OPEN

Treating Opioid Use Disorder With a Monthly Subcutaneous Buprenorphine Depot Injection: 12-Month Safety, Tolerability, and Efficacy Analysis

Anne C. Andorn, MD, Barbara R. Haight, PharmD,* Sunita Shinde, MD,* Paul J. Fudala, PhD,* Yue Zhao, DrPH,* Christian Heidbreder, PhD,* Susan M. Learned, MD,* Norma Lynn Fox, PhD,* Vijay R. Nadipelli, MS,* David Hassman, DO,† and Daniel Rutrick, MD‡*

Abstract:

Background: BUP-XR (RBP-6000 or SUBLOCADE) is the first Food and Drug Administration–approved subcutaneously administered monthly extended-release buprenorphine medication for the treatment of moderate or severe opioid use disorder. The primary objective of this phase III study was to assess the long-term safety, tolerability, and efficacy of BUP-XR.

Methods: This open-label multicenter study in adults with moderate or severe opioid use disorder enrolled 257 participants from a previously conducted placebo-controlled, double-blind phase III study (rollover group) and 412 de novo participants not previously treated with BUP-XR. Participants received an initial injection of BUP-XR 300 mg and subsequent monthly 300 mg or 100 mg flexible doses. By study end, participants received up to 12 injections.

Results: Overall, 66.8% of participants reported more than 1 treatment-emergent adverse event (TEAE). Injection-site TEAEs (13.2% of participants) were mostly mild or moderate in severity. There were no clinically meaningful changes in safety assessments. An integrated analysis of the double-blind and open-label study participants showed that the incidence of TEAEs, including injection-site TEAEs, was lower in the second 6 months of treatment versus the first 6 months. After 12 months of treatment, 61.5% of the rollover participants and 75.8% of the de novo participants were abstinent. Retention rates after 12 months were 50.6% for the participants who initiated BUP-XR in the double-blind study and 50.5% for de novo participants.

Conclusions: This study demonstrates that the clinical benefits and acceptable safety profile of BUP-XR demonstrated in the 6-month double-blind study are sustained over a 12-month open-label study, with lower incidence of TEAEs in the second 6 months of treatment.

Key Words: opioid use disorder, buprenorphine, long-term safety

(*J Clin Psychopharmacol* 2020;40: 231–239)

Opioid use disorder (OUD) is a neurobehavioral syndrome that is most commonly treated with methadone, buprenorphine, or naltrexone.[1,2] Although these medications can provide improved outcomes in patients treated for OUD, their use is limited because of lack of adherence to daily dosing regimens, subtherapeutic plasma concentrations over the dosing interval, abuse, misuse, diversion, and accidental poisoning.[2,3] Among these medications, buprenorphine, a partial agonist at the mu-opioid receptor, has demonstrated effectiveness in reducing signs and symptoms of opioid withdrawal and blocking opioid craving and drug-liking.[1,3] BUP-XR (RBP-6000 or SUBLOCADE), an extended-release formulation of buprenorphine, was approved by the US Food and Drug Administration for the treatment of moderate or severe OUD.

BUP-XR has been shown to provide consistent and therapeutically relevant plasma levels of buprenorphine over a monthly dosing interval.[4] In a 24-week randomized, double-blind, placebo-controlled study in adults with moderate or severe OUD (NCT02357901), BUP-XR significantly increased abstinence from illicit opioids.[3] In addition, participants reported statistically significant improvement in health status and health-related quality-of-life measures after treatment with BUP-XR.[1] With the exception of anticipated injection-site reactions, BUP-XR had a safety profile similar to that of transmucosal buprenorphine.[3] In that study, participants randomized to active treatment received 2 monthly doses of 300 mg BUP-XR and then 4 monthly doses of either 100 mg or 300 mg. The initial doses of 300 mg for the first 2 months were given to deliver the required plasma concentrations of buprenorphine (2–3 ng/mL) to provide opioid blockade.[5] Maintenance doses were selected to either maintain those plasma levels (100 mg) or to provide higher concentrations (300 mg) that may be required by some patients.[6]

The objective of this open-label phase III study (NCT02510014) was to assess the long-term safety and tolerability of BUP-XR in adults with moderate or severe OUD. Participants received an initial injection of BUP-XR 300 mg and subsequent injections of either 300 mg or 100 mg, in a flexible manner, up to 12 monthly injections. Long-term efficacy and retention were also assessed. Data from this study are presented for de novo (up to 12 months in the study) and rollover participants (up to 6 months in the present study in addition to the 6 months completed in the double-blind study).

MATERIALS AND METHODS

Study Design and Procedures

This multicenter phase III open-label long-term study (NCT02510014) was conducted at 39 sites in the United States between July 2015 and January 2017 in accordance with International Council for Harmonization Good Clinical Practice guidelines and US Food and Drug Administration regulations governing clinical study conduct. An institutional review board reviewed and approved the study protocol, amendments, informed consent form, and all other appropriate study-related information. All participants provided written informed consent before enrollment after procedures, and possible adverse effects were explained to them.

Participants enrolled in this study included rollover participants who completed the randomized, placebo-controlled,

From *Indivior Inc., North Chesterfield, VA; †Comprehensive Clinical Research, Berlin, NJ; and ‡Adams Clinical, Watertown, MA.

Received May 31, 2019; accepted after revision February 7, 2020.

Reprints: Anne C. Andorn, MD, Indivior Inc., 10710 Midlothian Turnpike, Suite 125, North Chesterfield, VA 23235 (e-mail: Anne.Andorn@Indivior.com).

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000001195

double-blind pivotal study[3] and de novo participants, who did not participate in the randomized double-blind study and whose first exposure to BUP-XR was in this open-label study. Rollover participants included those who had received 6 monthly doses of 300 mg (rollover 300/300 mg), 2 monthly doses of 300 mg followed by 4 monthly doses of 100 mg (rollover 300/100 mg), or 6 monthly doses of placebo (rollover placebo).

The study included a 3-day induction period with buprenorphine/naloxone sublingual film (2–24 mg) followed by a dosage adjustment period (8–24 mg) of up to 11 days, a 48-week BUP-XR treatment period, and a 4-week safety follow-up (Fig. 1). On day 1 of this study, participants received a BUP-XR 300 mg subcutaneous injection. Subsequent doses could be reduced to 100 mg with the possibility of increasing back to 300 mg, based on the medical judgment of the investigator ("flex dosing"). Doses were administered every 28 (−2/+4) days. De novo participants received up to 12 monthly injections, whereas rollover participants received up to 6 monthly injections (a total of up to 12 monthly injections when including double-blind treatment). All participants returned to the clinic weekly for the first 5 weeks, then every 2 weeks until injection 6 (Week 21), followed by monthly visits for the remainder of the study for urine drug screens (UDSs) and timeline follow-back (TLFB) interviews, which is a commonly used validated measure to recall drug consumption.[7] Individual drug counseling was provided throughout the study. De novo participants received individual drug counseling weekly for the first 5 weeks and then every 2 weeks until injection 6, followed by monthly for the remainder of the study (up to 12 injections); rollover participants received individual weekly counseling during the period they received the first 6 monthly injections, and once joining the study, they received individual drug counseling weekly for the first 5 weeks, followed by every 2 weeks until the end of the study.

