Converting patients from sublingual to injectable weekly and monthly buprenorphine

Michael P. Frost, MD[1]; Genie L. Bailey, MD[2]; Natalie R. Budilovsky-Kelley, PharmD[3]; Sonnie Kim, PharmD[3]; Fredrik Tiberg, MSc PhD[4]

[1]The Frost Medical Group, LLC, Conshohocken, PA, USA; [2]Warren Alpert Medical School of Brown University, Providence, RI, USA; Stanley Street Treatment and Resources, Inc., Fall River, MA, USA; [3]Braeburn, Plymouth Meeting, PA, USA; [4]Camurus AB, Lund, Sweden

BACKGROUND

- An estimated 2.1 million people in the US suffered from opioid use disorder (OUD) in 2016[1]
- OUD is an escalating public health crisis; provisional estimates of fatal overdoses involving opioids in 2017 were in excess of 49,000[2]
- The safety and efficacy of transmucosal buprenorphine (SL BPN) is well established for OUD treatment; however, daily dosing is a barrier to adherence and may limit the potential efficacy of buprenorphine[3]
- Extended-release buprenorphine has the potential to improve adherence by removing the need for daily treatment reminders, assuring healthcare providers that the dose given is the dose taken, and reducing the risk of pediatric exposure and misuse[4]
- CAM2038, a once-weekly or once-monthly extended-release, prefilled, small volume injection depot, is a ready-to-use, extended-release formulation of buprenorphine that can support the individualized treatment of OUD

METHODS

- Subgroup efficacy analysis of a phase 3, open-label, 12-month (48-week), flexible dosing, safety, and tolerability study (NCT02672111)
- This subgroup included participants who were currently receiving SL BPN treatment for OUD and willing to convert to CAM2038
- Inclusion criteria: moderate to severe OUD; age 18–65 years; current treatment with SL BPN or not on buprenorphine treatment for the last 60 days and seeking treatment
- Exclusion criteria: moderate to severe substance use disorder defined by DSM-5 for any substance other than opioids, caffeine, or nicotine; chronic pain requiring opioid treatment; acquired immune deficiency syndrome; and recent or current suicidal ideation or behavior based on the Columbia Suicide Severity Rating Scale
- Participants in this subgroup efficacy analysis were converted from their daily SL BPN treatment at baseline to treatment with CAM2038 weekly or monthly at corresponding doses (**Table 1**)
  - Individualized dose adjustments and changes in visit frequency were permitted as clinically indicated

Table 1: Doses of CAM2038 weekly and monthly for participants converted from sublingual buprenorphine or sublingual buprenorphine/naloxone

SL BPN or SL BPN/NX	CAM2038 weekly	CAM2038 monthly
≤6 mg	8 mg (0.16 mL)	-
8–10 mg	16 mg (0.32 mL)	64 mg (0.18 mL)
12–16 mg	24 mg (0.48 mL)	96 mg (0.27 mL)
18–24 mg	32 mg (0.64 mL)	128 mg (0.36 mL)
26–32 mg	-	160 mg (0.45 mL)

NX, naloxone; SL BPN, transmucosal buprenorphine.

- Secondary efficacy analyses included urine toxicology, self-reported illicit drug use, and measures of withdrawal and craving
  - Urine samples were quantitatively analyzed for opioids—including fentanyl—using liquid chromatography-tandem mass spectrometry
  - Other drugs of abuse were analyzed by immunoassay
  - Self-report of illicit opioid use and other drugs of abuse was recorded using a Timeline Followback Interview
  - Self-reported opioid craving was measured with unipolar “desire-to-use” and “need-to-use” 100-mm visual analogue scales (VAS), range 0 (none) to 100 (strongest possible)
  - Participants completed a satisfaction questionnaire at months 6 and 12 rating their experience with the study medication on a 5-unit scale
  - At screening, day 1, and monthly visits, opioid withdrawal was measured by the Subjective Opiate Withdrawal Scale (SOWS) and Clinical Opiate Withdrawal Scale (COWS); craving was measured by VAS
  - Urine samples were collected at weekly or monthly visits based on the frequency of CAM2038 injection
- Safety was assessed in all participants who received at least 1 dose of CAM2038
- Continuous data were summarized using descriptive statistics, and categorical data were presented using frequencies and percentages

