (13.29)	9.5 (16.94)
Week 1, day 2	N	192	195	96
	Mean (SD)	6.0 (1.71)	5.6 (11.80)	12.1 (21.07)
Week 2	N	183	193	84
	Mean (SD)	8.1 (17.23)	7.0 (14.89)	26.9 (28.88)
Week 3	N	175	185	76
	Mean (SD)	7.9 (15.70)	7.9 (17.91)	26.4 (28.38)
Week 4	N	174	181	68
	Mean (SD)	6.4 (14.67)	8.5 (19.07)	23.1 (26.73)

Week		Opioid Craving VAS Score		
Week 5, day 1	N	168	171	60
	Mean (SD)	6.3 (14.77)	7.4 (16.33)	22.5 (27.20)
Week 5, day 2	N	160	165	59
	Mean (SD)	3.1 (9.65)	3.5 (10.02)	14.2 (21.25)
Week 6	N	160	162	57
	Mean (SD)	4.9 (13.49)	3.7 (10.11)	18.5 (25.35)
Week 7	N	161	162	52
	Mean (SD)	4.0 (10.88)	4.7 (13.79)	18.8 (25.67)
Week 8	N	157	160	54
	Mean (SD)	4.4 (12.09)	5.4 (14.55)	18.9 (23.79)
Week 9, day 1	N	156	155	49
	Mean (SD)	4.8 (12.79)	4.4 (10.78)	18.6 (26.50)
Week 9, day 2	N	155	151	49
	Mean (SD)	3.2 (8.60)	3.0 (8.40)	16.3 (24.82)
Week 10	N	148	150	49
	Mean (SD)	3.5 (8.02)	3.7 (9.44)	20.9 (27.34)
Week 11	N	144	148	45
	Mean (SD)	4.2 (11.30)	3.3 (9.68)	24.8 (29.70)
Week 12	N	143	146	46
	Mean (SD)	4.2 (12.65)	3.6 (10.21)	22.5 (30.04)
Week 13, day 1	N	145	146	42
	Mean (SD)	3.6 (9.06)	4.7 (12.95)	23.8 (30.12)
Week 13, day 2	N	142	142	42
	Mean (SD)	2.2 (6.79)	3.5 (11.57)	17.3 (25.69)
Week 14	N	138	143	40
	Mean (SD)	4.7 (13.56)	4.7 (12.56)	20.8 (25.15)
Week 15	N	135	137	40
	Mean (SD)	5.0 (15.52)	4.1 (12.47)	21.1 (27.03)
Week 16	N	136	136	39
	Mean (SD)	4.3 (13.80)	4.6 (12.04)	20.7 (28.15)
Week 17, day 1	N	138	133	38
	Mean (SD)	4.3 (13.38)	5.2 (13.55)	18.7 (25.90)
Week 17, day 2	N	134	131	36
	Mean (SD)	3.6 (11.74)	4.5 (12.95)	16.9 (26.13)
Week 18	N	131	130	36
	Mean (SD)	4.7 (14.05)	3.4 (8.55)	21.1 (29.40)
Week 19	N	128	134	34
	Mean (SD)	4.5 (15.25)	3.4 (10.83)	18.0 (27.90)
Week 20	N	129	128	36
	Mean (SD)	5.2 (15.99)	4.1 (11.31)	17.3 (25.92)
Week 21, day 1	N	131	130	35
	Mean (SD)	5.1 (15.62)	5.2 (14.54)	18.8 (27.56)
Wek 21, day 2	N	126	125	35
	Mean (SD)	4.8 (15.60)	3.9 (11.37)	22.5 (30.45)
Week 22	N	126	125	34

Week		Opioid Craving VAS Score		
	Mean (SD)	5.8 (17.91)	3.4 (10.35)	21.0 (30.50)
Week 23	N	121	122	34
	Mean (SD)	6.1 (16.63)	2.6 (7.25)	16.2 (27.53)
Week 24	N	119	125	33
	Mean (SD)	6.8 (17.77)	3.2 (10.11)	17.1 (25.04)
LS mean change in opioid craving VAS from baseline to week 24 (SE) [95% CI]		2.1 (1.63) [–1.16 to 5.31]	–0.9 (1.63) [–4.11 to 2.34]	11.5 (2.48) [6.64 to 16.38]
Pairwise comparisons at week 24 compared with placebo + IDC groups		–9.4 (2.62) [–14.56 to –4.30]	–12.4 (2.61) [–17.51 to –7.28]	–
P value		0.0003	< 0.0001	–

BUP-ER = buprenorphine extended-release; CI = confidence interval; IDC = behavioural counselling/individual drug counselling; LS = least squares; mITT = modified intention-to-treat; SD = standard deviation; SE = standard error; VAS = Visual Analog Scale.

Note: *P* values derived from mixed model for repeated measures for change from baseline in opioid craving VAS score.

[a] Patients from Site 20 (n = 15) were excluded from the analysis.

Source: Clinical study report for Study 13-0001.[6]

The CGI-I was to be completed at five-week intervals by clinicians in order to determine the change in clinical status over time. The range on this scale begins at 1, to indicate very much improved, to a max of 7, to indicate very much worse.

Table 22 summarizes the results for CGI-I throughout the study. Mean values were similar between groups at baseline (2.1 to 2.2), and slightly decreased over time in the active treatment groups, while slightly increasing in the placebo group. Final values in the active treatment groups were 1.5 to 1.6, compared with 2.4 in the placebo group.

Table 22: Clinical Global Impression Scale for Improvement From Weeks 1 to 24 by Treatment Group — Full Analysis Set (mITT)[a]

Week		Mean (SD) CGI-I Score		
		BUP-ER 300 mg/100 mg + IDC (N = 194)	**BUP-ER 300 mg/300 mg + IDC (N = 196)**	**Placebo + IDC (N = 99)**
Week 1, day 1 (baseline)	N	190	192	97
	Mean (SD)	2.1 (0.91)	2.1 (0.95)	2.2 (0.94)
Week 5	N	166	170	60
	Mean (SD)	1.8 (0.79)	1.8 (0.77)	2.7 (1.20)
Week 9	N	155	155	49
	Mean (SD)	1.8 (0.73)	1.7 (0.79)	2.4 (1.10)
Week 13	N	145	146	42
	Mean (SD)	1.7 (0.78)	1.7 (0.72)	2.8 (1.27)
Week 17	N	138	133	38
	Mean (SD)	1.6 (0.70)	1.8 (0.82)	2.9 (1.12)
Week 21	N	131	130	35
	Mean (SD)	1.7 (0.77)	1.6 (0.74)	2.7 (1.28)
LS mean treatment effects at week 24 (SE) [95% CI]		1.6 (0.11) [1.43 to 1.87]	1.5 (0.11) [1.27 to 1.71]	2.4 (0.15) [2.07 to 2.65]

Week	Mean (SD) CGI-I Score		
Pairwise comparisons at week 24 compared with Placebo + IDC groups, [95% CI]	–0.7 (0.13) [–0.96 to –0.46]	–0.9 (0.13) [–1.12 to –0.62]	–
P value	< 0.0001	< 0.0001	–

BUP-ER = buprenorphine extended-release; CGI-I = Clinical Global Scale for Improvement; CI = confidence interval; IDC = behavioural counselling/individual drug counselling; LS = least squares; mITT = modified intention-to-treat; SD = standard deviation; SE = standard error.

Note: *P* values derived from mixed model for repeated measures for change from baseline in CGI-I score.

[a] Patients from Site 20 (n = 15) were excluded from the analysis.

Source: Clinical study report for Study 13-0001.[6]

The CGI-S was also to be completed at the same five-week intervals as the CGI-I scale by clinicians in order to rate the severity of patient symptoms. The range on this scale begins at 1, to indicate normal, to a max of 7, which interference in many life functions.

Table 23 summarizes results for CGI-S at various time points throughout the study. Mean values were similar between groups at baseline (2.5 to 2.7), and slightly decreased over time in the active treatment groups, while slightly increasing in the placebo group. Final values in the active treatment groups were 1.9 to 2.0, compared with 3.1 in the placebo group.

Table 23: Clinical Global Impression Scale for Severity From Weeks 1 to 24 by Treatment Group — Full Analysis Set (mITT)[a]

Week		Mean (SD) CGI-S Score		
		BUP-ER 300 mg/100 mg + IDC (N = 194)	**BUP-ER 300 mg/300 mg + IDC (N = 196)**	**Placebo + IDC (N = 99)**
Week 1, Day 1 (Baseline)	N	190	192	97
	Mean (SD)	2.6 (1.36)	2.5 (1.33)	2.7 (1.30)
Week 5	N	166	170	60
	Mean (SD)	2.2 (1.13)	2.2 (1.08)	3.0 (1.34)
Week 9	N	155	155	49
	Mean (SD)	2.1 (1.07)	2.1 (1.12)	2.8 (1.33)
Week 13	N	145	146	42
	Mean (SD)	2.0 (1.02)	2.1 (1.05)	3.2 (1.36)
Week 17	N	138	133	38
	Mean (SD)	1.9 (0.99)	2.0 (1.04)	3.1 (1.39)
Week 21	N	131	130	35
	Mean (SD)	2.0 (1.00)	1.9 (1.10)	3.1 (1.62)
LS mean treatment effects at week 24 (SE) [95% CI]		–0.7 (0.13) [–0.92 to –0.40]	–0.7 (0.13) [–1.00 to –0.48]	–0.0 (0.17) [0.35 to 0.29]
Pairwise comparisons at week 24 compared with Placebo + IDC groups, [95% CI]		–0.6 (0.14) [0.89 to –0.33]	–0.7 (0.14) [–0.97 to –0.41]	–
P value		< 0.0001	< 0.0001	–

BUP-ER = buprenorphine extended-release; CGI-I = Clinical Global Scale for Severity; CI = confidence interval; IDC = behavioural counselling/individual drug counselling; mITT = modified intention-to-treat; SD = standard deviation; SE = standard error.

Note: *P* values derived from mixed model for repeated measures for change from baseline in CGI-S score.

[a] Patients from Site 20 (n = 15) were excluded from the analysis.

Source: Clinical study report for Study 13-0001.[6]

Illicit Drug Use

One of the exploratory end points in this study investigated the proportion of patients with urine toxicology results that were non-negative for substances other than opioids from week 5 to week 24 in the full analysis set. There were no numerical differences identified between either treatment arm compared with placebo for this end point. The mean cumulative percentage of patients with urine toxicology results non-negative for substances other than opioids in the 300 mg/100 mg, 300 mg/300 mg, and placebo group were 71.0%, 70.7%, and 82.7%, respectively. It should be noted that all missing urine toxicology results for this outcome were considered non-negative.

Table 24 summarizes the percentage of patients with positive results for substances detected by urine toxicology (including opioids) from week 1 to week 24. The most common substances used among all patients enrolled were opiates, morphine, cannabinoids, hydromorphone, cocaine metabolites, and codeine.

Table 24: Patients with Positive Urine Toxicology Result by Any Substance (Including Opioids) From Week 1 to Week 24, n (%) — Full Analysis Set (mITT)[a]

Substance	Treatment Group[a]		
	BUP-ER 300 mg/100 mg + IDC (N = 194)	BUP-ER 300 mg/300 mg + IDC (N = 196)	Placebo + IDC (N = 99)
Amphetamine	68 (35.1)	47 (24.0)	23 (23.2)
Barbiturates	5 (2.6)	2 (1.0)	1 (1.0)
Benzodiazepine	51 (26.3)	49 (25.0)	18 (18.2)
Benzoylecgonine	92 (47.4)	106 (54.1)	44 (44.4)
Cannabinoids	103 (53.1)	111 (56.6)	56 (56.6)
Codeine	90 (46.4)	108 (55.1)	63 (63.6)
Hydrocodone	37 (19.1)	32 (16.3)	14 (14.1)
Hydromorphone	102 (52.6)	113 (57.7)	68 (68.7)
Methadone	2 (1.0)	0 (0.0)	6 (6.1)
Morphine	108 (55.7)	127 (64.8)	69 (69.7)
Opiates	131 (67.5)	140 (71.4)	74 (74.7)
Oxycodone	40 (20.6)	38 (19.4)	27 (27.3)
Oxymorphone	36 (18.6)	30 (15.3)	23 (23.2)
Phencyclidine	8 (4.1)	15 (7.7)	6 (6.1)

BUP-ER = buprenorphine extended-release; IDC= individual counselling; mITT = modified intention-to-treat.

[a] Patients from Site 20 were excluded from the analysis.

Source: Clinical study report for Study 13-0001.[6]

Subgroups

This study evaluated the primary outcome in the subgroup of patients aged 18 or older but younger than 30 years, 30 and older but younger than 45 years, younger than 60, and 60 years or older between week 5 and week 24 in the full analysis set. No appreciable differences in efficacy were observed among the age subgroups.

This study also evaluated the primary outcome in the subgroup of opioid source of access at screening, in patients using the non-injectable route and injectable route at screening, between week 5 and week 24. Results were supporting of the primary end point. Findings from this subgroup analysis are summarized in Table 25.

Table 25: Percentage Abstinence from Week 5 to Week 24 Based on Opioid Source of Access, n/N (%) — Full Analysis Set (mITT)[a]

Percentage Abstinence	Number (%) of Patients[a]		
Non-Injectable Opioid Users at Screening			
	BUP-ER 300 mg/100 mg + IDC (N = 138)	**BUP-ER 300 mg/300 mg + IDC (N = 136)**	**Placebo + IDC (N = 57)**
≥ 0%	138 (100.0)	136 (100.0)	57 (100.0)
≥ 10%	103 (74.6)	84 (61.8)	5 (8.8)
≥ 20%	87 (63.0)	73 (53.7)	2 (3.5)
≥ 30%	79 (50.7)	68 (50.0)	2 (3.5)
≥ 40%	70 (50.7)	60 (44.1)	2 (3.5)
≥ 50%	66 (47.8)	55 (40.4)	1 (1.8)
≥ 60%	62 (44.9)	47 (34.6)	1 (1.8)
≥ 70%	52 (37.7)	47 (34.6)	1 (1.8)
≥ 80%	43 (31.2)	38 (27.9)	1 (1.8)
≥ 90%	32 (23.2)	29 (21.3)	1 (1.8)
P value[b] (comparison with placebo + IDC)	< 0.0001	< 0.0001	–
Mean (SD)	46.2% (38.63%)	39.9% (39.64%)	3.1% (13.19%)
Median (range)	40.0% (0% to 100%)	27.5% (0% to 100%)	0.0% (0% to 90%)
Injectable Opioid Users at Screening			
	BUP-ER 300 mg/100 mg + IDC (N = 84)	**BUP-ER 300 mg/300 mg + IDC (N = 80)**	**Placebo + IDC (N = 50)**
≥ 0%	84 (100.0)	80 (100.0)	50 (100.0)
≥ 10%	55 (65.5)	57 (71.3)	7 (14.0)
≥ 20%	44 (52.4)	50 (62.5)	5 (10.0)
≥ 30%	36 (42.9)	43 (53.8)	4 (8.0)
≥ 40%	32 (38.1)	40 (50.0)	4 (8.0)
≥ 50%	31 (36.9)	37 (46.3)	3 (6.0)
≥ 60%	27 (32.1)	32 (40.0)	3 (6.0)
≥ 70%	22 (26.2)	29 (36.3)	1 (2.0)
≥ 80%	20 (23.8)	26 (32.5)	1 (2.0)
≥ 90%	14 (16.7)	25 (31.3)	1 (2.0)

Percentage Abstinence	Number (%) of Patients[a]		
P value (comparison with Placebo + IDC)	< 0.0001	< 0.0001	–
Mean (SD)	35.8% (37.11%)	45.4% (39.84%)	6.7% (19.39%)
Median (range)	20.0% (0% to 100%)	40.0% (0% to 100%)	0.0% (0% to 100%)

BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling; mITT = modified intention-to-treat; SD= standard deviation.

[a] Patients from Site 20 (n = 15) were excluded from the analysis. All missing results for self-reports were considered positive.

[b] Wilcoxon rank sum test was used to compare treatment groups. Each dose regimen was compared with placebo with respect to the composite primary end point at a significance level of alpha equals 0.025.

Source: Clinical study report for Study 13-0001.[6]

Harms

Only those harms identified in the review protocol are reported as follows (Table 3). See Table 26 for detailed harms data.

Adverse Events

The proportion of patients reporting AEs was 76.4% in the 300 mg/300 mg treatment group, 66.7% in the 300 mg/100 mg treatment group, and 56.0% in the placebo group (Table 26). Headache, constipation, and nausea were reported most frequently (8.4% to 8.9%) by patients in the BUP-ER groups.

No patients had early surgical removal of the BUP-ER depot.

Serious and Severe Adverse Events

Among patients who received BUP-ER, 2% and 3.5% experienced a serious AE compared with 5.0% in placebo. No single type of serious AE occurred at a frequency greater than one per cent (Table 26).

Withdrawals Due to Adverse Events

The proportion of patients who stopped treatment due to AEs was 3.4% and 5.0% in the BUP-ER treatment groups, and 2.0% in the placebo group. Two patients in the BUP-ER 300 mg/100 mg group discontinued treatment due to drug withdrawal syndrome.

Mortality

One death was reported in this study, in a patient belonging to the BUP-ER 300 mg/300 mg treatment group. The death was due to a gunshot wound, and considered unrelated to treatment.

Table 26: Adverse Events, Serious Adverse Events, Withdrawals Due to Adverse Events, and Deaths Observed in Study 13-0001 Throughout the Double-Blind Phase — Safety Analysis Set

	BUP-ER 300 mg/100 mg + IDC (N = 203)	BUP-ER 300 mg/300 mg + IDC (N = 201)	Placebo + IDC (N = 100)
AEs			
Patients with > 0 AEs, N (%)	155 (76.4)	134 (66.7)	56 (56.0)
Most Common AEs[a]			
Headache	19 (9.4)	17 (8.5)	6 (6.0)
Constipation	19 (9.4)	16 (8.0)	0 (0.0)
Nausea	18 (8.9)	16 (8.0)	5 (5.0)
Injection site pruritus	13 (6.4)	19 (9.5)	4 (4.0)
Vomiting	19 (9.4)	11 (5.5)	4 (4.0)
Insomnia	13 (6.4)	17 (8.5)	11 (11.0)
SAEs			
Patients with > 0 SAEs, N (%)	4 (2.0)	7 (3.5)	5 (5.0)
Most common SAEs[b]			
Gunshot wound	0 (0.0)	2 (1.0)	0 (0.0)
WDAEs			
WDAEs, N (%)	7 (3.4)	10 (5.0)	2 (2.0)
Most common WDAEs[b]			
Drug withdrawal syndrome	2 (1.0)	0 (0.0)	1 (1.0)
Increased aspartate aminotransferase	0 (0.0)	2 (1.0)	0 (0.0)
Deaths			
Number of deaths, N (%)	0 (0.0)	1 (0.5)	0 (0.0)
Gunshot wound	0 (0.0)	1 (0.5)	0 (0.0)
Fatal/Non-fatal Overdose			
Fatal overdose	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal overdose	0 (0.0)	0 (0.0)	0 (0.0)
Injection Site Reactions			
Mild	120 (59.1)	132 (65.7)	62 (62.0)
Moderate	16 (7.9)	19 (9.5)	11 (11.0)
Severe	0 (0.0)	4 (2.0)	0 (0.0)
Potentially life-threatening	0 (0.0)	1 (0.5)	0 (0.0)

AE = adverse event; BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency of greater than 6% in either BUP-ER treatment group.

[b] Frequency of 1% or greater in either BUP-ER treatment group.

Source: Clinical study report for Study 13-0001.[6]

Notable Harms

No overdoses, either fatal or non-fatal, were reported in either of the active treatment groups. Intravenous heroin overdose (referred to in the study as "accidental overdose") was reported as a serious AE in one patient in the placebo group at day 80. There were no changes made to the study treatment as a result of this event, and the patient eventually recovered. There were no overdoses of BUP-ER reported throughout the study.

Treatment-emergent AEs pertaining to central nervous system (CNS) depression were higher in the two active groups than those in the placebo group. The three most common AEs associated with CNS depression were somnolence, sedation, and dizziness. None of these AEs were deemed to be serious. Three patients taking BUP-ER withdrew from the study due to AEs related to CNS depression, which included two patients with sedation (one patient in the 300 mg/300 mg group and one in the 300 mg/100 mg group) and one patient with somnolence, belonging to the 300 mg/300 mg group.

No patients in this study experienced a treatment-emergent AE potentially related to respiratory depression.

Serum and free testosterone values were collected from all randomized patients at weeks 13, 21, and 25 and at any time during the double-blind phase from week 13 through week 21, respectively. Table 27 summarizes the proportions of patients with shifts in serum and free testosterone from normal at baseline to its worst value at any time after the first injection to week 25. There were similar proportions of patients with shifts from normal at baseline to low levels of testosterone between active and placebo groups throughout this time period.

Table 27: Summary of Patients With Shifts in Testosterone From Normal at Baseline to Worst Value at Any Time After First Injection to Week 25, n/N (%) — Safety Analysis Set

		BUP-ER 300 mg/100 mg + IDC (N = 203)	BUP-ER 300 mg/300 mg + IDC (N = 201)	Placebo + IDC (N = 100)
Testosterone	Low	41/135 (30.4)	38/137 (27.7)	22/65 (33.8)
	Normal	73/135 (54.1)	77/137 (56.2)	23/65 (35.4)
	High	2/135 (1.5)	2/137 (1.5)	1/65 (1.5)
Testosterone, free	Low	23/121 (19.0)	32/132 (24.2)	14/65 (50.8)
	Normal	68/121 (56.2)	79/132 (59.8)	33/65 (50.8)
	High	5/121 (4.1)	3/132 (2.3)	0/65 (0.0)

BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling.

Note: "At any time" includes all scheduled visits from week 1 (baseline) to week 29.

Source: Clinical study report for Study 13-0001.[6]

A higher proportion of patients in both 300 mg/100 mg and 300 mg/300 mg treatment groups reported elevated hepatic enzymes signalling potential hepatotoxicity at any time from week 1 to week 29, summarized in Table 28. There were a total of 27 patients in all three treatment groups with both alanine transaminase (ALT) and aspartate aminotransferase (AST) greater than three times the upper limit of normal. Of these 27 patients, 23 of them were reported to have had confounding factors for hepatic enzyme elevation such as hepatitis C; positive hepatitis C antibody; chronic alcohol use; elevated

liver function at screening and/or baseline; or a past history of alcoholic hepatitis, alcoholic pancreatitis, or gallstones. The four patients without any identifiable confounding factors were on BUP-ER treatment. Three of the four patients belonged to the 300 mg/100 mg group and one patient was in the 300 mg/300 mg group. Three of these patients belonging to 300 mg/300 mg group discontinued study treatment due to treatment-emergent AEs potentially related to liver dysfunction. There were no reported serious AEs potentially due to liver dysfunction in any patients throughout this study.

Table 28: Summary of Potential Hepatotoxicity at Screening and at Any Time From Week 1 to Week 29, n/N (%) — Safety Analysis Set

		BUP-ER 300 mg/100 mg + IDC (N = 203)	BUP-ER 300 mg/300 mg + IDC (N = 201)	Placebo + IDC (N = 100)
ALT > 3 x ULN	Screening	1/199 (0.5)	0/192 (0.0)	0/99 (0.0)
	At any time	11/202 (5.4)	24/201 (11.9)	5/100 (5.0)
AST > 3 x ULN	Screening	1/199 (0.5)	0/192 (0.0)	0/99 (0.0)
	At any time	17/202 (8.4)	23/201 (11.4)	5/100 (5.0)
ALT > 3 x ULN and AST > 3 x ULN	Screening	1/199 (0.5)	0/192 (0.0)	0/99 (0.0)
	At any time	9/202 (4.5)	15/201 (7.5)	3/100 (3.0)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling; ULN = upper limit of normal.

Note: "At any time" includes all scheduled visits from week 1 (baseline) to week 29.

Source: Clinical study report for Study 13-0001.[6]

Table 29 summarizes the AEs pertaining to injection site reactions occurring during the double-blind treatment phase. All AE events were deemed to be of mild or moderate severity with the exception of one event of severe injection site pruritis, occurring in the 300 mg/300 mg treatment group.

Table 29: Patients With Injection Site Reactions at Any Time, n/N (%) — Safety Analysis Set

Substance	BUP-ER 300 mg/100 mg + IDC (N = 203)	BUP-ER 300 mg/300 mg + IDC (N = 201)	Placebo + IDC (N = 100)
Pain at Injection Site			
Mild	120 (59.1)	132 (65.7)	62 (62.0)
Moderate	16 (7.9)	19 (9.5)	11 (11.0)
Severe	0 (0.0)	4 (2.0)	0 (0.0)
Potentially life-threatening	0 (0.0)	1 (0.5)	0 (0.0)
Tenderness at Injection Site			
Mild	122 (60.1)	117 (58.2)	54 (54.0)
Moderate	45 (22.2)	52 (25.9)	28 (28.0)
Severe	8 (3.9)	9 (4.5)	5 (5.0)
Potentially life-threatening	0 (0.0)	0 (0.0)	0 (0.0)
Erythema/Redness			
Mild	83 (40.9)	97 (48.3)	41 (41.0)
Moderate	19 (9.4)	28 (13.9)	7 (7.0)

Substance	BUP-ER 300 mg/100 mg + IDC (N = 203)	BUP-ER 300 mg/300 mg + IDC (N = 201)	Placebo + IDC (N = 100)
Severe	0 (0.0)	3 (1.5)	1 (1.0)
Potentially life-threatening	0 (0.0)	0 (0.0)	0 (0.0)
Induration			
Mild	114 (56.2)	103 (51.2)	52 (52.0)
Moderate	6 (3.0)	21 (10.4)	3 (3.0)
Severe	1 (0.5)	0 (0.0)	0 (0.0)
Potentially life-threatening	0 (0.0)	0 (0.0)	0 (0.0)
Swelling			
Mild	80 (39.4)	72 (35.8)	25 (25.0)
Moderate	10 (4.9)	16 (8.0)	3 (3.0)
Severe	1 (0.5)	2 (1.0)	0 (0.0)
Potentially life-threatening	0 (0.0)	0 (0.0)	0 (0.0)

BUP-ER = buprenorphine extended-release; IDC = behavioural counselling/individual drug counselling.

Source: Clinical study report for Study 13-0001.[6]

Discussion

Summary of Available Evidence

One RCT, Study 13.0001, was included in this review. Additional evidence in the form of an extension study, an indirect comparison, and a long-term observational study were also part of the review (see Appendices).

