Dosing to Effect with Subcutaneous and Sublingual Buprenorphine for Opioid Use Disorder

Michelle R. Lofwall,[1] Edward V. Nunes,[2] Sharon L. Walsh,[2] Genie Bailey,[3] Michael Frost,[4] Natalie Budilovsky-Kelley,[5] Elin Banke Nordbeck,[6] Fredrik Tiberg[6]

[1]University of Kentucky College of Medicine, Center on Drug and Alcohol Research, Lexington, KY, USA; [2]Columbia University Irving Medical Center, New York State Psychiatric Institute, New York, NY, USA; [3]Department of Psychiatry & Human Behavior, Warren Alpert Medical School, Brown University & Stanley Street Treatment and Resources (SSTAR), Fall River, MA, USA; [4]The Frost Medical Group, LLC, Conshohocken, PA, USA; [5]Braeburn, Philadelphia, PA, USA; [6]Camurus AB, Lund, Sweden

Background

- Around 2.7 million Americans have been reported to have opioid use disorder (OUD), with estimates suggesting the true number may be as high as 6–7 million.[1,2] Opioids caused over 83,000 opioid overdose deaths in the US in 2022[3]
- CAM2038 is a subcutaneous buprenorphine (BPN) depot shown to be efficacious in the treatment of OUD[4]
- In a phase 3 randomized clinical trial (**Figure 1**), weekly and monthly CAM2038 was shown to be non-inferior to sublingual BPN (SL-BPN) on the primary outcome of responder rate (i.e., no evidence of illicit opioid use for >8 of 10 prespecified points during weeks 9–24, with 2 of these at week 12 and during month 6 [weeks 21–24]) and superior on the planned *a priori* secondary outcome of urine tests negative for illicit opioids over weeks 4–24 evaluated by cumulative distribution function[4]
- A range of doses are available for both CAM2038 and SL-BPN, which allows flexible dosing to address the individual treatment needs of patients
- Further research is needed to better understand the association of buprenorphine dose with treatment outcomes for both formulations[5]

Objective

- To assess whether dose of CAM2038 and SL-BPN was associated with treatment outcomes

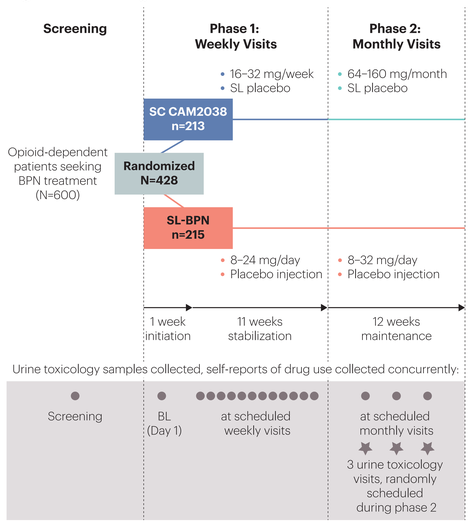
Methods

- This was a post-hoc analysis of a phase 3, 24-week, outpatient, randomized, double-blind, double-dummy, active-controlled, multicenter trial (NCT02651584)[4]
- Treatment-seeking adults with moderate to severe OUD were randomized to receive CAM2038 or daily SL-BPN with naloxone alongside appropriate placebo (**Figure 1**)
- Injections were given weekly for 12 weeks then monthly for 12 weeks
- Doses were flexible and individualized per clinical judgement at each site based on current practice guidelines (e.g., taking into account opioid withdrawal, cravings, illicit opioid use and if opioid effects are adequately blocked)[6]
- Starting in the second month of treatment, the effect of each dose given was evaluated at the end of the dosing interval by examining four outcomes:
  1. Urine drug test result (UDT)
  2. Clinical Opiate Withdrawal Scale (COWS, 0–48)
  3. Subjective Opiate Withdrawal Scale (SOWS, 0–64)
  4. Need- and desire-to-use opioid visual analog scales (VAS, 0–100)
- UDT results (mean percentage of urine samples negative for opioids, with missing urine samples handled as positive) and mean COWS, SOWS, and VAS scores were calculated for weeks 5–24
- Associations between dose and outcomes were assessed by descriptive statistics

