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Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder
A Randomized Clinical Trial

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IMPORTANCE Buprenorphine treatment for opioid use disorder may be improved by sustained-release formulations.

OBJECTIVE To determine whether treatment involving novel weekly and monthly subcutaneous (SC) buprenorphine depot formulations is noninferior to a daily sublingual (SL) combination of buprenorphine hydrochloride and naloxone hydrochloride in the treatment of opioid use disorder.

DESIGN, SETTING, AND PARTICIPANTS This outpatient, double-blind, double-dummy randomized clinical trial was conducted at 35 sites in the United States from December 29, 2015, through October 19, 2016. Participants were treatment-seeking adults with moderate-to-severe opioid use disorder.

INTERVENTIONS Randomization to daily SL placebo and weekly (first 12 weeks; phase 1) and monthly (last 12 weeks; phase 2) SC buprenorphine (SC-BPN group) or to daily SL buprenorphine with naloxone (24 weeks) with matched weekly and monthly SC placebo injections (SL-BPN/NX group).

MAIN OUTCOMES AND MEASURES Primary end points tested for noninferiority were response rate (10% margin) and the mean proportion of opioid-negative urine samples for 24 weeks (11% margin). Responder status was defined as having no evidence of illicit opioid use for at least 8 of 10 prespecified points during weeks 9 to 24, with 2 of these at week 12 and during month 6 (weeks 21-24). The mean proportion of samples with no evidence of illicit opioid use (weeks 4-24) evaluated by a cumulative distribution function (CDF) was an a priori secondary outcome with planned superiority testing if the response rate demonstrated noninferiority.

RESULTS A total of 428 participants (263 men [61.4%] and 165 women [38.6%]; mean [SD] age, 38.4 [11.0] years) were randomized to the SL-BPN/NX group (n = 215) or the SC-BPN group (n = 213). The response rates were 31 of 215 (14.4%) for the SL-BPN/NX group and 37 of 213 (17.4%) for the SC-BPN group, a 3.0% difference (95% CI, −4.0% to 9.9%; $P < .001$). The proportion of opioid-negative urine samples was 1099 of 3870 (28.4%) for the SL-BPN/NX group and 1347 of 3834 (35.1%) for the SC-BPN group, a 6.7% difference (95% CI, −0.1% to 13.6%; $P < .001$). The CDF for the SC-BPN group (26.7%) was statistically superior to the CDF for the SL-BPN/NX group (0; $P = .004$). Injection site adverse events (none severe) occurred in 48 participants (22.3%) in the SL-BPN/NX group and 40 (18.8%) in the SC-BPN group.

CONCLUSIONS AND RELEVANCE Compared with SL buprenorphine, depot buprenorphine did not result in an inferior likelihood of being a responder or having urine test results negative for opioids and produced superior results on the CDF of no illicit opioid use. These data suggest that depot buprenorphine is efficacious and may have advantages.

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Opioid use disorder (OUD) and opioid-related overdose deaths are escalating global health problems[1,2] contributing to significant mental, physical, and social adverse consequences that include transmission of infectious diseases, unintentional overdose, criminal activity, and incarceration.[3-5] An estimated 2.6 million people in the United States have an OUD, and more than 33 000 opioid-involved overdose deaths occur anually.[2,6] In the European Union, an estimated 1.3 million people engage in high-risk opioid use.[7]

Opioid use disorder can be effectively treated with pharmacotherapies, including sublingual (SL) buprenorphine hydrochloride, a partial μ-opioid receptor agonist on the World Health Organization's essential medications list.[8,9] Despite its efficacy, currently approved daily SL and buccal buprenorphine formulations have limitations, including suboptimal medication adherence, diversion, intravenous misuse, and unintended pediatric exposures.[10-12] These limitations may diminish the effectiveness of SL buprenorphine and contribute to negative perceptions, stigma, and barriers to treatment.[10,13,14]

Weekly and monthly subcutaneous (SC) buprenorphine (CAM2038) in small-volume (<1 mL), extended-release formulations are based on a nanoscale drug delivery system (FluidCrystal technology[15]; Camurus AB) in late-stage clinical development for OUD treatment that may address some of these limitations. The CAM2038 formulation is well tolerated locally and systemically, provides dose-proportional long-acting release of buprenorphine during the weekly and monthly treatment intervals, and has bioavailability 6 to 8 times higher than that of SL buprenorphine.[16] For example, a single 24-mg weekly injection or 96-mg monthly injection of CAM2038 delivers a similar dose exposure as 16 mg/d of buprenorphine hydrochloride during these treatment intervals.[16] Steady delivery for extended periods without daily peaks and troughs may improve the efficacy of buprenorphine, because buprenorphine implants produced higher cumulative rates of no illicit opioid use for 6 months compared with daily buprenorphine combined with naloxone hydrochloride.[17]

A recent double-blind randomized inpatient clinical trial among non-treatment-seeking adults with moderate-to-severe OUD demonstrated that a single dose of CAM2038 24 or 32 mg/wk (SL equivalent, approximately 16 or 24 mg/d) rapidly suppressed opioid withdrawal and craving within 24 hours, demonstrating its safety and efficacy for use in induction, and also blocked the drug liking of 18 mg of parenteral hydromorphone hydrochloride.[18] This study evaluated the efficacy of SC buprenorphine vs SL buprenorphine-naloxone for treatment of illicit opioid use in patients seeking OUD treatment.

Key Points

Question Are weekly and monthly subcutaneous buprenorphine depot formulations noninferior to a daily sublingual combination of buprenorphine and naloxone when comparing the proportion of urine samples negative for illicit opioids for 24 weeks and the response rate among treatment-seeking adults with moderate-to-severe opioid use disorder?