Study 13-0001 enrolled 504 patients with moderate-to-severe OUD as defined by the *DSM-5*, considered to be clinically stable and seeking treatment. Patients were randomized to receive either BUP-ER 300 mg for six doses every four weeks via subcutaneous injection (BUP-ER 300 mg/300 mg), BUP-ER 300 mg for two doses then BUP-ER 100 mg for four doses every four weeks via subcutaneous injection (BUP-ER 300 mg/100 mg), or volume-matched placebo for six doses every four weeks via subcutaneous injection. The primary outcome was percentage abstinence, defined as the CDF of the percentage urine samples negative for opioids combined with negative self-reports for illicit opioids use, referred to as percentage abstinence, from week 5 to week 24 of double-blind treatment.

The extension study, Study 13-0003 (Appendix 6), was an open-label safety study that included a combination of patients who had completed Study 13-0001 with BUP-ER treatment (referred to as "roll-over" patients) as well as newly enrolled patients (referred to as "de novo" patients). All patients had a diagnosis of moderate-to-severe OUD as defined in the *DSM-5*, and were considered to be clinically stable and seeking treatment. The primary outcome was the safety and tolerability throughout a period of 48 weeks over which BUP-ER was administered.

The manufacturer-submitted indirect treatment comparison in this report (Appendix 7) summarized the indirect evidence comparing BUP-ER with other drugs approved for use in OUD. The outcomes evaluated in this analysis included treatment retention and opioid test positivity.

The observational study, RECOVER (Appendix 8), was a longitudinal observational study assessing patients with OUD who had participated in Study 13-0001 and Study 13-0003 and received at least one study injection. This study was designed to assess the recovery process over a 24-month period. The outcomes of interest in this study included criminal activity, opioid abstinence and withdrawal, depression, psychological stress, work attendance and performance, and general physical and mental health.

Interpretation of Results

Efficacy

Pivotal Trial (Study 13-0001)

According to current treatment guidelines, the most common surrogate end point for establishing a baseline measure of addiction risk and to monitor adherence of opioid maintenance therapy is negative UDS results.[1,4] Urine drug sample results are also able to establish the reliability of self-reported illicit opioid use. In Study 13-0001, two regimens of BUP-ER, 300 mg/100 mg and 300 mg/300 mg, were compared against placebo in evaluating percentage abstinence from week 5 to week 24, defined as the CDF of the percentage of negative UDS combined with self-reports negative for illicit opioid use. Both treatment arms of BUP-ER were statistically significantly better than placebo in percentage

abstinence from week 5 to week 24 in the full analysis set, with a mean percentage abstinence of 42.7% and 41.3% in the 300 mg/100 mg and 300 mg/300 mg arms, respectively, compared with 5.0% in the placebo arm (*P* value < 0.0001 for each regimen compared with placebo). Similarly, treatment success (defined as any patient with 80% or more of UDS negative for opioids combined with negative self-reports) was significantly higher in 300 mg/100 mg (28%) and 300 mg/300 mg (29%) arms, respectively, compared with 2% in placebo (*P* < 0.0001).

The validity of these results remains uncertain due to the high dropout rate in Study 13-0001. First, there was a significant difference in the proportion of patients receiving placebo treatment who prematurely withdrew from the trial (66%) compared with in the BUP-ER groups (37%; *P* < 0.0001), with 50% of patients in the placebo group dropping out within the first six weeks of treatment compared with 21% in both BUP-ER groups. The most commonly cited reasons for withdrawal in the placebo group were lack of efficacy (18%), withdrawal of consent (18%), and lost to follow-up (12%). It is unclear whether blinding was maintained in the placebo group of this trial due to the nature of the intervention in this population, and the onset of opioid withdrawal-related symptoms. Furthermore, a protocol amendment was filed while this trial was being conducted in response to FDA feedback that all randomized patients receive a five-day buprenorphine/naloxone taper beginning on day 1 of treatment in order to reduce unblinding in patients receiving placebo. Only 163 (32%) patients in this study were able to receive this taper, making it difficult to rule out whether unblinding occurred in this group.

Due to a high volume of missing data from patient discontinuation in this study, its impact on the primary outcome was analyzed by an FDA reviewer in the statistical report for BUP-ER.[7] Three different sensitivity analyses were carried out. The first analysis based the per cent of negative opioid use of placebo dropouts on observed data prior to discontinuation, while active arm dropouts were treated as treatment failures. The second analysis assumed that the percentage of negative drug use was calculated based on available data, except patients who discontinued due to lack of efficacy, in which cases missing data were imputed as positive. The third analysis imputed all missing data as negative for opioid use except for those discontinuing due to lack of efficacy, representing the most unlikely case in favour of placebo. All three analyses were supportive of the primary analysis conclusion, with a statistically significant treatment effect noted for both arms of BUP-ER treatment compared with placebo; however, the methodological limitations and its associated risk of unblinding outlined above cannot be ruled out.

Additional limitations affect whether the significant results obtained in this trial are clinically meaningful. First, it is unclear what the MCID of UDS negative for opioids when comparing active opioid maintenance treatment with placebo in this patient population. The statistical analysis plan for this trial assumed that a clinically meaningful difference between at least one of the two dose regimens and placebo was 15%, citing previous placebo-controlled, double-dummy RCTs in this patient population where a non-inferiority margin of 20% was used, and reducing to 15% to avoid under-powering the study. The RCTs where the 20% margin was used were reviewed in a previous CDR report on buprenorphine implants (Probuphine).[40] Clinical reviewers for that report questioned the certainty of assumptions leading to the choice of the 20% margin, including that there would be a 100% abstinence rate among patients on sublingual buprenorphine treatment, and that 25% of patients would remain abstinent after treatment with sublingual buprenorphine was stopped. Second, although the use of UDS is common in patients with OUD, evidence for it as an useful surrogate marker for treatment effectiveness is somewhat limited.[41] The clinical experts

involved in this review cited improvements in social functioning as the most clinically meaningful outcome in this patient population; as noted, however, correlation of these outcomes to UDS results combined with self-reports of illicit opioid use is unclear. The primary efficacy outcome as a surrogate for determining a decrease in use of opioids was supported by the FDA. The Health Canada reviewers noted potential limitations with the CDF data and that interpretation of the results of Study 13-0001 should be done considering the primary and key secondary outcome, treatment success.[11]

Patients treated with BUP-ER were more likely to be abstinent, but relative to placebo in a single RCT over a relatively short duration (24 weeks). The choice of a placebo comparator group in Study 13-0001 limits the ability to determine how BUP-ER compares with other treatment options that Canadian patients with OUD currently have access to, and risks overestimating the treatment effect of BUP-ER. An indirect comparison and network meta-analysis (NMA) was submitted by the manufacturer in order to provide data on comparisons to current treatment options in Canada. Comparators in this study were BUP-ER 300 mg/100 mg, BUP-ER 300 mg/300 mg, variable-dose methadone, sublingual buprenorphine (BUP-V), buprenorphine implants (BUP-IMP), and a different buprenorphine depot injection (CAM2038) that was undergoing regulatory review in the US at the time the NMA was conducted. Using a fixed-effects model, BUP-ER 300 mg/100 mg was associated with a significantly decreased likelihood of opioid test positivity compared with placebo (odds ratio [OR], 0.12; 95% CI, 0.06 to 0.24), BUP-V (OR, 0.34; 95% CI, 0.12 to 0.90), and BUP-IMP (OR, 0.32; 95% CI, 0.12 to 0.78). Similar results were seen in the BUP-ER 300 mg/300 mg arm. Using a fixed-effects model neither BUP-ER dose arm was significantly different than BUP-V, BUP-IMP, and CAM2038 with respect to study dropout. Using the same model, treatment with variable-dose methadone was associated with a significantly lower rate of study dropout than both the BUP-ER 300 mg/100 mg and BUP-ER 300 mg/300 mg arms. Several limitations impacted the generalizability of this study's findings. First, transparency in reporting the systematic review methods and analysis, and the rationale for use of specific models in the clinical submission was not provided. Second, only a limited heterogeneity assessment was performed for one outcome (study dropout), and it was not specified a priori. Finally, the results for both study drop out and opioid test positivity were based on studies with sparse baseline data, which may prevent its generalizability to the Canadian population. As a result, the comparative evidence and analysis results in this report should be interpreted with caution due to notable uncertainty in the conduct and results from the NMA. Results for this analysis are summarized and appraised in Appendix 7.

A recent meta-analysis was undertaken by the Institute for Clinical and Economic Review, aiming to compare clinical effectiveness between extended-release opioid agonists and antagonist medications for addiction treatment in patients with OUD.[42] Due to the absence of any direct comparison of BUP-ER with buprenorphine/naloxone, the evidence base was considered to be insufficient, and BUP-ER was unable to be compared with other extended-release OUD treatments.

The duration of BUP-ER treatment in Study 13-0001 was limited to 24 weeks, and the extension study (Study 13-0003) provided additional longer-term data on the use of BUP-ER over 48 weeks. Study 13-0003 used the same efficacy end point as in the pivotal Study 13-0001, CDF for percentage negative UDS combined with self-reports negative for illicit opioid use; however, no formal statistical tests appear to have been performed for this analysis, limiting any inferences or conclusions on the results. Results for this trial are provided in Appendix 6. Overall, mean percentage abstinence was 46% in patients newly

initiated with BUP-ER treatment (de novo patients) compared with 57% of roll-over patients from Study 13-0001. About 8% of de novo patients achieved 100% abstinence compared with 18% of roll-over patients; however, results from the roll-over cohort should be interpreted with caution, as it is likely comprised of a selected group of patients who completed Study 13-0001 with a good response, good adherence, and few side effects. Patients in Study 13-0001 received a 300 mg dose of BUP-ER for at least one to two months before switching to a 100 mg dose. The results of the 100 mg dose are therefore difficult to interpret, potentially leading to overestimation because of potential carry-over effects of the 300 mg doses received. In Study 13-0003, all patients were to receive a 300 mg dose as an initial dose, and clinical staff were given the option of providing either 300 mg or 100 mg subsequently, depending on patient response. The doses patients received did not appear to be recorded. Although the Health Canada product monograph recommends patients be initiated with 300 mg for two months followed by 100 mg, there is a potential in these studies for perceived benefits in BUP-ER to have been misattributed to the 100 mg dose rather than the 300 mg dose.

Failure to manage withdrawal symptoms and reduce opioid cravings in patients with OUD can greatly affect patient satisfaction and contribute to relapse.[1,4] In Study 13-0001, mean COWS, SOWs, opioid craving VAS, and CGI scales for improvement and severity were recorded in order to assess the effect of treatment on withdrawal symptoms. Mean COWS and SOWS scores were relatively low at baseline and at week 24 in the all treatment groups (mean COWS 1.9 or lower; SOWS 4.9 or lower), indicating reduced withdrawal symptoms. Regarding desire- or need-to-use VAS scores, mean scores in the placebo group were numerically higher at baseline (9.5) compared with the active treatment groups (5.5 in the 300 mg/100 mg group and 7.1 in the 300 mg/100 mg group), indicating a slightly higher degree of desire or need to use opioids in the placebo group. There were numerically higher values noted in the placebo group at week 2 (26.9), and values remained high until week 24. Final mean scores in the placebo group for the desire- or need-to-use VAS scores at week 24 (17.1) were significantly higher than in active treatment groups (6.8 in the 300 mg/100 mg group and 3.2 in the 300 mg/300 mg group). Limited results were obtained for changes in the clinical status of patients, such as CGI-I and CGI-S. Mean values for these outcomes were similar between groups, and observed to slightly improve over time in the active treatment groups, while slightly worsening in the placebo group. Of note, analyses for these outcomes were not adjusted for multiplicity, and therefore should be interpreted with consideration of the risk of Type I errors. There was no MCID identified for any of these scoring scales in patients with OUD being treated with MAT. Regarding the scales used to measure patient withdrawal symptom scales, clinical experts consulted for this submission noted that the SOWS and COWS scores are used in practice to guide induction doses for opioid maintenance therapy, and not utilized as a measure of patient experience or treatment success.[37] Regarding the outcomes used to measure clinical status, CGI scoring scales have historically been criticized for lacking in reliability and validity.[33-35] There were no data on social function outcomes, health-related quality of life, or other patient-focused outcomes from Study 13-0001 available for this review. The manufacturer provided data related to patient-reported outcomes collected in Study 13-0001 at the time of providing comments on a draft version of this report. The data suggested that BUP-ER improved health-related quality of life (measured using the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) index and EQ-5D-5L VAS), and the proportion of patients with employment and health insurance as compared with placebo. However, there was insufficient information reported to assess the validity of these results.

Mean COWS, SOWS, and desire- or need-to-use opioid VAS scores were also recorded throughout Study 13-0003; however, according to the statistical analysis plan, statistical comparisons were not planned. Mean COWS and SOWS scores were generally low at baseline and remained low in both groups to the study end point. Mean opioid craving VAS scores were generally low in both groups at baseline (5.9 in de novo patients and 4.4 in roll-over patients); however, there was a slight increase from baseline in the mean VAS score at the end point (4.2) among roll-over patients (final mean score: 8.3) compared with a slight decrease from baseline in the mean score (–2.0) among de novo patients (final mean score: 3.0). There does not appear to be a clear explanation for this numerical difference between groups, given that both groups appeared to receive the same number of injections over the course of both studies 13-0001 and 13-0003.

Although no submissions were received in the call for patient input, many patients interviewed in a published report regarding their medication-assisted therapy for OUD stressed the importance of making positive social changes in their lives, such as engaging in work or volunteering, over the results of urine testing as a key measure of treatment success.[43] A longitudinal observational study, RECOVER, was provided by the manufacturer with data on these outcomes deemed clinically meaningful to patients. Results for this study are provided in Appendix 8. The RECOVER study measured missed work days in included patients and found that those who had received placebo injections as well as those who had received BUP-ER treatment for 13 months or longer had reported the fewest missed days of work compared with patients who had received BUP-ER treatment for one to two months, three to eight months, and nine to 12 months. Results for this outcome are limited by the fact that this data were self-reported, therefore limited by recall bias and truthfulness of responses.

Patients with OUD are linked to higher rates of criminality than the general population.[1,44,45] The RECOVER study evaluated change in criminal activity in patients enrolled in studies 13-0001 and 13-0003 from the 12 months leading up to study enrolment until up to 12 months after initiation of BUP-ER treatment. In the year prior to study enrolment, 10% of patients had been arrested, with 8.3% receiving misdemeanour charges and 2.4% receiving felony charges. In the time between the trial and up to 12 months after the trial, 6.8% of patients had been arrested, with 5.0% receiving misdemeanour charges and 2.4% receiving felony charges. Although there was a numerically lower number of total arrests, the proportion of patients receiving felony charges remained consistent before and after study enrolment. This data were limited by the fact that it was obtained from public records, of which only 65% for patients was found.

Emotional and mental health is an important component of care for patients with OUD, and there is a high prevalence of concurrent mental health diagnoses in this population, such as depression and anxiety.[1,36] Due to the lack of inclusion of patients with concurrent mental illness in studies 13-0001 and 13-0003, the known effect of BUP-ER in this population is limited. In the RECOVER study, it was found that patients with the longest recorded treatment duration with BUP-ER were associated with numerically lower mean scores on the Kessler-6 psychological distress scale (7.8 among patients in the one-to-two month group compared with 4.0 in the 13-to-18 month group), as well as a numerically lower proportion of patients with severe depression (Beck's Depression Inventory score of 29 or greater). Results from these outcomes should be interpreted with caution due to the fact that this data were self-reported, therefore limited by recall bias, as well as truthfulness of responses.

Studies 13-0001 and 13-0003 enrolled patients who were predominantly white and male, with a mean age of around 39 years.

A breakdown of social characteristics (i.e., housing, employment, past criminality) of the populations was not provided. Similarly, patients recruited in the RECOVER study were 66.1% male and 60% white, with the majority (59%) between the ages of 35 and 49 years. Almost one-half (47%) of patients in the RECOVER sample were employed either full- or part-time, with 76% being stably housed; the median monthly patient income was $879. Due to the diverse patient population with OUD, it may be difficult to extrapolate some of this data to a general Canadian OUD population. Furthermore, specific high-risk populations of interest, such as youth, Indigenous peoples, homeless or jobless patients, patients addicted to high potency opioids, and patients with chronic pain have not been represented in this study.[37]

There is additional uncertainty in the generalizability of the use of BUP-ER in patients with concurrent substance use disorders (excluding cocaine, cannabis, tobacco, and alcohol), as well as those meeting *DSM-5* criteria for either moderate or severe cocaine, alcohol, or cannabis use disorder. According to the clinical expert involved in this review, concurrent substance use disorders are very common in this patient population, and cannabis use is reported to be especially prevalent. However, it should be noted that approximately one-half of patients in each treatment group reported concomitant cannabis use at screening, between 40% and 50% reported cocaine use, and approximately 90% reported alcohol and tobacco use at screening. Details as to the nature and intensity of use of these substances was not provided, and given the eligibility criteria for the study it is difficult to fully assess how representative these patients are of the OUD population in Canada. A lower proportion of patients with depression (12.9%) and anxiety (9.6%) were represented in this study compared with the general population of patients with OUD. This may be due to the exclusion of patients with uncontrolled psychiatric comorbidities in studies 13-0001 and 13-0003, potentially resulting in a higher likelihood of positive outcomes.

BUP-ER provides another therapeutic option for patients with OUD. The potential added benefits of BUP-ER over existing drug therapies for OUD may include the formulation (monthly injectable administration), thereby reducing the impact of daily adherence to oral products, possibly improving treatment retention, and reducing the risk of diversion. However, limited (or no) evidence for these potential benefits means there is at present uncertainty about the long-term impact of BUP-ER relative to other available treatments for OUD.

Harms

AEs were measured in Study 13-0001 over 24 weeks, and were reported to have occurred by most patients at a frequency of 56.0% in the placebo group compared with 66.7% in the BUP-ER 300 mg/100 mg group and 76.4% in the BUP-ER 300 mg/300 mg group. The most common AEs were headache, constipation, and nausea. Among patients who received BUP-ER injections, 2.7% experienced a serious AE compared with 5.0% of patients in the placebo group. The proportion of patients who stopped treatment due to AEs was generally low and ranged from 2.0% to 5.0%.

Study 13-0003 was a long-term extension study observing safety outcomes in patients with OUD treated with BUP-ER over a total period of 48 weeks. Overall, patients newly treated with BUP-ER (de novo patients) reported a higher overall incidence of AEs (73%) compared with patients who completed Study 13-0001 (roll-over patients) (57%). The lower

percentage of patients experiencing an AE who completed Study 13-0001 is likely because of the select patient group (i.e., those who were able to tolerate 24 weeks of treatment prior to entering the extension study). The most common AEs were constipation, nausea, and injection site pain. Approximately 4% of all patients in the study experienced serious AEs, and the proportion of patients who withdrew from the study due to AEs was 2.5%.

The frequency of injection site AEs was high in patients receiving BUP-ER in Study 13-0001 and its extension study, 13-0003. Most of these reactions were described as mild or moderate, and resulting in pain, tenderness, redness, and induration. One patient in Study 13-0001 withdrew due to an injection site ulcer. Three patients in Study 13-0001 withdrew due to injection site reactions, such as pain and swelling. There were no reports of anaphylactic reactions in Study 13-0001, but one patient in the de novo treatment group in Study 13-0003 experienced an anaphylactic reaction following injection.

In Study 13-0001, the frequency of AEs associated with liver disorders was found to be 7.1% in the BUP-ER arms compared with 1% in the placebo arm. A total of nine patients (4.5%) in the 300 mg/100 mg arm and 16 patients (7.9%) in the 300 mg/300 mg arm were found to have experienced elevated ALT and AST levels greater than three times the upper limit of normal compared with three patients (3%) receiving placebo. Three patients in the 300 mg/300 mg arm withdrew due to AEs related to liver injury. Similar results were observed in Study 13-0003, where the frequency of AEs associated with liver disorders in all patients receiving BUP-ER was 8.2%, and 28 patients (4.3%) experienced elevated ALT and AST levels greater than three times the upper limit of normal. Two patients (both in the *de novo* arm) withdrew from the trial due to liver-related events. A total of 15 patients (2.2%) had to have their BUP-ER dose reduced due to liver-related AEs or liver-related enzyme issues (i.e., increased AST or ALT). It is presumed that these patients were reduced from the BUP-ER 300 mg dose to the 100 mg dose.

There is uncertainty regarding the safety of BUP-ER's use in pregnancy. BUP-ER contains the solvent N-methyl-2-pyrrolidone (NMP) a known teratogenic compound with confirmed developmental toxicity in animals. Studies with animals exposed to NMP have demonstrated fetotoxic effects at equivalent doses of NMP delivered by BUP-ER. High NMP exposure has also been linked to abnormal sperm parameters, including low motility, low mean number, and higher percentage of abnormal sperm.[5] In humans, it has not been established whether BUP-ER can harm reproductive capacity or fetal development as there are no controlled studies of its use in pregnant women. As a result, the use of BUP-ER in women of childbearing potential who are not using effective contraception is recommended to be avoided.[5] Considering the extended-release nature of this product, the potential for longer treatment duration and the high proportion of young patients affected by OUD should be important considerations before initiating treatment in young females of childbearing potential.

Of patients enrolled in the extension, Study 13-0003, the total duration of exposure to BUP-ER injections was up to 48 weeks. The suggested duration of treatment with BUP-ER is not specified in the product monograph; however, the clinical experts involved in this review expect that patients with OUD would need to be on this medication for at least a few years until they can achieve overall stability, due to the high overdose risk in this population. There is a significant risk of serious harm if BUP-ER is administered intravenously, as it can form a solid mass upon contact with body fluids, potentially causing occlusion, local tissue damage, and thrombo-embolic events, including life-threatening pulmonary emboli. As a result, it is stated in the product monograph that BUP-ER is not to be administered

intravenously or intramuscularly, and its use is limited to only be administered by a health care professional.[5]

Although buprenorphine has been available for a number of years and its risk profile is well-known, there are some potential adverse effects that are specific to this product. BUP-ER forms a solid mass upon subcutaneous administration to the abdominal area. Any evidence of tampering at the injection site or attempting to remove the mass is instructed to be clinically monitored throughout treatment. In the case that a depot must be removed, it can be surgically excised under local anesthesia within 14 days of administration.[5] According to the product monograph, residual plasma concentrations from previous injections will decrease gradually over the subsequent months.[5] No patients in either of the two clinical trials required depot removal throughout the 48-week period, and there were no reports of attempted removals of the depot.

Harms outcomes were not measured in either the RECOVER study or the manufacturer-submitted indirect comparison.

Potential Place in Therapy[2]

Subcutaneous monthly injections of a non-divertible formulation of 300 mg or 100 mg of buprenorphine after a minimum seven-day induction on sublingual buprenorphine for the management of moderate-to-severe OUD in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product is another option to address the current opioid epidemic. Most people with moderate-to-severe OUD do not access treatment due to systemic, clinical, and individual barriers. In addition, the treatment requirements paradoxically lead to disengagement from care with significant morbidity and mortality. Monthly injections might help address some of these gaps, including access for those in remote areas of the country who have difficulty with daily or weekly visits to pharmacies to be medicated.

Existing oral methadone or sublingual buprenorphine require regular observation and risk of diversion necessitating more urine testing for medication adherence. The potential benefits of buprenorphine monthly injection include an indication for induction of remission regardless of the dose of sublingual buprenorphine required, and more exposure to treatment, especially where the risk of dropout is high in the early induction phase of buprenorphine. This is very important in the rapid access clinics where they will be able to provide an injection after one week of transmucosal buprenorphine while they arrange for a transfer to a treatment program. Given the blocking effects observed after one injection, the monthly injection will potentially provide protection to those at highest risk of death from overdose (e.g., those who are using multiple substances, including alcohol, prescribed or street-obtained opioids, and who have comorbid mental health conditions).

An injection is likely to be associated with less stigma because there is no requirement to attend a pharmacy for weekly doses, and there will be a reduced need for urine toxicological drug testing allowing for more meaningful counselling and engagement in recovery-oriented treatment. The expectation with such a treatment is that patients will re-integrate more easily into the workforce, be able to travel, and engage in normal activities, which are key outcomes assessed in practice. In addition, it is expected that this formulation may allow care delivery to be better integrated in primary care settings, with

[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.

minimal burden on the practice. Collectively, this could expand treatment and address the unmet need of patients.

There are no special tests required to identify these patients other than insurance coverage and willingness to attend monthly for injections. Caution will be needed in prescribing buprenorphine monthly injection to those 65 years and older, and in those using sedative hypnotics or other depressants, such as alcohol, to prevent mixed drug overdose. Patients younger than 18 years of age are a growing population of those with OUD and who often go without treatment.[12,13] Although buprenorphine monthly injection is currently not indicated for use in this patient group because of a lack of data,[5] it is possible that physicians would consider using the drug for these patients. Another important subpopulation of patients is pregnant women with OUD, for whom buprenorphine is a preferred treatment.[12] However, the black box warning might limit the use of this product for these patients. Physicians will have to balance these risks against the continued exposure to buprenorphine/naloxone combinations that are currently marketed in Canada.

Conclusions

In adults with moderate or severe OUD inducted and clinically stabilized on 8 mg to 24 mg of sublingual buprenorphine/naloxone, BUP-ER injections (at either 300 mg every four weeks for six doses, or 300 mg every four weeks for two doses, followed by 100 mg every four weeks for four doses) administered subcutaneously was superior to volume-matched placebo injections based on the CDF of percentage abstinence, defined as a combination of percentage urine samples negative for opioids and negative self-reports for illicit opioid use at the end of 24 weeks. The proportion of patients completing treatment was significantly higher in patients treated with BUP-ER compared with placebo. Results appear to be supported by improvements in symptoms of withdrawal and desire or cravings to use opioids in patients on BUP-ER compared with placebo; however, these outcomes should be interpreted with consideration of the risk of Type I error and it is unclear whether the degree of difference is clinically relevant. Identified harms were consistent with the safety profile of buprenorphine. There was a numerically higher frequency of injection site reactions with the use of BUP-ER, most of which were mild to moderate in nature. BUP-ER is not recommended to be used in women of childbearing potential who are not using an effective and reliable method of contraception.

There is limited evidence on the longer-term benefits and harms associated with BUP-ER and the comparative effects versus non-placebo comparators. Significant limitations exist with the extension study, observational study, and NMA summarized within this review. As a result, the comparative effectiveness of BUP-ER in adults with moderate or severe OUD is uncertain.