At the end of the open-label study, participants could enroll in a 6-month extension study or transition to buprenorphine/naloxone sublingual film treatment.

Participant Eligibility

Inclusion criteria for both the double-blind study and for de novo participants in the present study included being a treatment-seeking adult 18 to 65 years of age who met, by medical history, the *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition* (*DSM-5*) criteria for moderate or severe OUD for the 3 months immediately before signing the informed consent form, with an opioid craving visual analog scale (VAS) score of 20 mm or less[8] and a Clinical Opiate Withdrawal Scale score of 12 or less[9] before receiving the first dose of BUP-XR. Exclusion criteria, in brief, included a current diagnosis (other than OUD) that required chronic opioid treatment; a positive UDS result for cocaine or cannabis and met *DSM-5* criteria for either moderate or severe cocaine or cannabis use disorder; moderate or severe alcohol use disorder, per *DSM-5* criteria; and/or a history of either suicidal ideation within 30 days or a suicide attempt within 6 months of informed consent.

Enrollment of rollover participants was based on the investigator's determination that continuation of study treatment was appropriate and that there had been no major protocol deviations or adverse events that would preclude inclusion of the participant in the study.

Safety Assessments

Safety assessments included treatment-emergent adverse events (TEAEs) rated for both intensity (mild, moderate, or severe) and whether the event was serious or not, local injection-site tolerability, local injection-site pain, clinical laboratory values, vital signs, suicidality, and electrocardiograms (ECGs). Injection sites were graded for pain and other reactions. Injection-site pain was measured using the injection-site pain VAS, with responses (0–100 mm) ranging from "no pain" to "pain as bad as it could be." Suicidal ideation and behavior were monitored using the electronic Columbia-Suicide Severity Rating Scale. Treatment-emergent adverse events were coded according to the Medical Dictionary for Regulatory Activities version 17.1.[10]

Efficacy Assessments

Efficacy was evaluated using UDS for opioids plus self-reported illicit opioid use combined into a single abstinence endpoint. Opioids assessed by UDS included codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Urine drug testing was performed with immunoassays to detect opioids and methadone (EMIT II Plus Opiate Assay and EMIT II

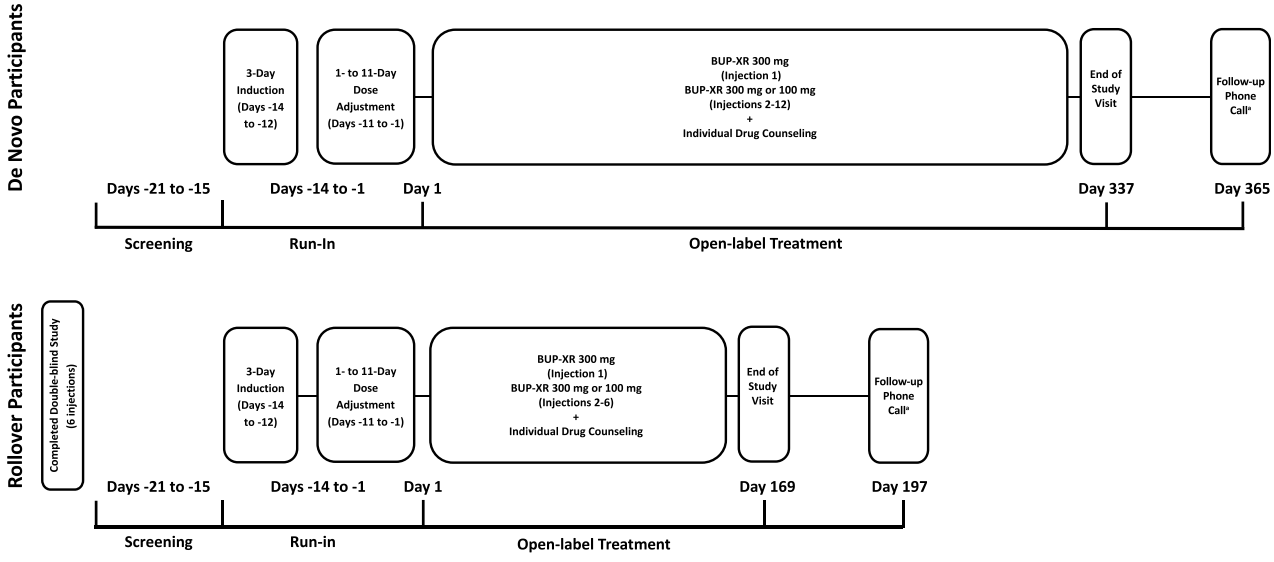

FIGURE 1. Study design. [a]Follow-up phone call not required for those entering the extension study. BUP/NAL SF, buprenorphine/naloxone sublingual film.

Plus Methadone Assay, respectively; Siemens Healthcare Diagnostics Ltd) and oxycodone (DRI Oxycodone Assay; Thermo Scientific). Confirmatory testing was done with gas chromatography/mass spectrometry for codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone; positive cutoff thresholds and limits of quantitation for all analytes were 300 ng/mL and 100 ng/mL, respectively. Testing was performed by ACM Global Central Laboratory (Rochester, NY). Use of amphetamine/methadone,* buprenorphine, methadone, and opioids (which may have included some opioids that were not specifically tested for [eg, fentanyl]) were assessed using the TLFB.[3]

Medication Satisfaction Assessment

Medication satisfaction was evaluated with the Medication Satisfaction Questionnaire, a single-item questionnaire that evaluates the participant's satisfaction with opioid medication categorized as satisfied (5–7), neutral (4), or dissatisfied (1–3).[11]

Data Analyses

The number of participants was planned to ensure that at least 100 participants reached 1 year of treatment with BUP-XR. No formal statistical hypothesis testing was performed. Descriptive summaries of the effects of open-label BUP-XR on safety and tolerability were performed on the safety analysis set (SAS), comprising all open-label study participants who received at least 1 BUP-XR injection.

In addition, a comparison of safety during the first and second 6-month treatment periods was performed on the SAS of the double-blind study (participants who received at least 1 dose of BUP-XR or placebo) and the SAS of de novo participants.

