THE UNIVERSITY OF SYDNEY

Long-term safety, tolerability and effectiveness of CAM2038 weekly and monthly buprenorphine depots for opioid use disorder

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Disclosure

- N. Lintzeris, M. Frost, A. Dunlop, R.Ali, P.Haber, E. Nunes, G. Bailey, J. Billeskov Jansen, L. Chemnitz Frey, B. Weber and J. Strang were investigators in the study sponsored by Braeburn Pharmaceuticals
- M. Frost is a consultant for Braeburn Pharmaceuticals
- S. Kim is a full-time employee of Braeburn Pharmaceuticals
- F. Tiberg is a full-time employee of Camurus
- N Lintzeris has received research funding support for investigator-led studies from Indivior and Mundipharma, and provided consultancy work for Mundipharma on unrelated topic.

Opioid dependence is a growing global health problem

- 33 million people misuse opioids globally
  - Largest society burden of all drugs[1]
  - About 4 million diagnosed patients in Europe and the US, less than half in treatment[2,3]
- Ongoing opioid crisis
  - 33,091 US opioid overdose deaths in 2015, 12,990 from heroin (+23% compared to 2014)[4]
  - Growing concerns in Europe with over 7000 overdose deaths in 2016[5]
  - In Australia, approximately 1200 overdose drug deaths in 2015
- A chronic relapsing disease
  - Opioid-use trajectories indicate chronic disease with less than 30% abstinence achieved over time
  - Opioid dependence mortality continues to increase over time[6]

Source: 1. UNODC, World Drug Report 2015; 2. SAHMSA, National Survey on Drug Use and Health (NSDUH) – 2014; 3. EMCDD, European Drug Report Trends and Developments 2015; 4. Center for Disease Control & Prevention 2016; 5. EMCDD, European Drug Report Trends and Developments 2017; 6. Hser et al. Harvard Review Psychiatry1 2015; 23: 76-89

Ongoing opioid crisis highlights unmet needs in the treatment of opioid use disorder (OUD)

Current standard treatments

- Sublingual buprenorphine, buprenorphine-naloxone or methadone
- Efficacy demonstrated in reducing illicit opioid use, spreading of BBV and mortality
- On the World Health Organization's Essential Medicines List
- Many treatment models require daily or near daily supervised dosing, and/or regular dispensing

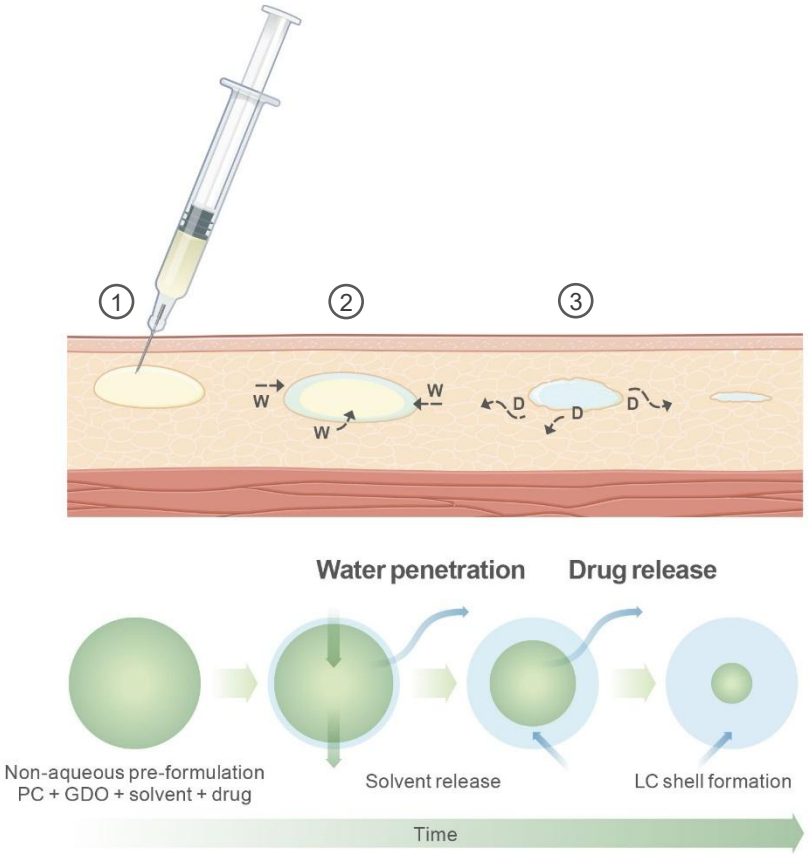
Limitations of standard treatments

- Poor medication adherence
  - Increased risk of relapse / overdose
  - Fear of accidental paediatric exposure & death
- Suboptimal quality of life
  - Inconvenience, cost & stigma of daily medication
  - Daily reminders of disease and addiction
- Public health impact
  - Opportunities for diversion, misuse and abuse
  - Huge healthcare and societal costs
  - Costs of daily supervised / dispensed medications

Source: 1. IMS 2015

CAM2038 – weekly and monthly BPN depots for opioid dependence

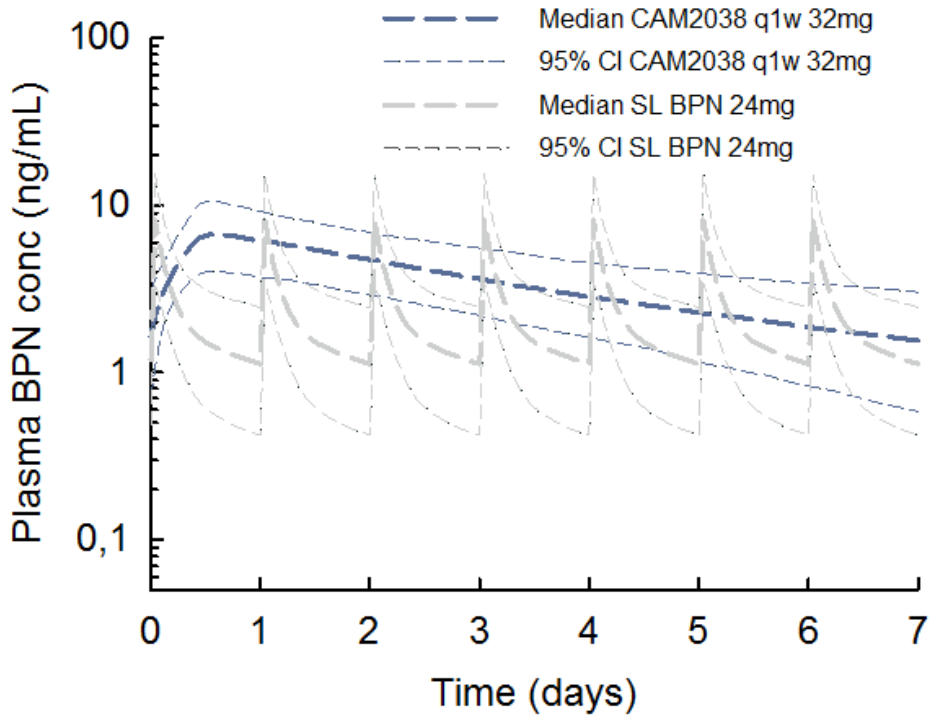
- Based on FluidCrystal® depot technology
- Flexible dosing for use across MAT treatment phases
  - From initiation and stabilization to long-term maintenance
- Ready-for-use in prefilled syringe
- Small volume fixed dosages (<0.16 – 0,67mL)
- 23 gauge needle
- Room temperature storage