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:	MEDLINE All (1946-present) Embase (1974-present) PsycINFO (1806-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid
Date of Search:	January 15, 2019
Alerts:	Weekly search updates from January 15, 2019 until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Humans Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
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
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY

Embase <1974 to 2019 January 25>

Ovid MEDLINE(R) ALL <1946 to January 25, 2019>

PsycINFO <1806 to January Week 3 2019>

1. buprenorphine/
2. 2. (sublocade* or buprenor* or brixadi* or buvidal* or 40D3SCR4GZ or CAM2038* or CAM 2038* or 6029M or 6029-M or RX6029* or RBP6000 or RBP-6000 or CI-112302 or CI112302 or "CI112,302" or "CI 112302" or UM952 or UM-952 or NIH-8805 or NIH8805).ti,ab,kf,ot,hw,rn,nm.
3. 3. 1 or 2

MULTI-DATABASE STRATEGY	
4.	4. ((extend* adj2 release) or (once adj2 month*) or (sustain* adj2 release) or SR or LP or (slow adj2 release) or (control* adj2 release) or CR or XL or XR or (delay* adj2 action) or (delay* adj2 release) or (prolong* adj2 action) or (prolong* adj2 release) or (timed adj2 release) or (long adj2 acting) or depot*).ti,ab,kf,ot,hw,rn,nm.
5.	controlled drug release/ or delayed-action preparations/
6.	4 or 5
7.	3 and 6
8.	7 use medall
9.	7 use psyh
10.	or/8-9
11.	exp *controlled release formulation/ or exp *controlled drug release/
12.	((extend* adj2 release) or (once adj2 month*) or (sustain* adj2 release) or SR or LP or (slow adj2 release) or (control* adj2 release) or CR or XL or XR or (delay* adj2 action) or (delay* adj2 release) or (prolong* adj2 action) or (prolong* adj2 release) or (timed adj2 release) or (long adj2 acting) or depot*).ti,ab,kw,dq.
13.	*buprenorphine/
14.	(sublocade* or buprenor* or brixadi* or buvidal* or 40D3SCR4GZ or CAM2038* or CAM 2038* or 6029M or 6029-M or RX6029* or RBP6000 or RBP-6000 or CI-112302 or CI112302 or "CI112,302" or "CI 112302" or UM952 or UM-952 or NIH-8805 or NIH8805).ti,ab,kw,dq.
15.	(buprenor* adj2 (injectable* or injection*)).ti,ab,kf,kw,ot,hw,rn,nm.
16.	11 or 12
17.	13 or 14
18.	16 and 17
19.	18 use oemezd
20.	10 or 19
21.	15 not 20
22.	20 or 21
23.	(conference abstract or conference review).pt.
24.	22 not 23
25.	exp animals/
26.	exp animal experimentation/ or exp animal experiment/
27.	exp models animal/
28.	nonhuman/
29.	exp vertebrate/ or exp vertebrates/
30.	animal.po.
31.	or/25-30
32.	exp humans/
33.	exp human experimentation/ or exp human experiment/
34.	human.po.
35.	or/32-34
36.	31 not 35
37.	24 NOT 36
38.	remove duplicates from 37

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. Search -- Studies with results | buprenorphine*
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.

Grey Literature

Dates for Search:	January 21, 2019 to January 22, 2019
Keywords:	buprenorphine
Limits:	No date limits used

Relevant websites from the following sections of the CADTH grey literature checklist, Grey matters: a practical tool for evidence-based searching (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- health statistics
- Internet search
- open access journals.

Appendix 3: Excluded Studies

Table 30: Excluded Studies

Reference	Reason for Exclusion
8	Not an RCT
9	Not an RCT
10	Not an RCT
46	Not an RCT

RCT = randomized controlled trial.

Appendix 4: Detailed Outcome Data

Table 31: Summary of Efficacy End Points and Analysis Strategy

	Statistical Method	Analysis Set	Approach to Missing Data
Primary Efficacy End Point			
CDF of the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use from week 5 through week 24	Wilcoxon rank sum test	FAS, PPS, and pre-specified subgroup	All missing data considered non-negative for opioids
Key Secondary Efficacy End Point			
Treatment success, defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioids use from week 5 through week 24	CMH test	FAS	All missing data considered non-negative for opioids
Additional Secondary Efficacy End Points			
CDF of the percentage of urine samples negative for opioids from week 5 through week 24	Wilcoxon rank sum test	FAS	All missing data considered non-negative for opioids
CDF of the percentage of self-reports negative for illicit opioids from week 5 through week 24	Wilcoxon rank sum test	FAS	All missing data considered non-negative for opioids
Change from baseline in opioid craving VAS (week 5 through week 24)	MMRM	FAS	Model-based
Percentage of completers	CMH test	FAS	No imputation
Percentage of patients abstinent	CMH test	FAS	No imputation
Change from baseline in CGI-S (week 5 through week 24)	MMRM	FAS	Model-based; no imputation
Change from baseline in total score on the COWS (week 5 through week 24)	MMRM	FAS	Model-based; no imputation
Change from baseline in total score on the SOWS (week 5 through week 24)	MMRM	FAS	Model-based; no imputation
Total number of weeks of abstinence as assessed from urine samples negative for opioids combined with self-reports negative for illicit opioid use from week 5 through week 24	ANOVA	FAS	All missing data considered non-negative for opioids
Exploratory Efficacy End Points			
Percentage of urine toxicology results positive for substance other than opioids	Wilcoxon rank sum test	FAS	All missing data considered non-negative for opioids
Time to first urine sample negative for illicit opioids combined with self-reports	Log-rank test	FAS	Censoring

	Statistical Method	Analysis Set	Approach to Missing Data
negative for illicit opioid use collected from week 5 through week 24			
Time to first urine sample negative for illicit opioids combined with self-reports negative for illicit opioid use collected from week 5 through week 24	Cox Proportional Hazards Model	FAS	Censoring

ANOVA = analysis of variance; CDF = cumulative distribution function; CGI-S = Clinical Global Impression – Severity; CMH = Cochran-Mantel-Haenszel; COWS = clinical opiate withdrawal scale; FAS = full analysis set; MMRM = mixed model for repeated measure; PPS = per-protocol set; SOWS = subjective opiate withdrawal scale; VAS = Visual Analog Scale.

Source: Clinical study report for Study 13-0001.[6]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Clinical Global Impressions scale (CGI): Severity (CGI-S) and Improvement (CGI-I)
- Clinical Opiate Withdrawal Scale (COWS)
- Subjective Opiate Withdrawal Scale (SOWS)
- Visual Analog Scale (VAS) for Cravings.

Findings

Instrument	Type	Evidence of Validity	MCID	References
CGI	**CGI-Improvement** • The investigator assesses the degree of the patient's global improvement since initiation of treatment (7-point Likert-type scale). Higher scores indicate worsening due to treatment. This is a single-item scale. **CGI-Severity** • The investigator rates the severity of illness at baseline and at time point(s) during (or at end of) treatment on a 7-point Likert-type scale. Higher scores indicate greater severity of illness. Change from baseline can be assessed. This is a single-item scale.	No evidence of validation in patients with substance abuse	Not identified	Guy (1976)[47]
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)[48]
SOWS	A self-administered, 16-item instrument used to rate the presence and intensity of opiate withdrawal symptoms. A higher score indicates a more severe withdrawal experience.	Yes (in men known to abuse opioids)	Not identified	Handelsman (1987)[49]
VAS for Cravings	An instrument used to quantify the state of craving a patient experienced in the previous 24 hours. For the 13-0001 trial, the scale was 100 mm. The scale is anchored on the left by "no craving at all" and anchored on the right by "strongest craving ever."	No	Not identified	McMillan (1996)[50]

CGI = Clinical Global Impressions; COWS = clinical opiate withdrawal scale; MCID = minimal clinically important difference; SOWS = Subjective Opiate Withdrawal Scale; VAS = Visual Analog Scale.

Clinical Global Impressions

The CGI outcome was originally developed during the Psychopharmacology Research Branch schizophrenic treatment studies. The CGI was modified for increased reliability by the Early Clinical Drug Evaluation program as a general tool for use in clinical trials. The CGI encompasses three global scales that can be used individually or in combination: Improvement (CGI-I), Severity (CGI-S), and Efficacy Index (CGI-EI). The scale items are

universal and thus the tool is intended for global assessment, in any research population, including adults and children. The CGI-I scale and CGI-EI require a minimum of one assessment (post-treatment), while the CGI-S scale requires a minimum of two, which must include pre- and post-treatment assessments. The CGI-I and CGI-S are similar one-item, 7-point Likert scales. Items are rated by the investigator. In the modified 1976 format, the CGI-S and CGI-EI should measure the patient's condition on the day of evaluation, or within the last week. The CGI-I was intended to measure improvement since admission to the study.[47] The CGI-I and CGI-S are often used as companion measures.

The CGI-S rates the severity of the psychopathology pre- and post-treatment. The investigator is asked to judge, based on their total clinical experience, the severity of illness relative to other patients of the specific study population (not relative to all types of patients); 0 means not assessed; 1 means normal, not at all ill; 2 means borderline mentally ill; 3 means mildly ill; 4 means moderately ill; 5 means markedly ill; 6 means severely ill; and 7 means among the most extremely ill patients.[47]

The CGI-I evaluates the change observed since the initiation of treatment and is intended to capture the improvement due to treatment, and not total improvement; 0 means not assessed; 1 means very much improved; 2 means much improved; 3 means minimally improved; 4 means no change; 5 means minimally worse; 6 means much worse; and 7 means very much worse.[47]

The CGI scales are among the most broadly used, rapid, and accessible measures for evaluating psychiatric outcomes in clinical trials. Despite wide acceptance, little psychometric validation of the scales has been performed, especially outside of specific disorders, such as schizophrenia, depression, and social anxiety. The scales have been criticized for lacking consistency, reliability, validity, scoring anchors, and responsiveness. It has been argued that CGI measures may not lend well to the establishment of a clinically important change as they are too simple to precisely measure treatment effects, especially as new drugs may only offer incremental benefits.[33-35] No evidence of a minimal clinically important difference (MCID) has been identified in patients with any specific indication, including those receiving treatment 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.[51] It can be administered in an office, clinic, or hospital setting and is quick to administer (generally within a few minutes).[48,51] It was originally published in a buprenorphine treatment training manual.[48,51] The COWS can also be used to track opioid withdrawal and differentiate it from opioid toxicity through serial measurements.[48] It is comprised of and rates 11 common signs and symptoms of opioid withdrawal, including resting pulse rate (beats/minutes), sweating (over past half an hour 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 (over last half an hour), tremor (observing outstretched hands), yawning (during assessment), anxiety or irritability (during assessment), and gooseflesh skin (during assessment).[51] 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 means mild; 13 to 24 means moderate; 25 to 36 means moderately severe; and more than 36 means severe

withdrawal; although these groupings have not been validated.[48,51] The overall score may be used to assess the physical level of opioid dependence.[51]

Tompkins et al.[48] 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.[48]

When analyzing the internal consistency of the COWS, an overall Cronbach's alpha of 0.78 indicated good reliability.[48] 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).[48] The COWS differentiates between mild opiate withdrawal and its absence.[48] The COWS has also been validated and found reliable when translated into other languages.[52]

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.[49] It is comprised of 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 meaning not at all, 1 meaning a little, 2 meaning moderately, 3 meaning quite a bit, and 4 meaning extremely. Patients are asked to rate: (1) I feel anxious, (2) I feel like yawning, (3) I'm perspiring, (4) My eyes are tearing, (5) My nose is running, (6) I have goose flesh, (7) I am shaking, (8) I have hot flashes, (9) I have cold flashes, (10) My bones and muscles ache, (11) I feel restless, (12) I feel nauseous, (13) I feel like vomiting, (14) My muscles twitch, (15) I have cramps in my stomach, and (16) I feel like shooting up now.[49] The wording of some of these items has since been modified to reflect more current terminology.

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.[49]

In order to assess the SOWS validity and reliability, Handelsman et al.[49] examined male patients in or entering treatment for substance abuse who were abusing only opioids or opioids and one or more other substance(s). 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. Construct 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. SOWS scores significantly

increased after receiving a naloxone challenge, although the net magnitude of the change was small and SOWS scores, overall, were largely variable.[49]

In order to examine the test-retest reliability of the SOWS, Handelsman et al.[49] administered the SOWS and the ARCI-WOWS on two occasions (one week separating the administration of the tests) in patients who were expected to maintain stable levels of opiate withdrawal symptoms. The intra-class correlation coefficients (ICC) were moderate for the SOWS (ICC = 0.60) and strong for the ACRI-WOWS (ICC = 0.85); the ARCI-WOWS displayed a higher degree of test-retest reliability over one week.[49]

The aforementioned results indicate that the SOWS (and the ARCI-WOWS) is sensitive to changes in opiate withdrawal symptom severity that occur spontaneously and in response to naloxone. However, the publication discussing the development and validation of the SOWS measure presents a number of deficiencies. First, the development of this measure is not sufficiently discussed to evaluate the content validity of the instrument, nor the face validity. Insufficient information is published to assess whether pre-testing of exploratory factor analysis, confirmatory factor analysis, and other methods of instrument development were undertaken. Second, all participants were male, ranging from 27 to 42 years of age; thus, the instrument testing lacks external validity.[49]

While the SOWS was validated for construct validity (comparing groups before and after treatment, and theoretically comparing groups with and without increased withdrawal symptoms), the investigators did not control for timing of naloxone challenge relative to last opioid drug intake. Patients likely experienced varying degrees of withdrawal, possibly blunting the effects of naloxone at the time of the SOWS administration. Furthermore, during validation testing, patients met the self-reported criteria for opioid abuse, but not necessarily for dependence, and no physiological measure of dependence was taken at time of test administration. The investigators did not attempt to calculate correlation between expert-observed or physiological opioid withdrawal symptoms and SOWS results; nor was criterion validity assessed by correlation of the SOWS with the previously validated ARCI-WOWS.[49] By current standards, the SOWS lacks a number of validation steps.[53]

Of note, a group in the Netherlands translated and refined the original English 16-item SOWS[49] to generate a contemporary consensus version of the Dutch SOWS.[54] The investigators administered the SOWS to 272 opioid-dependent in-patients at multiple stages during rapid detoxification treatment. Exploratory factor analysis identified three items that did not reliably load onto the same four factors throughout the treatment period. After removal of these three items, the 13-item SOWS was found to have good construct and criterion validity as well as high internal consistency and test-retest reliability as a measure of withdrawal symptoms at various stages during rapid detoxification.[54]

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

Visual Analog Scale for Cravings

In the only study identified that had used the VAS for Cravings, McMillan and Gilmore-Thomas[50] 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 their peak craving level along the time of day at which this peak craving occurred. 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-dosage change requests or time since dose.[55] 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,[56] 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 a patient with substance abuse undergoing methadone maintenance treatment.[55]

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

Conclusion

The COWS is a clinician-assessment instrument used to assess the signs and symptoms associated with opioid withdrawal in a 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 patient-completed instrument that is used to rate the intensity and presence of opiate withdrawal symptoms. It has been partially validated. 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. 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 Extension Study

Included Studies

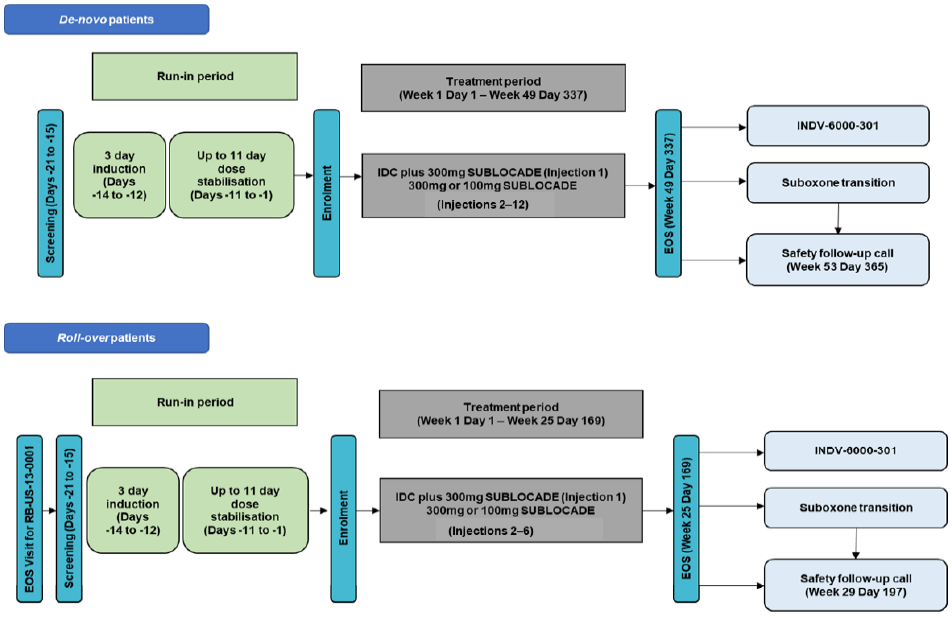
Description of Studies

Pivotal Trial (Study 13-0003)

Study 13-0003 was a multi-centre, open-label, long-term safety trial that was designed to assess the safety and tolerability of buprenorphine extended-release (BUP-ER) subcutaneous injection (100 mg and 300 mg) over one year in treatment-seeking patients with opioid use disorder (OUD). This study included a combination of patients who had completed Study 13-0001 (referred to as "roll-over" patients) and newly enrolled patients (referred to as "de novo" patients).

This study design consisted of a seven-day screening period, a run-in phase for up to two weeks, and a treatment period of 25 weeks for roll-over patients and 49 weeks for de novo patients. The screening visit occurred up to three days after the end-of-study visit for Study 13-0001 for roll-over patients that had been deemed by study investigators that initiation or continuation of treatment was appropriate, and that there had been no significant protocol deviations or clinically relevant adverse events precluding inclusion into the study. Both roll-over and de novo patients were reviewed for eligibility against inclusion and exclusion criteria at this time. The run-in period included a three-day induction with buprenorphine/naloxone followed by a dosage adjustment period of up to 11 days, and the treatment period involved monthly injections of up to 12 injections for de novo patients, and up to six injections for roll-over patients. Further study details are described in Table 32.

Figure 3: Study Design of Study 13-0003



EOS = end of study; IDC = behavioural counselling/individual drug counselling.

Source: Clinical study report for Study 13-0003.

Table 32: Details of Long-Term Extension Study

		13-0003
Designs and Populations	**Study Design**	Multi-centre, OL, long-term safety study
	Locations	US
	Population (N)	669
	Inclusion Criteria	Roll-over cohort: • Previous enrolment in study 13-0001 De novo cohort: • Moderate or severe OUD[a], seeking treatment • ≥ 18 to ≤ 65 years, and BMI ≥ 18.0 to ≤ 35.0kg/m^2 • Women of childbearing potential to have a negative pregnancy test prior to enrolment • All men and women of childbearing potential agreed contraception use
	Exclusion Criteria	De Novo cohort: • Current diagnosis, other than OUD, requiring chronic opioid treatment • Current substance use disorder[a], other than opioids, cocaine, cannabis, tobacco, or alcohol • Positive UDS results at screening for cocaine or cannabis and either moderate or severe cocaine use disorder or cannabis use disorder[a] • Moderate or severe alcohol use disorder[a] • Treatment for OUD required by court order • Pregnant or lactating female • Current incarceration or pending incarceration/ legal action • History of suicidal ideation within 30 days • Chest pain, palpitations with either exertion or drug use, peripheral or generalized edema, or major cardiovascular event (including IE) within 6 months • Significantly abnormal BP in opinion of investigator
Drugs	**Intervention**	Roll-over BUP-ER cohort from 13-0001: Buprenorphine extended-release 300 mg x one dose every four weeks followed by 300 mg or 100 mg every four weeks x 5 doses De novo BUP-ER cohort: buprenorphine extended-release 300 mg x one dose every four week followed by 300 mg or 100 mg every four weeks SC x 11 doses
	Comparator(s)	No comparison group
Duration	**Phase**	
	Run-in	2 weeks
	Double-blind	49 weeks
	Follow-up	4 weeks
Outcomes	**Primary End Point**	Safety and tolerability
	Other End Points	CDF of percentage of urine samples negative for opioids combined with negative self-reports for illicit opioid use; treatment success
Notes	**Publications**	Ling (2018)[31]

BMI = body mass index; BP = blood pressure; BUP-ER - buprenorphine extended-release; CDF = cumulative distribution function; IE = infective endocarditis; OL = open-label; OUD = opioid use disorder; SC = subcutaneous; UDS = urine drug screen.

Note: Two additional report were included (Health Canada Reviewer's Report for Sublocade,[11] Ling 2018[31]).

[a] Based on *DSM-5* criteria.

Source: Clinical study report for Study 13-0003.[8]

Populations

Inclusion and Exclusion Criteria

Patients in the roll-over cohort had to have successfully completed Study 13-0001 in its entirety, including the end-of-study assessments who belonged to either the placebo, 300 mg/300 mg, or 300 mg/100 mg arms, as well as agree to continue to use medically acceptable contraception throughout the trial duration for inclusion into Study 13-0003.

The de novo cohort had identical inclusion/exclusion criteria to Study 13-0001. This included adults meeting the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* criteria for current opioid dependence (Table 4) between 18 and 65 years of age who could tolerate buprenorphine, reach a stable buprenorphine dose within about two weeks, and comply with returning to the study site through the run-in period. Exclusion criteria in this study included an existing diagnosis requiring chronic opioid treatment, those meeting *DSM-5* criteria for moderate or severe cocaine, alcohol, or cannabis use disorder, receiving medication-assisted treatment for opioid use disorder in the past 90 days, and patients who had use of barbiturates, benzodiazepines, methadone, or buprenorphine within the past 30 days.

Baseline Characteristics

Study 13-0003 enrolled a total of 669 patients, 412 to the de novo arm of the study and 257 roll-over patients. The demographic and baseline characteristics appeared to be comparable between groups (Table 33). Overall, there were 432 patients who were male (64.6%), 462 who were white (69.1%), and patients had a mean age of 39.6 years (range, 19 to 65 years). Overall, 46.2% patients had a history of injectable opioid use, compared with 53.8% of patients who were non-injectable opioid users. Regarding medical history, the most commonly reported conditions were drug abuse (87.1%), hepatitis C (15.2%), and depression (14.1%). All prior medications including over the counter medication, dietary supplements, and herbal preparations taken within 30 days prior to screening were recorded.

Table 33: Summary of Baseline Characteristics — Safety Analysis Set

	De Novo Patients (N = 412)	Roll-Over Patients (N = 257)
Age, years, Mean (SD)	38.4 (12.10)	41.6 (11.07)
Male, n (%)	263 (63.8)	169 (65.8)
Race, n (%)		
White	295 (71.6)	167 (65.0)
Black	107 (26.0)	85 (33.1)
Other	10 (2.5)	4 (1.6)
Mean weight, kg (SD)	75.49 (14.658)	78.43 (18.097)
Mean BMI, kg/m^2 (SD)	25.38 (4.286)	26.14 (5.067)
Substance use at screening, n (%)		
Caffeine	365 (88.6)	229 (89.1)
Tobacco	354 (85.9)	222 (86.4)
Alcohol	193 (46.8)	144 (56.0)

	De Novo Patients (N = 412)	Roll-Over Patients (N = 257)
Opioid Users at Screening, n (%)		
Non-injectable opioid users	217 (52.7)	143 (55.6)
Injectable opioid users	195 (47.3)	114 (44.4)
Positive UDS on day 1[a]	199 (48.3)	98 (38.1)
Negative UDS on day 1[b]	213 (51.7)	158 (61.5)
Self-Reported Use 30 Days Prior to Screening, n (%)		
Amphetamine	29 (7.0)	9 (3.5)
Benzodiazepines	0 (0.0)	1 (0.4)
Cannabinoids	130 (31.6)	87 (33.9)
Cocaine	105 (25.5)	74 (28.8)
Methamphetamine	38 (9.2)	18 (7.0)
Phencyclidine	0	2 (0.8)
Medical History at Screening n, (%)		
Drug abuse	366 (88.8)	217 (84.4)
Depression	61 (14.8)	33 (12.8)
Anxiety	44 (10.7)	19 (7.4)
Drug dependence	46 (11.2)	39 (15.2)
Hepatitis C	60 (14.6)	42 (16.3)
At Least One Concomitant Medication, n (%)	272 (66.0)	154 (59.9)
Ibuprofen	24 (5.8)	21 (8.2)
Hydroxyzine	1 (0.2)	16 (6.2)
Acetaminophen	28 (6.8)	14 (5.4)
Amoxicillin	16 (3.9)	5 (1.9)
Benzodiazepines	11 (2.7)	6 (2.3)
Natural opium alkaloids	22 (5.3)	7 (2.7)
Morphine	4 (1.0)	1 (0.4)
Oxycodone/ acetaminophen	6 (1.5)	5 (1.9)
Oxycodone	5 (1.2)	1 (0.4)
Hydromorphone	5 (1.2)	0
SSRIs		
Citalopram	9 (2.2)	4 (1.6)
Sertraline	3 (0.7)	2 (0.8)
Other antidepressants		
Buproprion	7 (1.7)	2 (0.8)
Trazodone	16 (3.9)	4 (1.6)
Venlafaxine	6 (1.5)	3 (1.2)
Desvenlafaxine	2 (0.5)	0
Mirtazapine	3 (0.7)	1 (0.4)

BMI = body mass index; SD = standard deviation; SSRIs = selective serotonin reuptake inhibitors; UDS = urine drug screening.

[a] Indicative of illicit opioid use in addition to run-in medication up until day 1.

[b] Indicative of no illicit opioid use in addition to run-in medication up until day 1.

Source: Clinical study report for Study 13-0003.[8]

Table 34 depicts the drug use history in the safety analysis set of patients within Study 13-0003. Apart from opioids, the most frequently reported illicit drugs used were cannabinoids, cocaine, and amphetamines/methamphetamine. A total 48.4% of patients previously used cannabinoids, 41.6% of patients previously used cocaine, and 21.0% previously used amphetamines/methamphetamine.