Efficacy and treatment retention were evaluated in the population of participants who either entered the double-blind randomized study or the long-term safety study, more specifically the full analysis set (FAS) for the double-blind study and the SAS of the open-label study. Participant satisfaction was evaluated on the SAS of the open-label study. The FAS for the double-blind study comprised randomized participants who received at least 1 dose of BUP-XR or placebo, excluding 15 participants from one site because of compliance issues (these 15 participants discontinued the double-blind study prematurely). Proportion (in %) of participants achieving abstinence was summarized by week using available data approach in which participants with both missing UDS and self-report at a specific visit were excluded from the percentage denominator for that visit. Participants with a missing value for either UDS or self-report (but not both) were considered as positive (nonabstinent).

The Kaplan-Meier method was used to estimate treatment retention rates, based on the FAS of the double-blind study and the SAS of the open-label study, for all participants who received at least 1 injection of BUP-XR or placebo, from the first injection of active BUP-XR or placebo treatment and over the entire exposure period for the corresponding treatment. Four cohorts were considered for the analyses, those who initiated treatment during the double-blind study (separate cohorts for each of the maintenance dose assignments in that study), those on placebo during the double-blind study, and the de novo participants who initiated treatment during the open-label study. Participants who completed the 6 months of active treatment in the double-blind study but did not continue into the open-label study were censored at the end of 6 months (day 169). Participants treated with placebo and without discontinuation in the double-blind study were censored at their last observed time point in the double-blind study or the end of 6 months (day 169), whichever was earlier. Participants treated with active BUP-XR and without discontinuation during the 12 months treatment period were censored at their last observed time point or the end of 12 months (day 337), whichever was earlier.

*In the electronic patient-reported outcomes (ePRO) for the TLFB interview, "methadone" was erroneously substituted for "methamphetamine" (ie, the ePRO read "amphetamine/methadone" when it should have read "amphetamine/methamphetamine"). As a result, there was the potential for variability in the interpretation of the "amphetamine/methadone" data point. Therefore, a response of "use" of amphetamine/methadone was considered positive for opioids. A sensitivity analysis, excluding the question of amphetamine/methadone, revealed similar results for percentage abstinence as when 'use' of amphetamine/methadone was considered non-negative and 'not use' of amphetamine/methadone was considered positive.

RESULTS

Disposition, Demographics, and Extent of Exposure

A total of 669 participants entered the study and 406 (60.7%) completed it (Supplementary Figure, Supplemental Digital Content, http://links.lww.com/JCP/A662). The number of participants (n) in each group was as follows: de novo (412), rollover placebo (32), rollover 300/300 mg (113), and rollover 300/100 mg (112). The most common reasons for discontinuation were lost to follow up (14.8%) and withdrawal of consent (13.6%).

Demographics and baseline characteristics were similar among the 4 SAS participant groups (Table 1). Most participants were male (64.6%), white (69.1%), current tobacco users (86.1%), and current alcohol users (50.4%); 46.2% used opioids via an injectable route based on reported use during the 30 days before screening and reported lifetime use.

Participants in the de novo group received a mean (SD) of 8.4 (4.4) injections. The mean (SD) number of BUP-XR injections was 11.2 (1.5) for the rollover 300/300 group, 11.5 (1.1) for the rollover 300/100 mg group, and 5.3 (1.6) for the rollover placebo group (excluding injections of placebo). The majority of both de novo participants (75.7%) and rollover participants (60.7%) received the 300 mg maintenance dose throughout the open-label study. Of all participants who completed the study (n = 406), 60.3% (n = 245) remained on 300 mg throughout the study. A total of 201 participants had a dose reduction from 300 mg to 100 mg. Of these, 25 participants had their dose increased back to 300 mg. Of these, 5 had their dose decreased again to 100 mg.

Safety

Safety results for this open-label study are presented for de novo (up to 12 months in the study) and rollover participants (up to 6 months in the study). In addition, an integrated comparison of TEAEs from months 1 to 6 and months 7 to 12 of treatment is presented for participants in this study and in the double-blind study.

Adverse Events in the Open-Label Study

Among the SAS de novo participants, 73.8% had a reported TEAE during the 12-month treatment period (Table 2). During 6 months in the open-label study, 53.1% of participants in the rollover 300/300 mg group, 58.0% in the rollover 300/100 mg group, and 62.5% in the rollover placebo group had a reported TEAE. Serious TEAEs ranged from 2.7% to 4.4% and were highest in the rollover 300/300 mg group. There was no individual serious TEAE that was reported in 1% or greater of participants in any group. Two participants in the de novo group had serious adverse events (SAEs) leading to discontinuation (gallbladder perforation and accidental overdose); neither event was considered related to study treatment. The incidence of severe TEAEs was highest in the de novo group (8.7%). The majority of TEAEs were mild to moderate in severity. There were no deaths and no individual

TABLE 1. Baseline Demographics and Characteristics, SAS of Open-Label Study

Participant Characteristics	De Novo (n = 412)	Rollover			
		Rollover BUP-XR 300/300 mg (n = 113)	Rollover BUP-XR 300/100 mg (n = 112)	Rollover Placebo (n = 32)	Rollover Total (n = 257)
Age, mean (SD), y	38.4 (12.1)	40.4 (11.1)	42.2 (11.1)	43.8 (10.7)	41.6 (11.1)
BMI, mean (SD), kg/m^2	25.4 (4.3)	26.6 (5.5)	25.6 (4.6)	26.4 (4.8)	26.1 (5.1)
Sex, n (%)					
Male	263 (63.8%)	77 (68.1%)	70 (62.5%)	22 (68.8%)	169 (65.8%)
Female	149 (36.2%)	36 (31.9%)	42 (37.5%)	10 (31.3%)	88 (34.2%)
Race, n (%)					
White	295 (71.6%)	75 (66.4%)	70 (62.5%)	22 (68.8%)	167 (65.0%)
Black/African American	107 (26.0%)	36 (31.9%)	39 (34.8%)	10 (31.3%)	85 (33.1%)
Multiple/other	10 (2.4%)	2 (1.8%)	3 (2.7%)	0	5 (1.9%)
Ethnicity, n (%)					
Non-Hispanic/Latino	369 (89.6%)	105 (92.9%)	106 (94.6%)	30 (93.8%)	241 (93.8%)
Hispanic or Latino	43 (10.4%)	8 (7.1%)	6 (5.4%)	2 (6.3%)	16 (6.2%)
Use of opioids by an injectable route, n (%)	195 (47.3%)	48 (42.5%)	45 (40.2%)	21 (65.6%)	114 (44.4%)
Alcohol use, n (%)					
Never	122 (29.6%)	22 (19.5%)	20 (17.9%)	6 (18.8%)	48 (18.7%)
Former	97 (23.5%)	29 (25.7%)	28 (25.0%)	8 (25.0%)	65 (25.3%)
Current	193 (46.8%)	62 (54.9%)	64 (57.1%)	18 (56.3%)	144 (56.0%)
Tobacco use, n (%)					
Never	40 (9.7%)	11 (9.7%)	10 (8.9%)	2 (6.3%)	23 (8.9%)
Former	18 (4.4%)	5 (4.4%)	7 (6.3%)	0	12 (4.7%)
Current	354 (85.9%)	97 (85.8%)	95 (84.8%)	30 (93.8%)	222 (86.4%)

The SAS comprises all participants who received at least 1 dose of BUP-XR during the treatment period of the study.