RESULTS

- A total of 227 adult participants were enrolled from December 14, 2015, to April 12, 2017; 190 participants were receiving SL BPN at entry
  - 167/227 (73.6%) participants completed 48 weeks of treatment; 157/227 (69.2%) completed 48 weeks of treatment with 4 weeks of follow-up
- Of the 190 participants converted from SL BPN, 138 (72.6%) completed 48 weeks of treatment; 132 (69.5%) completed 48 weeks of treatment with 4 weeks of follow-up
  - Reasons for discontinuation were withdrawal by participant (n = 31), lack of efficacy (n = 12), physician decision (n = 5), lost to follow-up (n = 4), adverse event (n = 3), pregnancy (n = 1), and other (n = 2)

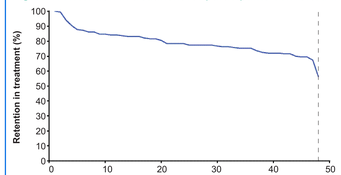
Table 2: Demographic and clinical characteristics at baseline in the overall safety population

Characteristic	Converted from SL BPN N = 190	Overall N = 227
Age, y, mean (SD)	41.3 (9.64)	41.4 (9.59)
Sex		
Male	119 (62.6)	143 (63.0)
Female	71 (37.4)	84 (37.0)
Race		
White	183 (96.3)	203 (89.4)
Black or African American	3 (1.6)	20 (8.8)
Other	4 (2.1)	4 (1.8)
Ethnicity		
Hispanic or Latino	2 (1.1)	4 (1.8)
Not Hispanic or Latino	187 (98.4)	222 (97.8)
Other	1 (0.5)	1 (0.4)
BMI, kg/m², mean (SD)	26.7 (5.84)	26.5 (5.77)
Region		
Australia	23 (12.1)	24 (10.6)
Europe	76 (40.0)	76 (33.5)
United States	91 (47.9)	127 (55.9)
Substance abuse history		
Opioid use disorder (DSM-5) diagnosis	157 (82.6)	194 (85.5)
Time to first opioid abuse, years, mean (SD)	14.7 (8.48)	14.8 (8.55)
Time to first diagnosis, years, mean (SD)	9.8 (7.60)	9.8 (7.75)
Heroin as primary opioid of use	97 (51.1)	134 (59.0)
Injection as route of abuse	83 (43.7)	N/A
Meets DSM-5 criteria for current use		
Benzodiazepines	9 (4.7)	9 (4.0)
Cannabinoids	15 (7.9)	16 (7.0)
Cocaine	0	1 (0.4)
Heroin	15 (7.9)	52 (22.9)
Nicotine	129 (67.9)	161 (70.9)
Other	2 (1.1)	2 (0.9)
Baseline withdrawal and cravings, mean (SD)		
COWS at baseline	2.0 (2.7)	3.4 (4.3)
SOWS at baseline	4.7 (8.1)	8.3 (12.7)
Desire to use VAS at baseline	11.7 (24.2)	22.0 (33.7)
Need to use VAS at baseline	11.7 (23.8)	22.3 (33.8)

Unless otherwise noted, data presented as n (%).
BMI, body mass index; COWS, Clinical Opiate Withdrawal Scale (0–48); DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; N/A, not available; SD, standard deviation; SL BPN, transmucosal buprenorphine; SOWS, Subjective Opiate Withdrawal Scale (0–64); VAS, visual analogue scale (0–100 mm).