Findings In this randomized clinical trial of 428 participants, the proportion of opioid-negative urine samples was 1347 of 3834 (35.1%) and response rate was 37 of 213 participants (17.4%) for the subcutaneous depot buprenorphine group compared with 1099 of 3870 (28.4%) and 31 of 215 participants (14.4%), respectively, for the sublingual buprenorphine-naloxone group. Both primary outcomes demonstrated noninferiority.

Meaning Long-acting buprenorphine depot formulations appear to be efficacious for treatment of opioid use disorder.

Methods

Study Design

This 24-week, double-blind, double-dummy, active-controlled, multisite, phase 3 randomized clinical trial evaluated the efficacy and safety of weekly and monthly SC buprenorphine compared with daily SL buprenorphine-naloxone. The trial protocol is given in Supplement 1. Participants enrolled at 35 outpatient clinical sites in the United States (24 office-based clinics [1 primary care, 3 academic] and 11 research clinics [1 academic]) (listed in eTable in Supplement 2) from December 29, 2015, through October 19, 2016. Protocol approval was obtained from the central and local institutional review boards of the participating sites. Written informed consent was obtained, and attendance stipends were provided (mean stipend per visit, $50; range, $0-$75).

Participants

Eligible participants were aged 18 to 65 years, diagnosed with and seeking treatment for moderate-to-severe OUD,[19] considered to be good candidates for buprenorphine treatment based on medical and psychosocial history, and willing to use reliable contraception. Exclusion criteria consisted of receiving pharmacotherapy for OUD within 60 days or any investigational drug within 4 weeks; AIDS; chronic pain requiring opioid therapy; pregnancy, lactation, or planned pregnancy; hypersensitivity or allergy to buprenorphine, other opioids, or excipients in CAM2038; use of strong cytochrome P450 3A4 inhibitors (azole antifungals, macrolide antibiotics, or protease inhibitors); recent or current suicidal ideation or behavior; risk for torsades de pointes (heart failure, hypokalemia, or family history of long QT syndrome); electrocardiogram with Fridericia formula QTc of greater than 450 milliseconds in men and greater than 470 milliseconds in women; aspartate aminotransferase or alanine aminotransferase levels 3-fold higher than the upper limits of the reference range; total bilirubin or creatinine level 1.5-fold higher than the upper limits of the reference range; or pending legal action or other factors or conditions that could adversely affect participant safety and adequate adherence.

Intervention Groups and Medication Dosing

Eligible participants presented on randomization day (week 0-day 1; start of phase 1) in opioid withdrawal and received an open-label SL dose of 4 mg of buprenorphine hydrochloride with 1 mg of naloxone hydrochloride. If buprenorphine-naloxone was tolerated, participants were randomized using a centralized computer system 1:1 to receive SC buprenorphine injections plus daily SL placebo tablets or SC placebo injections plus SL buprenorphine-naloxone tablets (ie, double-dummy design).

Unblinded staff not participating in study evaluations dispensed and administered SC injections to avoid the risk of unblinding owing to small variations in the appearance of active and placebo injections. Placebo and SL buprenorphine were matched in appearance.

The first week's target dosages were 16 mg of SL buprenorphine hydrochloride–naloxone hydrochloride (achieved day 2) and 24 mg weekly of SC buprenorphine (achieved day 4). After randomization on day 1, participants randomized to SL buprenorphine-naloxone (SL-BPN/NX group) received 4 mg of SL buprenorphine hydrochloride and naloxone hydrochloride, and those randomized to SC buprenorphine (SC-BPN group) received 16 mg of SC buprenorphine in a weekly injection (estimated equivalent of 8 mg/d SL buprenorphine hydrochloride[16]). On day 2, the SL-BPN/NX group was titrated to a dosage of 16 mg/d; the SC-BPN group received matched SL placebo. Take-home SL medication was provided for day 3. On day 4, the SC-BPN group received an 8-mg SC buprenorphine weekly injection (estimated equivalent, 4-6 mg/d SL buprenorphine); the SL-BPN/NX group received an SC placebo injection.

Dosages thereafter were flexible, based on patient needs and using clinical judgment, as would occur in clinical practice. On days 5 to 7, double-dummy titration to 24 mg/d of SL buprenorphine hydrochloride–naloxone hydrochloride or 32 mg/wk of SC buprenorphine was permitted. During weeks 1 to 11 (phase 1), visits were weekly, with weekly SC buprenorphine and placebo injections (SC buprenorphine of 16, 24, or 32 mg, approximating SL buprenorphine hydrochloride of 8, 16, and 24 mg/d, respectively) and a 1-week supply of SL buprenorphine-naloxone placebo. During weeks 12 to 24 (phase 2), visits were once monthly, with monthly SC buprenorphine or placebo injections (SC buprenorphine of 64, 96, 128, or 160 mg, approximating SL buprenorphine hydrochloride of 8, 16, 24, and 32 mg/d, respectively) and a 4-week supply of SL buprenorphine-naloxone or SL placebo. Blinded dose adjustments (up or down) were made at scheduled visits as needed. A window of 2 days for weekly visits and 7 days for monthly visits was allowed. Reinductions were prohibited. If the visit window was missed, the site physician or principal investigator and study medical monitor determined whether treatment could continue safely without reinduction. Medication therapy was discontinued at week 24, with standard clinical care offered until follow-up at week 28.

During phase 2, 1 supplemental dose per month using 8 mg/wk of open-label SC buprenorphine was available as needed for both groups, per the investigator's clinical judgment. All participants received on-site, manual-guided individual addiction counseling at each weekly and monthly visit.[20] Counseling aimed to address OUD symptoms and functioning along with the patient's recovery. Additional visits for counseling and other medical concerns were accommodated and documented.