% was calculated using n as the denominator.

Study procedures completed at EOS/day 169 for the double-blind study served as screening assessments for the rollover group.

Use of opioids by an injectable route is based on reported use during the 30 days before screening as well as reported lifetime use.

BMI indicates body mass index; EOS, end of study.

severe TEAE was reported in 1% or greater of participants in any group. Discontinuations due to a TEAE were less than 4% in all groups. The most common TEAEs (≥5% of de novo participants) were constipation, injection-site pain, nausea, headache, insomnia, nasopharyngitis, and injection-site erythema, many of which were considered treatment-related (Table 2). The mean (SD) number of doses among the 520 participants with at least 1 TEAE was 9.7 (3.6).

A TEAE of drug withdrawal syndrome was reported for 8 participants (1.2%), and none were considered severe. Three de novo participants (0.4%) discontinued the study because of drug withdrawal syndrome.

During the study, 46 participants (6.9%) had their dose reduced from 300 mg to 100 mg because of a TEAE. None of the TEAEs leading to dose reduction were SAEs, and most had resolved or were resolving by study end. The most commonly reported TEAEs (≥1%) that led to dose reduction were sedation/lethargy/somnolence (1.9%) and an increased liver function value (1.5%). Of the 46 participants who had a dose reduction due to TEAEs, 37 completed the study, 5 withdrew consent, 2 were withdrawn because of pregnancy, 1 was withdrawn because of TEAEs, and the remaining participant was withdrawn because of other reasons (incarceration). Of the 37 participants who completed the study, 30 continued the 100 mg dose after dose reduction, wheras 7 had their dose increased back to 300 mg at some point.

Injection-Site Tolerability in the Open-Label Study

Injection-site reaction TEAEs were reported in 67 de novo (16.3%) and 21 rollover participants (8.2%). The most commonly reported were pain (6.9%), erythema (4.0%), and pruritus (3.9%). Only 2 of these were severe; none were serious and 2 resulted in discontinuation.

The overall mean worst injection-site pain VAS scores within 60 minutes postinjection ranged from 44.0/100 after injection 1 to 24.7 after injection 12 for de novo participants and ranged from 33.5 after injection 1 to 30.5 after injection 6 for rollover participants. Mean injection-site pain scores decreased over the first hour after injection and further lessened with each injection, as shown for injections 1 and 12 for the de novo group in Figure 2.

Additional Safety Assessments in the Open-Label Study

There were no unexpected safety signals detected and no TEAEs potentially related to respiratory depression. Vital signs and ECG parameters remained generally within normal reference ranges. Individual TEAEs pertaining to ECG or cardiac disorders were rare (each occurring in ≤1.5% of participants overall); 1 SAE of myocardial infarction was reported, which was considered not related to study treatment. One de novo participant had a single postbaseline QT interval, Fridericia correction value of greater than 500 milliseconds without sequelae. No BUP-XR overdoses occurred; 3 participants had an overdose with another substance

TABLE 2. Treatment-Emergent Adverse Events, SAS of Open-Label Study

n (%)	De Novo Participants (n = 412)	Rollover Participants: Rollover BUP-XR 300/300 mg (n = 113)	Rollover BUP-XR 300/100 mg (n = 112)	Rollover Placebo (n = 32)	Rollover Total (n = 257)
Any TEAE	304 (73.8)	60 (53.1)	65 (58.0)	20 (62.5)	145 (56.4)
Treatment-related TEAE	172 (41.7)	22 (19.5)	31 (27.7)	9 (28.1)	62 (24.1)
Serious TEAE	17 (4.1)	5 (4.4)	3 (2.7)	1 (3.1)	9 (3.5)
Severe TEAE	36 (8.7)	5 (4.4)	2 (1.8)	1 (3.1)	8 (3.1)
TEAE leading to discontinuation	14 (3.4)	3 (2.7)	0	1 (3.1)	4 (1.6)
Death	0	0	0	0	0
TEAEs (≥5% for any of the groups) by MedDRA preferred term, n (%)					
Constipation	50 (12.1)	4 (3.5)	5 (4.5)	0	9 (3.5)
Decreased appetite	6 (1.5)	0	1 (0.9)	2 (6.3)	3 (1.2)
γ-Glutamyltransferase increased	12 (2.9)	5 (4.4)	6 (5.4)	1 (3.1)	12 (4.7)
Headache	36 (8.7)	1 (0.9)	4 (3.6)	0	5 (1.9)
Injection-site erythema	22 (5.3)	1 (0.9)	4 (3.6)	0	5 (1.9)
Injection-site pain	39 (9.5)	4 (3.5)	1 (0.9)	2 (6.3)	7 (2.7)
Injection-site pruritus	17 (4.1)	2 (1.8)	6 (5.4)	1 (3.1)	9 (3.5)
Insomnia	28 (6.8)	1 (0.9)	10 (8.9)	0	11 (4.3)
Nasopharyngitis	24 (5.8)	1 (0.9)	5 (4.5)	0	6 (2.3)
Nausea	38 (9.2)	4 (3.5)	4 (3.6)	3 (9.4)	11 (4.3)

The SAS comprises all participants who received at least 1 dose of BUP-XR during the open-label treatment period of the study.
Treatment-emergent adverse events are for 6 months of open-label treatment in rollover participants and 12 months of treatment in de novo participants.
MedDRA indicates Medical Dictionary for Regulatory Activities.

(one each with diazepam, trazadone [suspected], and heroin). There were 2 participants (0.3%) with a TEAE of suicidal ideation. There were no TEAEs of suicidal behavior or attempt, and no clinically meaningful changes in the electronic Columbia-Suicide Severity Rating Scale were observed.