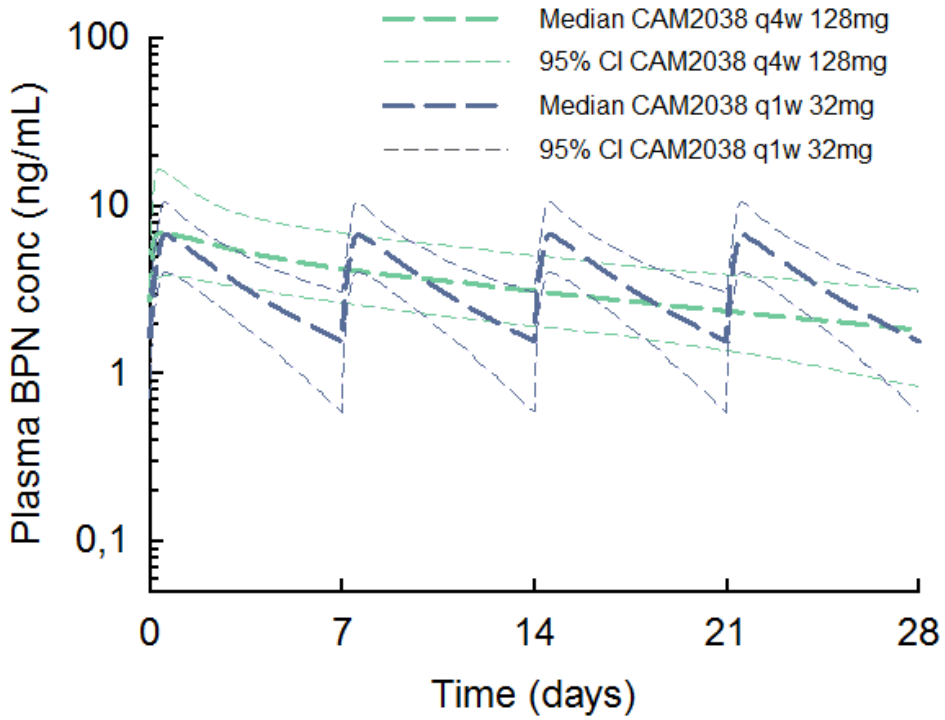
1. Subcutaneous injection of lipid-based formulation
2. Liquid crystal gel formation on water absorption (w)
3. Slow release of drug compound (D), biodegradation of depot

Steady-state population PK profiles after weekly and monthly dosing of CAM2038 vs. daily SL BPN

Weekly CAM2038 – Daily SL BPN



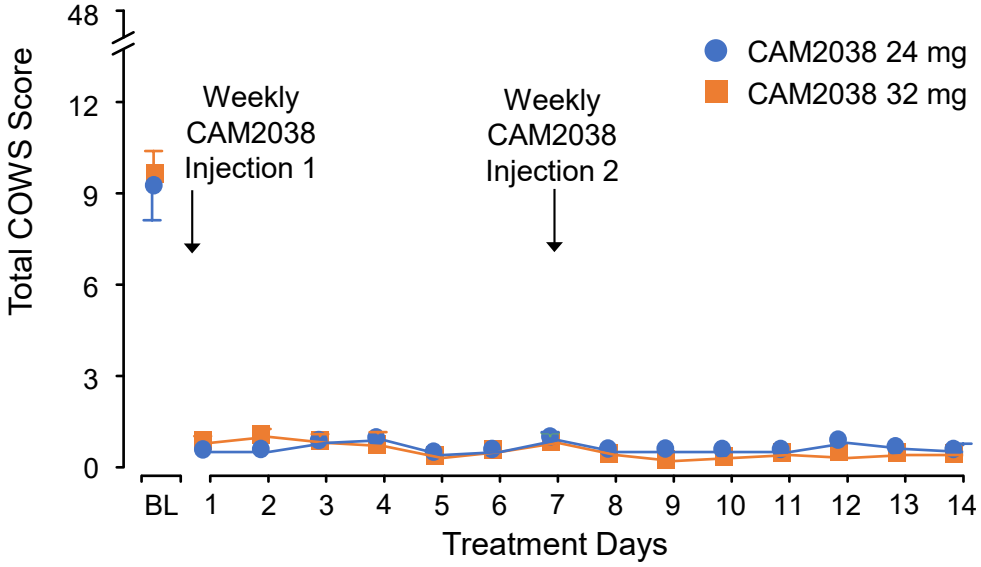
Monthly CAM2038 – Weekly CAM2038



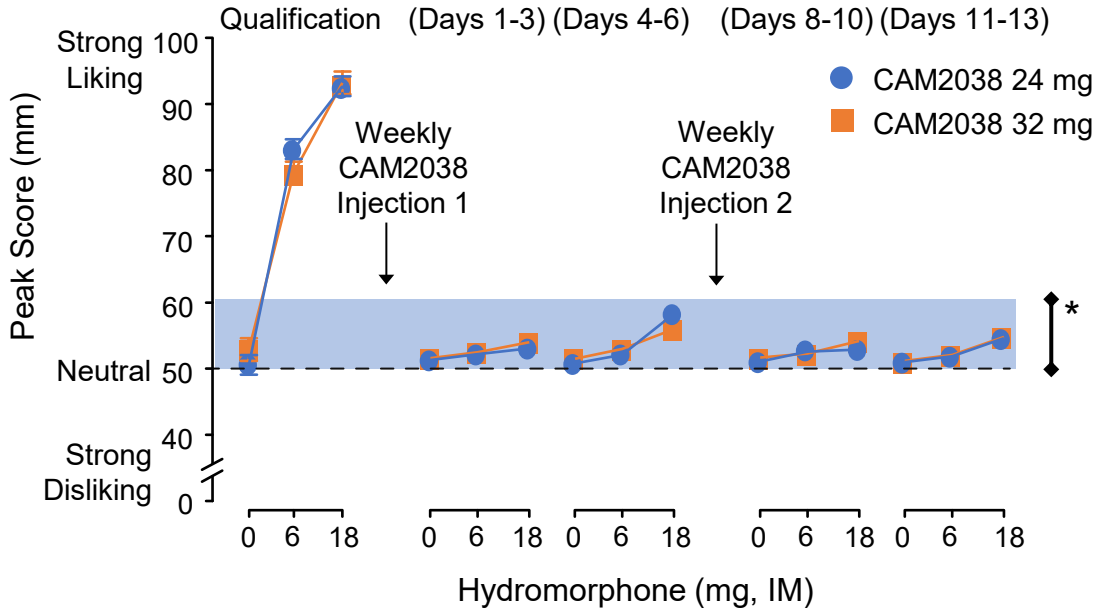
Population PK analysis and modelling based on data from four clinical studies (N=236). Diagnostic testing demonstrated predictive BPN concentrations and good agreement between observed and predicted data percentiles