Table 34: Drug Use History — Safety Analysis Set, n (%)

	De Novo Patients (N = 412)	Roll-Over Patients (N = 257)
Opioids	412 (100)	257 (100)
Cannabinoids	198 (48.1)	126 (49.0)
Cocaine	158 (38.3)	120 (46.7)
Amphetamines/ methamphetamine	95 (23.1)	46 (17.9)
Methadone	40 (9.7)	33 (12.8)
Benzodiazepines	61 (14.8)	34 (13.2)
Buprenorphine	67 (16.3)	35 (13.2)
Barbiturates	12 (2.9)	2 (0.8)
Phencyclidine	4 (1.0)	2 (0.8)
Other	6 (1.5)	2 (0.8)

Source: Clinical study report for Study 13-0003.[8]

Interventions

Patients enrolled in this study were administered buprenorphine/naloxone sublingual film, buprenorphine long-acting depot (BUP-ER), and behavioural counselling/individual drug counselling identical to Study 13-0001. For a detailed account of treatments administered throughout the induction, dosage adjustment, and treatment phases to patients in the de novo arm of the trial, see Table 7. Patients enrolled in the roll-over arm of this trial were to be inducted with buprenorphine/naloxone sublingual film on the same day they completed the end-of-study visit for Study 13-0001, provided they met all appropriate inclusion criteria, and none of the exclusion criteria. Dosages for these patients were to be titrated to a minimum of 8 mg buprenorphine/naloxone sublingual film by the end of the three-day induction period, regardless of their clinical opiate withdrawal scale (COWS) scores and the presence or absence of withdrawal symptoms. After the end of the induction period, the dosage adjustment and treatment phases for these patients followed those outlined in Table 7.

During the treatment phase of this study, patients received BUP-ER (300 mg, 100 mg) as well as behavioural counselling/individual drug counselling based on the medical judgment of the study investigator.

Buprenorphine / Naloxone Sublingual Film

Buprenorphine / naloxone sublingual film (Suboxone) was supplied as an orange, rectangular sublingual film with a white printed logo. This product was manufactured by Indivior. Each sublingual film contained buprenorphine hydrochloride and naloxone hydrochloride dehydrate at a 4:1 ratio expressed as the free bases. In this trial, films were available in four dosage strengths, which were 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, and 12 mg/3 mg buprenorphine/naloxone.

Buprenorphine Extended-Release Injection

BUP-ER was supplied as buprenorphine in an Atrigel delivery system. This was a single-syringe system, the entire contents of which were administered with each dose. BUP-ER contains buprenorphine in two dosage strengths, 300 mg and 100 mg. The approximate volume delivered is 0.5 mL for 100 mg injection and 1.5 mL for the 300 mg injection.

On day 1 of the study (initiation of study treatment injections), all patients, including roll-over patients from Study 13-0001 who had previously received placebo, were to receive an initial 300 mg subcutaneous injection of BUP-ER. Subsequent doses of BUP-ER were able to be adjusted down to 100 mg and, if required, back up to 300 mg based on the medical judgment of the investigator, as long as all patients were to receive injections separated by 28 (–2/+4) days.

Behavioural Counselling / Individual Drug Counselling

Patients in this study received once weekly individual behavioural counselling and individual drug counselling (IDC) in accompaniment to pharmacotherapy. Therapy was administered by appropriately qualified and trained staff members on-site who were blinded to patient's urine drug screen (UDS) results. Behavioural counselling / IDC were to continue once weekly until an early termination or end-of-study visit.

Outcomes

The primary objective in this study was to establish the long-term safety and tolerability of subcutaneous administration of BUP-ER in patients with OUD.

Secondary objectives were to collect clinical outcome data after subcutaneous administration of BUP-ER in patients with OUD. One efficacy outcome, the percentage of urine samples, was combined with negative self-reports of illicit opioid use. The self-reports were conducted via a timeline follow-back interview. Derivation of this composite efficacy end point was identical to that of the primary efficacy end point in Study 13-0001 (Table 35). Other efficacy outcomes included other drugs and alcohol on the timeline follow-back, COWS, subjective opiate withdrawal scale (SOWS), and opioid craving Visual Analog Scale (VAS).

Table 35: Composite Efficacy End Point Derivation

Urine Drug Screen Result[a]	Self-Report of Illicit Opioid Use Result	Primary Efficacy End Point
Non-negative	Non-negative	Non-negative
Non-negative	Negative	Non-negative
Negative	Non-negative	Non-negative
Negative	Non-negative	Non-negative
Negative	Negative	Negative

[a] Missing urine drug screen samples and/or self-reports were counted as non-negative.

[b] The self-reports of illicit opioid use were obtained from timeline follow-back interviews.

Source: Clinical study report for Study 13-0003.[8]

Statistical Analysis

Categorical variables were summarized using counts as well as percentages. Continuous variables were summarized using the number of observations, mean, standard deviation, median, minimum, and maximum. No formal statistical comparisons were conducted.

Analysis Populations

The following analysis sets were used for data analysis.

Run-in safety analysis set: All patients who received at least one dose of buprenorphine/naloxone sublingual film during the run-in period of the study.

Safety analysis set: All patients who received at least one dose of BUP-ER during the open-label treatment period of the study. This analysis was used for all safety analyses for the open-label treatment period.

Patient Disposition

Table 36 summarizes patient disposition in Study 13-0003. There were 994 patients screened for this study, of which 22.0% were screen failures. Following this, 775 patients were scheduled to enter the run-in period, of which 13.7% were run-in failures. Finally, 669 patients were included in the safety analysis set. In the de novo arm, 50.0% of patients discontinued the trial prematurely, most commonly citing loss to follow-up, withdrawal of consent, and other as reasons. A lower proportion of patients discontinued prematurely in the roll-over group (22.2%), citing similar reasons to those in the de novo group. Common "other" reasons included incarceration (19 patients) and pregnancy (13 patients). A total of 15 patients were withdrawn due to an adverse event.

Table 36: Patient Disposition in Study 13-0003

	De Novo Patients	Roll-Over Patients
Screened, N	994	
Screen failures	219 (22.0)	
Entered run-in period	508	267
Run-in failure, n (%)	96 (18.9)	10 (3.7)
Adverse event	1 (0.2)	1 (0.4)
Death	0	0
Withdrawal symptoms	1 (0.2)	0
Lost to follow-up	44 (8.7)	3 (1.1)
Consent withdrawn	22 (4.3)	3 (1.1)
Withdrawn by investigator	7 (1.4)	1 (0.4)
Protocol violation	2 (0.4)	0
Physician decision	0	1 (0.4)
Other	19 (3.7)	1 (0.4)
Entered BUP-ER treatment period, n (%)	412 (81.1)	257 (96.3)
Completed	206 (50.0)	200 (77.8)
Discontinued, N (%)	206 (50.0)	57 (22.2)
Reason for discontinuation		
Adverse event	11 (2.7)	4 (1.6)
Death	0	0
Withdrawal symptoms	3 (0.7)	0
Lost to follow-up	80 (19.4)	19 (7.4)
Noncompliance with study drug	0	0

	De Novo Patients	Roll-Over Patients
Physician decision	5 (1.2)	0
Patient withdrew consent	67 (16.3)	24 (9.3)
Patient withdrawn by investigator	7 (1.7)	1 (0.4)
Lack of efficacy	0	0
Protocol violation	4 (1.0)	4 (1.6)
Study terminated by sponsor	0	0
Other[a]	28 (6.8)	5 (1.9)
Run-in safety analysis set, N	508	267
Safety analysis set, N	412	257

BUP-ER = extended-release buprenorphine injection.

[a] "Other" reasons included incarceration (n = 19), pregnancy (n = 13), and patient unable to continue trial due to new job (n = 1).

Source: Clinical study report for Study 13-0003.[8]

Exposure to Study Treatments

The exposure of patients to study treatment during the open-label treatment phase in Study 13-0003 by four week intervals is summarized in Table 37. Due to the design of the study, patients in the roll-over cohort were included for only a total of six injections, or a duration of at least 24 weeks. There were no early surgical removals of the BUP-ER depot throughout the duration of the study.

Table 37: Exposure to Study Drug over Treatment Period — Safety Analysis Set

Duration of Exposure		Number (%) of Patients[a]	
		De Novo Patients (N = 412)	Roll-Over Patients (N = 257)
4 to < 8 weeks	N	48	10
	Mean number of weeks (SD)	4.3 (0.75)	4.8 (1.45)
8 to < 12 weeks	N	24	13
	Mean number of weeks (SD)	8.5 (1.01)	8.9 (1.34)
12 to < 16 weeks	N	27	14
	Mean number of weeks (SD)	12.6 (0.95)	12.6 (1.01)
16 to < 20 weeks	N	19	10
	Mean number of weeks (SD)	16.6 (0.96)	16.3 (0.34)
20 to < 24 weeks	N	15	22
	Mean number of weeks (SD)	20.8 (0.97)	22.9 (1.55)
24 to < 28 weeks	N	18	187
	Mean number of weeks (SD)	25.5 (1.53)	24.3 (0.39)
28 to < 32 weeks	N	9	1
	Mean number of weeks (SD)	28.3 (0.39)	28.7
32 to < 36 weeks	N	9	NA
	Mean number of weeks (SD)	32.3 (0.52)	
36 to < 40 weeks	N	10	NA
	Mean number of weeks (SD)	37.3 (0.97)	
40 to < 44 weeks	N	5	NA

Duration of Exposure		Number (%) of Patients[a]	
	Mean number of weeks (SD)	41.6 (1.03)	
44 to < 48 weeks	N	18	NA
	Mean number of weeks (SD)	46.4 (1.53)	
≥ 48 weeks	N	210	NA
	Mean number of weeks (SD)	48.8 (1.02)	

NA = not applicable; SD = standard deviation.

Source: Clinical study report for Study 13-0003.[8]

The total number of doses administered to patients during the open-label treatment phase in Study 13-0003 is summarized in Table 38. Due to the design of the study, patients in the roll-over cohort were included for only a total of six injections, while patients in the de novo cohort were expected to be administered 12 injections through the course of the trial.

Table 38: Total Number of Doses Administered in the Open-label Treatment Period — Safety Analysis Set

Number of Doses Administered in Treatment Period	De Novo Patients, N (%) (N = 412)	Roll-Over Patients, N (%) (N = 257)
1	46 (11.2)	8 (3.1)
2	24 (5.8)	13 (5.1)
3	27 (6.6)	15 (5.8)
4	20 (4.9)	11 (4.3)
5	15 (3.6)	7 (2.7)
6	15 (3.6)	203 (79.0)
7	13 (3.2)	NA
8	10 (2.4)	NA
9	9 (2.2)	NA
10	5 (1.2)	NA
11	9 (2.2)	NA
12	219 (53.2)	NA

NA = not applicable.

Note: Roll-over patients only received six injections as per protocol.

Source: Clinical study report for Study 13-0003.[8]

Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Table 3.

Key Efficacy End Point

Table 39 summarizes results for the key efficacy end point. Using the same primary efficacy end point as in Study 13-0001, the mean cumulative distribution function of percentage abstinence (UDS negative for opioids combined with self-reports negative for illicit opioid use) was found to be 45.59% (median, 42.11%) in de novo patients and 56.45% (median, 36.42%) in roll-over patients. Overall, 7.8% of de novo patients were able to achieve 100% abstinence compared with 18% of roll-over patients.

Table 39: Cumulative Distribution Function of the Percentage Urine Drug Samples Negative for Opioids Combined With Self-Reports Negative for Illicit Opioid Use at the End of Study[a] — Safety Analysis Set

Percentage UDS Negative and Self-Reports Negative for Illicit Opioid Use	Number (%) of Patients[a]	
	De Novo Patients (N = 412)	Roll-Over Patients (N = 257)
≥ 0%	412 (100)	257 (100)
≥ 10%	315 (76.5)	206 (80.2)
≥ 20%	278 (67.5)	200 (77.8)
≥ 30%	239 (58.0)	189 (73.5)
≥ 40%	217 (52.7)	159 (61.9)
≥ 50%	187 (45.4)	150 (58.4)
≥ 60%	166 (40.3)	137 (53.3)
≥ 70%	132 (32.0)	110 (42.8)
≥ 80%	98 (23.8)	96 (37.4)
≥ 90%	62 (15.0)	74 (28.8)
100%	32 (7.8)	47 (18.3)
Mean (SD)	45.59 (35.872)	56.45 (36.423)
Median	42.11	61.54
Minimum, Maximum	0% to 100%	0% to 100%

UDS = urine drug samples; SD = standard deviation.

[a] Patients in the roll-over group participated in this study for six months. Patients in the de novo group participated in this study for 12 months.

Source: Clinical study report for Study 13-0003.[8]

Table 40 represents the breakdown of the proportion of patients by treatment group considered abstinent (with a UDS sample negative for opioids combined with self-reports negative for illicit opioids) collected at different time points throughout the open-label treatment period. All missing results for urine drug samples or negative self-reports were considered to be non-negative for opioids.

Table 40: Number and Percentage of Patients achieving Abstinence by Visit — Safety Analysis Set

Week	Number (%) of Patients	
	De Novo Patients (N = 412)	Roll-Over Patients (N = 257)
Screening	0	148 (57.6)
Baseline[a]	196 (47.6)	147 (57.2)
Week 2 day 8	221 (53.6)	156 (60.7)
Week 3 day 15	218 (52.9)	154 (59.9)
Week 4 day 22	223 (54.1)	152 (59.1)
Week 5 day 29	208 (50.5)	157 (61.1)
Week 7 day 43	213 (51.7)	155 (60.3)
Week 9 day 57	202 (49.0)	148 (57.6)
Week 11 day 71	198 (48.1)	145 (56.4)

Week	Number (%) of Patients	
Week 13 day 85	198 (48.1)	147 (57.2)
Week 15 day 99	189 (45.9)	143 (55.6)
Week 17 day 113	187 (45.4)	140 (54.5)
Week 19 day 127	181 (43.9)	133 (51.8)
Week 21 day 141	178 (43.2)	139 (54.1)
Roll-over end of study, day 169	NA	117 (45.5)
Week 25 day 169	168 (40.8)	NA
Week 29 day 197	163 (39.6)	NA
Week 33 day 225	174 (42.2)	NA
Week 37 day 253	171 (41.5)	NA
Week 41 day 281	161 (39.1)	NA
Week 45 day 309	159 (38.6)	NA
De novo end of study day 337	157 (38.1)	NA

NA = not applicable.

Note: All missing results for opioids were considered non-negative for opioids. Opioids non-negative indicates detection of codeine, hydrocodone, hydromorphone, methadone, morphine, opiates, oxycodone, and oxymorphone in the urine drug screen, as well as amphetamine/methadone, buprenorphine, and opioids in the timeline follow-back assessment.

[a] Baseline result was week 1, day 1.

Source: Clinical study report for Study 13-0003.[8]

Other Efficacy Outcomes

The total SOWS scores by visit in the safety analysis set is provided in Table 41. The mean total SOWS scores remained low in both groups throughout the duration of the trial, which suggests that patients experienced minimal withdrawal symptoms. At the end of the study, mean total scores were numerically lower in the de novo arm (2.0) compared with the roll-over arm (3.9).

Table 41: Mean Subjective Opiate Withdrawal Scale by Treatment Group — Full Analysis Set

Week	Mean (SD) SOWS Score	
	De Novo Patients (N = 412)	**Roll-Over Patients (N = 257)**
Week 1 day 1 (baseline)	3.8 (5.27)	2.8 (5.44)
Week 2 day 8	2.4 (3.85)	1.7 (4.35)
Week 3 day 15	2.2 (3.89)	1.5 (3.81)
Week 4 day 22	2.3 (4.45)	1.7 (4.52)
Week 5 day 29	3.9 (6.98)	2.2 (5.25)
Week 7 day 43	1.7 (3.29)	1.7 (4.61)
Week 9 day 57	2.7 (5.20)	2.8 (6.77)
Week 11 day 71	1.3 (2.83)	1.6 (3.90)
Week 13 day 85	2.6 (5.31)	2.2 (5.00)
Week 15 day 99	1.5 (3.69)	1.7 (3.93)
Week 17 day 113	2.3 (4.77)	2.3 (5.36)
Week 19 day 127	1.5 (3.66)	1.9 (6.19)
Week 21 day 141	1.8 (4.47)	2.7 (7.29)

Week	Mean (SD) SOWS Score	
Roll-over end of study, day 169	NA	3.9 (8.90)
Week 25 day 169	2.3 (5.39)	NA
Week 29 day 197	2.2 (5.01)	NA
Week 33 day 225	1.7 (3.62)	NA
Week 37 day 253	2.1 (4.66)	NA
Week 41 day 281	2.2 (4.76)	NA
Week 45 day 309	2.3 (6.35)	NA
De novo end of study day 337	2.0 (4.08)	NA
Mean change from baseline to end of study	–1.6 (5.05)	+1.1 (7.17)

NA = not applicable SD = standard deviation; SOWS = subjective opiate withdrawal scale.

Source: Clinical study report for Study 13-0003.[8]

Table 42 displays the mean total COWS scores recorded by visit during the open-blind treatment period. Mean COWS scores at baseline remained low throughout the study, indicating minimal withdrawal symptoms. Similar mean scores at the end of study were obtained in the de novo treatment arm (1.0) and the roll-over treatment arm (1.2).

Table 42: Mean Clinical Opiate Withdrawal Scale by Treatment Group — Safety Analysis Set

Week	Mean (SD) COWS Score	
	De Novo Patients (N = 412)	**Roll-over Patients (N = 257)**
Week 1 day 1 (baseline)	2.1 (2.43)	1.5 (1.98)
Week 2 day 8	1.4 (1.89)	0.9 (1.57)
Week 3 day 15	1.3 (2.11)	0.9 (1.57)
Week 4 day 22	1.1 (1.67)	1.0 (1.66)
Week 5 day 29	1.7 (2.51)	1.2 (2.27)
Week 7 day 43	1.0 (1.58)	0.8 (1.34)
Week 9 day 57	1.6 (2.44)	1.1 (1.74)
Week 11 day 71	0.9 (1.34)	0.7 (1.23)
Week 13 day 85	1.1 (1.66)	1.0 (1.90)
Week 15 day 99	0.7 (1.28)	0.9 (1.56)
Week 17 day 113	1.1 (2.00)	1.0 (1.90)
Week 19 day 127	0.8 (1.13)	0.9 (1.82)
Week 21 day 141	1.0 (1.67)	1.1 (2.22)
Roll-over end of study, day 169	NA	1.2 (2.26)
Week 25 day 169	1.0 (1.95)	NA
Week 29 day 197	1.1 (2.25)	NA
Week 33 day 225	0.9 (1.53)	NA
Week 37 day 253	0.9 (1.67)	NA
Week 41 day 281	1.1 (1.74)	NA
Week 45 day 309	1.0 (2.03)	NA
De novo end of study day 337	1.0 (1.49)	NA
Mean change from baseline to end of study	–1.0 (2.41)	–0.3 (2.37)

COWS = clinical opiate withdrawal scale; NA= not applicable; SD= standard deviation.

Source: Clinical study report for Study 13-0003.[8]

Mean opioid craving VAS scores are summarized in Table 43. In both arms of the trial, opioid craving VAS scores were low, which indicated that there was a minimal craving for opioids throughout the duration of the trial. It should be noted that at the end of the study, mean scores were 8.3 for patients in the roll-over group, compared with 3.0 for patients in the de novo group.

Table 43: Mean Opioid Craving Visual Analog Scale by Treatment Group — Safety Analysis Set

Week	Mean (SD) Opioid Craving VAS Score	
	De Novo Patients (N = 412)	Roll-Over Patients (N = 257)
Week 1 day 1 (baseline)	5.9 (10.59)	4.4 (9.62)
Week 2 day 8	5.3 (12.92)	3.8 (10.43)
Week 3 day 15	5.1 (12.17)	3.7 (10.00)
Week 4 day 22	5.2 (12.66)	3.6 (9.68)
Week 5 day 29	7.2 (15.80)	4.8 (11.29)
Week 7 day 43	3.6 (11.29)	3.6 (11.28)
Week 9 day 57	6.0 (14.51)	4.9 (14.48)
Week 11 day 71	2.2 (6.43)	3.4 (10.93)
Week 13 day 85	4.9 (13.20)	5.0 (13.06)
Week 15 day 99	2.9 (9.66)	3.1 (9.65)
Week 17 day 113	4.4 (12.43)	4.9 (12.50)
Week 19 day 127	3.0 (8.87)	3.5 (10.75)
Week 21 day 141	3.7 (10.91)	4.8 (11.29)
Roll-over end of study, day 169	NA	8.3 (18.57)
Week 25 day 169	5.0 (14.97)	NA
Week 29 day 197	4.4 (12.84)	NA
Week 33 day 225	2.8 (8.10)	NA
Week 37 day 253	4.3 (11.98)	NA
Week 41 day 281	4.0 (11.03)	NA
Week 45 day 309	3.9 (11.65)	NA
De novo end of study day 337	3.0 (9.79)	NA
Mean change from baseline to end of study	–2.0 (10.83)	4.2 (16.77)

NA = not applicable; SD = standard deviation; VAS = Visual Analog Scale.

Source: Clinical study report for Study 13-0003.[8]

Table 44 summarizes the percentage of patients with positive results for substances detected by urine toxicology (including opioids) for all visits. The most common substances used among all patients enrolled were opiates, morphine, cannabinoids, hydromorphone, and codeine.

Table 44: Urine Toxicology for Substance Use for All Visits — Safety Analysis Set

Substance	Treatment Group, N (%)	
	De Novo Patients (N = 412)	Roll-Over Patients (N = 197)
Amphetamine	156 (37.9)	73 (28.4)
Barbiturates	8 (1.9)	4 (1.6)
Benzodiazepine	105 (25.5)	69 (26.8)
Benzoylecgonine	207 (50.2)	123 (47.9)
Cannabinoids	233 (56.6)	135 (52.5)
Codeine	265 (64.3)	100 (38.9)
Hydrocodone	72 (17.5)	31 (12.1)
Hydromorphone	300 (72.8)	107 (41.6)
Methadone	9 (2.2)	2 (0.8)
Morphine	315 (76.5)	129 (50.2)
Opiate	364 (88.3)	149 (58.0)
Oxycodone	102 (24.8)	44 (17.1)
Oxymorphone	91 (22.1)	29 (11.3)
Phencyclidine	22 (5.3)	12 (4.7)

Source: Clinical study report for Study 13-0003.[8]

Harms

Only those harms identified in the review protocol are reported in the following (see Protocol). Relevant harms data are summarized in Table 45.

Adverse Events

Throughout the open-label treatment phase of Study 13-0003, 447 (66.8%) of patients enrolled reported at least one adverse event. There was a numerically higher proportion of patients in the de novo group (73.3%) experiencing an adverse event compared with patients in the roll-over group (56.4%). The most common adverse events cited were constipation (8.4%), nausea (7.0%), injection site pain (6.9%), and insomnia (5.5%).

Serious Adverse Events

Regarding serious adverse events, a total of 25 (3.7%) patients in both arms reported occurrences during the treatment phase. The most common serious adverse events were cellulitis and accidental overdose, all of which occurred among patients in the de novo arm. A total of 43 (6.4%) patients in both arms experienced severe adverse events, the most common of which were constipation and muscle spasms.

Withdrawals Due to Adverse Events

Withdrawal due to adverse events occurred in 17 (2.5%) of the patients enrolled. There was a numerically higher proportion of patients in the de novo group who withdrew due to adverse events (3.2%) than roll-over patients (1.6%). The most common adverse event leading to withdrawal was cited as drug withdrawal syndrome. No patients had early surgical removal of the BUP-ER depot.

Mortality

There were no reported deaths throughout the course of this trial.

Notable Harms

There were no adverse events reported that pertained to respiratory depression.

During the treatment period, there were 165 patients (24.7%) with adverse events pertaining to withdrawal symptoms (120 patients in the de novo group and 45 patients in the roll-over group). The most common adverse events potentially pertaining to withdrawal symptoms were nausea (7.0%), insomnia (5.5), anxiety (3.6%), and vomiting (3.4%).

There were three patients reporting overdose, one each of heroin, trazodone and diazepam, all of which were reported as serious adverse events.

Potential hepatoxicity was reported in 28 patients (4.2%) who had both alanine transaminase (ALT) and aspartate aminotransferase (AST) greater than three times the upper limit of normal at some point during the study. The majority of these patients had confounding factors such as hepatitis C; positive hepatitis C antibody; previous medical history of hepatitis C, alcohol use, cholelithiasis, and/or concomitant use of hepatoxic drugs, any of which could have impacted the liver function serum tests. Four patients (1.4%) had no identifiable coexisting factors for this elevation in hepatic enzymes. Two patients in the de novo group discontinued due to liver-related events (AST increased and liver function test was found to be abnormal) compared with none in the roll-over arm. A total of 12 patients in the de novo group (2.9%) had to have their dose reduced due to liver-related adverse events or liver-related enzyme issues (i.e., increased AST or ALT) compared with three patients (1.2%) in the roll-over group.

Table 45: Adverse Events, Serious Adverse Events, Withdrawals Due to Adverse Events, and Deaths Observed in Study 13-0003 Throughout Treatment Phase — Safety Analysis Set

	De Novo Patients (N = 412)	Roll-over Patients (N = 257)
AEs		
Patients with > 0 AEs, N (%)	302 (73.3)	145 (56.4)
Most common AEs[a]	Constipation, nausea, injection site pain, insomnia, headache, nasopharyngitis	
Constipation	47 (11.4)	9 (3.5)
Nausea	37 (9.0)	10 (3.9)
Injection site pain	39 (9.5)	7 (2.7)
Insomnia	27 (6.6)	10 (3.9)
Headache	31 (7.5)	5 (1.9)
Nasopharyngitis	24 (5.8)	6 (2.3)
Serious Adverse Events		
Patients with > 0 serious AEs, N (%)	16 (3.9)	9 (3.5)
Most common SAEs[a]	Cellulitis, accidental overdose	
Cellulitis	2 (0.5)	1 (0.4)
Accidental overdose	2 (0.5)	0
Severe Adverse Events		
Patients with > 0 severe AEs, N (%)	36 (8.7)	7 (2.7)

	De Novo Patients (N = 412)	Roll-over Patients (N = 257)
Most common serious adverse events	Constipation, muscle spasms, asthma, arthropod bite, back pain, sleep disorder, cellulitis	
Constipation	3 (0.7)	0
Muscle spasms	3 (0.7)	0
Asthma	2 (0.5)	0
Arthropod bite	2 (0.5)	0
Back pain	2 (0.5)	0
Sleep disorder	2 (0.5)	0
Cellulitis	1 (0.2)	1 (0.4)
WDAEs		
WDAEs, N (%)	13 (3.2)	4 (1.6)
Most common reasons	Drug withdrawal syndrome, injection site ulcer, sedation, somnolence, abnormal LFTs, increased aspartate aminotransferase, constipation, nausea, vomiting, rash, lymphadenitis	
Drug withdrawal syndrome	3 (0.7)	0
Injection site pain	0	1 (0.4)
Injection site reaction	1 (0.2)	0
Injection site swelling	0	1 (0.4)
Aspartate aminotransferase increased	1 (0.2)	0
Lipase increased	1 (0.2)	0
Abnormal LFTs	1 (0.2)	0
Weight decreased	0	1 (0.4)
Migraine	0	1 (0.4)
Sedation	0	1 (0.4)
Somnolence	1 (0.2)	0
Gallbladder perforation	1 (0.2)	0
Jaundice	1 (0.2)	0
Constipation	1 (0.2)	0
Accidental overdose	1 (0.2)	0
Diabetes mellitus	1 (0.2)	0
Deaths		
Number of deaths, N (%)	0 (0.0)	0

AE = adverse event; LFT = liver function test; SAE = serious adverse events; WDAE = withdrawals due to adverse events.