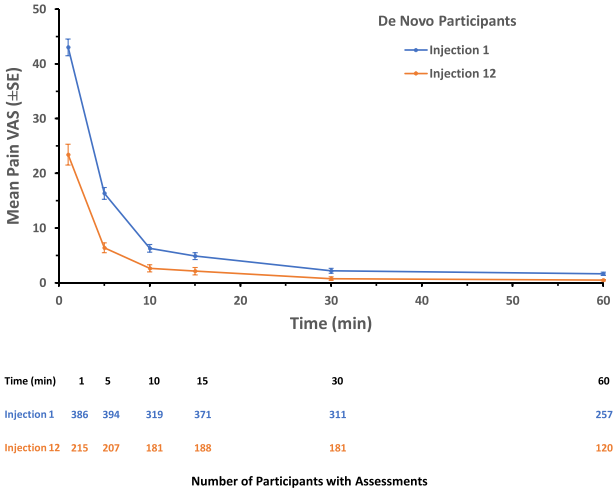

FIGURE 2. Injection-site pain VAS scores over time: de novo participants after injections 1 and 12, SAS of the open-label study. Injection-site pain was measured using the injection-site pain VAS, with responses (0–100 mm) ranging from "no pain" to "pain as bad as it could be" and was assessed at 6 time intervals over 60 minutes after injection.

Safety Across the Double-Blind and Open-Label Studies

Among those who received active treatment during the double-blind study, a lower percentage of participants reported at least 1 TEAE during the second 6 months of treatment (open label) than during the first 6 months of treatment (BUP-XR 300/300 mg, 68.2% for months 1 to 6 vs 53.1% for months 7 to 12; BUP-XR 300/100 mg, 76.8% for months 1 to 6 vs 58.0% for months 7 to 12).

In the cohort of participants who received placebo during months 1 to 6 of the double-blind study and the active treatment during months 7 to 12 of the open-label study, a lower percentage of participants reported at least 1 TEAE during the first 6 months compared with the next 6 months (56.0%, placebo vs 62.5%, active). The percentage of de novo participants reporting at least 1 TEAE was lower during the second 6 months of open-label treatment (38.1%) than during the initial 6 months of open-label treatment (69.4%). The percentage of participants experiencing the most commonly reported TEAEs was lower in the second 6 months of treatment than in the first 6 months of treatment (Fig. 3). Similarly, the incidence of most injection-site TEAEs was lower during months 7 to 12 of treatment than during months 1 to 6 of treatment in all participant groups (Fig. 4). For the participants who received active treatment, among the de novo participants, 8.3% and 3.0% of participants had hepatic disorder TEAEs in the first 6 months and during months 7 to 12, respectively, compared with 7.5% and 6.9% from the BUP-XR 300/300 mg and 300/100 mg participants during the months 1 to 6 treatment in the double-blind study and 5.3% and 5.4% from the rollover 300/300 mg and 300/100 mg groups during the months 7 to 12

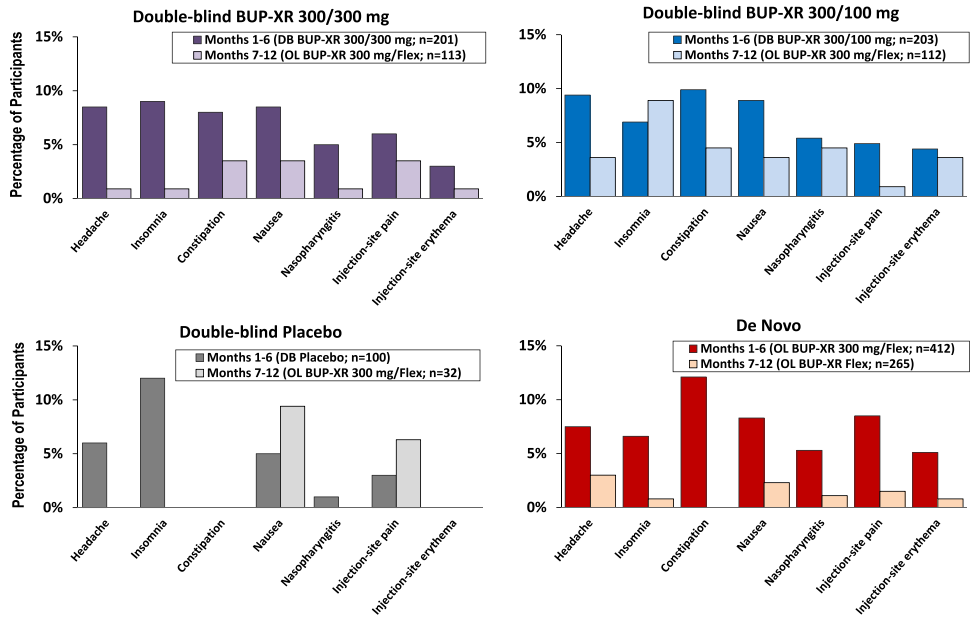

FIGURE 3. Commonly reported TEAEs by treatment period, SAS of the double-blind and open-label studies combined. Participants received placebo or BUP-XR 300/300 mg or 300/100 mg at injections 1 to 6 (months 1–6) in the double-blind study, and then the rollovers received BUP-XR 300 mg at injection 7, and BUP-XR 300 mg or 100 mg flex dosing at injections 8 to 12 (months 7–12) in the open-label study. De novo participants received BUP-XR 300 mg at injection 1 and BUP-XR 300 mg or 100 mg flex dosing at injections 2 to 12 in the open-label study. DB, double blind; OL, open label.

in the open-label study (Table 3). Among these hepatic disorder TEAEs, 0.5% and 0% of de novo participants had severe TEAEs in the first 6 months and during months 7 to 12, respectively, and 1% had severe TEAEs in the BUP-XR 300/300 mg group in the double-blind study. In addition, 0.9% of de novo participants from the open-label study (0.5% in the first 6 months and 0.4% during months 7 to 12) had events leading to discontinuation. None of the participants receiving active treatment in the rollover group in the