Sustained suppression of withdrawal and blockade of opioid effects from first dose

Clinical opiate withdrawal scale (COWS)



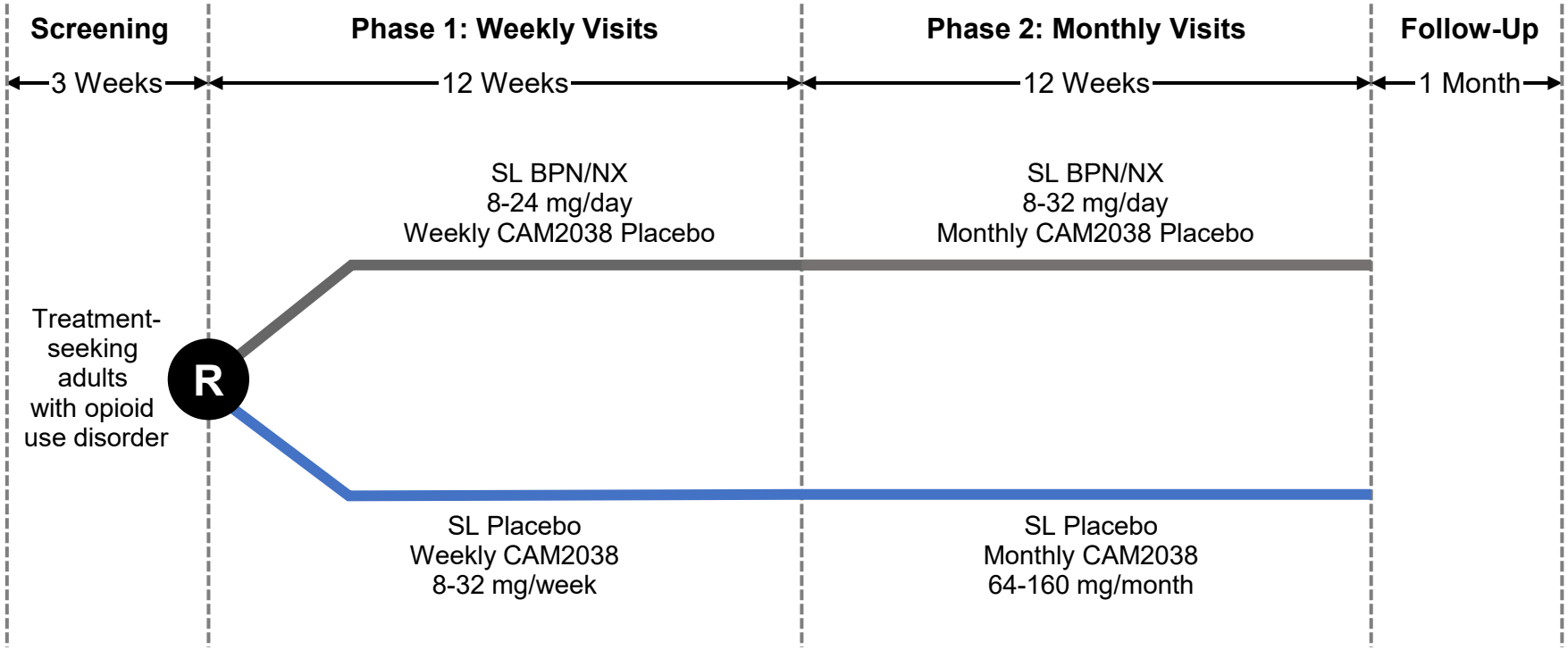
Measure of drug liking VAS



** 11 pt. difference: Prespecified complete blocking criteria*

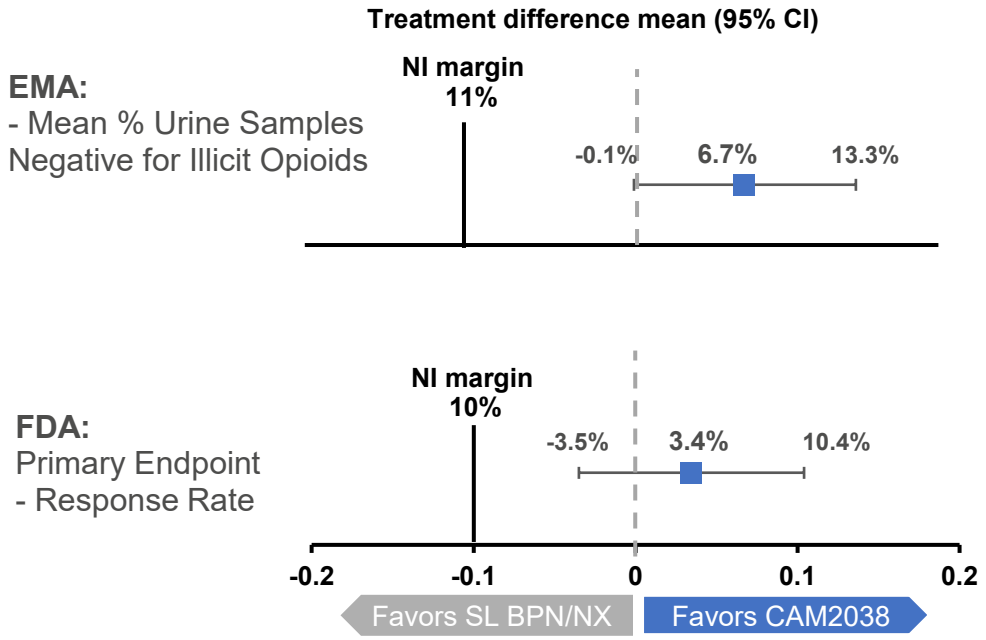
Head-to-head efficacy study of a long-acting injection versus daily sublingual buprenorphine/naloxone