Study End Points

The primary end points, defined a priori (before database lock) using data from the European Medicines Agency (EMA) and US Food and Drug Administration (FDA), were the mean percentage of urine samples with test results negative for illicit opioids for weeks 1 to 24 (EMA) and the responder rate (FDA). The responder definition was developed in collaboration with the FDA and required no illicit drug use at prespecified times while participants received the weekly (phase 1) and monthly (phase 2) injections. Specifically, a responder was defined as having no evidence of illicit opioid use (ie, urine test result and self-report of drug use both negative for illicit opioids) in phase 1 at week 12 and for at least 2 of 3 assessments at weeks 9 to 11 and in phase 2 for at least 5 of 6 assessments from weeks 12 to 24, including month 6 (ie, weeks 21-24).

Secondary end points included the mean percentage of opioid-negative samples examined by a cumulative distribution function (CDF) for weeks 4 to 24 and study retention. Cumulative distribution function values are an established end point used in earlier placebo-controlled, phase 3 clinical trials for OUD treatment.[21,22] Exploratory outcomes included opioid-negative urine samples by time and phase, desire- and need-to-use opioid visual analog scales (VAS), Clinical and Subjective Opiate Withdrawal Scales,[23] and frequency of supplemental 8-mg SC buprenorphine use and additional psychosocial counseling. All urine test results negative for opioids were affirmed with self-reports of no illicit opioid use except for the EMA primary outcome analysis and other analyses as indicated.

Assessment

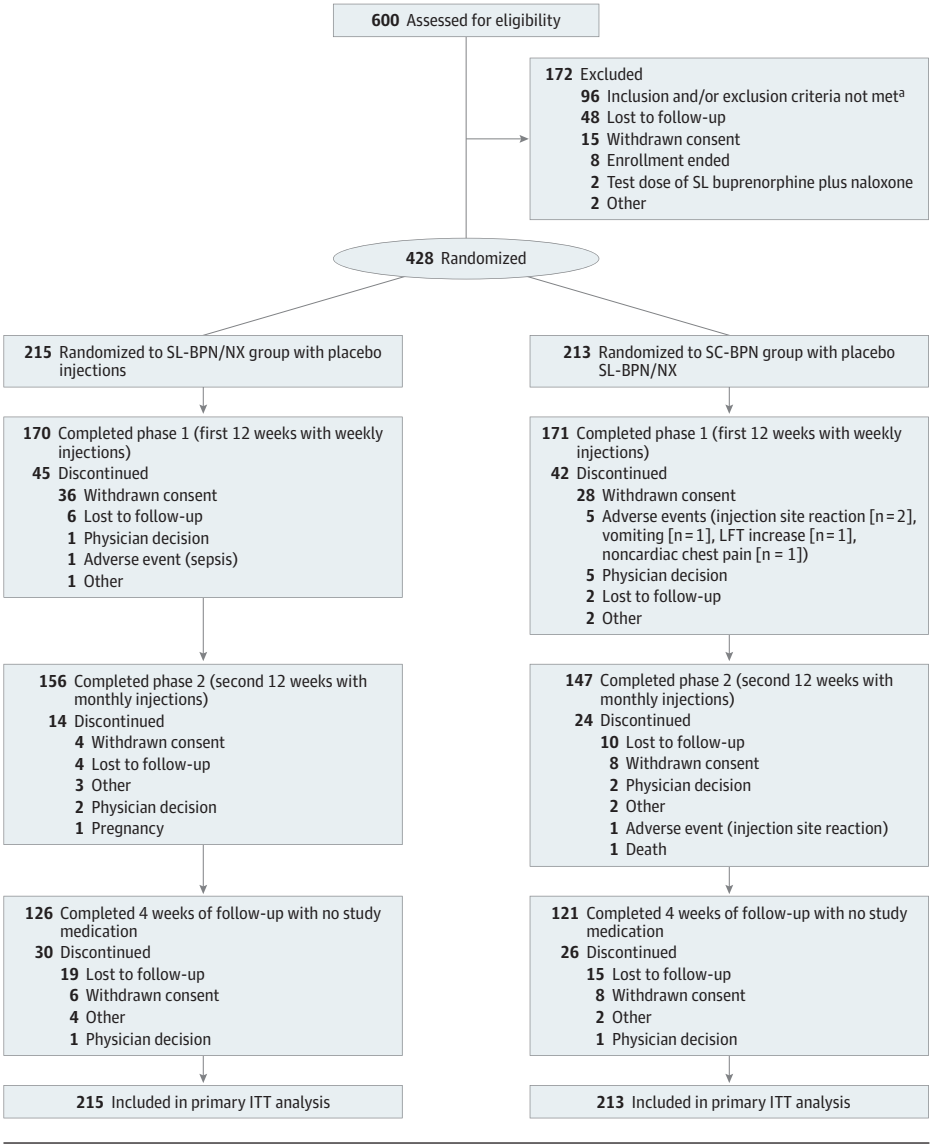
After initial dose titration, study visits were scheduled weekly during weeks 1 to 12 and monthly at weeks 16, 20, and 24. Urine samples collected with temperature verification at each scheduled visit and at 3 additional randomly scheduled visits in phase 2 were analyzed quantitatively by a central laboratory with gas chromatography–mass spectrometry with a lower limit of quantification of approximately 5 ng/mL for dihydrocodeine bitartrate, codeine, morphine sulfate, hydrocodone, and oxycodone hydrochloride and 1 ng/mL for oxymorphone hydrochloride, and by liquid chromatography–tandem mass spectrometry with a lower limit of quantification of 0.1 ng/mL for fentanyl, 0.2 ng/mL for norfentanyl, and approximately 20 ng/mL for methadone and its metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.