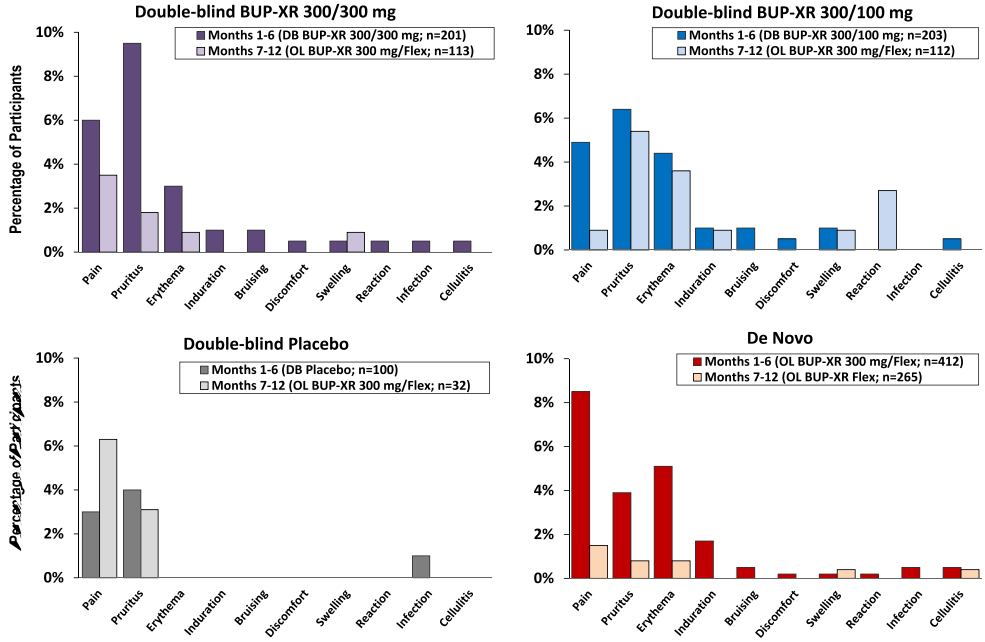

FIGURE 4. Injection-site TEAEs by treatment period, SAS of the double-blind and open-label studies combined. Participants received placebo or BUP-XR 300/300 mg or 300/100 mg at injections 1 to 6 during the double-blind study, and then the rollovers received BUP-XR 300 mg at injection 7, and BUP-XR 300 mg or 100 mg flex dosing at injections 8 to 12 (months 7–12) in the open-label study. De novo participants received BUP-XR 300 mg at injection 1 and BUP-XR 300 mg or 100 mg flex dosing at injections 2 to 12 in the open-label study. DB, double blind; OL, open label.

TABLE 3. Summary of Severity and Seriousness of Hepatic Disorder TEAEs, SASs of the Double-Blind and Open-Label Studies Combined

Study	Phase III Double Blind			Phase III Open Label				
Treatment Period	Months 1–6			Months 7–12			Months 1–6	Months 7–12
Event, Participants, n (%)	BUP-XR 300/300 mg (n = 201)	BUP-XR 300/100 mg (n = 203)	Placebo (n = 100)	Rollover BUP-XR 300/300 mg (n = 113)	Rollover BUP-XR 300/100 mg (n = 112)	Rollover Placebo (n = 32)	De Novo (n = 412)	De Novo (n = 265)
Hepatic disorder TEAEs	15 (7.5)	14 (6.9)	1 (1.0)	6 (5.3)	6 (5.4)	2 (6.3)	34 (8.3)	8 (3.0)
SAEs	0	0	0	0	0	0	0	0
Severe TEAE	2 (1.0)	0	0	0	0	1 (3.1)	2 (0.5)	0
Events leading to discontinuation	3 (1.5)	0	0	0	0	0	2 (0.5)	1 (0.4)

The SAS comprises all participants who received at least 1 dose of BUP-XR/placebo.

open-label study and 1.5% of participants in the BUP-XR 300/300 mg group during the double-blind study discontinued because of hepatic disorder TEAEs (Table 3). There were no SAEs potentially related to liver dysfunction during either study. Among the de novo patients, the rate of elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) decreased numerically from the first 6 months to the next 6 months (8.5% vs 6.4% with both AST and ALT ≥3 upper limit of normal [ULN]), whereas it remained similar in the BUP-XR 300/300 mg group, and it generally increased in the BUP-XR 300/100 mg and placebo groups to the second 6 months during the open-label study, 8.0%, 3.9%, and 1.0% in the BUP-XR 300/300 mg, BUP-XR 300/100 mg, and placebo groups, respectively, in the double-blind study; and 8.8%, 7.1%, and 3.1% in the rollover 300/300 mg, 300/100 mg, and placebo groups, respectively, in the open-label study. In total, 1.2% of the De novo participants in the first 6 months and none of the De novo participants during months 7 to 12 of the open-label study had increased total bilirubin values of more than 2 times the ULN. None of the rollover participants in the open-label study and 1% of the participants in the double-blind study receiving active treatment had increased total bilirubin values of more than 2 times the ULN (Table 4). One participant in these studies with bilirubin of more than 5 times the ULN had a TEAE of hepatitis A. Although there were intermittent

TABLE 4. Participants With Liver Function Assessments Meeting Specified Criteria for Worst Case Postbaseline, SASs of the Double-Blind and Open-Label Studies Combined

Study	Phase III Double Blind			Phase III Open Label				
Treatment Period	Months 1–6			Months 7–12			Months 1–6	Months 7–12
Parameter and Criteria, n (%)	BUP-XR 300/300 mg (n = 201)	BUP-XR 300/100 mg (n = 203)	Placebo (n = 100)	Rollover BUP-XR 300/300 mg (n = 113)	Rollover BUP-XR 300/100 mg (n = 112)	Rollover Placebo (n = 32)	De Novo (n = 412)	De Novo (n = 265)
ALT								
≥8× ULN	4 (2.0)	3 (1.5)	1 (1.0)	2 (1.8)	1 (0.9)	1 (3.1)	12 (2.9)	3 (1.1)
≥5× ULN to <8× ULN	3 (1.5)	2 (1.0)	1 (1.0)	1 (0.9)	3 (2.7)	1 (3.1)	15 (3.6)	3 (1.1)
>3× ULN to <5× ULN	18 (9.0)	6 (3.0)	2 (2.0)	9 (8.0)	4 (3.6)	0	20 (4.9)	15 (5.7)
AST								
≥8× ULN	4 (2.0)	3 (1.5)	1 (1.0)	0	1 (0.9)	1 (3.1)	12 (2.9)	4 (1.5)
≥5× ULN to <8× ULN	5 (2.5)	4 (2.0)	0	6 (5.3)	5 (4.5)	0	7 (1.7)	5 (1.9)
>3× ULN to <5× ULN	14 (7.0)	9 (4.4)	0	5 (4.4)	7 (6.3)	1 (3.1)	22 (5.3)	16 (6.0)
ALT and AST								
≥3× ULN at same time	16 (8.0)	8 (3.9)	1 (1.0)	10 (8.8)	8 (7.1)	1 (3.1)	35 (8.5)	17 (6.4)
Both ≥8× ULN	4 (2.0)	2 (1.0)	1 (1.0)	0	0	1 (3.1)	7 (1.7)	2 (0.8)
Both ≥5× ULN and not both ≥8× ULN	1 (0.5)	1 (0.5)	0	3 (2.7)	4 (3.6)	0	7 (1.7)	1 (0.4)
Both ≥3× ULN and not both ≥5× ULN	11 (5.5)	5 (2.5)	0	7 (6.2)	4 (3.6)	0	21 (5.1)	14 (5.3)
Total bilirubin								
≥5× ULN	0	0	0	0	0	0	1 (0.2)	0
>2× ULN to <5× ULN	1 (0.5)	1 (0.5)	0	0	0	0	4 (1.0)	0

The SAS comprises all participants who received at least 1 dose of BUP-XR/placebo.

n, number of participants who received 1 injection during the specific time period. If there were multiple assessments for a laboratory parameter at the same time, the worst result was used. A participant was included in the highest/worst applicable toxicity grade per criterion, among the postbaseline visits including unscheduled visits.