- Participants converted from SL BPN to CAM2038 at study entry maintained their level of clinical stability based on efficacy measures at baseline
- Of the 190 participants converted from SL BPN, 113/190 (59.5%) converted to CAM2038 weekly and 77/190 (40.5%) converted to CAM2038 monthly. During the study, participants were allowed to transition from weekly to monthly CAM2038 based on investigator discretion. A total of 63/190 (33.2%) participants converted from SL BPN, transitioned from weekly to monthly injections; 49 (25.8%) transitioned from monthly to weekly injections; 124 (65.3%) did not transition in injection schedule
- Of the 113 participants converted to CAM2038 weekly from SL BPN, 51/113 (45.1%) remained on CAM2038 weekly

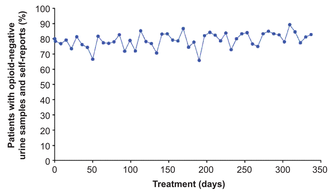
Figure 1: Retention in treatment for participants converted from SL BPN



Dashed line indicates end of study.
SL BPN, transmucosal buprenorphine.

- Mean (standard deviation [SD]) duration of retention in treatment was 38.3 (16.85) weeks for the overall safety/efficacy population
- The majority of participants in the full exposure safety population (n = 128, 67.0%) completed 48 weeks of treatment

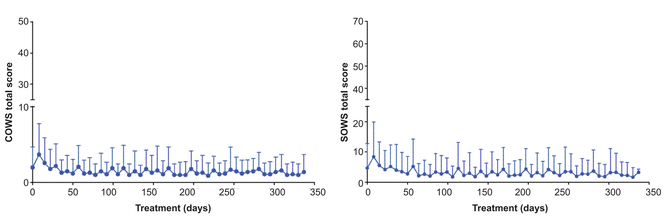
Figure 2: Negative opioid urine toxicology results confirmed by self-reports for participants converted from SL BPN



SL BPN, transmucosal buprenorphine.

- Participants had a high percentage of opioid-negative urine samples from baseline (72.8%) through end of treatment (78.3%, range 75.0%–83.6%)
- Self-reported illicit opioid use was low; the mean (SD) percentage of no illicit use was 92.5% (19.78) over the course of the study
- The percentage of participants with positive samples for other drugs of abuse were low and remained stable from baseline through end of treatment

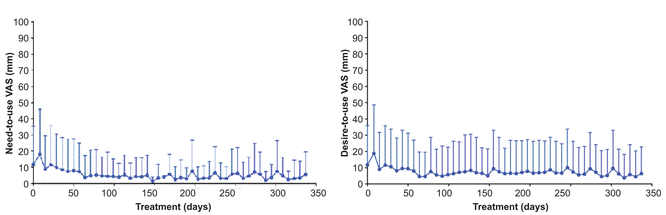
Figure 3: Clinically evaluated (A) and subjective (B) ratings of withdrawal for participants converted from SL BPN



COWS, Clinical Opiate Withdrawal Scale (0–48); SL BPN, transmucosal buprenorphine; SOWS, Subjective Opiate Withdrawal Scale (0–64).

- The mean (SD) COWS score was 2.0 (2.7) at baseline and decreased to 1.4 (2.3) at end of treatment
- The mean (SD) SOWS score was 4.7 (8.1) at baseline and decreased to 3.3 (6.3) at end of treatment

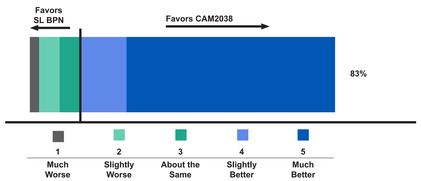
Figure 4: Measurements of craving by need-to-use (A) and desire-to-use (B) visual analog scales for participants converted from SL BPN



SL BPN, transmucosal buprenorphine; VAS, visual analog scale.