Scheduled visit assessments included urine drug and pregnancy testing, self-report of drug use by Timeline Followback interview,[24] Clinical Opiate Withdrawal Scale (range, 0 [no withdrawal] to 48 [severe withdrawal]), Subjective Opiate Withdrawal Scale (range, 0 [no withdrawal] to 64 [severe withdrawal]), VAS craving items (range, 0 [no need or desire to use] to 100 [maximum need or desire to use since the last visit]), vital signs, Columbia Suicide Severity Rating Scale,[25] 12-lead electrocardiogram, assessment of adverse events, and injection-site examination with pain scale (range, 0 [no pain] to 10 [worst possible pain]).

Statistical Analysis

Analyses included all randomized participants (intention to treat) and followed the FDA statistical analysis plan. The EMA primary end point aimed to establish noninferiority with an 11% margin by an analysis of variance model with a treatment effect consistent with that of other buprenorphine trials.[21] The FDA primary end point of responder rate aimed to establish noninferiority with a 10% margin by χ^2 test for proportions of responders. For secondary outcomes, a closed testing procedure[26] controlled for overall type I error rate (5%, 2 sided) with a prespecified order for superiority testing of SC buprenorphine (only if primary outcomes achieved noninferiority) on the CDF of the mean

Figure 1. Enrollment and Study Retention Through Follow-up



The SL-BPN/NX group received a sublingual (SL) combination of buprenorphine and naloxone plus subcutaneous (SC) placebo injections; the SC-BPN group, SC buprenorphine injections plus SL placebo. ITT indicates intention to treat; LFT, liver function test.

[a] The 3 most common reasons for not meeting inclusion and/or exclusion criteria were abnormal laboratory values (n = 24), factors or medical conditions that could adversely affect participant safety and adequate adherence (n = 21), and not being a good candidate for buprenorphine treatment per the site investigator (n = 9).

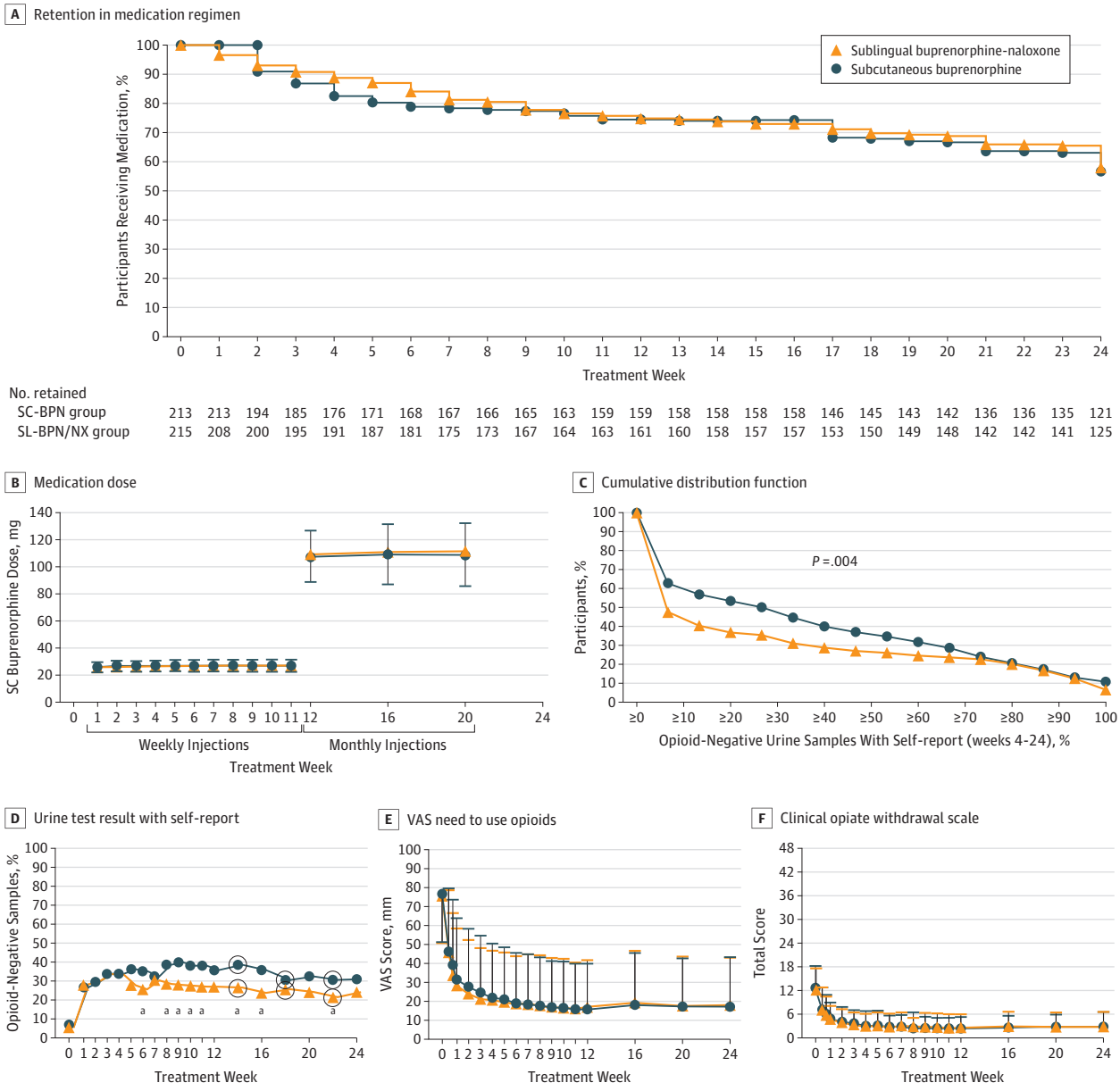
percentage of opioid-negative urine samples from weeks 4 to 24 (Wilcoxon rank sum test) and FDA responder rate. Study retention was analyzed with a χ^2 test for noninferiority with a 15% margin. Post hoc sensitivity analyses were conducted on urine test results from weeks 1 to 24. Other exploratory analyses included evaluating treatment effect on opioid-negative urine samples by time (χ^2 test) and overall treatment difference by the Wei and Lachin test, opioid-negative urine samples by phase (χ^2 test), and withdrawal and craving measures (controlling for baseline values) using the analysis of covariance model. A total of 1988 of 7704 urine samples (25.8%) were missing and imputed as positive for illicit opioids because return to illicit opioid use is common when patients leave treatment.[27-30] In specified sensitivity analyses, missing values were deleted and not imputed. Treatment exposure was calculated based on SC buprenorphine doses administered and SL buprenorphine-naloxone doses dispensed at scheduled visits from weeks 1 to 21, assuming that all SL doses dispensed were taken as prescribed. Supplemental SC buprenorphine use, counseling sessions, and safety evaluations (eg, adverse events) were tabulated. Analyses, conducted with SAS software (version 9.2; SAS Institute, Inc), were 2-sided with significance levels of $P < .05$.