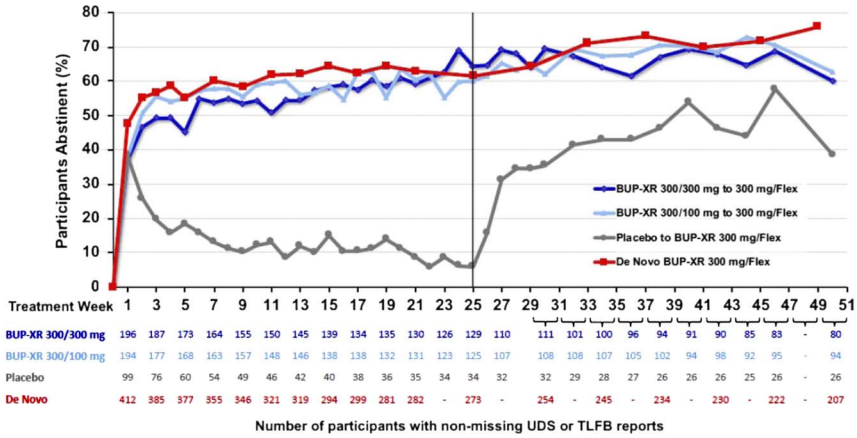

FIGURE 5. Weekly abstinence in the randomized double-blind and long-term safety studies, FAS of the double-blind study and SAS of the open-label study combined. Available data approach. Abstinence defined as negative UDS combined with TLFB negative for illicit opioid use. Participants received placebo or BUP-XR 300/300 mg or 300/100 mg at injections 1 to 6 during the double-blind study (weeks 0–25), and then the rollovers received BUP-XR 300 mg at injection 7, and BUP-XR 300 mg or 100 mg flex dosing at injections 8 to 12 (weeks 26–50) in the open-label study. De novo participants received BUP-XR 300 mg at injection 1 and BUP-XR 300 mg or 100 mg flex dosing at injections 2 to 12 (weeks 0–49) in the open-label study. TLFB, timeline follow-back; UDS, urine drug screen.

elevations of ALT and AST or isolated elevations of bilirubin, no cases of hepatocellular injury based on elevated AST/ALT with jaundice (which can indicate serious drug-induced hepatoxicity) were observed, and no depot removal was necessary.

Efficacy, Retention, and Participant Satisfaction

A total of 901 participants were included in the efficacy analyses. The percentage abstinent from opioids at the end of open-label treatment was as follows: de novo, 75.8%; rollover 300/300 mg, 60.0%; rollover 300/100 mg, 62.8%; and rollover placebo, 38.5% (Fig. 5). The percentage of participants abstinent after the first 6 injections of BUP-XR was similar in the double-blind and open-label studies: de novo, 61.5%; BUP-XR 300/300 mg, 64.3%; and BUP-XR 300/100 mg, 60%. The percentage of participants abstinent in the placebo group was 57.7% at the week of receiving the sixth BUP-XR injection. At the week of receiving the 12th injection in the open-label study, the percentage of participants abstinent was as follows: de novo, 71.6%; rollover 300/300 mg, 68.7%; rollover 300/100 mg, 70.5% (Fig. 5).

De novo participants and those treated with BUP-XR in the double-blind study had similar treatment retention rates (Fig. 6). Retention after 6 and 12 months of open-label treatment for de novo participants was 65.5% and 50.5%, respectively. Retention after 6 months for the BUP-XR 300/300 mg and BUP-XR 300/100 mg groups in the double-blind study was 66.3% and 66.0%, respectively, and 36.4% in the placebo group. Retention after 12 months was 47.1% and 53.9% for the BUP-XR 300/300 mg and 300/100 mg participants, respectively. Among the 32 placebo participants who enrolled in the open-label study, 26 completed 12 months.

Participant satisfaction with medication measured in the open-label study was high at all time points, with 85.0% to 89.7% of de novo participants and 85.0% to 85.2% of rollover participants satisfied, very satisfied, or extremely satisfied with

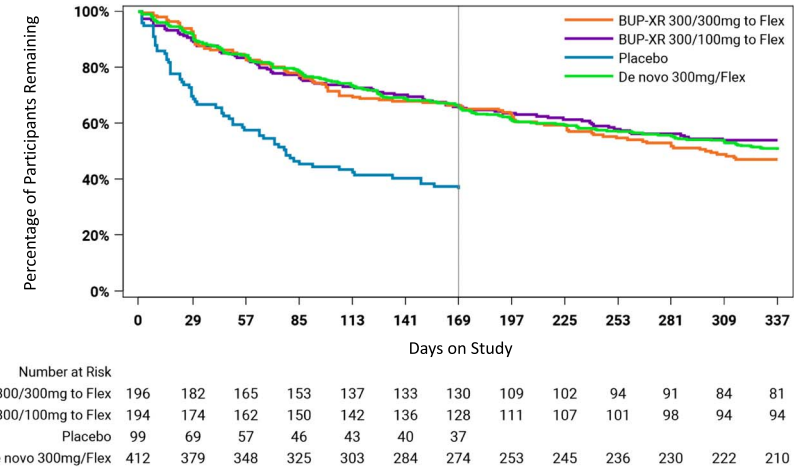

FIGURE 6. Twelve-month treatment retention from initiation to discontinuation using the Kaplan-Meier approach. Full analysis set of the double-blind study and SAS of the open-label study combined. Participants who completed the 6 months of active treatment in the double-blind study but did not continue into the open-label study were censored at the end of 6 months (day 169). Participants treated with placebo and without discontinuation in the double-blinded study were censored at their last observed time point in the double-blinded study or the end of 6 months (day 169), whichever was earlier. Participants treated with active BUP-XR and without discontinuation during the 12 months treatment period were censored at their last observed time point or the end of 12 months (day 337), whichever was earlier.

BUP-XR treatment across time points. Of the 404 participants (204 de novo, 200 rollover) completing assessments at the end of study, 88.8% de novo and 85.0% rollover participants were satisfied, very satisfied, or extremely satisfied with BUP-XR treatment.