Results

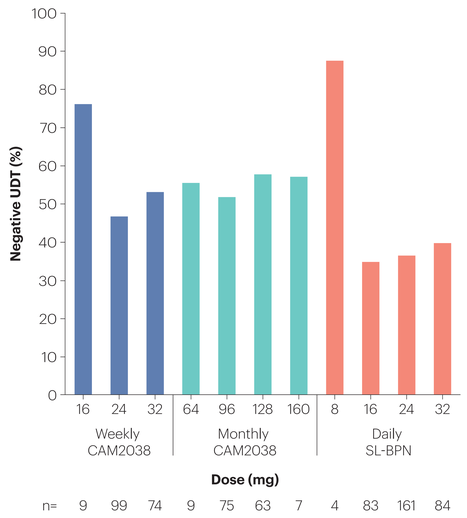
- Demographics and baseline characteristics were comparable between groups (**Table 1**)
- COWS, SOWS, and opioid craving scores were elevated and clinically significant at baseline (**Table 1**), indicating clear treatment need as expected[4,7]
- Higher percentages of negative urine tests were observed in patients treated with CAM2038 compared with SL-BPN (**Figure 2**). The particularly high percentages seen for the lowest doses are likely related to small patient numbers and high stability of these patients
- No clinically significant associations of dose with mean percentage of negative urine samples (**Figure 2**), mean COWS scores (**Figure 3**), mean SOWS scores (**Figure 3**), or mean need-to-use and desire-to-use scores (**Figure 4**) were found for any BPN formulation/dosing regimen. However, there was a trend of increasing disease severity with increasing BPN dose indicated by slight increases in these parameters, likely reflecting that patients on higher doses had more severe disease
- In the primary analysis, withdrawal and craving decreased over time while on weekly and monthly CAM2038 and SL-BPN[4]

Figure 1 Trial design



There was a 1-month follow-up after phase 2. Adapted from: Lofwall et al. JAMA Intern. Med. 2018;178(6): 764–73.

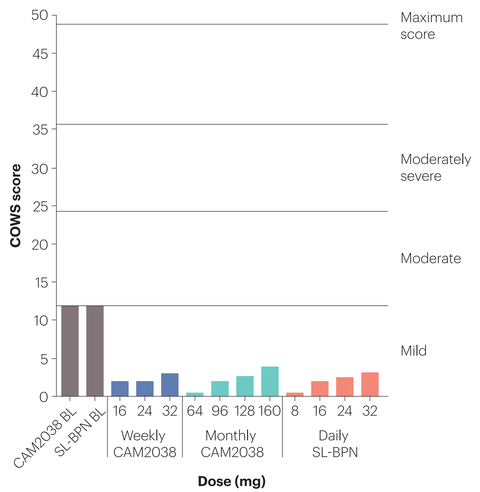
Figure 2 Percentage of urine samples negative for opioids



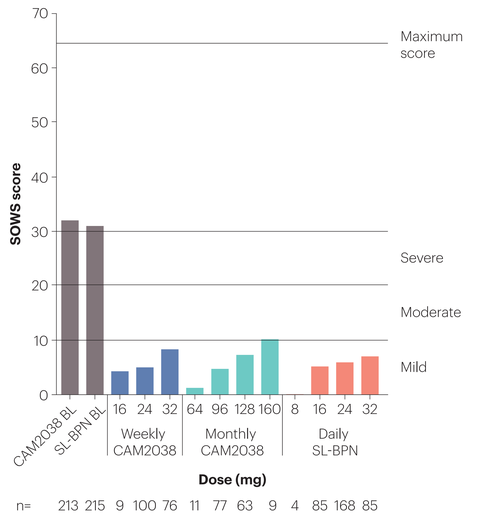
Data represent mean percentage of negative UDT tests from weeks 5–24 of the trial (excluding the 4-week grace period at the beginning of the trial). As participants' doses could have changed over time, the same participant may be present at different times in the different dose categories within the assigned group. Numbers below the x-axis label represent the number of participants making up each dose category.

Figure 3 Withdrawal scores

A) COWS scores



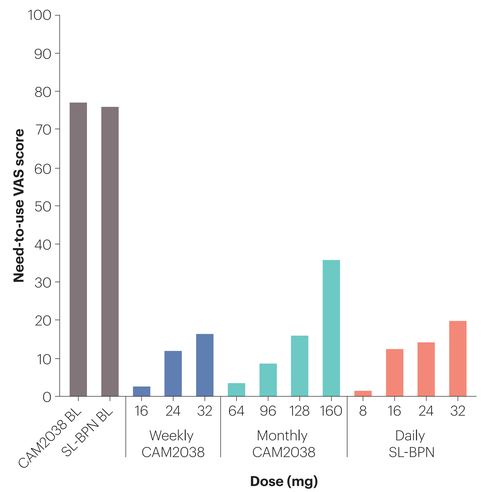
B) SOWS scores



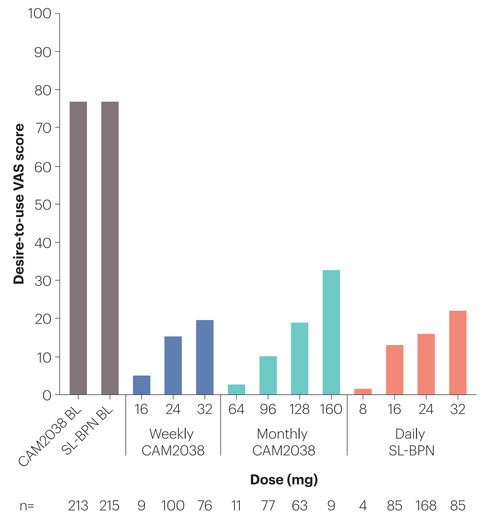
Data represent mean COWS and SOWS scores recorded for patients the visit after they received the specified dose, from weeks 5–24 of the trial (excluding the 4-week grace period at the beginning of the trial).