Results

Participants

Of the 428 participants randomized (263 men [61.4%] and 165 women [38.6%]; mean [SD] age, 38.4 [11.0] years), all received at least 1 medication dose, and 147 of 213 (69.0%) randomized to the SC-BPN group and 156 of 215 (72.6%) randomized to the SL-BPN/NX group completed the 24-week treatment period (**Figure 1**). Of these completers, 4 in the SL-BPN/NX group and 7 in the SC-BPN group stopped study

Figure 2. Study Outcomes



Treatment week 0 indicates randomization day. Triangles indicate sublingual (SL) buprenorphine hydrochloride-naloxone, and circles are subcutaneous (SC) buprenorphine. A, Participants receiving study medication over time. B, Mean (SD) SL buprenorphine-naloxone doses were converted to SC buprenorphine dose equivalents based on the following conversions: SL buprenorphine hydrochloride daily doses of 8, 16, and 24 mg were converted to weekly SC buprenorphine hydrochloride doses of 16, 24, and 32 mg, respectively, and monthly SC buprenorphine hydrochloride doses of 64, 96, and 128 mg, respectively. Sublingual buprenorphine hydrochloride at a dosage of 32 mg/d was converted to SC buprenorphine hydrochloride, 160 mg/mo. C, Cumulative distribution function of percentage of opioid-negative urine samples affirmed with no illicit opioid use by self-report from weeks 4 to 24. D, For the mean percentage of opioid-negative samples affirmed with self-report of no illicit opioid use by time point, missing values were imputed as positive. Circled values indicate random urine tests. E, Mean (SD) visual analog scale (VAS) score of worst or strongest need to use opioids since the last visit (0 indicates no need to use; 100, maximum need to use) over time, with the first 2 values plotted after day 0 representing days 2 and 4 of week 0 (analysis of covariance [ANCOVA] shows no significant treatment effect). F, Mean (SD) Clinical Opiate Withdrawal Scale total score over time, with the first 2 values plotted after week 0 representing days 2 and 4. Scores of 5 to 12 indicate mild withdrawal (ANCOVA shows no significant treatment effect).

[a] $P \leq .05$ per time point (using analysis of variance) between groups; overall $P = .02$ (Wei Lachin test).

treatment but continued study participation, minimizing missing data. Retention with medication (**Figure 2**A) and participant characteristics were similar between groups (**Table 1**). Although morphine (the primary metabolite of heroin) was the most common opioid in baseline urine samples, a significant portion of study participants tested

positive for fentanyl (49 [22.8%] in the SL-BPN/NX group and 62 [29.1%] in the SC-BPN group).

Treatment Outcomes

Both primary outcomes met prespecified criteria for noninferiority (**Figure 3**). Subsequent analysis of secondary outcomes demonstrated superiority of SC buprenorphine vs SL buprenorphine-naloxone on the CDF of the proportion of opioid-negative urine samples during weeks 4 to 24 (Figure 3). The next outcome tested, superiority of response rate, was not significant. Sensitivity analyses of the primary EMA end point and CDF were consistent with the main findings (Figure 3). In addition, the CDF for weeks 1 to 24 demonstrated significantly less illicit opioid use in the SC-BPN group.

Evaluation of the percentage of opioid-negative urine samples by phase demonstrated that SC buprenorphine was noninferior in phase 1 and superior in phase 2 to SL buprenorphine-naloxone (Figure 3). The percentage of negative illicit opioid urine samples over time (Figure 2D) showed a separation between groups after the first 4 treatment weeks, whereby the SC-BPN group frequently had a significantly higher percentage of opioid-negative results. Exploratory analysis of the CDF from weeks 4 to 24 demonstrated that, among participants reporting intravenous drug use at baseline, those in the SC-BPN group achieved a higher percentage of urine samples negative for illicit opioids (mean [SD], 34.2% [2.4%]) (Figure 3) compared with the SL-BPN/NX group (mean [SD], 27.4% [2.5%]). Opioid craving (need-to-use VAS item) and withdrawal (eg, Clinical Opiate Withdrawal Scale) were suppressed immediately in both groups from day 1 throughout the study (Figure 2E and F), without significant group differences.

Mean (SD) doses of SL buprenorphine hydrochloride in phases 1 and 2 were 18.5 (4.2) and 19.6 (4.9) mg/d, respectively; for SC buprenorphine, 26.6 (4.4) mg/week (approximately 18.6 [4.4] mg/d of SL buprenorphine) and 108.4 (21.1) mg/mo (approximately 19.1 [5.3] mg/d SL buprenorphine), respectively (Figure 2B). In phase 2, supplemental weekly 8-mg SC injections of buprenorphine were administered to 17 of 215 participants (7.9%) in the SL-BPN/NX group (28 total doses) and 14 of 213 (6.6%) in the SC-BPN group (23 total doses). Both groups had similar mean (SD) durations of medication exposure (SL-BPN/NX group, 131.7 [61.0] days; SC-BPN group, 128.4 [63.2] days).