Source: Clinical study report for Study 13-0003.[8]

Patients with injection site reactions at any time throughout Study 13-0003 are summarized in Table 46. During the treatment period, 88 total patients (13.2%) reported to have adverse events related to injection site reactions (15.5% in the de novo group and 8.2% in the roll-over group). The most commonly reported injection site reactions were injection site pain (46 patients, 6.9%), injection site erythema (27 patients, 4.0%), and injection site pruritis (26 patients. 3.9%), all of which were generally mild in severity. Two patients reportedly withdrew due to injection site reactions. One patient in the de novo group experienced an anaphylactic reaction following injection.

Table 46: Patients with Injection Site Reactions at Any Time — Safety Analysis Set, N (%)

	De Novo Patients (N = 412)	Roll-Over Patient (N = 257)
Pain at Injection Site		
Mild	257 (62.4)	140 (54.5)
Moderate	26 (6.3)	9 (3.5)
Severe	4 (1.0)	0
Potentially life-threatening	0	0
Tenderness at Injection Site		
Mild	269 (65.3)	165 (64.2)
Moderate	83 (20.1)	39 (15.2)
Severe	17 (4.1)	5 (1.9)
Potentially life-threatening	0	0
Erythema/Redness		
Mild	169 (41.0)	72 (28.0)
Moderate	30 (7.3)	24 (9.3)
Severe	5 (1.2)	0
Potentially life-threatening	0	0
Induration		
Mild	185 (44.9)	120 (46.7)
Moderate	10 (2.4)	10 (3.9)
Severe	3 (0.7)	0
Potentially life-threatening	0	0
Swelling		
Mild	98 (23.8)	50 (19.5)
Moderate	8 (1.9)	50 (19.5)
Severe	1 (0.2)	0
Potentially life-threatening	0	0

Source: Clinical study report for Study 13-0003.[8]

Critical Appraisal

Internal Validity

- The characteristics of patients at baseline appeared to be generally balanced between treatment groups, although there was a slightly higher proportion of patients with a positive UDS on day 1 (48.3% in the de novo group and 38.1% in the roll-over group).
- Study 13-0003 was an open-label study designed to examine long-term safety and tolerability outcomes of BUP-ER treatment over a period of 48 weeks. As a result, this was an uncontrolled cohort study of two groups of patients both receiving BUP-ER injections, with no statistical comparisons between the two groups defined a priori.
- There was a high number of patients with missing data for UDS results, self-reports for illicit opioid use, and opioid craving scores (i.e., COWS, SOWS, opioid craving VAS). For the UDS results and self-reports for illicit opioid use outcomes that were dichotomous, missing data (including early dropouts) was imputed as non-negative.

The clinical expert involved in this review believed this to be a reasonable assumption to make in this patient population. Missing data for other continuous outcomes (i.e., COWS, SOWS, and opioid craving VAS) were not imputed for their analysis; however, there is a possibility that patients who prematurely withdrew from this study and those who did not were different patient populations. Potential impact on these results is uncertain since there were no sensitivity analyses conducted.

- Results from patients in the roll-over group should be interpreted with caution, as this population is largely comprised of patients who had completed Study 13-0001 with a good response, good adherence, and low side effects from study treatment. Therefore, efficacy results may be overestimated in this group compared with all users due to the fact that it is highly selected, and harms may be underestimated.
- Withdrawal symptoms, such as change from baseline in COWS, SOWS, and opioid craving VAS, as well as change in clinical global impression scales for improvement and severity were recorded in this study. The COWS and SOWS scales used throughout this trial have been validated in this patient population; however, minimal clinically important difference is unknown. The clinical expert involved in this review added that these scales are typically only employed in practice to decide on what dosage to induct patients on opioid maintenance therapy. The validity and reliability of the need- or desire-to-use VAS remains uncertain. Further information on the validity of these outcomes is provided in Appendix 5.
- Self-reports of illicit opioid use was collected in the format of a timeline follow-back interview, which was administered electronically by an interviewer. The interview instrument required patients to retrospectively estimate they drug use in the 30 days prior to screening, as well as the last visit at all subsequent visits, by answering with use or no use. As a result, this interview format may have been impacted by the truthfulness of responses, as well as non-response bias.

External Validity

- Of the 994 patients screened for inclusion into Study 13-0003, 669 entered the BUP-ER treatment phase. Of those, 219 (22.2%) were recorded as screen failures. The exclusion criteria in this study was extended to patients with any concurrent substance use disorder (excluding cocaine, cannabis, tobacco, and alcohol), as well as those meeting *DSM-5* criteria for either moderate or severe cocaine, alcohol, or cannabis use disorder. According to the clinical expert involved in this review, concurrent substance use disorders are very common in this patient population, and cannabis use is especially prevalent. Furthermore, patients with uncontrolled psychiatric comorbidities (i.e., depression, post-traumatic stress disorder, anxiety) were also excluded from this trial, which are well-known to occur among patients with OUD.[1,36,37] Stringent inclusion and exclusion criteria can potentially lead to the inclusion of a select group of patients that may not be representative of the population of patients with moderate-to-severe OUD in Canada who are seeking medication-assisted treatment and can potentially limit the generalizability of the trial results.
- The majority of patients who were enrolled in Study 13-0003 were white (69.1%) and male (64.6%), with a mean age of 39.6 years. Regarding concurrent medical history, 15.2% of patients in the study had hepatitis C and, regarding concurrent psychiatric history, 14.1% had depression documented. These rates are much lower than what is found in the general population,[1,36-38] and therefore may be more likely to have positive outcomes. Generalizability is also uncertain for patients who may belong to a more marginalized, or specific high-risk population of interest, such as youth or Indigenous

peoples, or those with chronic pain, who have not been represented in this study.[37] Finally, this trial was 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.

- Patients enrolled in this study were scheduled to receive BUP-ER 300 mg as an initial dose. Subsequent doses were able to be adjusted either down to 100 mg or maintained at 300 mg based on the medical judgment of the investigator. This is not in line with recommended dosages in the product monograph approved by Health Canada, which recommends that patients start with 300 mg per month for two months followed by a maintenance dose of 100 mg per month thereafter.[5] The product monograph goes on to recommend that the maintenance dose be increased to 300 mg monthly only if the patient does not demonstrate satisfactory clinical response and can tolerate the 100 mg dose. There were no comparisons made between patients maintained on 300 mg per month and 100 mg per month in this study to determine significant differences in tolerability or efficacy between the two doses.
- The included study focused on short-term outcomes and does not provide evidence of observed reductions or patient control of drug use that are of clinical and social benefit, even if opioid use has not completely stopped. In addition, questions around the impact of BUP-ER on critically important outcomes, such as health-related quality of life, work productivity, and incarceration rates, have not been recorded in this trial.

Conclusions

Study 13-0003 was an open-label, long-term safety and tolerability study evaluating the use of BUP-ER in patients with moderate-to-severe OUD who are treatment-seeking. Safety findings from this trial were consistent with the other studies evaluating BUP-ER. The incidence of hepatic-related adverse events and injection site reactions were notable in this study population. Regarding efficacy outcomes, the mean percentage abstinence was 46% in the de novo group compared with 57% in the roll-over group. Overall, 24% of de novo patients and 37% of roll-over patients met the criterion for treatment success. However, due to the open-label study design and the highly selected patient sample, results of safety and efficacy should be interpreted with caution.

Appendix 7: Summary of Indirect Comparisons

Aim

Given the lack of head-to-head studies for buprenorphine extended-release (BUP-ER) subcutaneous injection, this review was conducted to summarize and appraise the indirect evidence comparing BUP-ER subcutaneous injection to other drugs approved for use in opioid use disorder (OUD).

Methods

A literature search was conducted to identify relevant indirect treatment comparisons (ITCs) that included the patients, interventions, and outcomes as identified in the CADTH Common Drug Review Clinical Review protocol (Table 3). One manufacturer-supplied systematic review and ITC met the criteria for inclusion.[9]

Description of Indirect Treatment Comparison Identified

One ITC submitted by the manufacturer was included for critical appraisal. Table 47 summarizes the key aspects of the ITC. The ITC included was sponsored by the manufacturer of BUP-ER subcutaneous injection.

Table 47: Overview of Included Indirect Treatment Comparison

Population	Intervention	Comparators	Outcomes	Study Design
Patients with opioid dependence or opioid use disorder	Buprenorphine depots (i.e., BUP-ER, CAM2038)	• Buprenorphine implants (i.e., Probuphine) • Buprenorphine tablets (e.g., Subutex) oral tablets (e.g., Subutex) • Buprenorphine plus naloxone (e.g., Suboxone) • Methadone • Naltrexone • Levacetylmethadol • Placebo • None	• Treatment retention • Abstinence from opioids other than OAT • Relapse • Compliance/adherence • Withdrawal • Cravings • Addiction severity index • Quality of life	• RCTs • SRs and MAs of RCTs

BUP-ER = buprenorphine extended-release; MAs = meta-analyses; OAT = opioid agonist treatment; RCTs = randomized control trials; SRs = systematic reviews.

Source: Manufacturer-supplied indirect treatment comparison.[9]

Review and Appraisal of Indirect Treatment Comparison

The manufacturer-submitted ITC[9] was critically appraised in part using recommendations from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons as a guide.[57]

Review of Manufacturer-Supplied Indirect Treatment Comparison

Objectives and Rationale for the Manufacturer-Supplied Indirect Treatment Comparison

The objective of the manufacturer-supplied ITC was to compare the efficacy of BUP-ER subcutaneous injection with sublingual buprenorphine, methadone, and CAM2038 for abstinence and treatment retention.

Methods for Manufacturer-Supplied Indirect Treatment Comparison

Study Eligibility, Selection Process, and Data Extraction

Studies for the manufacturer's ITC were identified via systematic literature. The authors searched MEDLINE, Embase, PyscInfo, The Cochrane Database of Systematic Reviews (CDSR), The Database of Abstracts of Reviews of Effectiveness (DARE), and Cochrane Central Register of Controlled Trials (CENTRAL) for potentially relevant English-language randomized controlled trails or clinical trials published from January 1, 2000, to July 12, 2017. Abstracts from the 2016 College on Problems of Drug Dependence Conference and 2016 International Council on Alcohol, Drugs and Traffic Safety Conference were also reviewed for relevant studies. Reference lists of published systematic reviews and meta-analyses were manually searched to identify additional trials.

The manufacturer provided clear eligibility criteria for the inclusion of studies in the ITC. Studies were included if they had opioid dependence or OUD. Studies were included if they studied any relevant pharmaceutical intervention compared with any other pharmaceutical intervention, placebo, or nothing. Studies on patients receiving treatment for detoxification (as opposed to maintenance) as part of the intervention were excluded. Studies were excluded if they specifically examined patients who were involved in the criminal justice system, pregnant, or HIV-positive. Studies were excluded if patients were required to have co-dependence or co-abuse of other drugs. Non-randomized controlled trails, observational studies, case series, case reports, studies of non-original data, and non-systematic reviews were also excluded. Studies were excluded based on patient characteristics or outcome data as assessed by expert clinician opinion. Consultation with clinical experts resulted in excluding one study that was unbalanced with respect to the proportion of male patients in treatment arms and excluding one study that had 52-week retention data that was much higher than what was reported in other studies. It is unclear how the inclusion of these studies may have altered the study results.

Two independent researchers reviewed titles, abstracts, and full-text articles for studies that met the protocol-specified inclusion criteria. Discrepancies were resolved through consensus with a third reviewer. Data were extracted by one reviewer and reviewed for accuracy by a second reviewer.

Comparators

The ITC included studies that compared the following:

- buprenorphine depots (i.e., BUP-ER, CAM2038)
- buprenorphine implants (BUP-IMP)
- buprenorphine tablets (variable-dose sublingual buprenorphine [BUP-V])
- buprenorphine plus naloxone (e.g., Suboxone)
- methadone (variable-dose methadone [MET-V])
- naltrexone
- levacetylmethadol
- placebo.

Fixed-dose sublingual buprenorphine and fixed-dose methadone were not considered as these are not considered to be standard of care in Canada. CAM2038 was included as it allowed for data from the sublingual buprenorphine arm to be added into the network.

Outcomes

The ITC evaluated the following efficacy and safety outcomes: treatment retention, abstinence from opioids other than opioid agonist treatment, relapse, compliance, adherence, withdrawal, cravings, addiction severity index, and quality of life.

Quality Assessment of Included Studies

Risk of bias in the trials was assessed using the Cochrane Risk of Bias Tool. The number of reviewers carrying out the assessment was not reported, nor was the process for reconciling discrepancies. An a priori assessment for clinical heterogeneity in the included studies was not reported. Characteristics of studies were reported (e.g., blinding, duration of dependence, number of previous treatment attempts, duration of study) but were not used to refine the inclusion criteria. No statistical adjustment for any potential confounders or study quality was considered.

Indirect Comparison Methods

Study Dropout (Treatment Retention)

For this analysis, treatment retention was defined as study dropout within each study, consistent with prior systematic reviews and meta-analyses of trials evaluating OUD. Treatment retention was used to assess the network meta-analysis (NMA) outcome for study dropout. The proportion of patients still on treatment at various time points throughout the trial were depicted in several original publications as Kaplan-Meier survival curves. The data were digitally extracted using UN-SCAN-IT graph digitizer software. Some studies did not have Kaplan-Meier curves available for scanning, for these studies' retention data at individual time points were extracted.

Retention data were analyzed using a Weibull proportional hazards model. The ITC was conducted in WinBUGS software (version 1.4.3) using a Bayesian-based analysis with vague prior distributions for the NMA. Fixed- and random-effects models were conducted. The proportion of patients retained in the study at each time point was analyzed using the binomial distribution and the cloglog link function; this methodology includes weighting by sample size. The Weibull proportional hazards framework assumes the data are Weibull distributed and the hazards of events for each treatment are proportional. All study dropouts were assumed to be non-retained regardless of the reason for study withdrawal.

It is unclear if sensitivity analyses to examine heterogeneity were planned a priori. The Q-statistic was calculated to assess potential heterogeneity associated with the studies (n = 7) that included a BUP-V to MET-V comparison. Convergence was assessed visually via autocorrelation diagnostics within the WinBUGS program. Reported results included at least 40,000 posterior samples after a burn in of at least 10,000 samples.

Consistency between indirect and direct effects were not assessed. The NMA for study dropout appears to support the assumption of transitivity as patient baseline characteristics were similar. Model fit was evaluated using the deviance information criterion (DIC); however, details on number of models examined and how the best model was selected (e.g., based on the DIC alone) were unclear.

The use of the Weibull approach was rationalized as it allowed for the incorporation of all available data, including multiple time points reported from a single study, and is advantageous over other methods such as fractional polynomials because comparative efficacy estimates can be expressed as constant hazard ratios, which are more readily interpretable than polynomial slopes.

The hazard ratios were presented with 95% credible intervals where a hazard ratio (HR) greater than 1.0 indicated increased hazard of study dropout relative to the comparison arm. HRs were presented for placebo, BUP-ER 300 mg/300 mg, and BUP-ER 300 mg/100 mg compared with various treatments.

Opioid Positivity (Overall Abstinence by Urinalysis)

For this analysis, the assessment of opioid abstinence was defined as the percentage of negative urine samples during the entire study duration, which was the most commonly and consistently reported outcome for abstinence that was suitable for analysis. Overall abstinence by urinalysis was used to assess the NMA outcome for opioid positivity.

Binary data for this outcome was assessed as the total number of positive urinalysis samples divided by the total number of samples scheduled to be collected. The NMA was performed using a Bayesian-based analysis. The proportions were modelled using a binomial distribution with logit link. A fixed-effect model was used due to only three studies in the network; this prevented a reliable estimation of the random-effect parameter. The NMA was designed to be weighted by the number of patients rather than the number of collected urinalysis samples by using the number of patients within each treatment arm as the denominator of each of the proportions rather than the total number of samples collected. Odds ratios (ORs) were presented for placebo, BUP-ER 300 mg/300 mg, and BUP-ER 300 mg/100 mg compared with various treatments.

No sensitivity analyses were performed. Similar to the study dropout NMA, for opioid positivity convergence was assessed visually via autocorrelation diagnostics within the WinBUGS program. Reported results included at least 40,000 posterior samples after a burn in of at least 10,000 samples.

Consistency between indirect and direct effects were not assessed. The NMA for study dropout appears to support the assumption of transitivity as patient baseline characteristics were similar. Model fit was evaluated using the DIC; however, details on number of models examined and how the best model was selected (e.g., based on the DIC alone) were unclear.

Results

The systematic review identified a total of 119 publications. Overall, 12 trials met the criteria for inclusion.

A summary of the patient characteristics of the patients included in the ITCs and study details are provided in Table 48 and Table 49. The included studies took place across the US, Europe, and Australia with the majority from the US.

For the two NMAs performed, comparisons were made for the following treatments: MET-V, BUP-V, BUP-IMP, CAM2038, BUP-ER 300 mg/300 mg, and BUP-ER 300 mg/100 mg. Across trial arms, the MET-V dose ranged from 20 mg to 150 mg per day; the BUP-V dose ranged from 12 mg to 32 mg per day, and BUP-IMP was consistent at four doses of 80 mg.

Included studies often excluded patients with acute medical conditions, significant chronic comorbidities, use of prescribed or illicit drugs that may interfere with OUD treatment, mental illness, and poor liver or cardiovascular health. In several studies, concurrent counselling was offered; however, the specific type and intensity of the counselling intervention varied widely between studies or was not well described.

Patients were generally similar based on demographics and baseline characteristics. The mean age ranged from 26 years to 40 years, male patients were consistently over-represented and accounted for 50% to 84% of patients, and white patients accounted for 34% to 83% of patients. Severity of OUD at baseline was not commonly reported across trials; however, most patients in the studies were diagnosed using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria. The included studies in the retention analysis differed by several factors, including blinding status (open-label, single-blind, double-blind), length of induction period (0 to 21 days), the timing of randomization relative to induction/stabilization (before or after), the reported time points for outcome assessment (6 to 26 weeks), and treatment retention proportion by arm (27% to 90%).

For the overall abstinence by urinalysis analysis, studies were similar with respect to the following important characteristics: missing samples and study dropouts were counted as positive; timing of assessment for overall urinalysis was at 24 weeks; and timing of randomization was after induction/dose stabilization. The extent of missing data was not presented.

The overall risk of bias assessment was determined to be “low” for the ITC outcomes across studies. One study by Cameron et al. was determined to have high risk of bias specific to allocation concealment as the study was described as “non-blinded” for treatment allocation.

Table 48: Demographics and Baseline Characteristics by Treatment for Studies Included in the Indirect Treatment Comparison

Study	Treatment[a,b]	Patients (n)	Mean Age, Years	Male, %	White, %	Primary Opioid Use at Study Entry	Mean Duration of Dependence, Years	Patients with Previous Tx, %	No. of Previous Tx Attempts, Mean
13-0001	Placebo BUP-ER 300 mg/ 300 mg BUP-ER 300 mg/ 100 mg	99 196 194	39 39 40	65 67 66	78 71 68	Opioid[a]	NR	NR	NR
Cameron et al. (2006)	BUP avg 12 mg per day MET avg 36 mg per day	11 10	NR	NR	NR	Opioid[a]	NR	NR	NR
Compton (2012)	BUP 16 mg to 24 mg per day MET 70 mg to 90 mg per day	64 18	33.4 34.6	65.6 66.7	82.1 66.7	Heroin[b]	NR	NR	NR
Lofwall et al. (2018) FDA Advisory Committee: CAM2038 Briefing Document	CAM2038 BUP 8 mg to 32 mg per day	213 215	39 38	57 66	75 76	Opioid, with 71% heroin patients	4.3 4.7	NR	NR
Johnson et al. (2000) Lott et al. (2006)	LAAM 75 mg to 161 mg per day MET 60 mg to 100 mg per day MET 20 mg per day BUP 16 mg to 32 mg per day (oral solution)	55 55 55 55	37.0 36.0 36.0 36.0	60 74 63 66	44 46 34 34	Opioid[a]	NR	NR	2.5 2.4 1.6
Ling et al. (2010)	BUP implant (4 × 80 mg) Placebo	108 55	35.8 39.3	66.7 72.7	75.9 72.7	Opioid, with 63% heroin patients[a]	NR	23.1 to 25.5	NR
Lintzeris et al. (2004)	BUP avg 13.2 mg per day MET avg 49.4 mg per day	46 36	28.8 28.8	61 61	NR	Heroin	8.4 8.4	NR	8.6 8.6

Study	Treatment[a,b]	Patients (n)	Mean Age, Years	Male, %	White, %	Primary Opioid Use at Study Entry	Mean Duration of Dependence, Years	Patients with Previous Tx, %	No. of Previous Tx Attempts, Mean
Mattick et al. (2003) Dean et al. (2004)	MET 20 mg to 150 mg per day BUP 2 mg to 32 mg per day	205 200	30 30	69 70	NR	Opioid[a]	7.58 7.67	NR	1 1
Petitjean et al. (2001)	BUP 8 mg to 16 mg per day MET 30 mg to 120 mg per day	27 31	28.1 26.7	81.0 84.0	NR	Opioid[a]	4.7 4.6	NR	NR
Rosenthal et al. (2013)	BUP implant (4 × 80 mg) Placebo BUP/NAL 12 mg to 16 mg per day	114 54 119	36.4 35.2 35.3	63.2 57.4 60.5	83.3 83.3 81.5	Opioid with 62% heroin patients[a]	NR	NR	NR
Saxon et al. (2013) Hser et al. (2014)	BUP/NAL 2 mg to 32 mg per day MET avg 93 mg per day	738 529	39.3 38.4	71.2 64.7	72.9 79.3	Opioid	9.8 to 9.9	NR	NR
Soyka et al. (2008)	BUP 9.5 mg to 10.7 mg per day MET 46.8 mg to 49.8 mg per day	64 76	31.2 27.9	66.0 66.0	NR	Opioid	NR	NR	NR

Avg = average; BUP = buprenorphine; ER = extended release; LAAM = Levacetylmethadol; MET = methadone; NAL = naloxone; No. = number; NR = not reported; OUD = opioid use disorder; tx = treatment.

[a] Refers to studies that did not exclusively focus on heroin-dependent patients and can include both prescription opioid- and heroin-dependent patients. Unless stated, the percentage distribution of prescription opioid and heroin use was not reported and therefore is uncertain.

[b] Refers to studies that are focused explicitly on heroin-dependent patients.

Source: Manufacturer-supplied indirect treatment comparison.[9]

Table 49: Included Study Details

Study	Study Country	Study Setting	Blinding	Induction Period, Days	Randomization Timing Relative to Induction/ Stabilization	Induction/ Stabilization Period Included in Retention Measurement	Reported Time Point(s), Weeks	Retention on Tx, %	KM Retention Curve Available
13-0001	US	Outpatient Clinic	Double	7 to 14	After	No	24	–	Yes
Cameron et al. (2006)	UK	Substance misuse service and pharmacy	Open label	2 to 5 flexible up to 6 weeks	Before	No	12	45.5 60.0	No
Compton (2012)	US	NR	NR	4	Before	Unclear	18	39.1 27.8	No
Lofwall et al. (2018) FDA Advisory Committee: CAM2038 Briefing Document	US	Outpatient clinic	Double	None	Before	Unknown	24	56.8 58.6	No
Johnson et al. (2000) Lott et al. (2006)	US	Outpatient clinic	Double	14	Before				
Ling et al. (2010)	US	Outpatient clinic	Double	≥ 3	After	No	16/24	50.9/30.9 81.5/65.7	Yes
Lintzeris et al. (2004)	Australia	Outpatient clinic	Open label	NR	Before	Unclear	13/26	63/46 72/58	No
Mattick et al. (2003) Dean et al. (2004)	Australia	MET clinic	Double	NR	Before	Unclear	13	50.0 59.4	Yes
Petitjean et al. (2001)	Switzerland	Outpatient clinic	Double	21	Before	Yes	6	56.0 90.0	No
Rosenthal et al. (2013)	US	Substance treatment centre	Double	≥ 3	After	No	24	25.9 60.4 63.9	No

Study	Study Country	Study Setting	Blinding	Induction Period, Days	Randomization Timing Relative to Induction/ Stabilization	Induction/ Stabilization Period Included in Retention Measurement	Reported Time Point(s), Weeks	Retention on Tx, %	KM Retention Curve Available
Saxon et al. (2013) Hser et al. (2014)	US	Opioid treatment clinic	Open label	3 (BUP/NAL) > 14 (MET)	Before	Yes	24	45.9 73.9	No
Soyka et al. (2008)	Germany	Outpatient clinic	Unclear	7	Before	Yes	26	48.4 55.3	No

BUP = buprenorphine; KM = Kaplan-Meier; MET = methadone; NAL = naloxone; NR = not reported; tx = treatment.

[a] Refers to studies that did not exclusively focus on heroin-dependent patients and can include both prescription opioid- and heroin-dependent patients. Unless stated, the percentage distribution of prescription opioid and heroin use was not reported and therefore is uncertain.

[b] Refers to studies that are focused explicitly on heroin-dependent patients.

Source: Manufacturer-supplied indirect treatment comparison.[9]

Study Dropout

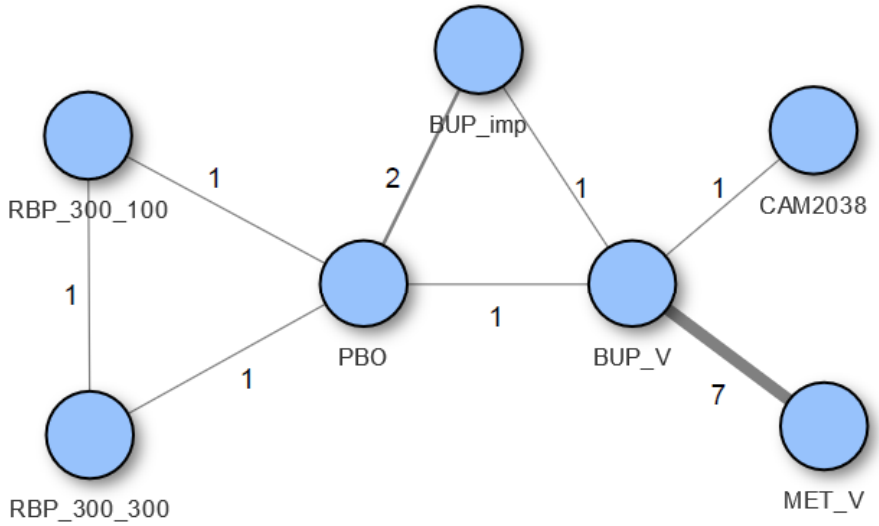
For the analysis related to study dropout, 11 trials were included (N = 3,413). The network of evidence the treatment retention outcome is presented in Figure 4.