DISCUSSION

Effective OUD treatment is an important part of the solution to the opioid epidemic. Use of BUP-XR may contribute to treatment success by providing consistent therapeutic plasma concentrations, ensuring medication adherence, and potentially reducing the risk of abuse, misuse, and diversion. The efficacy and safety profile of BUP-XR in this open-label study was consistent with that previously reported for the double-blind study.[3]

With the exception of the anticipated injection-site reactions, treatment with up to 12 monthly BUP-XR injections was well tolerated, with a safety profile consistent with that of transmucosal buprenorphine.[3] The finding that the incidence of TEAEs was lower during the second 6 months of exposure to BUP-XR could be due to differential dropout during the first 6 months and/or that longer exposure to BUP-XR does not increase the frequency of TEAEs. Notably, the graded injection-site reactions also improved over time. In addition, opioid-induced respiratory depression is a major limiting factor in the effective management of analgesia with potentially fatal consequences[12,13]; therefore, the absence of safety signals related to respiratory depression provides strong support for the use of BUP-XR in the treatment of OUD.

The hepatic safety profile of BUP-XR in the present study was comparable with that reported for transmucosal buprenorphine/naloxone.[14] It is noteworthy that longer exposure to the highest dose of BUP-XR did not worsen hepatic laboratory assessments. Importantly, no cases of hepatocellular injury indicated by increased AST/ALT with jaundice were noted, and no removal of BUP-XR was required in these studies.

In the double-blind study, abstinence rates were significantly improved in participants maintained on BUP-XR 100 mg or 300 mg compared with placebo.[3] In this open-label study, the percentage of participants abstinent from opioids continued to increase over an additional 6 months of treatment. A marked increase in abstinence was noted for participants who rolled over from placebo to BUP-XR after starting BUP-XR treatment. Abstinence rate, the time-course of improvement, and the retention rate for the de novo group were similar to those of the rollover group. Sustained abstinence from opioids has been reported to be associated with a number of positive outcomes including decreased mortality, improved medical status, marital status, and social functioning; reduced crime; and increased employment.[15–19] Therefore, longer treatment durations can provide better rates of abstinence and improved outcomes for those treated for more than 6 months.

In summary, this study shows that the clinical benefits and acceptable safety profile of BUP-XR demonstrated in the 6-month double-blind study were sustained over a 12-month open-label study, with lower incidence of TEAEs in the second 6 months of treatment. The current data support the use of BUP-XR as an effective long-term treatment for patients with moderate or severe OUD. (Appendix, Supplemental Digital Content, http://links.lww.com/JCP/A663).

AUTHOR DISCLOSURE INFORMATION

This work was funded by Indivior Inc. Editorial and graphics assistance was provided by Prescott Medical Communications Group (Chicago, IL), funded by Indivior Inc. A.C.A., B.R.H., S.S., P.J.F., Y.Z., C.H., S.M.L., and V.R.N. are employees of Indivior Inc. N.L.F was an employee of Indivior Inc. at the time the study was conducted. D.H. reports no conflicts. D.R. has received associated research compensation for late phase clinical trials from Indivior Inc. as well as 12 other pharmaceutical companies, listed in order of largest to smallest grant: Allergan, Indivior, Janssen, Shire, Sunovion, Novartis, Alkermes, Otsuka, Supernus, Palatin, Roche, Takeda, and Teva.

REFERENCES

1. Ling W, Nadipelli VR, Solem CT, et al. Patient-centered outcomes in participants of a buprenorphine monthly depot (BUP-XR) double-blind, placebo-controlled, multicenter, phase 3 study. *J Addict Med*. 2019;13:442–449.
2. Blanco C, Volkow ND. Management of opioid use disorder in the USA: present status and future directions. *Lancet*. 2019;393:1760–1772.
3. Haight BR, Learned SM, Laffont CM, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2019;393:778–790.
4. Laffont CM, Gomeni R, Heidbreder C, et al. Population pharmacokinetic modeling after repeated administrations of RBP-6000, a new, subcutaneously injectable, long-acting, sustained-release formulation of buprenorphine, for the treatment of opioid use disorder. *J Clin Pharmacol*. 2016;56:806–815.
5. Nasser AF, Greenwald MK, Vince B, et al. Sustained-release buprenorphine (RBP-6000) blocks the effects of opioid challenge with hydromorphone in subjects with opioid use disorder. *J Clin Psychopharmacol*. 2016;36:18–26.
6. Hillhouse M, Canamar CP, Doraimani G, et al. Participant characteristics and buprenorphine dose. *Am J Drug Alcohol Abuse*. 2011;37:453–459.
7. O'Farrell TJ, Fals-Stewart W, Murphy M. Concurrent validity of a brief self-report drug use frequency measure. *Addict Behav*. 2003;28:327–337.
8. McHugh RK, Fitzmaurice GM, Carroll KM, et al. Assessing craving and its relationship to subsequent prescription opioid use among treatment-seeking prescription opioid dependent patients. *Drug Alcohol Depend*. 2014;145:121–126.
9. Wesson DR, Ling W. The clinical opiate withdrawal scale (COWS). *J Psychoactive Drugs*. 2003;35:253–259.
10. Posner K, Brown GK, Stanley B, et al. The Columbia-suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168:1266–1277.
11. Vernon MK, Revicki DA, Awad AG, et al. Psychometric evaluation of the medication satisfaction questionnaire (MSQ) to assess satisfaction with antipsychotic medication among schizophrenia patients. *Schizophr Res*. 2010;118:271–278.
12. Pattinson KT. Opioids and the control of respiration. *Br J Anaesth*. 2008; 100:747–758.
13. Wiest K, Algera MH, Moss L, et al. High plasma buprenorphine concentrations decrease respiratory effects of intravenous fentanyl [poster]. In: Annual Meeting of the American Society of Addiction Medicine; April 4-7, 2019; Orlando, FL.
14. Saxon AJ, Ling W, Hillhouse M, et al. Buprenorphine/naloxone and methadone effects on laboratory indices of liver health: a randomized trial. *Drug Alcohol Depend*. 2013;128:71–76.
15. Barr HL, Antes D, Ottenberg DJ, et al. Mortality of treated alcoholics and drug addicts: the benefits of abstinence. *J Stud Alcohol*. 1984;45:440–452.
16. Rounsaville BJ, Kosten TR, Kleber HD. The antecedents and benefits of achieving abstinence in opioid addicts: a 2.5-year follow-up study. *Am J Drug Alcohol Abuse*. 1987;13:213–229.
17. Hser YI, Hoffman V, Grella CE, et al. A 33-year follow-up of narcotics addicts. *Arch Gen Psychiatry*. 2001;58:503–508.
18. Sheehan M, Oppenheimer E, Taylor C. Opiate users and the first years after treatment: outcome analysis of the proportion of follow up time spent in abstinence. *Addiction*. 1993;88:1679–1689.
19. Ling W, Nadipelli VR, Solem CT, et al. Effects of monthly buprenorphine extended-release injections on patient-centered outcomes: a long-term study. *J Subst Abuse Treat*. 2020;110:1–8.