Phase 3 randomized, double-blind, double-dummy efficacy study (HS-11-421), N=428

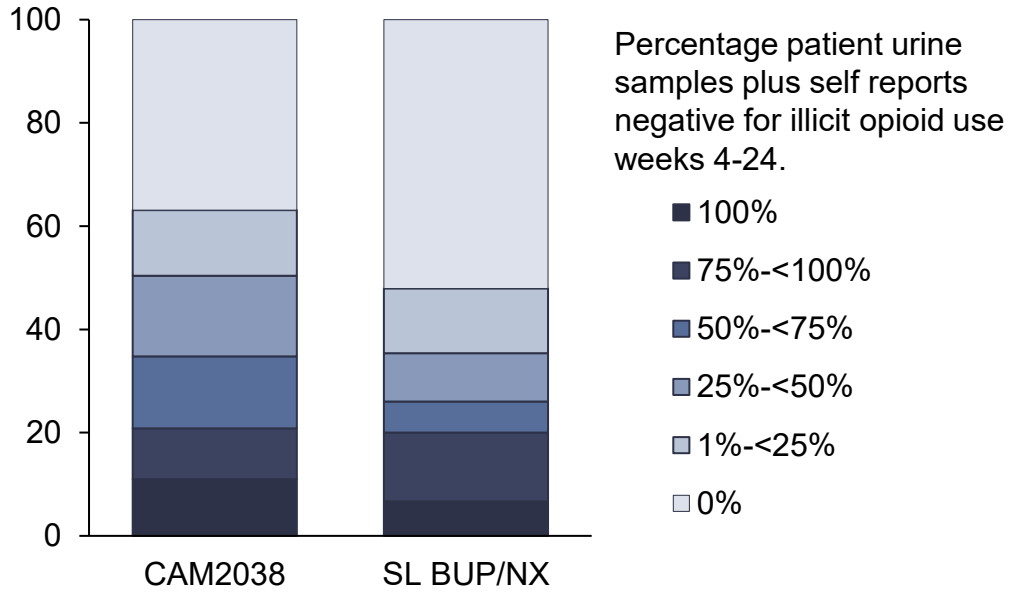


CAM2038 met primary and secondary endpoints of noninferiority and superiority versus daily SL BPN/NX

Noninferiority for mean % urines negative for illicit opioids and response rate P<0.001



Superiority demonstrated for first secondary endpoint of percentage weeks abstinent, P=0.004

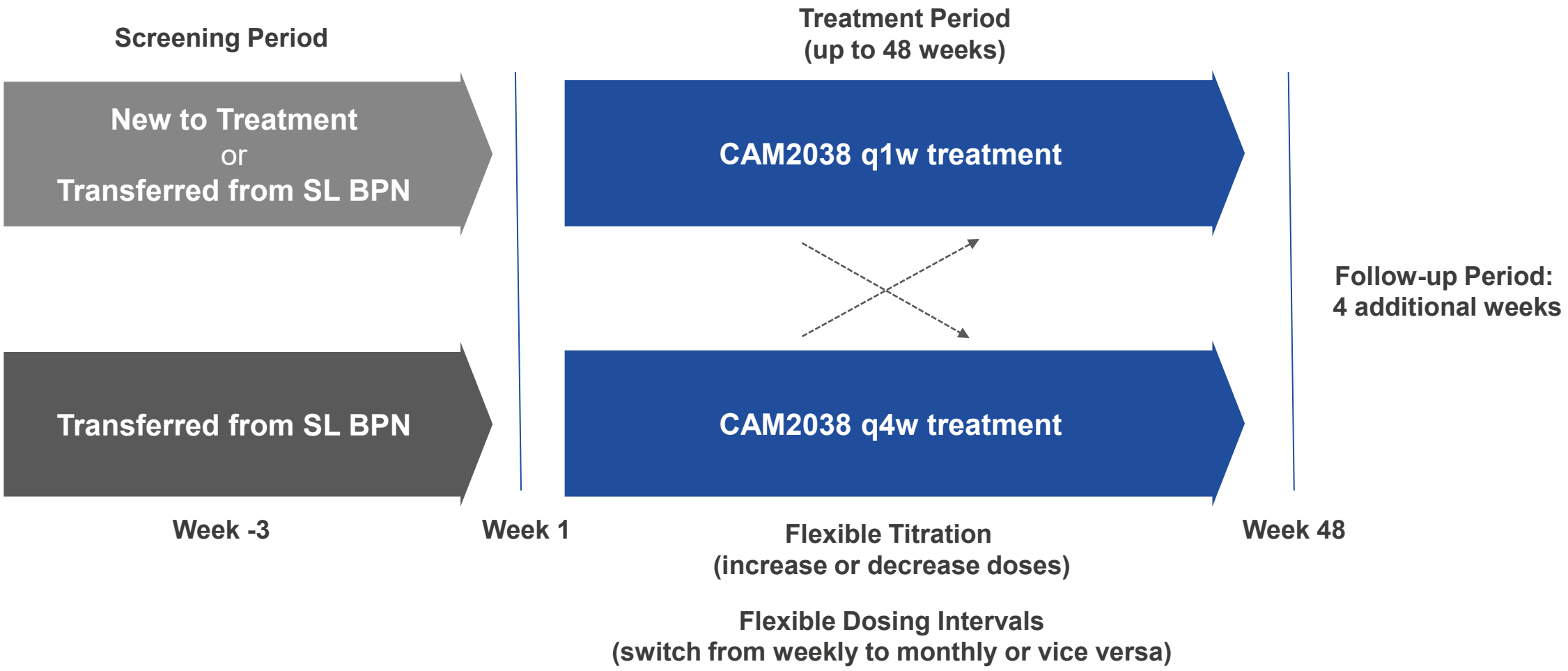


Study 499: 48-week, open-label, safety study performed in the Unites States, Europe and Australia

Study summary

Objective	To assess the long-term safety and efficacy of subcutaneous buprenorphine injection depots of CAM2038 q1w and q4w in adult outpatients with opioid use disorder
Main parameters	**Safety:** • adverse event (AE) and serious AE (SAE) • injection site examinations • clinical laboratory tests, electrocardiogram (ECG) • vital signs, physical examinations • suicidal ideation (C-SSRS) and pregnancy reporting **Efficacy:** • urine toxicology for opioids • urine toxicology for other psychoactive drugs • self-reported illicit drug use • retention in treatment • measures of withdrawal and measures of cravings
Duration	48 weeks followed by 4 weeks of follow-up during 2015-2017
Territory	Australia, Europe (UK, Hungary, Denmark, Sweden, Germany), Unites States
Centres	29 sites
Therapy	Prefilled syringes of CAM2038 q1w (50 mg/mL) and CAM2038 q4w (356 mg/mL)
Sponsors	Braeburn Pharmaceuticals