Using random-effect models (DIC = 276) neither BUP-ER 300 mg/100 mg nor BUP-ER 300 mg/300 mg were statistically more efficacious than each other or any of the following treatments: placebo, BUP-V, BUP-IMP, MET-V, and CAM2038 (Table 50), indicating no statistical difference in likelihood of study dropout associated with BUP-ER 300 mg/100 mg and BUP-ER 300 mg/300 mg. Comparison with treatment with MET-V favoured MET-V; however, the results were not statistically significant.

Using a fixed-effect model (DIC = 316), both BUP-ER 300 mg/100 mg and BUP-ER 300 mg/300 mg were more efficacious than placebo with respect to study dropout and were not significantly superior to each other, or to treatment with BUP-V, BUP-IMP, and CAM2038 (Table 50). Using this model treatment with MET-V was significantly superior to treatment with both BUP-ER 300 mg/100 mg and BUP-ER 300 mg/300 mg.

Statistically significant heterogeneity ($P < 0.0001$) was observed and was driven by two studies (Petitjean [2001] and Saxon [2013]/Hser [2014]) where the HR of MET-V compared with BUP-V was lower than the HRs observed in the other five studies. With the removal of the two studies in sensitivity analyses, the majority of the results remained relatively unchanged; however, treatment with both BUP-ER 300 mg/100 mg and BUP-ER 300 mg/300 was statistically efficacious compared with placebo in both random- and fixed-effect models. The sensitivity analyses showed no statistically significant difference for treatment with both BUP-ER 300 mg/100 mg and BUP-ER 300 mg/300 compared with MET-V.

Figure 4: Network of Evidence for Retention



BUP_imp = subcutaneous buprenorphine implant; BUP_V = variable SL buprenorphine; MET_V: variable methadone; PBO = placebo; RBP_300_100 = Sublocade BUP-ER 300 mg/100 mg dose; RBP_300_300 = sublocade BUP-ER 300 mg/300 mg dose.

Note: Each circle represents a treatment of interest. The lines between circles indicate a clinical trial comparison. Numbers indicate the number of trials including each comparison.

Source: Manufacturer-supplied indirect treatment comparison.[9]

Table 50: Network Meta-Analysis Hazard Ratios of Study Dropout

Treatment	Comparator	Random-Effect Model Hazard Ratio (95% CrI)	Fixed-Effect Model Hazard Ratio (95% CrI)
BUP-ER 300 mg/100 mg	Placebo	0.35 (0.11 to 1.08)	**0.35 (0.32 to 0.37)**
BUP-ER 300 mg/100 mg	BUP-IMP	1.09 (0.27 to 4.39)	**1.12 (0.95 to 1.32)**
BUP-ER 300 mg/100 mg	BUP-V	1.06 (0.21 to 5.07)	1.08 (0.73 to 1.62)
BUP-ER 300 mg/100 mg	MET-V	1.67 (0.32 to 8.73)	**1.58 (1.07 to 2.39)**
BUP-ER 300 mg/100 mg	BUP-ER 300 mg/300 mg	1.01 (0.33 to 3.15)	1.01 (0.94 to 1.09)
BUP-ER 300 mg/100 mg	CAM2038	1.0 (0.14 to 6.87)	1.02 (0.66 to 1.60)
BUP-ER 300 mg/300 mg	Placebo	0.34 (0.11 to 1.06)	**0.34 (0.32 to 0.37)**
BUP-ER 300 mg/300 mg	BUP-IMP	1.08 (0.27 to 4.34)	1.11 (0.94 to 1.30)
BUP-ER 300 mg/300 mg	BUP-V	1.05 (0.21 to 5.03)	1.07 (0.73 to 1.60)
BUP-ER 300 mg/300 mg	MET-V	1.65 (0.32 to 8.71)	**1.56 (1.06 to 2.37)**
BUP-ER 300 mg/300 mg	BUP-ER 300 mg/100 mg	0.99 (0.32 to 3.07)	0.99 (0.92 to 1.07)
BUP-ER 300 mg/300 mg	CAM2038	0.98 (0.14 to 6.75)	1.01 (0.65 to 1.59)
Placebo	BUP-IMP	**0.32 (0.14 to 0.73)**	**0.31 (0.27 to 0.36)**
Placebo	BUP-V	0.33 (0.11 to 1.02)	**0.32 (0.21 to 0.47)**
Placebo	MET-V	**0.22 (0.06 to 0.70)**	**0.22 (0.15 to 0.32)**
Placebo	BUP-ER 300 mg/100 mg	0.35 (0.11 to 1.08)	**0.35 (0.32 to 0.37)**
Placebo	BUP-ER 300 mg/300 mg	0.34 (0.11 to 1.06)	**0.34 (0.32 to 0.37)**
Placebo	CAM2038	0.35 (0.07 to 1.76)	**0.34 (0.22 to 0.52)**

BUP = buprenorphine; CrI = credible interval; ER = extended-release; IMP = implant; MET = methadone; V = variable dose.

Note: Random-effect model, deviance information criterion equals 276; fixed-effect model, deviance information criterion equals 316.

Source: Manufacturer-supplied indirect treatment comparison.[9]

Table 51: Network Meta-Analysis Hazard Ratios of Study Dropout Sensitivity Analysis[a]

Treatment	Comparator	Random-effects model Hazard Ratio (95% CrI)	Fixed-effects model Hazard Ratio (95% CrI)
BUP-ER 300 mg/100 mg	Placebo	**0.35 (0.23 to 0.53)**	**0.35 (0.32 to 0.37)**
BUP-ER 300 mg/100 mg	BUP-IMP	1.11 (0.63 to 1.88)	1.12 (0.95 to 1.32)
BUP-ER 300 mg/100 mg	BUP-V	1.08 (0.55 to 2.09)	1.09 (0.74 to 1.62)
BUP-ER 300 mg/100 mg	MET-V	1.37 (0.64 to 2.68)	1.4 (0.94 to 2.11)
BUP-ER 300 mg/100 mg	BUP-ER 300 mg/300 mg	1.01 (0.66 to 1.54)	1.01 (0.94 to 1.09)
BUP-ER 300 mg/100 mg	CAM2038	1.02 (0.45 to 2.24)	1.02 (0.66 to 1.6)
BUP-ER 300 mg/300 mg	Placebo	**0.34 (0.23 to 0.52)**	**0.34 (0.32 to 0.37)**
BUP-ER 300 mg/300 mg	BUP-IMP	1.1 (0.63 to 1.86)	1.11 (0.94 to 1.3)
BUP-ER 300 mg/300 mg	BUP-V	1.07 (0.55 to 2.05)	1.07 (0.73 to 1.6)
BUP-ER 300 mg/300 mg	MET-V	1.36 (0.64 to 2.64)	1.39 (0.93 to 2.09)
BUP-ER 300 mg/300 mg	BUP-ER 300 mg/100 mg	0.99 (0.65 to 1.51)	0.99 (0.92 to 1.07)
BUP-ER 300 mg/300 mg	CAM2038	1.01 (0.45 to 2.22)	1.02 (0.66 to 1.58)

BUP = buprenorphine; CrI = credible interval; ER = extended-release; IMP = implant; MET = methadone; V = variable dose.

Note: Random-effect model, deviance information criterion equals 264; fixed-effect model, deviance information criterion equals 263.

[a] Petitjean (2001) and Saxon (2013)/Hser (2014) studies removed.

Source: Manufacturer-supplied indirect treatment comparison.[9]

Opioid Positivity

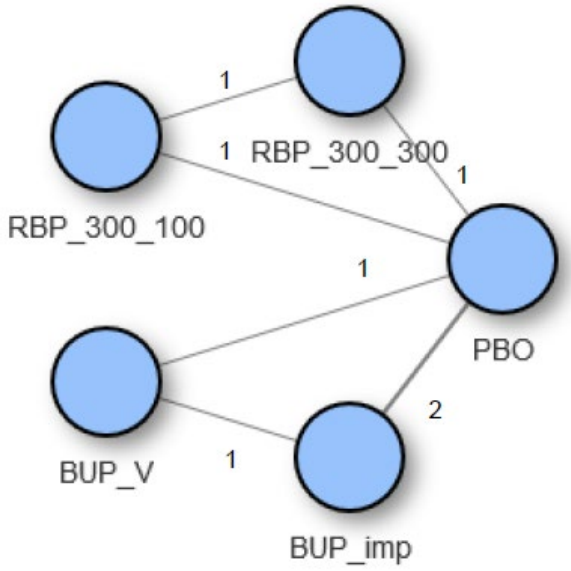
For the analysis related to opioid positivity three trials were included (N = 939). The network of evidence the treatment retention outcome is presented in Figure 5.

Using a fixed-effect model (DIC not reported), both BUP-ER 300 mg/100 mg and BUP-ER 300 mg/300 mg were statistically more efficacious compared with placebo, BUP-V, and BUP-IMP, indicating a decreased likelihood of opioid positivity associated with BUP-ER 300 mg/100 mg and BUP-ER 300 mg/300 mg (Table 52).

An increase in odds for opioid positivity was found for BUP-ER 300 mg/100 mg compared with placebo, OR was 0.12 (95% credible interval [CrI], 0.06 to 0.24). Similarly, when BUP-ER 300 mg/100 mg was compared with BUP-V, the OR was 0.34 (95% CrI, 0.12 to 0.90); and when compared with BUP-IMP, the OR was 0.32 (95% CrI, 0.12 to 0.78). Similar findings were identified for BUP-ER 300 mg/300 mg.

With respect to opioid positivity, placebo was less efficacious than all comparators: BUP-ER 300 mg/100 mg, BUP-ER 300 mg/300 mg BUP-V, and BUP-IMP.

Figure 5: Network of Evidence for Overall Abstinence by Urinalysis Data at Week 24



BUP_V = buprenorphine with variable dose; imp = implant; PBO = placebo; RBP_300_100 = sublocade BUP-ER 300 mg/100 mg dose; RBP_300_300 = sublocade BUP-ER 300 mg/300 mg dose.

Note: Numbers indicate the number of studies including each comparison.

Source: Manufacturer-supplied indirect treatment comparison.[9]

Table 52: Network Meta-Analysis Odds Ratios for Overall Opioid Positivity

Treatment	Comparator	Odds Ratio (95% CrI)
BUP-ER 300 mg/100 mg	Placebo	**0.12 (0.06 to 0.24)**
BUP-ER 300 mg/100 mg	BUP-IMP	**0.32 (0.12 to 0.78)**
BUP-ER 300 mg/100 mg	BUP-V	**0.34 (0.12 to 0.90)**
BUP-ER 300 mg/100 mg	BUP-ER 300 mg/300 mg	0.90 (0.60 to 1.35)
BUP-ER 300 mg/300 mg	Placebo	**0.13 (0.06 to 0.26)**
BUP-ER 300 mg/300 mg	BUP-IMP	**0.35 (0.14 to 0.86)**
BUP-ER 300 mg/300 mg	BUP-V	**0.37 (0.13 to 1.0)**
BUP-ER 300 mg/300 mg	BUP-ER 300 mg/100 mg	1.11 (0.74 to 1.65)

BUP = buprenorphine; CrI = credible interval; ER = extended-release; IMP = implant; V = variable doses.

Source: Manufacturer-supplied indirect treatment comparison.[9]

Critical Appraisal

The methods used to conduct the systematic review appear to be sufficient, and included a search of multiple databases and the screening completed by two reviewers. A search of grey literature was not performed. Data extraction was performed by one reviewer and reviewed for accuracy by a second reviewer. The number of reviewers carrying out the risk of bias assessment was not reported, nor was the process for reconciling discrepancies. The authors provided detailed summary tables of relevant data from the included trials that facilitated the assessment of the similarity between trials. The treatments and dosages included were relevant to this CADTH Common Drug Review. Fixed-dose sublingual buprenorphine and fixed-dose methadone were not included in the NMA as they are not a standard of care in Canada. CAM2038 was only included as it was required to allow data from the sublingual buprenorphine arm to be added into the network.

The risk of bias of most trials was rated as low risk by the authors of the systematic review; however, risk of bias attributed to treatment allocation concealment was high in one study, and unclear in six of the studies. The study with high risk of bias for treatment allocation concealment was described as “non-blinded.” The risk of bias attributed to random sequence generation was unclear in six studies. Sensitivity analyses were not performed based on the findings of the risk of bias assessment.

Prior to conducting the NMA, two clinical experts were consulted to determine if there were differences in study characteristics that would be thought to affect the meta-analysis outcomes. This consultation resulted in post hoc exclusion of one study that was unbalanced with respect to the proportion of male patients in treatment arms and the exclusion of one study that had 52-week retention data that was much higher than what was reported in other studies. It is unclear how the inclusion of these studies may have altered the study results as sensitivity analyses including these studies was not performed.

The authors rationalized not adjusting for potential confounders by using input from two clinical experts to guide the included studies. The authors stated that the collection of studies was expected to not include outliers or be different with respect to potential treatment effect modifiers. The authors also stated that the patient and study characteristics were too sparse to quantitatively identify and adjust for factors (e.g., severity of OUD at baseline) that could potentially be associated with the study outcomes. Clinical experts

confirmed that the limited data that was available was insufficient to reflect severity. Trials were not excluded from the analysis based on the timing of randomization (before or after the induction/dose stabilization period) as clinical experts did not expect this to impact the difference in long-term study retention between trial arms. The NMAs for both study dropout and opioid positivity appear to support the assumption of transitivity as patient baseline characteristics were similar. The included studies differed by the following study design characteristics: blinding status, length of induction period, the timing of randomization relative to induction/stabilization, the reported time points for outcome assessment, and treatment retention proportion. The impact of not adjusting for potential confounders is unclear.

A number of issues were identified with the conduct of the NMA. In the study dropout NMA, potential discrepancies between indirect and direct comparisons were not assessed, thereby making it unclear if the consistency assumption was met. In the opioid positivity NMA, potential discrepancies between indirect and direct comparisons could not be assessed as there were no closed loops within the network.

For the study dropout NMA, model fit was evaluated using the DIC; however, details on number of models examined and how the best model was selected was unclear. Alternatively, the authors rationalized the use of the Weibull approach, stating that it allowed for the incorporation of all available data, including multiple time points reported from a single study, and is advantageous over other methods such as fractional polynomials because comparative efficacy estimates can be expressed as constant hazard ratios, which are more readily interpretable than polynomial slopes. The use of the Weibull distribution was rationalized based on visual inspection; however, the use of the Weibull was not compared with any other distribution. Statistical support for the use of the Weibull distribution compared with selected distributions was supplied as supplementary material. For BUP-ER 300 mg/100 mg the tested distributions fit the observed data with similar precision based on Akaike information criterion (AIC) (range = 961.7 to 963.7). The AIC for the Weibull distribution was 963.3; however, a complete listing of the distributions tested was not provided. For BUP-ER 300 mg/300 mg a range for the tested distributions fit was not provided. It was stated that the AIC for the Weibull was 939.7, and the AIC for the generalized gamma was 919.6. The manufacturer stated that the observed difference must be a random anomaly. Conversely, in the manufacturer's pharmacoeconomic submission, the Weibull distribution was not used, and in its place they based their economic analysis on a generalized gamma model for the analysis of BUP-ER 300 mg/100 mg, and a Gompertz model for BUP-ER 300 mg/300 mg. In the pharmacoeconomic submission, the manufacturer rationalized the use of these models based on visual fit, AIC, and clinical reasonableness. The manufacturer rationalizes that the use of different models for the clinical and pharmacoeconomic submissions is based on the economic model relying on a survival distribution that considers both the observed data and extrapolated data, while the indirect treatment comparison considers the observed data only. The use of the generalized gamma model appears to be the best fit for the BUP-ER 300 mg/300 mg arm. The distribution fit for BUP-ER 300 mg/100 mg was similar between models and it is unclear which model had the best fit; therefore, the results presented in the NMA for the clinical submission (based on the Weibull distribution) regarding retention may not be appropriate to use (particularly for the BUP-ER 300 mg/300 mg arm) as the impact on the results is unclear.

The ITC was limited with respect to patient-reported outcomes. Health-related quality of life outcomes, which are generally a priority for patients, were not assessed.

The retention (study dropout) NMA was performed for both random- and fixed-effect models using the data from all 11 studies. As reported previously, the results for this outcome were quite different depending on which model was used, and the authors did not clearly identify a primary analysis, making it unclear which results should take precedence. The random-effect model appears to be the most appropriate based on the DIC (276 for random-effect; 316 for fixed-effect) and the ability of the random-effect model to allow for more heterogeneity as expected based on the (study design) differences observed between the included studies. Sensitivity analysis was performed to remove two studies in the MET-V/BUP-V comparison that contributed to heterogeneity ($P < 0.0001$); these studies had HRs for MET-V compared with BUP-V that were much lower than the HRs observed in the other five studies. The sensitivity analysis was well aligned with the findings of the full analysis set using the random-effect model.

Similar to the study dropout NMA, for the opioid positivity model fit was evaluated using the DIC; however, details on number of models examined and how the best model was selected (e.g., based on the DIC alone) was unclear. The NMA for opioid positivity was designed to be weighted by the number of patients rather than the number of collected urinalysis samples. The opioid positivity NMA was performed with a fixed-effect model using data from three studies. The limited amount of included data creates a sparse and/or weak network with most nodes connected with one study. DIC values were not presented for the analysis of opioid positivity making it unclear if the model adequately fit the data. Additionally, the extent of missing data were not presented for this outcome.

Several studies included in the ITC have exclusion criteria that resulted in the exclusion of patients with acute medical conditions, significant chronic comorbidities, use of prescribed or illicit drugs that may interfere with OUD treatment, mental illness, and poor liver or cardiovascular health. The extensive exclusion criteria in the trials created a population that was not representative of the population in Canada that would be expected to use the study drug, thereby limiting the applicability of the ITC findings.

Conclusion

The applicability of manufacturer's ITCs is impacted by the potential limitations in the submitted analysis. As previously described, the manufacturer ITC was not transparent in its systematic review methods and analysis and did not rationalize the use of specific models in the clinical submission. The results for both study dropout and opioid positivity were based on studies with sparse baseline data using a patient population not necessarily consistent with the Canadian population expected to use the study drug. Limited heterogeneity analysis was performed for one outcome (study dropout) but was not specified a priori. Overall, the results of this analysis must be interpreted with caution. Based on the results of the submitted ITC, it is unlikely that there are differences in efficacy by dose for BUP-ER (300 mg/100 mg, 300 mg/300 mg). It is unclear if BUP-ER 300 mg/100 mg or BUP-ER 300 mg/300 mg are more efficacious than placebo with respect to study dropout. A sparse network, limited reporting of analysis results, and problematic construction of the study outcome for the overall opioid positivity prevent conclusions from being made for this outcome. Little can be elucidated on the comparative efficacy with other products based solely on this submitted ITC.

Appendix 8: Summary of Observational Study

Aim

To summarize the details and findings of RECOVER[10], a longitudinal observational study of patients treated for opioid use disorder (OUD).

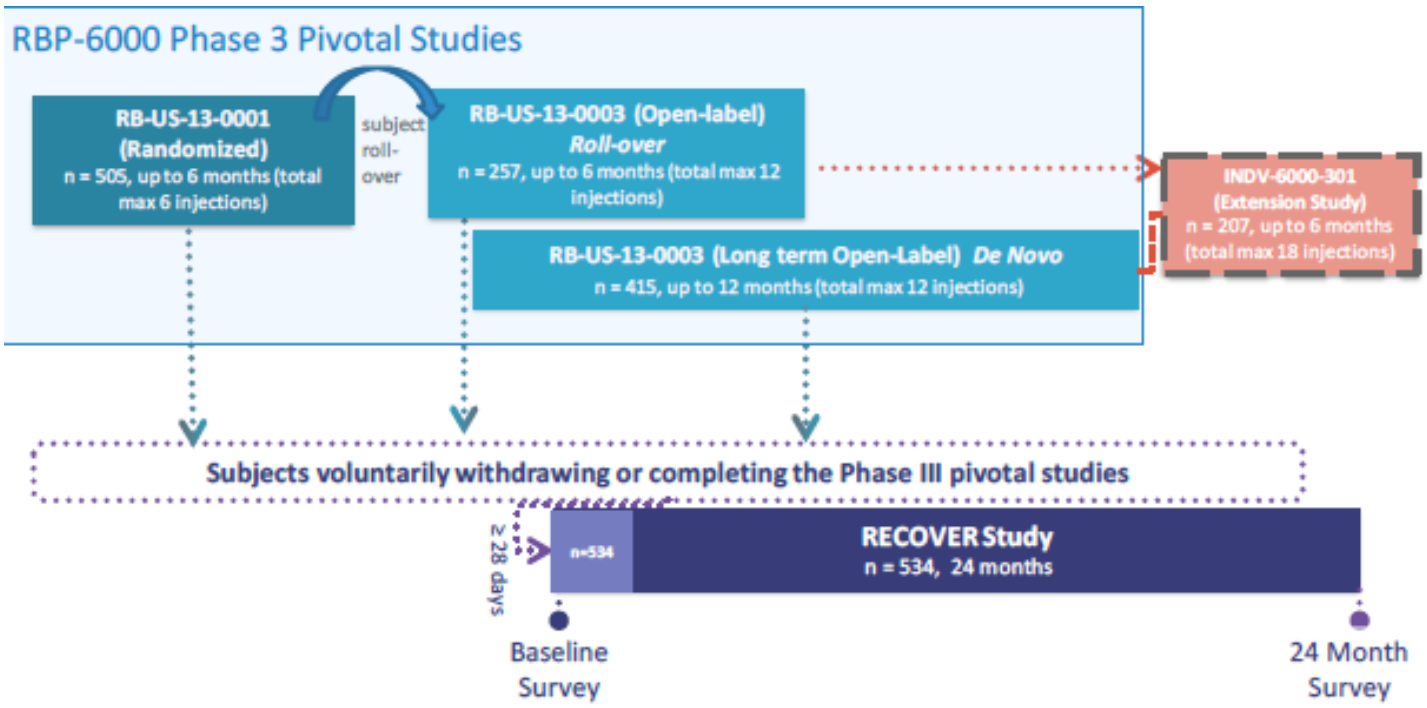
Methods

The RECOVER study was a multi-centre, non-interventional observational study for patients treated for OUD.

RECOVER was designed to assess the recovery process over a 24-month period for patients who participated in one of two phase III clinical trials for buprenorphine extended-release injection (BUP-ER; 13-0001 and 13-0003). Patients were eligible for RECOVER if they completed or dropped out of 13-0001 or 13-0003 and had received at least one study injection (Figure 6).

Assessments were made at baseline, and at six, 12, 18, and 24 months post-enrolment.

Figure 6: RECOVER Study Design and Patient Flow



Source: Clinical study report for RECOVER.[10]

Baseline Characteristics

In the RECOVER study, male patients made up 66% of the sample (Table 53). Most patients fell in the 35 to 45 year (45%) and 45 to 58 year (31%) age categories. White, non-Hispanic patients were over-represented (60%), and 51% of patients were single. Approximately half of the sample was composed of employed patients (47%), and most patients were high school graduates or equivalent (67%). For 76% of patients, housing was considered stable. Criminal behaviour was reported for 54% of patients.

Table 53: Summary of Baseline Characteristics

	Overall Sample N = 534
Male, n (%)	353 (66%)
Age, years (%)	
18 to 29 years	88 (16%)
30 to 45 years	241 (45%)
46 to 59 years	163 (31%)
60 years or older	42 (8%)
Race/Ethnicity, n (%)	
White, non-Hispanic	321 (60%)
Black, non-Hispanic	161 (30%)
Hispanic	50 (9%)
Other race	18 (3%)
Marital Status, n (%)	
Single	271 (51%)
Married	111 (21%)
Divorced/separated/widowed/other	152 (28%)
Employment, n (%)	
Full- or part-time	250 (47%)
Not employed	284 (53%)
Education, n (%)	
Less than high school education	86 (16%)
High school graduate or equivalent	357 (67%)
College degree or more	91 (17%)
Housing (Past Month), n (%)	
Stable	405 (76%)
Marginal	129 (24%)
Criminal Behaviour, n (%)	
Ever committed, arrested or convicted	291 (54%)
Living Status (past month), n (%)	
With family	105 (20%)
With parents	48 (9%)
With spouse/partner only	100 (19%)
With spouse/partner and children	127 (24%)
Alone/alone with children	100 (19%)

	Overall Sample N = 534
Other	54 (10%)
Volunteerism (past month), n (%)	110 (21%)
Valid driver's license (past month)	306 (57%)
Health Insurance (current)	
Public	249 (47%)
Private	89 (17%)
Other	21 (4%)
None	175 (33%)

Source: Clinical study report for RECOVER.[10]

Outcomes

The outcomes in RECOVER that were relevant to the protocol for this review included:

- criminal activity before and after clinical trials
  - this outcome was assessed using public data. Specifically, an online court record clearinghouse (BeenVerified) was used to match patients to their criminal and driver's license status histories
- abstinence from opioids in the past week and past month
  - last week point prevalence abstinence was defined as at least seven consecutive days of abstinence from opioids (prescription opioids or heroin excluding buprenorphine) in the past week (no use)
  - last month point prevalence abstinence was defined as at least 28 consecutive days of abstinence from opioids (prescription opioids or heroin excluding buprenorphine) in the past month (no use)
- general, physical, and mental health
  - assessed using the Medical Outcomes Study Short Form 12 (SF-12) version 1
- psychological distress
  - assessed using the Kessler-6 (K6)
- depression
  - assessed using Beck's Depression Inventory (BDI-II)
- opioid withdrawal
  - assessed using the Subjective Opiate Withdrawal Scale (SOWS)
- work attendance and performance
- self-reported abstinence (multivariate)
  - assessed using the previously described last week point prevalence abstinence and last month point prevalence abstinence measures
- abstinence in past seven days and urine drug screen (UDS; multivariate)
  - last week point prevalence abstinence self-report combined with UDS was achieved if neither self-report nor UDS panels indicate opioid use
  - patients provided a urine specimen using the T-Cup Multi-Drug Urine Test. The specimen was left at rest on a flat surface for five minutes. The UDS results (positive, negative, or invalid) were then recorded into an online data collection form.