Counseling attendance was high at scheduled visits (SL-BPN/NX group mean attendance, 94.1% [range, 84%-98%]; SC-BPN group mean attendance, 96.1% [range, 87%-100%]). Additional counseling visit frequency was similar (14 in the SL-BPN group; 15 in the SC-BPN/NX group; 1-3 visits/participant) between groups.

Table 1. Patient Demographics and Baseline Clinical Characteristics

Characteristic	Study Group[a] SL-BPN/NX (n = 215)	SC-BPN (n = 213)
Age, mean (SD), y	38.0 (10.9)	38.7 (11.2)
Male, No. (%)	142 (66.0)	121 (56.8)
White, No. (%)	164 (76.3)	159 (74.6)
BMI, mean (SD)	26.0 (5.6)	26.0 (5.0)
Employed full or part time, No. (%)	72 (33.5)	76 (35.7)
Education level, No. (%)		
Did not complete high school	37 (17.2)	36 (16.9)
High school diploma or GED	79 (36.7)	82 (38.5)
Some college or certificate	69 (32.1)	77 (36.2)
College, university, or graduate degree	29 (13.5)	18 (8.4)
History of any arrest, No. (%)	144 (67.0)	130 (61.0)
Duration since OUD diagnosis, mean (SD), y	4.7 (6.0)	4.3 (7.8)
History of injection opioid use at screening, No. (%)	110 (51.2)	114 (53.5)
Primary opioid of use, No. (%)		
Heroin	151 (70.2)	152 (71.4)
Prescription opioids	64 (29.8)	61 (28.6)
Nonopioid drug use at screening, No. (%)[b]	149 (69.3)	155 (72.8)
Amphetamine	32 (14.9)	38 (18.0)
Benzodiazepine	35 (16.3)	30 (14.2)
Cocaine	53 (24.7)	53 (25.1)
Marijuana	64 (29.8)	57 (27.0)
Hepatitis C antibody positive at screening, No. (%)	81 (37.7)	81 (38.0)
Medical history of depression, No. (%)	28 (13.0)	25 (11.7)
Baseline craving and withdrawal scores, mean (SD)		
Opioid craving: need-to-use VAS[c]	76 (24.9)	77 (25.4)
Opioid craving: desire-to-use VAS[d]	77 (25.4)	77 (26.2)
COWS score[e]	12 (6.0)	12 (5.4)
SOWS score[f]	31 (16.1)	32 (15.4)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COWS, Clinical Opiate Withdrawal Scale; GED, General Education Development; OUD, opioid use disorder; SC-BPN, subcutaneous buprenorphine; SL-BPN/NX, sublingual buprenorphine-naloxone; SOWS, Subjective Opiate Withdrawal Scale; VAS, visual analog scale.

[a] No significant differences between groups.

[b] For this study measure, 211 patients in the SC-BPN group were included.

[c] Scores range from 0 (no need to use) to 100 (maximum need to use since the last visit).

[d] Scores range from 0 (no desire to use) to 100 (maximum desire to use since the last visit).

[e] Scores range from 0 (no withdrawal) to 48 (severe withdrawal).

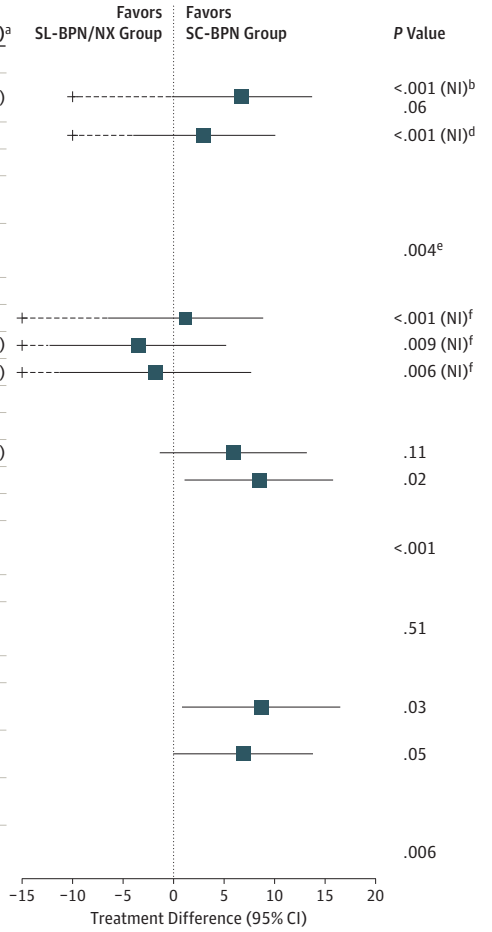
[f] Scores range from 0 (no withdrawal) to 64 (severe withdrawal).