Study design with flexible dosing regimen



Study dose conversion table for switching between SL BPN, Weekly or Monthly CAM2038

Daily SL BPN Dose	CAM2038 q1w	CAM2038 q4w
< 6 mg	8 mg	–
8 – 10 mg	16 mg	64 mg
12 – 16 mg	24 mg	96 mg
18 – 24 mg	32 mg	128 mg
26 – 32 mg	32 mg	160 mg

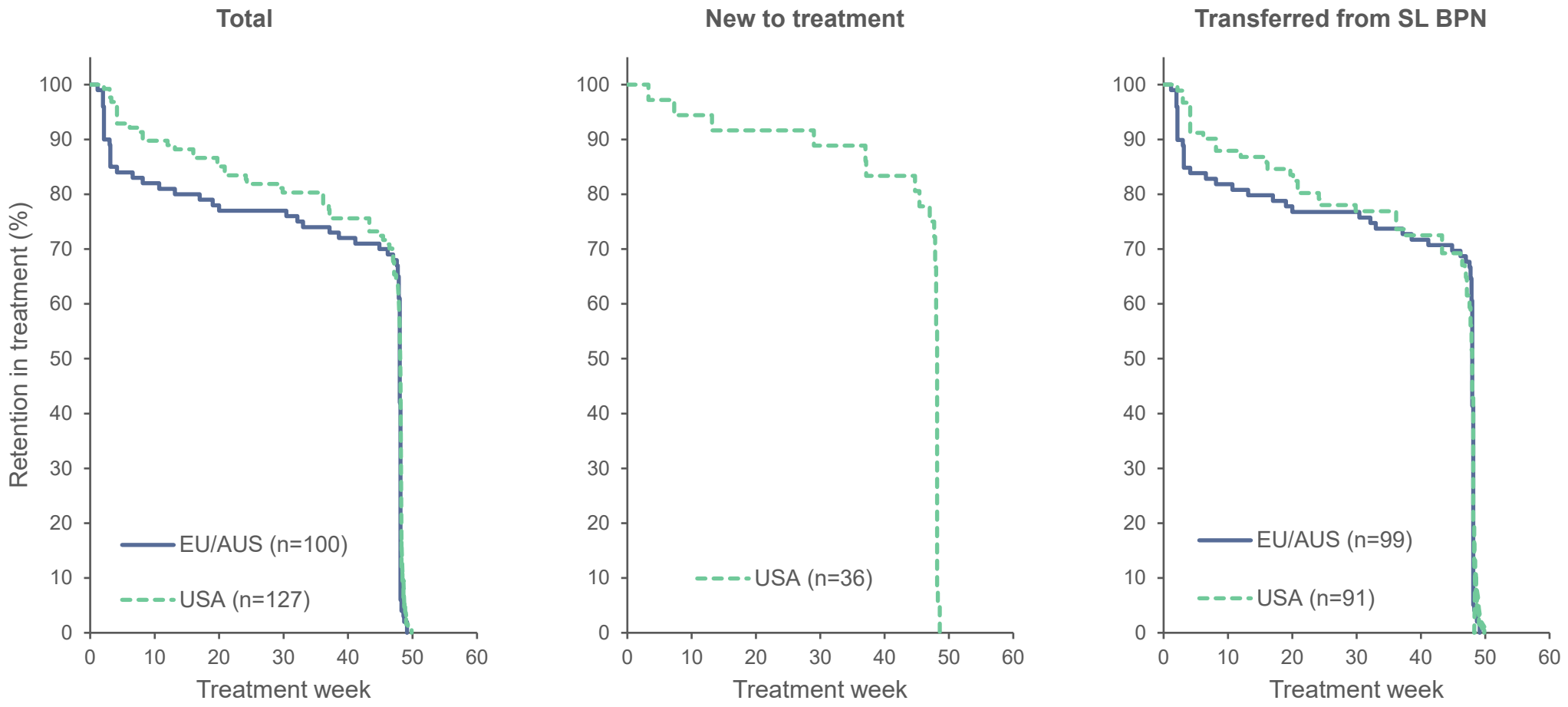
Demographics and baseline clinical characteristics

Characteristic	Transferred from SL BPN treatment N=190	New to BPN treatment N=37	Overall N=227
Age, y, mean (SD)	41.3 (9.64)	41.8 (9.41)	41.4 (9.59)
Sex (Male)	119 (62.6)	24 (64.9)	143 (63.0)
Race			
White	183 (96.3)	20 (54.1)	203 (89.4)
Black or African American	3 (1.6)	17 (45.9)	20 (8.8)
Other	4 (2.1)	0 (0)	4 (1.8)
BMI, kg/m^2, mean (SD)	26.7 (5.84)	25.3 (5.33)	26.5 (5.77)
Region			
Australia	23 (12.1)	1 (2.7)	24 (10.6)
Europe	76 (40.0)	0 (0)	76 (33.5)
United States	91 (47.9)	36 (97.3)	127 (55.9)
Substance abuse history			
Time to first opioid abuse, y, mean (SD)	14.7 (8.48)	15.7 (8.98)	14.8 (8.55)
Time to first diagnosis, y, mean (SD)	9.8 (7.60)	10.0 (8.60)	9.8 (7.75)
Heroin as primary opioid of use	97 (51.1)	37 (100.0)	134 (59.0)
Baseline withdrawal and cravings, mean (SD)			
COWS at baseline	2.0 (2.7)	10.6 (3.7)	3.4 (4.3)
SOWS at baseline	4.7 (8.1)	27.1 (15.3)	8.3 (12.7)
Desire to use VAS at baseline	11.7 (24.2)	74.8 (24.8)	22.0 (33.7)
Need to use VAS at baseline	11.7 (23.8)	76.3 (24.9)	22.3 (33.8)

Unless otherwise noted, data presented as n (%).
BMI, body mass index; BPN, buprenorphine; COWS, clinical opioid withdrawal scale (0–48); SD, standard deviation; SL BPN, sublingual buprenorphine; SOWS, subjective opioid withdrawal scale (0–64); VAS, visual analogue scale (0–100 mm).