Treatment Duration Groups

Patients that entered RECOVER were categorized based on treatments received in the previous clinical trials in the following groups:

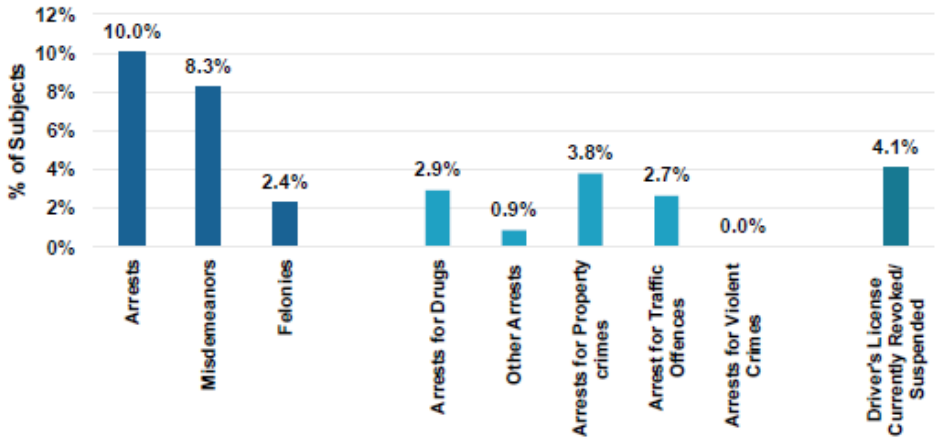
- placebo injections (only placebo injections) — 6.2% of patients in RECOVER
- one to two months (one to two active injections) — 15.7% of patients in RECOVER
- three to eight months (three to eight active injections) — 23.8% of patients in RECOVER
- nine months or longer including:
  - nine to 12 active injections — 29.0% of patients in RECOVER
  - 13 to 18 active injections (extension study participants) — 25.3% of patients in RECOVER.

Results

Criminal Activity Before and After Clinical Trials

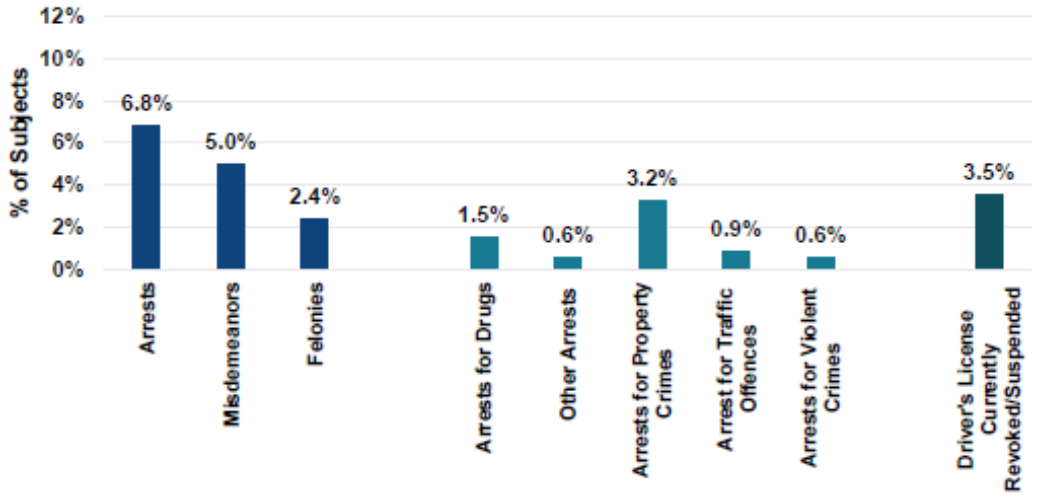
Within the 12 months prior to starting a BUP-ER clinical trial 10% of patients had been arrested with 8.3% of arrests attributed to misdemeanours, and 2.4% attributed to felonies (Figure 7). Conversely, within the time between exiting the clinical trial and up to 12 months later (11 months on average) 6.8% of patients had been arrested with 5.0% of arrests attributed to misdemeanours, and 2.4% attributed to felonies).[10] In both time frames the most common arrest was attributed to property crimes. It is unclear if the results suggest a decrease in criminal activity after participation in a BUP-ER clinical trial, and it is uncertain how use of a placebo could have resulted in a reduction in criminal activity. Moreover, there is potential for a Hawthorne effect to occur, whereby behaviours are modified simply by an individual being enrolled and actively followed/monitored in the clinical trial itself.

Figure 7: Arrests by Type in the 12 Months Prior to Starting Buprenorphine Extended-Release Injection Clinical Trials



Source: Clinical study report for RECOVER.[10]

Figure 8: Arrests by Type Since Exiting Buprenorphine Extended-Release Injection Clinical Trials (in Mean Observational Window of 11 Months)

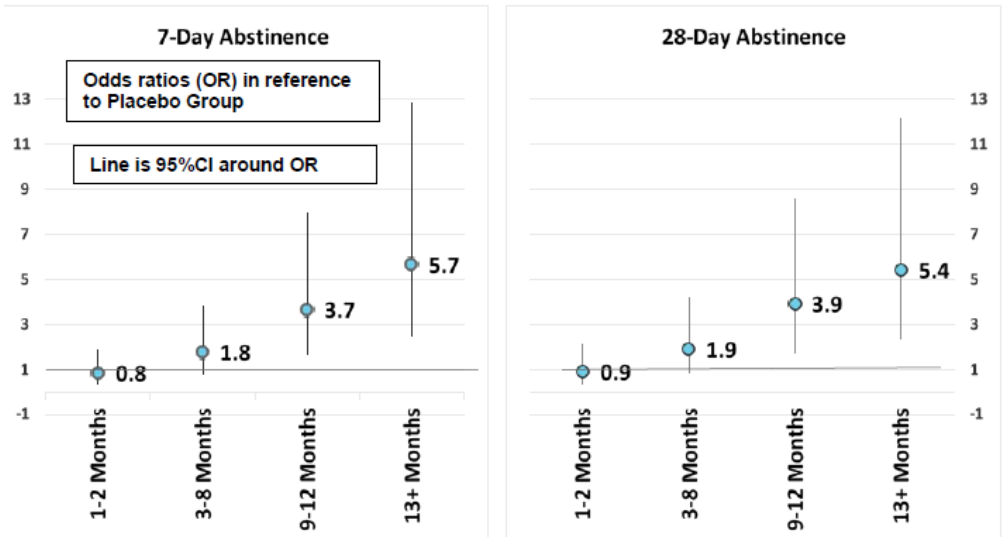


Source: Clinical study report for RECOVER.[10]

Abstinence From Opioids in Past Week and Past Month

In the one-to-two month group, 38% and 35% of patients had abstained from opioids in the past seven and 28 days respectively. In the 13-to-18 month group, 81% and 76% of patients had abstained from opioids in the past seven and 28 days respectively. Using bivariate analyses with seven-day and 28-day abstinence as a function of BUP-ER treatment duration determined that longer durations of treatment (nine to 12 and 13 to 18 months) have higher odds of achieving seven-day and 28-day abstinence (Figure 9). There was an increase of odds of 5.7 for achieving seven-day abstinence for those treated 13 months or more compared with placebo. An increase in odds of 5.4 was determined for achieving 28-day abstinence for those treated 13 months or more compared with placebo. Similar findings were determined using models that controlled for age, gender, age of onset, and time since last injection; however, the multivariate analyses were extremely limited and unlikely to control for major confounding factors that would be expected to substantially bias all study results (Figure 9 and Figure 10).

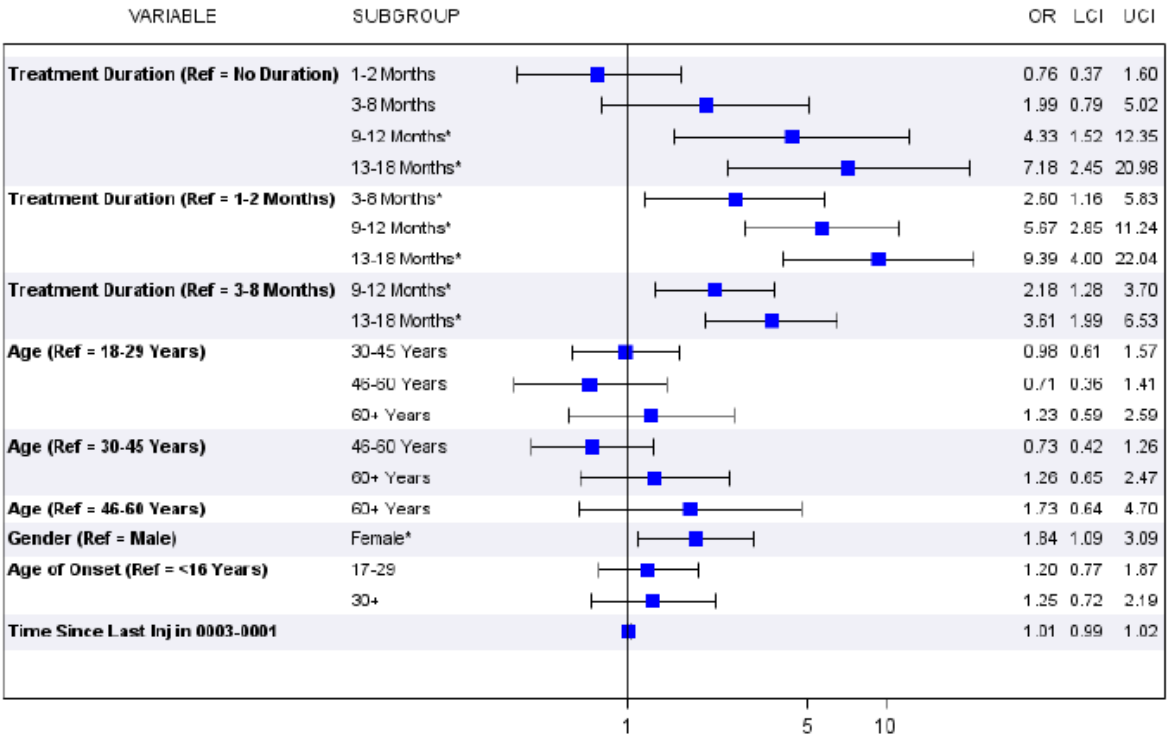
Figure 9: Associations Between Opioid Abstinence and Treatment Duration Group (Bivariate Analysis)



CrI = confidence interval; OR = odds ratio.

Source: Clinical study report for RECOVER.[10]

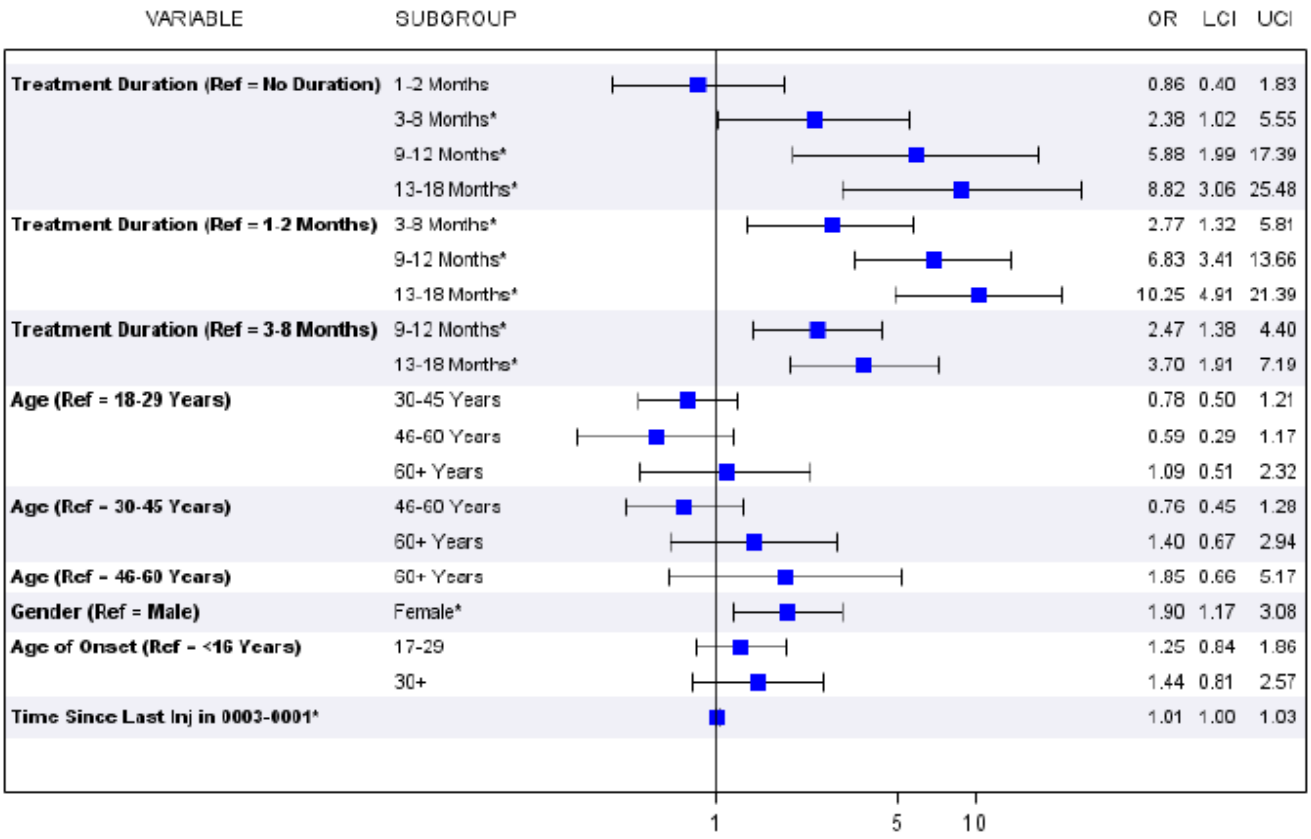
Figure 10: Predictors of Self-Reported Seven-Day Abstinence at Baseline



LCI = lower confidence interval; OR = odds ratio, Ref = reference; UCI = upper confidence interval.

Source: Clinical study report for RECOVER.[10]

Figure 11: Predictors of Self-Reported 28-Day Abstinence at Baseline



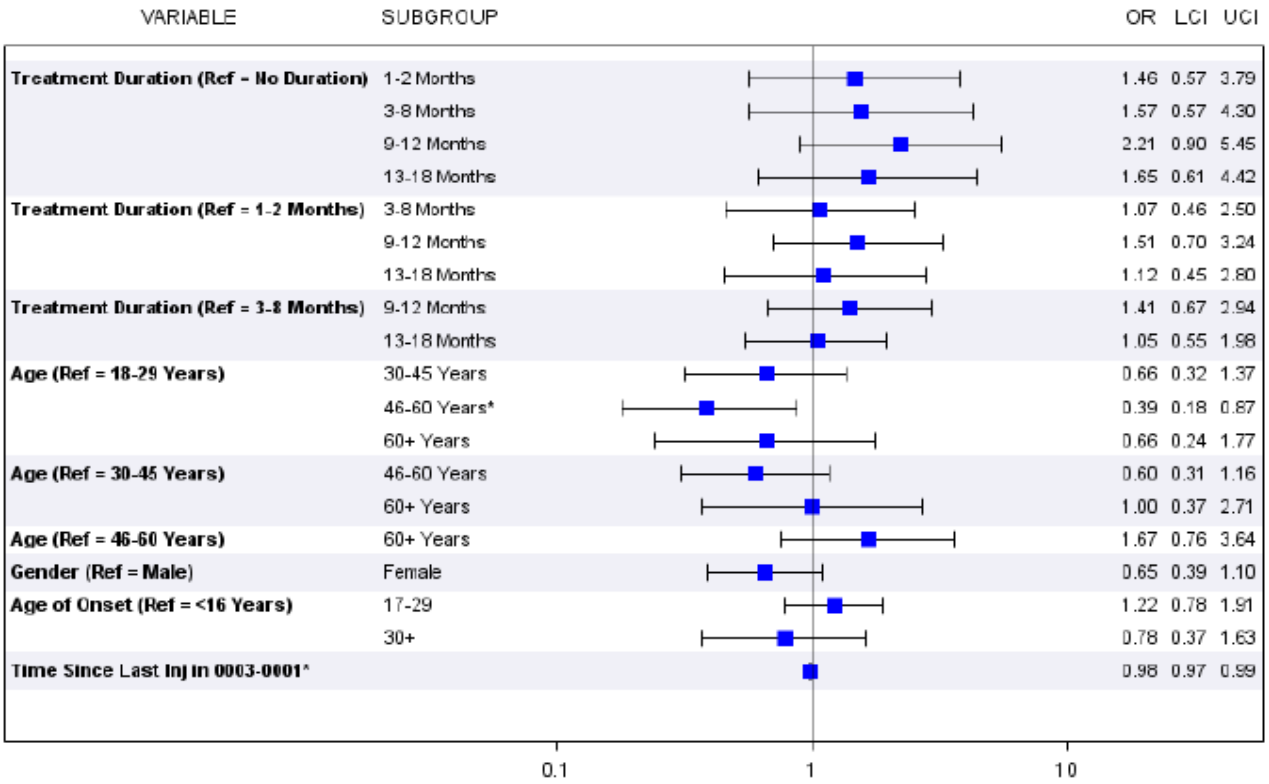
LCL = lower confidence interval; OR= odds ratio, UCI = upper confidence interval.

Source: Clinical study report for RECOVER[10]

General, Physical, and Mental Health (Short Form 12)

General, physical and mental health as assessed by the SF-12 was not associated with treatment duration using raw data and multivariate analysis (Figure 12). Using a multivariate assessment that included age, gender, age of onset, and time since last injection, it was determined that older people have lower (worse) physical health scores than those aged 18 to 29 years.

Figure 12: Associations Between General Health (Short Form 12) and Treatment Duration and Other Subject Characteristics



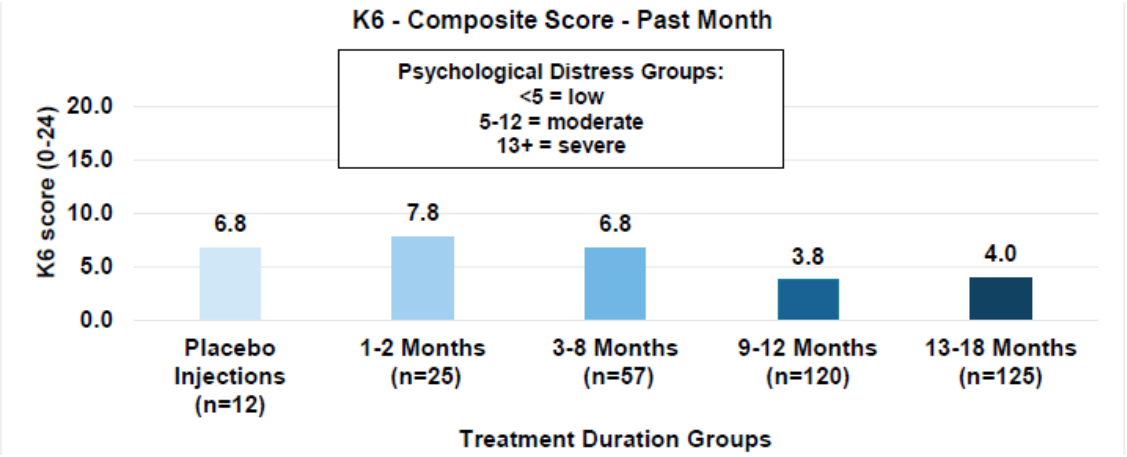
LCI = lower confidence interval; OR= odds ratio; Ref = reference; UCI = upper confidence interval.

Source: Clinical study report for RECOVER.[10]

Psychological Distress (Kessler 6)

Patients with the longest treatment durations had the lowest average scores on the K6 psychological distress scale, which suggests a lower level of psychological distress (Table 11). Patients in the one-to-two month group had a K6 score of 7.8, while patients in the 13-to-18 month group had a K6 score of 4.0.

Figure 13: Psychological Distress (Kessler 6) Score



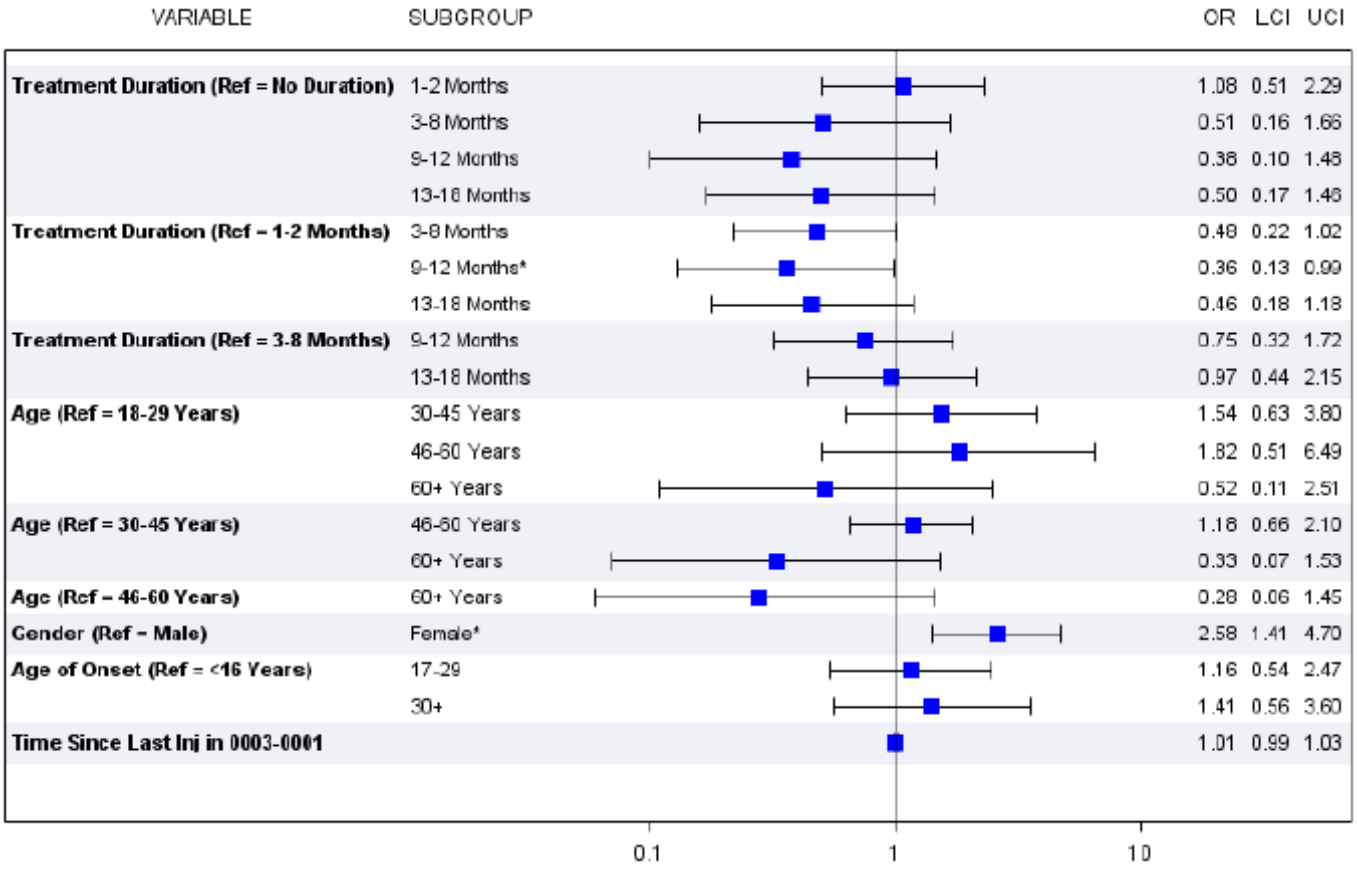
K6 = Kessler 6.

Source: Clinical study report for RECOVER.[10]

Depression (Beck's Depression Inventory)

Patients with the longest treatment durations had the lowest proportion of severe depression (BDI = 29 or more). In the one-to-two month group, 13.1% of patients had severe depression compared with 3.0% of patients in the 13-to-18 month group. Being treated for at least three months was associated with a lower likelihood of having severe depression than being treated for only one to two months, although this was only significant for the nine-to-12 month patients (Figure 14). This analysis also showed that being female was associated with severe depression.

Figure 14: Association between Severe Depression (Beck's Depression Inventory of 29 or more) and Treatment Duration and Other Subject Characteristics



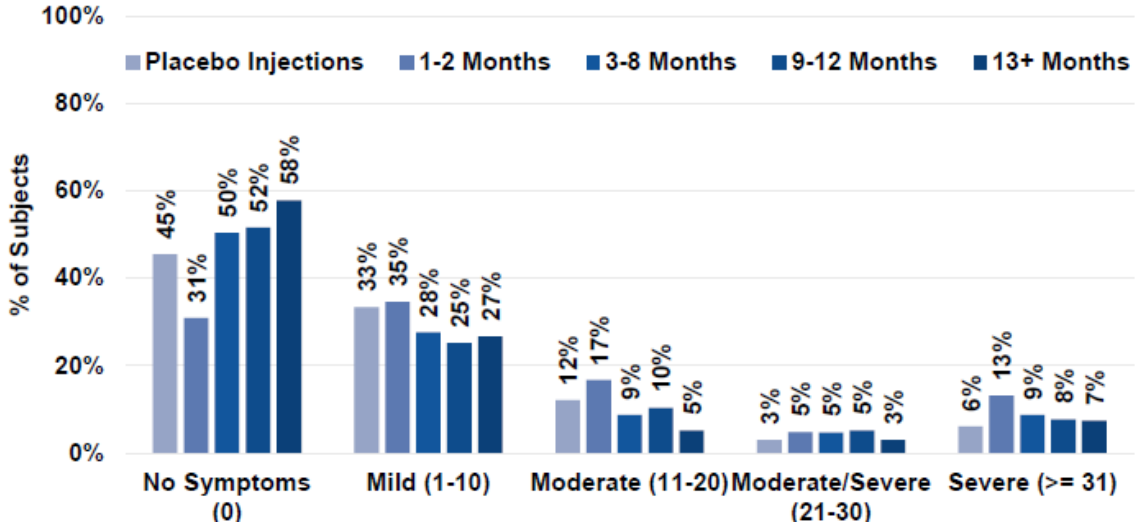
BDI = Beck's Depression Inventory; LCI = lower confidence interval; OR = odds ratio, Ref = reference; UCI = upper confidence interval.

Source: Clinical study report for RECOVER.[10]

Opioid Withdrawal (Subjective Opiate Withdrawal Scale)

The majority of patients did not experience opioid withdrawal symptoms in the month prior to baseline (Table 12). Differences by treatment duration group were not observed.