Safety Outcomes

The most common adverse events (regardless of study medication) were injection-site pain, headache, constipation, nausea, and injection-site pruritus and erythema (**Table 2**). All injection-site adverse events were mild (65 of 88 [73.9%]) or moderate (23 of 88 [26.1%]) in intensity. Eighteen participants (4.2%) experienced at least 1 nonfatal serious adverse event; only 1 such event was related to study drug (vomiting of moderate intensity in the SC-BPN group). One participant in the SC-BPN group was hit by a car and died; the death was assessed as unlikely related to the study drug. Fifteen participants (12 in the SL-BPN/NX group and 3 in the SC-BPN group) were hospitalized. Six hospitalizations were for infections that may have been related to injection drug use (eg, osteomyelitis, cellulitis, and sepsis); all but 1 of these occurred in the SL-BPN/NX group (the 1 hospitalization in the SL-BPN/NX group occurred after consent but before randomization). Five nonfatal drug overdoses were reported (4 accidental [3 involving heroin and 1 involving

Figure 3. Clinical Outcomes from Noninferiority and Superiority Analyses

Outcome	SL BPN/NX Group (n = 215)	SC-BPN Group (n = 213)	Treatment Difference (95% CI)[a]	P Value
Primary outcomes				
Opioid-negative urine samples (wk 1-24)	28.4 (2.5)	35.1 (2.5)	6.7 (−0.1 to 13.6)	<.001 (NI)[b] .06
No. (%) of responders[c]	31.0 (14.4)	37.0 (17.4)	3.0 (−4.0 to 9.9)	<.001 (NI)[d]
Secondary outcomes				
Weeks 4-24 opioid-negative urine samples with self-report, CDF, %[c]				
Median	0	27.6	NA	.004[e]
Mean (SE)	26.7 (2.5)	35.1 (2.5)		
Study retention, No. (%)				
Week 12 (phase 1)	170 (79.1)	171 (80.3)	1.2 (−6.4 to 8.8)	<.001 (NI)[f]
Week 24 (phase 2)	156 (72.6)	147 (69.0)	−3.5 (−12.2 to 5.1)	.009 (NI)[f]
Week 28 (follow-up)	126 (58.6)	121 (56.8)	−1.8 (−11.2 to 7.6)	.006 (NI)[f]
Other outcomes				
Opioid-negative urine samples, %				
Weeks 1-12 (phase 1), mean (SE)	29.9 (2.6)	35.8 (2.6)	5.9 (−1.3 to 13.1)	.11
Weeks 13-24 (phase 2), mean (SE)	25.4 (2.6)	33.9 (2.6)	8.5 (1.2 to 15.7)	.02
Weeks 4-24, IV use, CDF[c,g]				
Median	0	16.7	NA	<.001
Mean (SE)	15.4 (2.7)	30.9 (3.3)		
Weeks 4-24, no IV use, CDF[c,g]				
Median	13.3	33.3	NA	.51
Mean (SE)	38.5 (4.05)	39.9 (3.88)		
Sensitivity analyses				
Weeks 1-24 opioid-negative urine samples (missing not imputed), %	35.9 (2.77)	44.6 (2.8)	8.7 (0.9 to 16.4)	.03
Weeks 1-24 opioid-negative urine samples with self-report, %[c]	27.4 (2.45)	34.2 (2.46)	6.9 (0.0 to 13.7)	.05
Weeks 1-24 opioid-negative urine samples with self-report, CDF, %[c]				
Median	5.6	22.2	NA	.006
Mean (SE)	27.4 (2.47)	34.2 (2.43)		



Missing urine samples are counted as positive, and *P* values are 2 sided for superiority, unless otherwise specified. Dashed gray lines indicate prespecified noninferiority (NI) margins. CDF indicates cumulative distribution function; SC-BPN, group randomized to subcutaneous buprenorphine; and SL-BPN/NX, group randomized to sublingual combined buprenorphine and naloxone.

[a] Treatment difference between SC-BPN and SL-BPN/NX groups for location variables and risk difference for proportions.

[b] Margin of 11% using analysis of variance model.

[c] Negative illicit opioid urine test results affirmed by self-report of no illicit opioid use.

[d] Margin of 10% using the χ^2 test for responders defined as participants with opioid-negative urine samples in phase 1 (at week 12 and for at least 2 of 3 weeks from weeks 9 to 11) and in phase 2 (at least 5 of 6 assessments from weeks 12-24, including month 6).

[e] Calculated using the Wilcoxon rank sum test.

[f] Margin of 15% for study retention (χ^2 test).

[g] Intravenous (IV) drug use identified at baseline among 114 participants in the SC-BPN group and 110 in the SL-BPN/NX group.

clonazepam] and 1 intentional[involving doxepin hydrochloride, prazosin hydrochloride, and venlafaxine]); all occurred in the SL-BPN/NX group. Of note, 1 heroin overdose occurred after a participant was jailed for several days without access to their SL buprenorphine-naloxone and, on release, used heroin to self-treat withdrawal symptoms and overdosed.

Twenty-one participants had at least 1 adverse event rated as severe; only 2 of these were potentially related to the study drug. Both occurred in the SL-BPN/NX group. One of these participants experienced decreased libido, and the other experienced increased alanine aminotransferase and γ-glutamyltransferase levels. Ten participants discontinued the study treatment regimen owing to an adverse event; 4 of these were attributed to an injection-site reaction (1 in the SL-BPN/NX group and 3 in the SC-BPN group), and the remaining 6 were attributable to noncardiac chest pain (1 in the SC-BPN group), sedation (1 in the SC-BPN group), nausea with vomiting (1 in the SC-BPN group), nausea and self-induced vomiting with subsequent esophageal rupture (1 in the SC-BPN group), sepsis (1 in the SL-BPN/NX group), and drug withdrawal after being jailed without access to study medication (1 in the SL-BPN/NX group). One participant in the SL-BPN/NX group with an injection-site reaction discontinued the study treatment but completed the study.