Key study ’safety’ outcomes

High retention in treatment by time point and region (EU and AUS combined)



Long-term safety data

Category	Overall Safety Population		
	Transferred from SL BPN (n, (%)) N=190	New to BPN treatment (n, (%)) N=37	Overall (n, (%)) N=227
A least 1 TEAE	131 (68.9)	12 (32.4)	143 (63.0)
At least 1 drug-related TEAE	58 (30.5)	2 (5.4)	60 (26.4)
Injection site TEAE	43 (22.6)	2 (5.4)	45 (19.8)
Non-injection site TEAE	23 (12.1)	1 (2.7)	24 (10.6)
TEAEs leading to study drug discontinuations	3 (1.6)	0 (0)	3 (1.3)
At least 1 SAE	10 (5.3)	2 (5.4)	12 (5.3)
Hospitalisations	9 (4.7)	1 (2.7)	10 (4.4)
At least 1 drug-related SAE	0 (0)	0 (0)	0 (0)
Deaths	0 (0)	0 (0)	0 (0)

BPN, buprenorphine; SL BPN, sublingual buprenorphine; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

Long-term safety data

Category	Overall Safety Population		
	Transferred from SL BPN (n, (%)) N=190	New to BPN treatment (n, (%)) N=37	Overall (n, (%)) N=227
TEAEs in ≥5% of participants			
Injection site pain	33 (17.4)	2 (5.4)	35 (15.4)
Injection site swelling	25 (13.2)	2 (5.4)	27 (11.9)
Injection site erythema	20 (10.5)	1 (2.7)	21 (9.3)
Headache	18 (9.5)	0 (0)	18 (7.9)
Nasopharyngitis	17 (8.9)	1 (2.7)	18 (7.9)
Nausea	16 (8.4)	0 (0)	16 (7.0)
Vomiting	12 (6.3)	0 (0)	12 (5.3)
Urinary tract infection	9 (4.7)	3 (8.1)	12 (5.3)

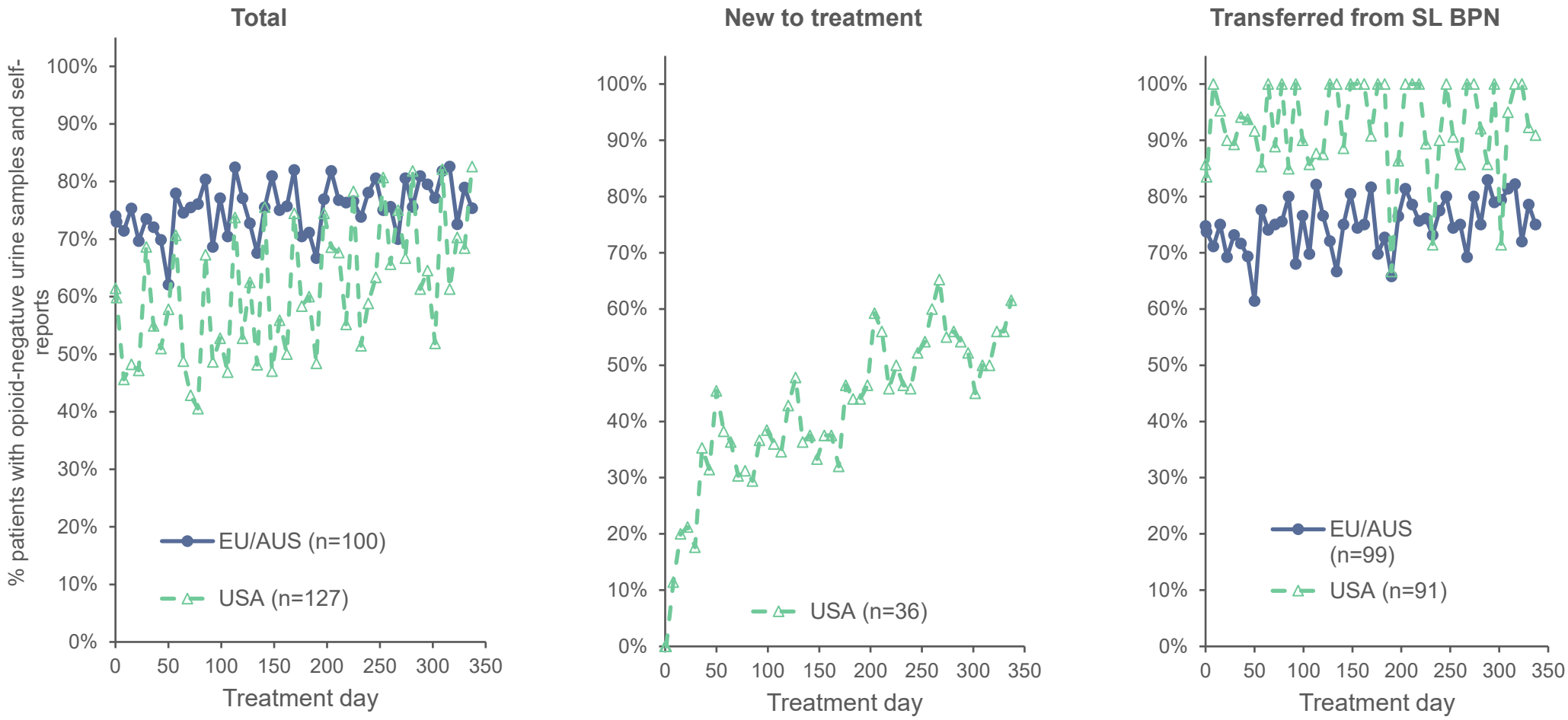
BPN, buprenorphine; SL BPN, sublingual buprenorphine; TEAE, treatment-emergent adverse event.

AEs Leading to Treatment Withdrawal: Study 499

	N=227 (n, (%))
Any AE leading to drug withdrawal	3.0 (1.3)
Injection site swelling, pain	1.0 (0.4)
Injection site swelling erythema, pruritis	1.0 (0.4)
Road traffic accident, with skull fractured base, pharyngeal injury, spinal fracture, interverterbral disk fracture, upper & lower limb fracture, multiple injuries	1.0 (0.4)