Figure 4 Craving scores

A) Need-to-use VAS scores



B) Desire-to-use VAS scores



Data represent mean need- and desire-to-use VAS scores recorded for patients the visit after they received the specified dose, from weeks 5–24 of the trial (excluding the 4-week grace period at the beginning of the trial).

Table 1 Patient demographics and baseline clinical characteristics

Characteristic	Treatment group[a] CAM2038 (n=213)	SL-BPN (n=215)
Age, years, mean (SD)	38.7 (11.2)	38.0 (10.9)
Male, n (%)	121 (56.8)	142 (66.0)
White, n (%)	159 (74.6)	164 (76.3)
History of injection opioid use at screening, n (%)	114 (53.5)	110 (51.2)
Primary opioid of use, n (%)		
Heroin	152 (71.4)	151 (70.2)
Prescription opioids	61 (28.6)	64 (29.8)
Baseline craving and withdrawal scores, mean (SD)		
COWS score[b]	12 (5.4)	12 (6.0)
SOWS score[c]	32 (15.4)	31 (16.1)
Need-to-use VAS[d]	77 (25.4)	76 (24.9)
Desire-to-use VAS[e]	77 (26.2)	77 (25.4)

[a]No significant differences between groups; [b]Scores range from 0 (no withdrawal) to 48 (severe withdrawal); [c]Scores range from 0 (no withdrawal) to 64 (severe withdrawal); [d]Scores range from 0 (no need to use) to 100 (maximum need to use since the last visit); [e]Scores range from 0 (no desire to use) to 100 (maximum desire to use since the last visit).

Conclusions

Efficacy was observed across all doses of CAM2038 and SL-BPN, consistent with previous reports of the efficacy of CAM2038, and all doses after titration were effective. However, there was a tendency towards slight withdrawal and cravings for patients on higher doses

This supports current practice guidelines for OUD treatment that emphasize the importance of individualizing dosing to effect based on clinical response[8]

BPN: buprenorphine; **BL:** baseline; **COWS:** Clinical Opiate Withdrawal Scale; **OUD:** opioid use disorder; **SC:** subcutaneous; **SD:** standard deviation; **SL-BPN:** sublingual BPN; **SOWS:** Subjective Opiate Withdrawal Scale; **UDT:** urine drug test; **VAS:** visual analog scale.

References: 1. Substance Abuse and Mental Health Services Administration. Results from the National Survey on Drug Use and Health 2020; **2.** Keyes KM. Drug Alcohol Depen Rep 2022;3:100052; **3.** Ahmad FB. National Center for Health Statistics 2023; **4.** Lofwall MR. JAMA Intern Med 2018;178:764–73; **5.** Hjelmström P. Drug Dev Ind Pharm 2020;46:1–7 **6.** Substance Abuse and Mental Health Services Administration. Treatment Improvement Protocol (TIP) 63 2021; **7.** Boyett B. Drug Alcohol Depen 2021;229:109057 **Author Contributions:** All authors made substantial contributions to study conception and design, or the acquisition, analysis, or interpretation of data; drafting the poster or revising it critically for important intellectual content; and final approval of the version of the poster to be published. **Disclosures: MRL:** Received scientific consultant fees from Berkshire Biomedical, Braeburn, Journey Colab, and Titan Pharmaceuticals in the last three years. **EN:** Investigator on NIH-funded studies that have received in-kind donations of medications or digital therapeutics from Alkermes, Braeburn, Camurus AB, CHESS Health, Indivior, and Pear Therapeutics, and has served as a consultant without compensation for Alkermes, Camurus AB, Indivior, and Pear Therapeutics. **SLW:** Received consultant fees for advising on the development and use of products for the treatment of opioid use disorder from Cerevel Therapeutics, AstraZeneca, Braeburn Pharmaceuticals, Titan, and Opiant in the past three years. **GB:** Investigator on NIH-funded studies that have received in-kind donations of medications or digital therapeutics from Alkermes, Braeburn, Camurus AB, CHESS Health, Indivior, and Pear Therapeutics, and received consultant fees from Braeburn and Titan Pharmaceuticals in the last three years. **MF:** Received consulting/speaking honoraria from Braeburn, received consultant fees from Molteni Farmaceutici and Accord Healthcare, and is a shareholder of Pocket Naloxone. **NBK:** Current employee of Braeburn, Inc. **EBN, FT:** Current employee and shareholder of Camurus AB. **Funding:** This study was funded by Camurus AB. Medical writing support was provided by Costello Medical and funded by Camurus AB. **Acknowledgements:** The authors thank Melanie Seaton, PhD, Costello Medical, Manchester, UK, and James Evry, MSc, Costello Medical, Cambridge, UK, for medical writing and editorial assistance, and Fay Angel, BA, Costello Medical, London, UK, from the Creative Team for graphic design assistance.