- Need-to-use and desire-to-use measurements were low at baseline and decreased over the course of the study
- The mean (SD) need-to-use VAS decreased from 11.7 (23.8) at baseline to 5.4 (14.3) at end of treatment
- The mean (SD) desire-to-use VAS decreased from 11.7 (24.2) at baseline to 6.4 (16.5) at end of treatment

Figure 5: Patient satisfaction for participants converted from SL BPN



SL BPN, transmucosal buprenorphine.

- At month 12, of the 133 responding participants who were receiving SL BPN at entry, 91 (68.4%) answered that CAM2038 was “much better” than their previous SL BPN treatment, 20 (15%) responded that CAM2038 was “slightly better,” 4 (3.0%) responded that CAM2038 was “much worse” compared with their previous SL BPN treatment, while 9 (6.8%) responded that CAM2038 was “slightly worse”

Table 3: Summary of adverse events (AEs)

Category	Converted from SL BPN N = 190	Overall N = 227
≥1 AE	131 (68.9)	143 (63.0)
≥1 drug-related AE	58 (30.5)	60 (26.4)
Injection site AE	43 (22.6)	45 (19.8)
Non-injection site AE	23 (12.1)	24 (10.6)
≥1 severe AE	13 (6.8)	15 (6.6)
Deaths	0	0
≥1 SAE	10 (5.3)	12 (5.3)
≥1 drug-related SAE	0	0
Hospitalizations	9 (4.7)	10 (4.4)
AEs leading to discontinuation	3 (1.6)	4 (1.8)
AEs in ≥5% of participants		
Gastrointestinal disorders	42 (22.1)	44 (19.4)
Injection site pain	33 (17.4)	35 (15.4)
Injection site swelling	25 (13.2)	27 (11.9)
Injection site erythema	20 (10.5)	21 (9.3)
Headache	18 (9.5)	18 (7.9)
Nasopharyngitis	17 (8.9)	18 (7.9)
Urinary tract infection	9 (4.7)	12 (5.3)
Vomiting	12 (6.3)	12 (5.3)

Data presented as n (%).
SAE, serious adverse event; SL BPN, transmucosal buprenorphine; AE, adverse event.

- With the exception of injection site adverse events, the long-term safety profile observed with CAM2038 was consistent with the known safety profile of SL BPN; no unexpected adverse events were observed

CONCLUSIONS

- CAM2038 was well-tolerated and had a systemic safety profile consistent with the known profile of BPN for participants converted to CAM2038 from daily SL BPN
- Participants with moderate to severe OUD who are being treated with daily SL BPN can be safely and effectively converted to corresponding doses of extended-release injectable weekly or monthly buprenorphine to continue their treatment and be assured dosing can be either up- or down-titrated for their needs at each time of clinical visit
- In participants converted from SL BPN, CAM2038 weekly and monthly demonstrated sustained withdrawal and craving suppression during conversion from SL BPN and throughout the study
- CAM2038 was associated with high treatment period retention rates and low levels of continued illicit opioid use throughout the study period for participants converted from SL BPN
- Based on participants on weekly dosing regimens thoughout the study, continued individualization of dose as well as dosing frequency may be important with extended-release formulations of buprenorphine as well as with daily self-administered buprenorphine

REFERENCES

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DISCLOSURES

GB has received grant support from the National Institutes of Drug Abuse, Reckitt-Benckiser/Indivior and Braeburn; consulting fees and travel support from Alkermes, Braeburn and Indivior; and speaker bureaus for Alkermes, Indivior and BioDelivey Sciences International. MF has received fees from BioDelivery Sciences, Braeburn, Indivior, and Knight Therapeutics; and served as an advisor for Kaleo. NB-K and SK are employees of and may hold stock in Braeburn. FT is an employee of and shareholder in Camurus AB.

ACKNOWLEDGEMENTS

This study was sponsored by Braeburn. The authors would like to thank study participants and investigators for their contribution to research and Camurus AB for their support. Writing and editorial support was funded by Braeburn.