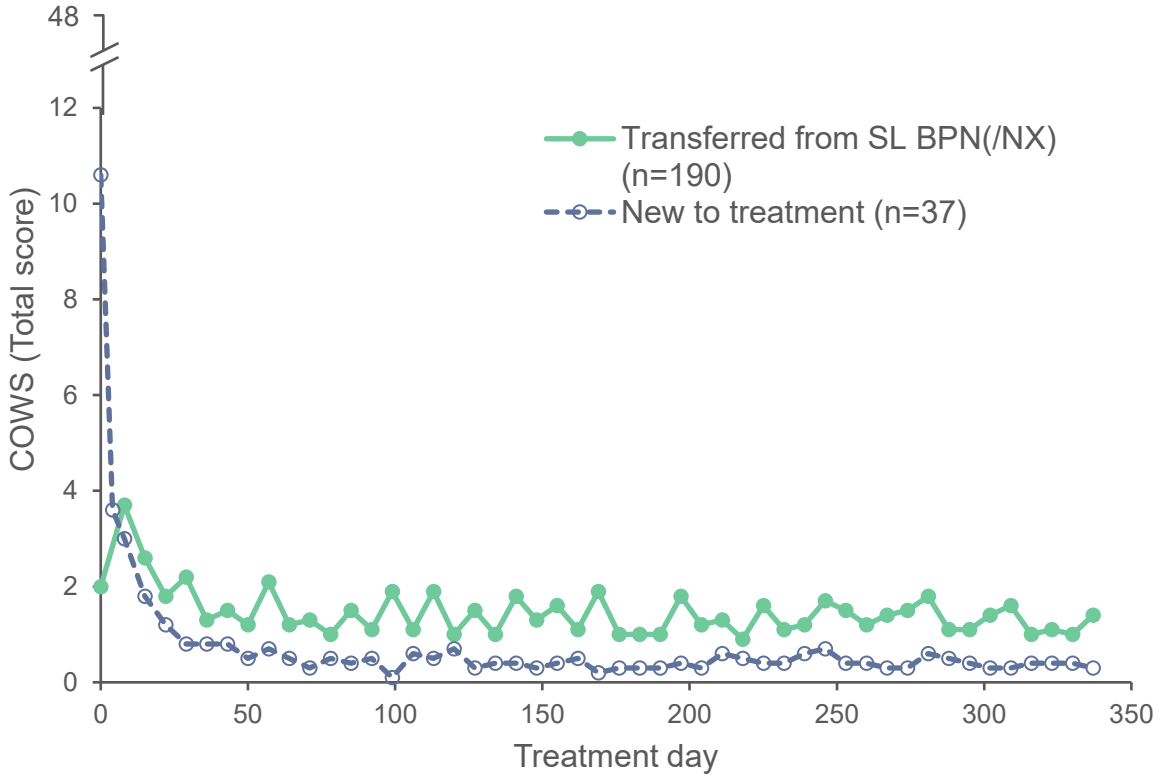
Key study ’efficacy’ outcomes

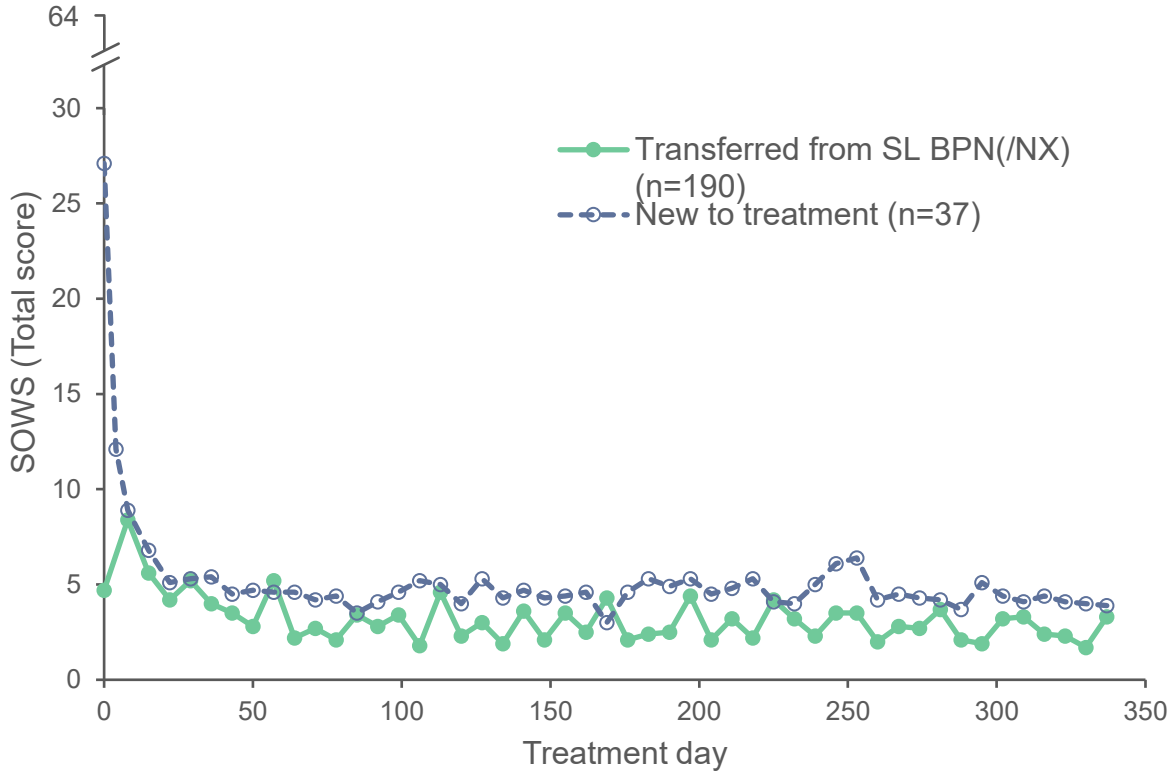
Percentage of patients with no illicit opioid use by time point and region (EU and AUS combined)



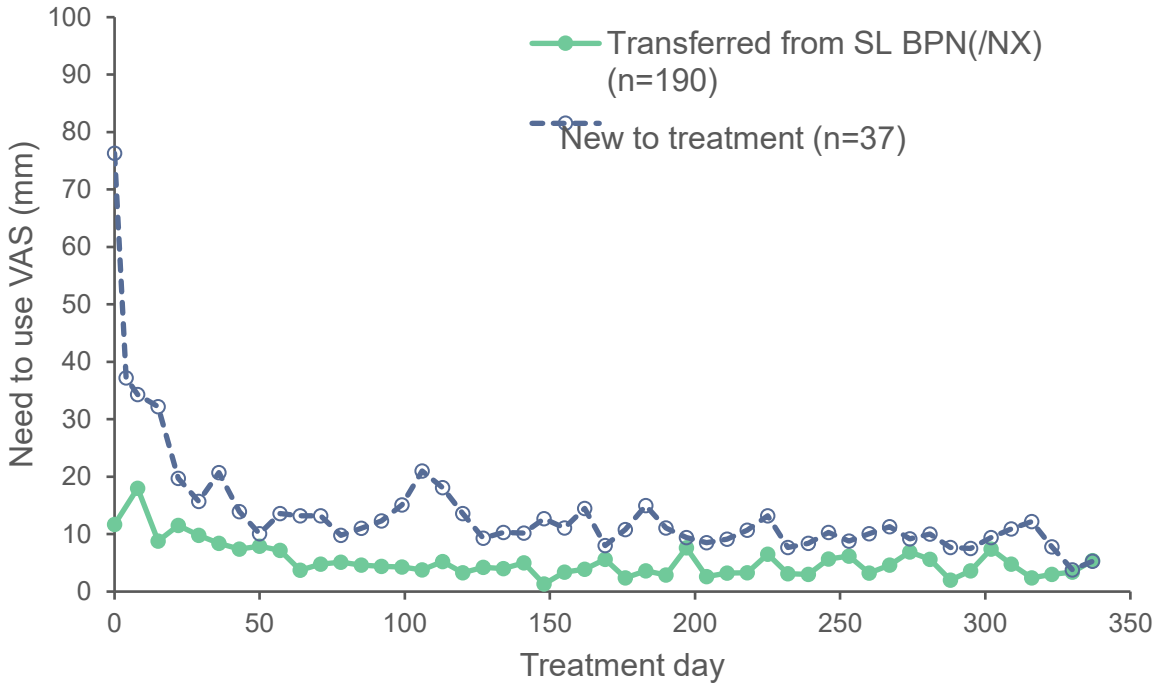
Data combines patients on weekly and monthly visit schedules. Missing values not imputed.