Discussion

This study is, to our knowledge, the first double-blind, double-dummy, randomized clinical trial that compared a weekly and monthly SC buprenorphine depot formulation with daily SL

Table 2. Summary of Treatment-Emergent Adverse Events

Adverse Event Characteristic	Study Group, No. (%) of Participants		
	SL-BPN/NX (n = 215)	SC-BPN (n = 213)	All (N = 428)
≥1 Any	119 (55.3)	128 (60.1)	247 (57.7)
≥1 Drug-related	64 (29.8)	70 (32.9)	134 (31.3)
≥1 Severe	15 (7.0)	6 (2.8)	21 (4.9)
Nonfatal serious	13 (6.0)	5 (2.3)	18 (4.2)
Deaths[a]	0	1 (0.5)	1 (0.2)
Hospitalizations	12 (5.6)	3 (1.4)	15 (3.5)
Drug overdoses[b]	5 (2.3)	0	5 (1.2)
Led to discontinuation of treatment	3 (1.4)	7 (3.3)	10 (2.3)
Occurred in ≥5% of participants	56 (26.0)	46 (21.6)	102 (23.8)
Injection-site pain	17 (7.9)	19 (8.9)	36 (8.4)
Headache	17 (7.9)	16 (7.5)	33 (7.7)
Constipation	16 (7.4)	16 (7.5)	32 (7.5)
Nausea	17 (7.9)	15 (7.0)	32 (7.5)
Injection-site pruritus	13 (6.0)	13 (6.1)	26 (6.1)
Injection-site erythema	12 (5.6)	12 (5.6)	24 (5.6)
Urinary tract infection	10 (4.7)	11 (5.2)	21 (4.9)
Insomnia	6 (2.8)	12 (5.6)	18 (4.2)

Abbreviations: SC-BPN, subcutaneous buprenorphine; SL-BPN/NX, sublingual buprenorphine-naloxone.

[a] Owing to a traffic accident assessed as unlikely to be related to the study drug.

[b] Includes 4 accidental drug overdoses (3 involving heroin and 1 involving clonazepam) and 1 intentional overdose (involving doxepin, prazosin, and venlafaxine).

buprenorphine-naloxone, an FDA-approved treatment for OUD, using a flexible treatment regimen, as is recommended in current practice guidelines.[31] Subcutaneous buprenorphine was noninferior to daily SL buprenorphine-naloxone on EMA and FDA primary outcomes, was superior to SL buprenorphine-naloxone on the CDF for illicit opioid use, and showed similar study retention.

Weekly SC buprenorphine depot provided rapid suppression of opioid withdrawal and craving within the first treatment week and throughout the study, comparable to that of SL buprenorphine-naloxone. Despite the availability of supplemental 8-mg injections to both groups during phase 2, few patients received these, suggesting that physicians were able to individualize and titrate each participant's weekly and monthly injection dose as they did with those receiving daily SL buprenorphine-naloxone. For SL buprenorphine hydrochloride-naloxone hydrochloride (the active control), the mean treatment dosage was 18 to 20 mg/d across both phases, known efficacious dosages for the treatment of OUD.[32,33]

The finding of superiority of SC buprenorphine depot to SL buprenorphine-naloxone on the CDF of urine samples negative for illicit opioids (Figure 2C) is not entirely surprising, because adherence is achieved for a week or month on the basis of a single dose administered by a clinician rather than a daily dosing adherence decision by a patient. These CDF results are likely to have been driven by significantly higher rates of urine samples negative for illicit opioids seen after the initial month in treatment (Figure 2D) and throughout phase 2 among those receiving the monthly SC buprenorphine injection (433 of 1278 negative [33.9%]) vs SL buprenorphine-naloxone (328 of 1290 negative [25.4%]) (Figure 3). Similar benefits of long-acting buprenorphine were demonstrated in a study of the 6-month buprenorphine implant,[17] which improved 6-month rates of opioid abstinence compared with daily SL buprenorphine-naloxone (85.7% vs 71.9%) among stable patients with OUD.

The safety profile of SC buprenorphine was generally comparable to that of SL buprenorphine-naloxone with the exception of some mild-to-moderate injection-site reactions, most commonly transient pain. Of note, 5 participants reported nonfatal overdoses, all of whom were in the SL-BPN/NX group; 1 overdose occurred in the context of withdrawal after being jailed without study medication.

Despite the inherent benefits of sustained-release buprenorphine treatment for OUD, future research will be needed to support widespread implementation of depot buprenorphine formulations across varied settings and populations, for example, those in hospitals and emergency departments with complications of OUD (eg, endocarditis and overdose) for whom initiating treatment with SC buprenorphine may facilitate continuation of treatment in an outpatient, in-office setting after discharge.[34-36] Persons at risk for unwanted disruptions in treatment and/or loss of opioid tolerance (eg, during incarceration or residential treatment programs not allowing maintenance medication), who have difficulty adhering to or dislike taking daily medication, who are unable to safely store their medication, who are concerned about theft and confidentiality (eg, while traveling or at the pharmacy), or who are at risk to divert, abuse, or inject their medication may also be favorable candidates for sustained-release buprenorphine formulations. Finally, depot buprenorphine may also reduce some of the burdens and stigma to patients imposed by current daily medications, which in some treatment settings require supervised administration.[37]

Strengths and Limitations

Strengths of the study included the double-blind, double-dummy design; large sample size; geographically diverse study sites; enrollment of a sample characteristic of the population of persons with OUD (ie, intravenous use and fentanyl frequently detected); use of highly sensitive opioid urine testing; an active control group receiving known therapeutic doses; and flexible individualized treatment regimens. Strong placebo responses are uncommon in

patients with OUD, and overdose deaths have occurred with placebo even when accompanied by intensive psychosocial treatments.[38] Limitations include lack of assessment of SL medication adherence, and only 1 site was primary care based. The study evaluated efficacy, not effectiveness, so it cannot assess whether treatment retention and outcomes could be improved without the double-blind and double-dummy treatment administration as occurs in standard clinical practice.

Conclusions

These results support the efficacy of long-acting weekly and monthly subcutaneous depot buprenorphine formulations as an additional OUD treatment option. These formulations may also address potential limitations and concerns about daily dosing, including diversion, misuse, and accidental exposure of medication to children.

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