Figure 15: Subjective Opiate Withdrawal Scale Scores in Past Month

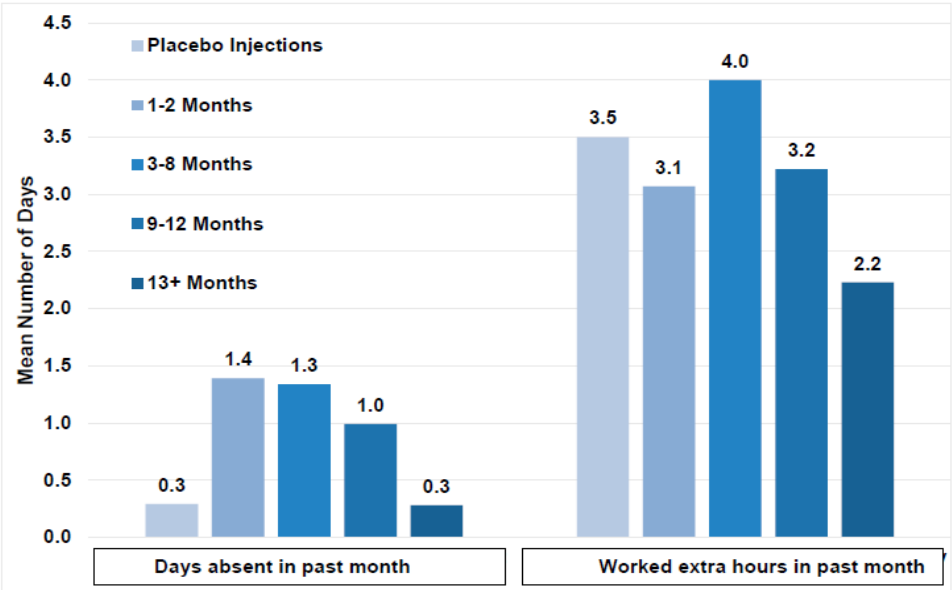


Source: Clinical study report for RECOVER.[10]

Work Attendance and Performance

Among patients who worked, those who received placebo injections and those in the 13-to-18 month group reported missing the fewest whole days of work (0.3 days). No clear trends in absenteeism (Figure 16) or perception of work (Figure 17) was noted by treatment group.

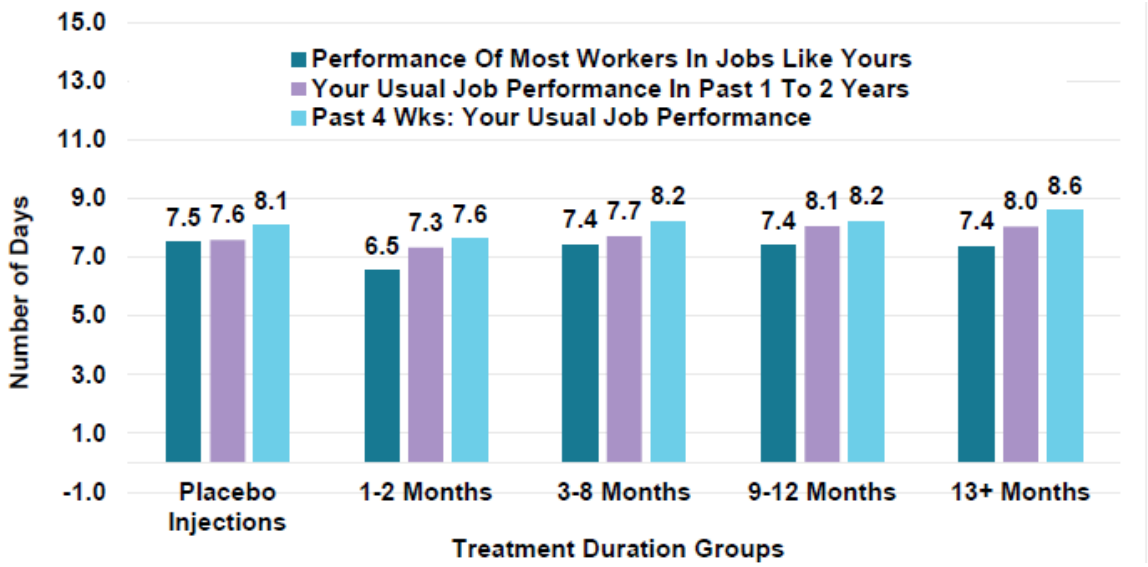
Figure 16: Work Attendance in Past Month



Note: Worked extra hours includes arriving early, staying late, and/or working extra hours.

Source: Clinical study report for RECOVER.[10]

Figure 17: Perception of Work Performance by Treatment Duration Group



wks = weeks.

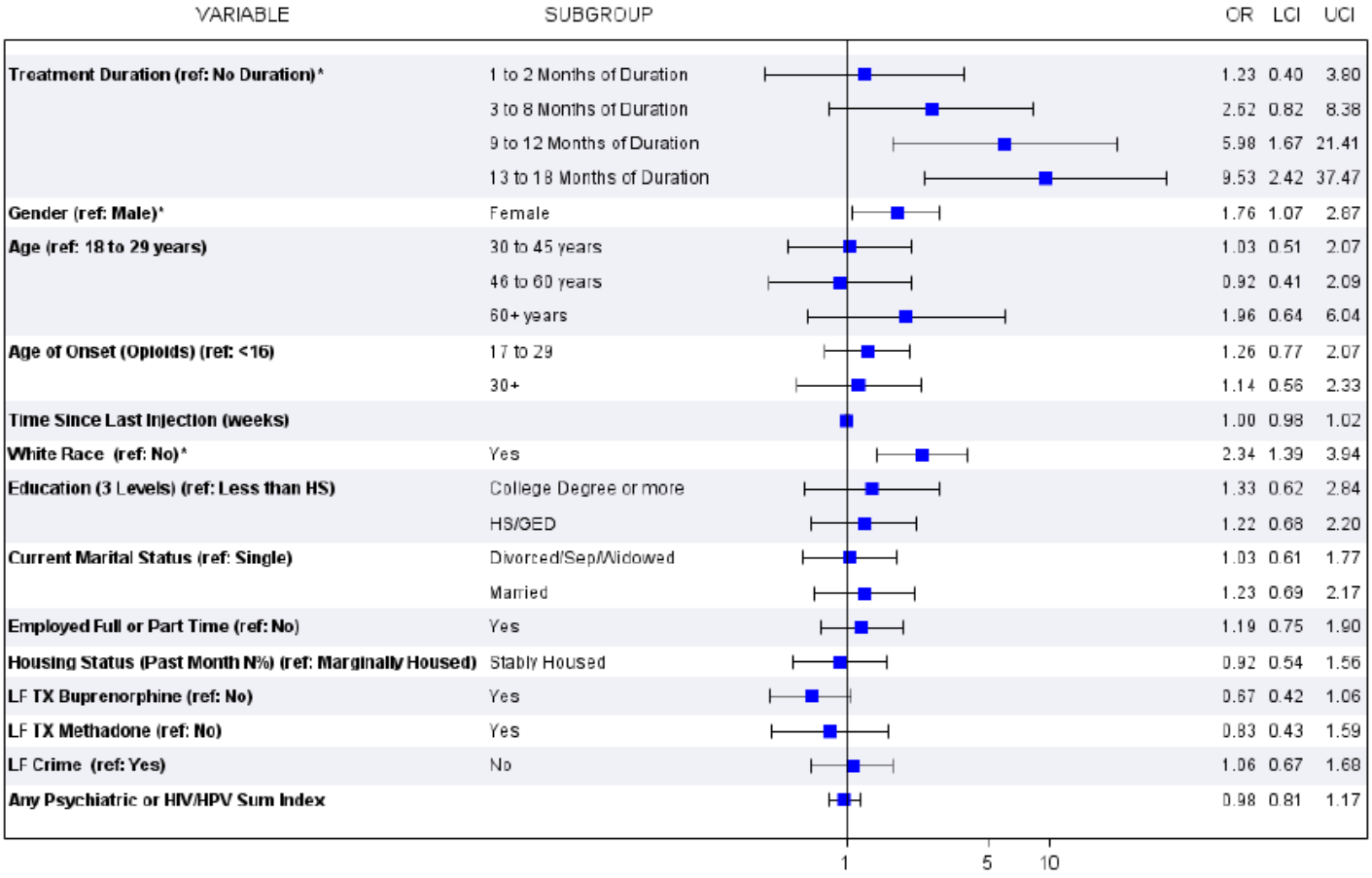
Source: Clinical study report for RECOVER.[10]

Self-Reported Abstinence

Multivariate models assessed past-week and past-month abstinence controlling for the following key demographic, clinical, and psychosocial characteristics: demographics, lifetime OUD treatments received, lifetime crime, age of onset of opioid use, education, employment, stable housing, comorbidity statuses, and study site. While these characteristics were controlled for, it is likely that these analyses were limited and unlikely to control for major confounding factors that would be expected to substantially bias the study results.

After controlling for these characteristics revealed that patients who received longer durations of BUP-ER treatment (nine to 12 months and 13 or more months) were significantly more likely to achieve both seven-day and 28-day abstinence based on self-report (Figure 18 and Figure 19).There was an increase of odds of 9.5 (95% CI, 2.42 to 37.47) for achieving seven-day abstinence for those treated 13 months or more compared with placebo. Similarly, an increase in odds of 9.82 (95% CI, 2.31 to 34.54) was determined for achieving 28-day abstinence for those treated 13 months or more compared with placebo. Similar findings were determined for the nine-to-12 month group compared with placebo for both seven-day and 28-day abstinence. In both sets of analyses, white race was associated with higher odds of abstinence. A sensitivity analysis for a combination of both self-report and UDS for the past seven days to assess seven-abstinence found consistent results with the main analysis.

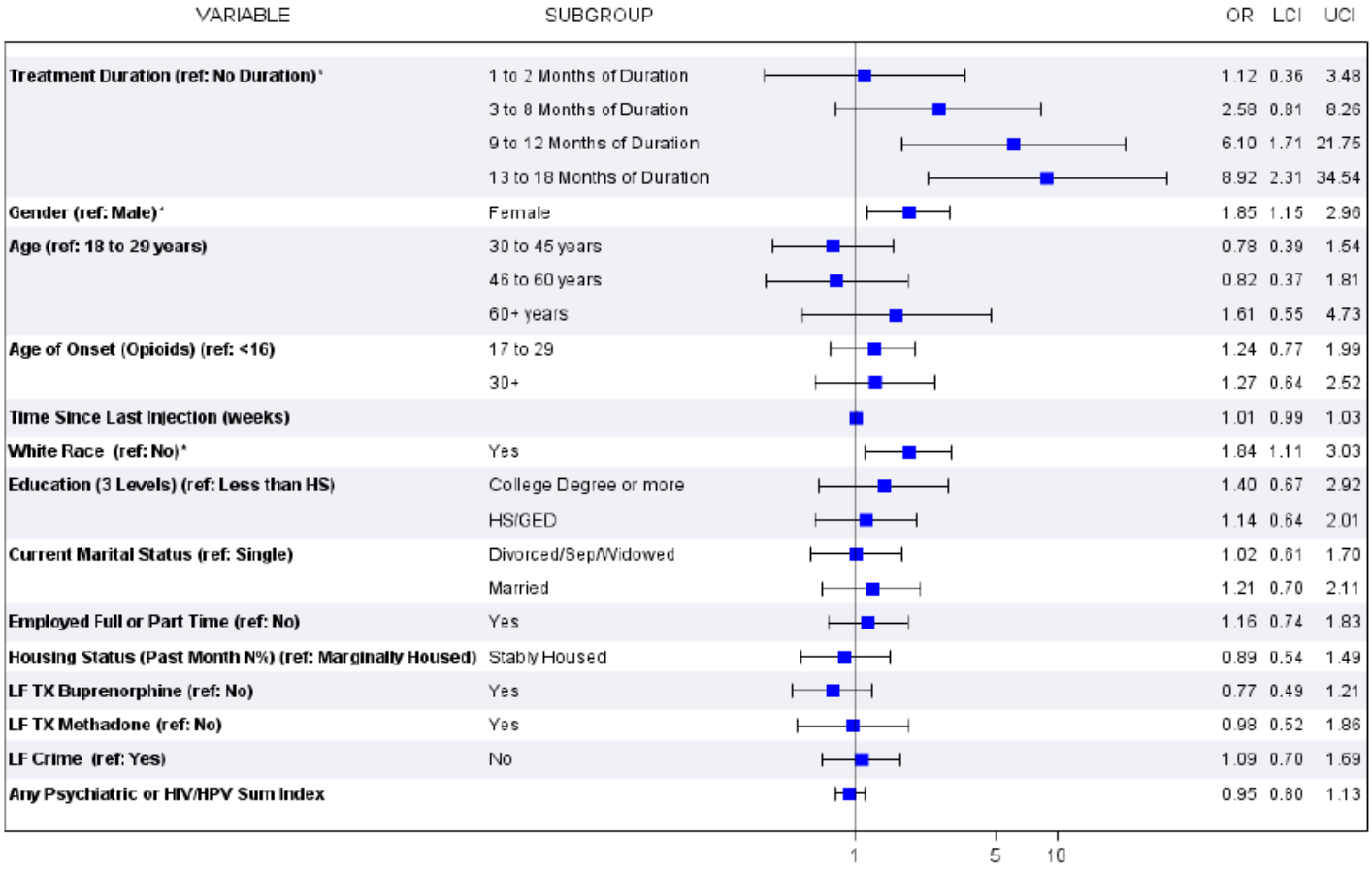
Figure 18: Multivariate Predictors of Past Seven-Day Abstinence



LCI = lower confidence interval; OR= odds ratio; ref = reference; UCI = upper confidence interval.

Source: Clinical study report for RECOVER.[10]

Figure 19: Multivariate Predictors of Past 28-day Abstinence



LCI = lower confidence interval; OR= odds ratio, ref = reference; UCI = upper confidence interval.

Source: Clinical study report for RECOVER.[10]

Harms

Adverse events, serious adverse events, and withdrawals due to adverse events were not assessed and were not relevant as RECOVER was non-interventional.

Limitations

The observational design of the RECOVER study is associated with major limitations when assessing recovery among patients who participated in phase III randomized controlled trials for BUP-ER. The patient population in RECOVER was largely comprised of patients who had completed the phase III trials with good response, good adherence, and low side effects from study treatment. Therefore, this patient population was highly selected, and not representative of the Canadian population that would be likely to use BUP-ER.

While multivariate analysis was performed for key outcomes (self-reported abstinence), the analyses were limited and unlikely to control for major confounding factors that would be expected to substantially bias all study results.

This study was largely based on self-reported data that can be limited with respect to accuracy due to recall bias. This is particularly problematic when the period of recall is long, as is the case with the 28-day outcomes. Additionally, RECOVER assessed sensitive topics that may produce issues with truthfulness of responses.

Missing data were excluded from analysis with no attempt to impute the data. This is of minimal concern as almost all survey questions were answered by 98% or more of the patients. For the UDS data, only 34 patients out of 534 had missing data.

The outcome related to criminal activity before and after clinical trials was limited as the data obtained from public records, which was found for 65% of patients.

Conclusion

The RECOVER study was a multi-centre, non-interventional observational study for patients treated for OUD who had participated in one of two phase III clinical trials for BUP-ER. RECOVER was designed to assess the recovery process over a 24-month period.

Based on public records, 10% of patients had been arrested within one year before screening eligible for the trial, with misdemeanour charges accounting for 8.3%. Conversely, within the time between exiting the clinical trial and up to 12 months later (11 months on average) 6.8% of patients had been arrested with 5.0% of arrests attributed to misdemeanours. Seven-day and 28-day abstinence were associated with increased treatment duration. There was an increase in odds of 5.7 for achieving seven-day abstinence for those treated 13 months or more compared with placebo. An increase in odds of 5.4 was determined for achieving 28-day abstinence for those treated 13 months or more compared with placebo. Longer treatment duration (specifically the nine-to-12 month and 13-to-18 month groups) was also associated with less psychological distress and less depression.

After controlling for some key demographic, clinical, and psychosocial characteristics, it was determined that patients who received longer durations of BUP-ER treatment (nine to 12 months and 13 or more months) were significantly more likely to achieve both seven-day and 28-day abstinence based on self-report (Figure 18 and Figure 19).

There was an increase of odds of 9.5 (95% CrI, 2.42 to 37.47) for achieving seven-day abstinence for those treated 13 months or more compared with placebo. Similarly, an increase in odds of 9.82 (95% CrI, 2.31 to 34.54) was determined for achieving 28-day abstinence for those treated 13 months or more compared with placebo. Similar findings were determined for the nine-to-12 month group compared with placebo for both seven-day and 28-day abstinence.

A sensitivity analysis for a combination of both self-report and UDS for the past seven days to assess seven-abstinence found consistent results with the main analysis.

The main limitations of RECOVER related to the observational design of the study, minimal control for confounding variables, and a highly selected study population not representative of the Canadian population. All results of the RECOVER study should be interpreted with caution.

Appendix 9: Summary and Critical Appraisal of Studies Used in Economic Analysis

Aim

To examine the validity of relevant clinical results found in the three key studies used in the pharmacoeconomic analyses.[58-60]

Findings

Kelty (2017)

Aim

To examine the validity of the results for fatal and non-fatal overdose rates per 1,000 person-years (ptpy), by treatment, in Kelty (2017).[58]

Study Characteristics

This was a retrospective-prospective cohort study conducted using state health hospital mortality data of Australian opioid-dependent patients between 2001 and 2010 (inclusive). The patients in this cohort were treated with methadone, buprenorphine, or implant naltrexone. Treatment data for patients who received buprenorphine and methadone was obtained from the Monitoring of Drugs of Dependence Systems. Treatment data for implant naltrexone were obtained from patient treatment lists from a drug and alcohol clinic. Data for fatal and non-fatal opioid overdose were obtained from mortality and hospital records, and collated by treatment.

The primary outcome of interest for this study were rates of fatal and non-fatal (requiring hospital admission) opioid overdose per 1,000 patient-years by treatment group. Comparisons of rates of fatal opioid overdose between treatment groups were carried out using univariate and multivariate Cox proportional hazard regression, while rates of non-fatal opioid overdose were compared using generalized estimating equations, with negative binomial distributions. Univariate and multivariate Cox proportional hazard regression was used to identify potential risk factors, such as gender, age at first treatment, hospital admissions for opioid overdose, non-opioid drug overdose, intentional self-harm, and cardiovascular or respiratory problems in the two years prior to initial treatment and following commencement of initial treatment. Fatal and non-fatal opioid overdoses and the ratio between the two were calculated for patients during “induction” (defined as the first 28 days after starting treatment), “on treatment” (defined as the period between induction and cessation of treatment), and “off treatment” (defined as the cessation of treatment period to either the commencement of a subsequent treatment or December 31, 2012). Treatment periods were only included when the average dose of methadone was 20 mg or more and the average dose of buprenorphine was 2 mg or more.

This analysis included 8,226 patient episodes, of which 3, 515 were treated with methadone, 3,250 were treated with buprenorphine, and 1,461 were treated with naltrexone. Patients were predominantly male (mean, 64.4% to 66.7%) and with a mean starting age between 30.3 and 31.9 years. The median dose per treatment was 47.0 mg (interquartile range [IQR], 34.6 mg to 65.0 mg) buprenorphine, and not reported in the methadone group, with a median treatment length per episode of 0.50 years (IQR, 0.46 to

0.50 years) in the methadone group and 0.63 years (IQR, 0.18 to 1.72 years) in the buprenorphine group.

Rates of fatal opioid overdose were similar between groups, and rates of non-fatal overdose were not significantly different between the methadone and buprenorphine groups. There were higher rates of fatal opioid overdose in the induction period within the methadone group (16.2 ptpy) compared with the buprenorphine group (0). Both fatal and non-fatal opioid overdoses occurred predominantly in the first two weeks after initiating treatment.

Critical Appraisal

This study evaluated a clearly focused, objective outcome (fatal and non-fatal opioid overdose), taking into account relevant risk factors and comparing relevant treatments used in opioid use disorder (OUD). Methods of regression used to control for risk factors and compare between groups appeared to be appropriate. Cases were clearly defined and reliable database systems were used to collect information.

Several limitations impact the interpretation of the study's findings. First, there was no power calculation provided to determine whether differences between groups were clinically significant. Second, the design of the study allowed patients to have multiple episodes, meaning that the same patient could have been captured more than once in a non-random way. Due to the nature of OUD treatment, it is likely that patients would have been trialled on a different pharmacotherapeutic option at a second or third time. It remains unclear which treatment was considered first-line for patients in Australia during this period. As a result, the possibility of patient populations being different between treatment arms cannot be ruled out. Finally, data in this study was from an Australian patient population, potently limiting the generalizability of the study's findings.

Sordo (2017)

Aim

To examine the validity of the results for all-cause mortality rates per 1,000 ptpy, by treatment, in Sordo (2017).[60]

Study Characteristics

This was a systematic review and meta-analysis designed to compare the risks for all-cause and overdose mortality in patients with OUD during and after treatment with methadone (MET) or buprenorphine (BUP). The data sources for this study were retrospective and prospective cohort studies comparing mortality during and after initiation of treatment with MET or BUP, with a follow-up period. Sources of data in the literature search were MEDLINE, Embase, PsycINFO, and LILACS.

Crude all-cause and overdose mortality rates were calculated during periods in and out of treatment (by dividing the number of deaths registered in each period by person-years contributed by all patients). Cause-specific mortality rates in and out of treatment were combined across MET and BUP cohorts using a bivariate random-effects meta-analysis on log transformed mortality rates in both treatment period. Heterogeneity was contrasted in these pooled mortality rates by location, prevalence of opioid injection, gender, age, average methadone dose, percentage of inpatient injection, follow-up period, and loss to follow-up in methadone cohorts. Given the limited number of buprenorphine cohorts, there

was no heterogeneity analysis performed. Cause-specific mortality rates before and after four weeks of treatment were calculated using a multivariate random-effects meta-analysis on log transformed mortality rates in time-to-treatment intervals. For pooled trends in all-cause mortality risk over time in and out of methadone treatment, a fitted bivariate random-effects meta-regression of log transformed rates on a quadratic linear spline function of log time was used, with a knot at four weeks. Heterogeneity was further evaluated with a multivariate extension of the Cochran chi-squared test and quantified with an extended I^2 statistic. Publication bias and genuine small study effects were assessed with an extended Egger test.

The meta-analysis included 19 cohort studies; 11 were from Europe and Israel, four were from North America, and four were from Australia. Methadone was prescribed in 18 cohorts, including 122,885 patients from 1965 to 2010 with an average daily dose between 47 mg to 116 mg, while buprenorphine was used in three cohorts, including 15,831 patients from 1990 to 2010 with an average daily dose between 10 mg to 12 mg. The average duration of follow-up in the methadone group was 1.3 to 13.9 years, compared with 1.1 to 4.5 years in the buprenorphine group. Most studies were deemed to be of moderate quality.

All-cause mortality during follow-up periods in and out of treatment were reported in 17 methadone cohorts and two buprenorphine cohorts, while overdose mortality was reported in 11 methadone cohorts and one buprenorphine cohort. All-cause mortality rates between methadone cohorts had significant heterogeneity (I^2 = 98%, P < 0.001), and not calculated for buprenorphine cohorts (one study). Overdose mortality between methadone cohorts had moderate heterogeneity (I^2 = 66%, P = 0.001) for in-treatment rates and significant heterogeneity (I^2 = 97%; P < 0.001) for out-of-treatment rates.

Critical Appraisal

This study had a focused aim, examining an objective outcome (all-cause and overdose mortality) as an end point. Eligibility criteria for study inclusion and exclusion were defined, and information sources were generally provided. The statistical analysis defined a priori for this data set appeared to be appropriate in taking into account relevant risk factors. Heterogeneity was assessed as well as publication bias. Results were presented with confidence intervals and measures of consistency.

The small evidence base, and reduced duration of exposure identified for buprenorphine cohorts, greatly impact the interpretation of these results. Furthermore, the methadone evidence base was gathered from studies published as far back as 1965, when treatment practices for patients with opioid use disorder may not be generalizable to the present day, and all-cause mortality or overdose mortality rates were different. In contrast, data from buprenorphine ranged from 1990 to 2010. With the smaller evidence base in the buprenorphine cohort, there is a greater likelihood of confounding risk factors having a greater effect. It is also important to consider how readily available methadone was compared with buprenorphine in some of these jurisdictions.

Other limitations of this study include the high degree of heterogeneity identified in the methadone cohorts, and variable countries of origin within the evidence base.

Public Health England Evidence Review (2017)[59]

Aim

To examine the validity of the results for annual probability of abstinence, by treatment, in Public Health England evidence review.[59]

Study Characteristics

This was an evidence review undertaken by Public Health England (commissioned by the UK Department of Health) aiming to review the evidence base for what is to be expected of drug treatment and recovery systems in order to inform future policy. This included establishing the current prevalence of drug misuse and projected outcomes of treatment and abstinence (successful completion of treatment) in the opioid treatment population.

Models for opioid use were constructed for the period between January 2011 and August 2016 and tested for the period between September 2014 and August 2016, with assumptions that there would be no unforeseeable changes in external influences leading to a significant increase in treatment demand, and that incidence and prevalence would continue to follow existing trends (which, at the time, were declining in England).

The definition of patients who had successfully completed treatment (abstinence) was those who had been assessed as no longer requiring structured drug treatment interventions; and those who were abstinent from heroin, other non-medical opioids, opioid substitution therapy, and crack cocaine; and were not dependent on any other substance, including alcohol.

Abstinence rates were reported taken from a model examining the annual likelihood of study treatment completion by the length of time using opiate. In this report, it was generally found that as length of use increases, the likelihood of successful treatment completion decreases. The specific value used in the economic analysis (7%) was the rate modelled for patients who had misused opiates for 21 years or more. It also appears that the rate affects the proportion of all patients in treatment during that year.

Critical Appraisal

This was a thorough review that used established sources for its database. Reviewers clearly reported the assumptions in their model. However, there are some limitations with the application of the use of abstinence rates in the pharmacoeconomic model. First, the model was based on the assumption that prevalence would follow existing declining trends in the UK; however, in Canada, prevalence rates are increasing, and more potent opioids are being used. Second, the abstinence rate used (7%) was based on patients who had been misusing opiates for 21 years or more. It is unlikely that this population can be generalized to current Canadian patients with OUD, who are a generally very young patient population, with different opioid use histories. Finally, there may be a problematic assumption in the way this rate is being applied, as the value is an estimated proportion of all patients in treatment over the time frame of a year, rather than the proportion of all patients initiating treatment that year.

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