Clinical and subjective opiate withdrawal scales; COWS and SOWS scores





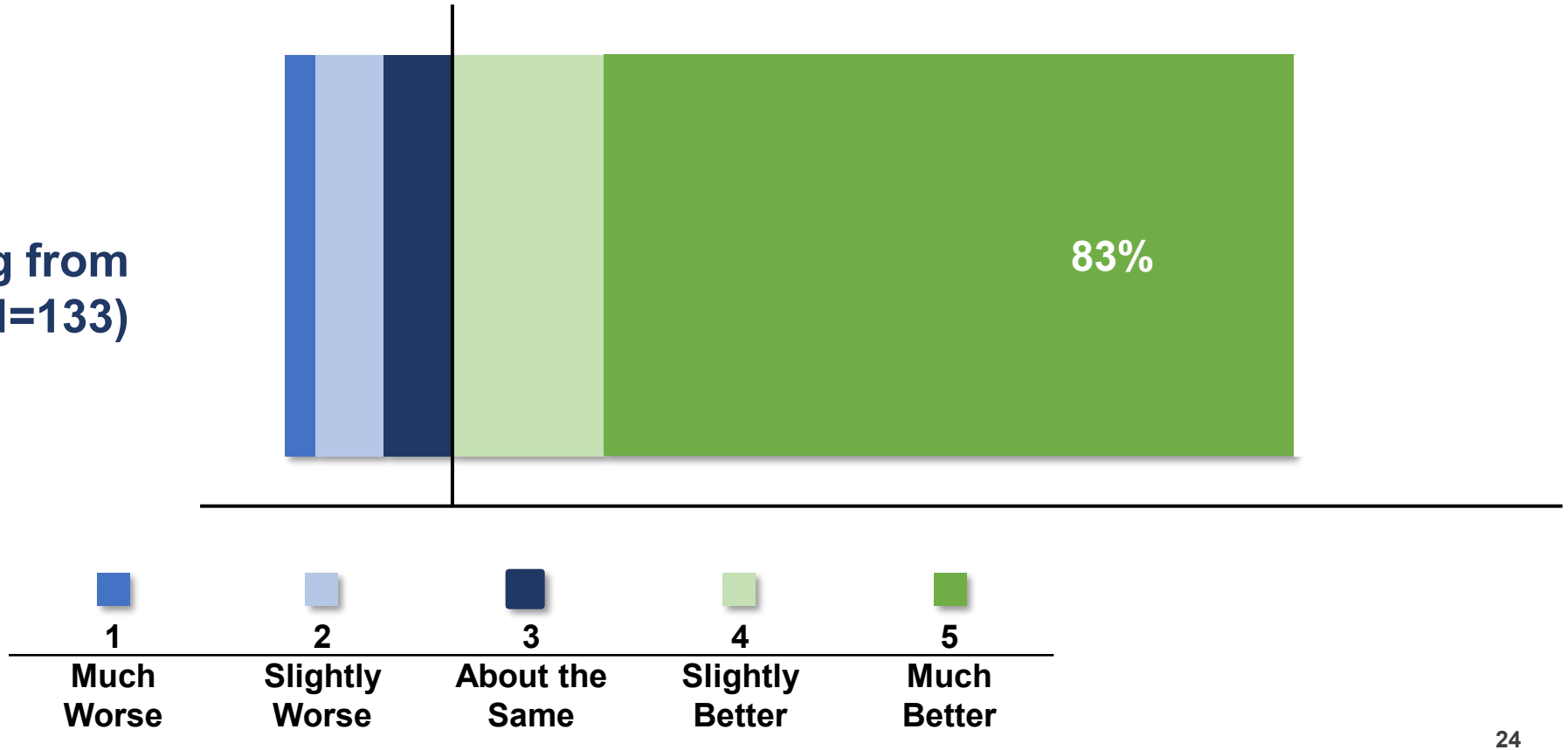
Opioid cravings; need to use VAS



Patient satisfaction with CAM2038 at 6 months compared to previous sublingual buprenorphine

The study medication compared to my previously prescribed SL BPN treatment is:

Patients transferring from sublingual BPN (N=133)



Personal clinician perspective

- CAM2038 easy to ‘handle’ and administer
- Flexible weekly / monthly doses and choice of 4 doses within each interval facilitated patient care
- Booster and ‘bridging’ doses as required
- Missed appointments by patients
- Titrating doses to achieve clinical outcomes
- Transfer doses a reasonable guide but minority required dose adjustments

Conclusions

- **Long-term safety**
  - Comparable to shorter term CAM2038 studies and SL BPN:
  - Injection site reactions observed in up to 20% of subjects
  - No drug related SAEs; few treatment discontinuation due to adverse events (1.3%)
- **Efficacy**
  - High retention for both new to treatment and transferred patients from SL BPN/NX
  - Percentage of illicit opioid-negative urine drug screens and self-reports well maintained in transferred patients and increasing in ‘new to treatment’ patients
  - Well controlled cravings and withdrawals across the study
- **Patient satisfaction**
  - High satisfaction with CAM2038 versus previous SL BPN treatment
- **Administration by healthcare professionals**
  - Minimizes potential for diversion, misuse, and accidental pediatric exposure

Thank you!

Acknowledgement

- Study participants and clinical staff
- Stefan Peterson and Michael Chen, statistical support
- Sonia Oosman, study co-ordination and operations