Innovations in opioid dependence treatment
Prolonged-release buprenorphine

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Disclosures

Prof D’Agnone has been scientific adviser and speaker for: Gilead Sciences, Britannia Pharmaceuticals, Indivior, Martindale Pharma, Shire & Camurus

Prolonged release buprenorphine profiling for ODT patients

Ensure compliance[1,2,3]

Reduce burden and stigma of daily pick ups and supervised consumption[4]

- Cost[5]
- Time commitment[4]
- Stigma[4]

Need to ensure opioid receptor blockade

- Preventing overdose[6,7]
- Alternative options: naltrexone tablets or implant?*

Transport and storage of CDs[3]

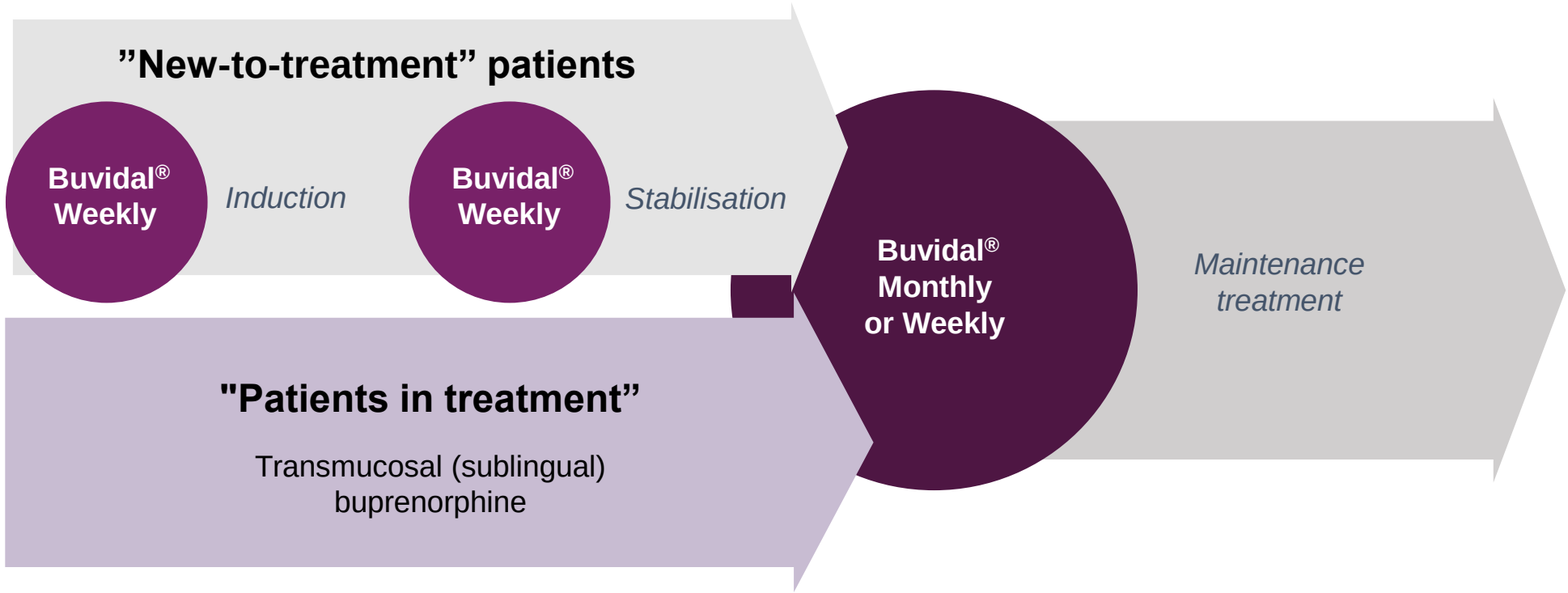
- Commuters[5]
- Domestic and international flyers[5]
- Child safeguarding issues[5]
- Prison population[3,6]

**Not approved in Europe*

CD, controlled drug; ODT, opioid dependence therapy

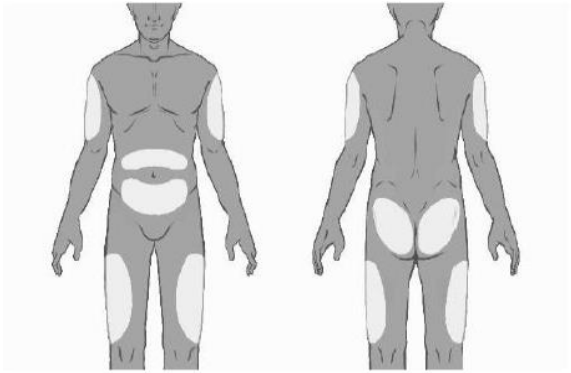
1. Albayaty M, et al. *Adv ther* 2017;34:560–75; 2. Frost M, et al. *Addiction* 2019 (in print); 3. NICE. ES19. 2019; 4. Gilman M, et al. *Patient prefer adherence* 2018;12:2123–29; 5. Bailey GL, et al. AAAP 2018 (poster presentation); 6. Dematteis M, et al. *Expert opin pharmacother* 2017;18:1987–99; 7. Lofwall MR, et al. *JAMA intern med* 2018;178:764–73

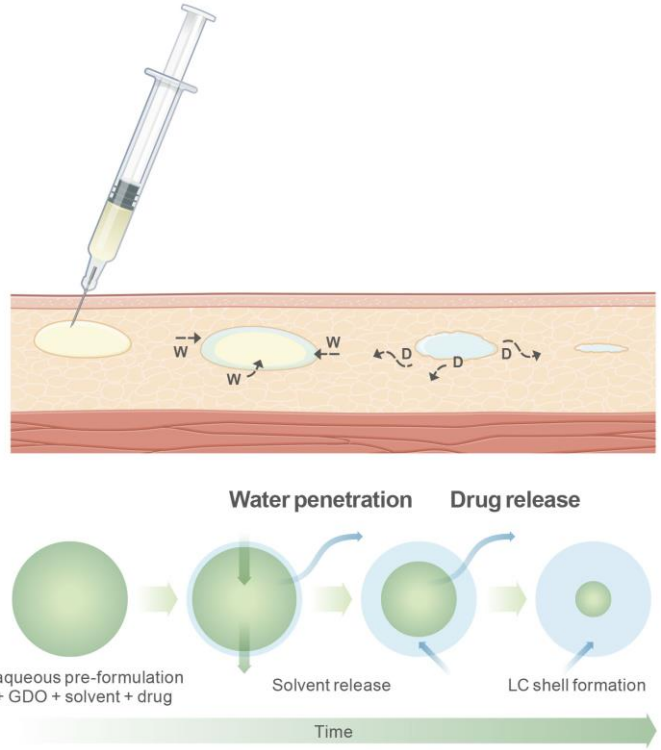
Buvidal® – developed for treatment of opioid dependence across treatment phases



Buvidal® – weekly and monthly buprenorphine depots for treatment of opioid dependence

- Multiple dose options: 4 x weekly, 3 x monthly
  - Weekly: 8mg, 16mg, 24mg, 32mg
  - Monthly: 64mg, 96mg, 128mg
- Ready for use – pre-filled syringe
  - Retractable, 23 gauge, stored at room temperature





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

Buvidal® (CAM2038) clinical evidence

Phase I/2 pharmacokinetics

Four clinical trials in healthy volunteers and opioid dependent patients[1,2]

Phase 2 pharmacodynamics

A double-blind, randomised within-patient, opioid challenge study in adults with moderate-to-severe opioid use disorder[3]

Phase 3 efficacy

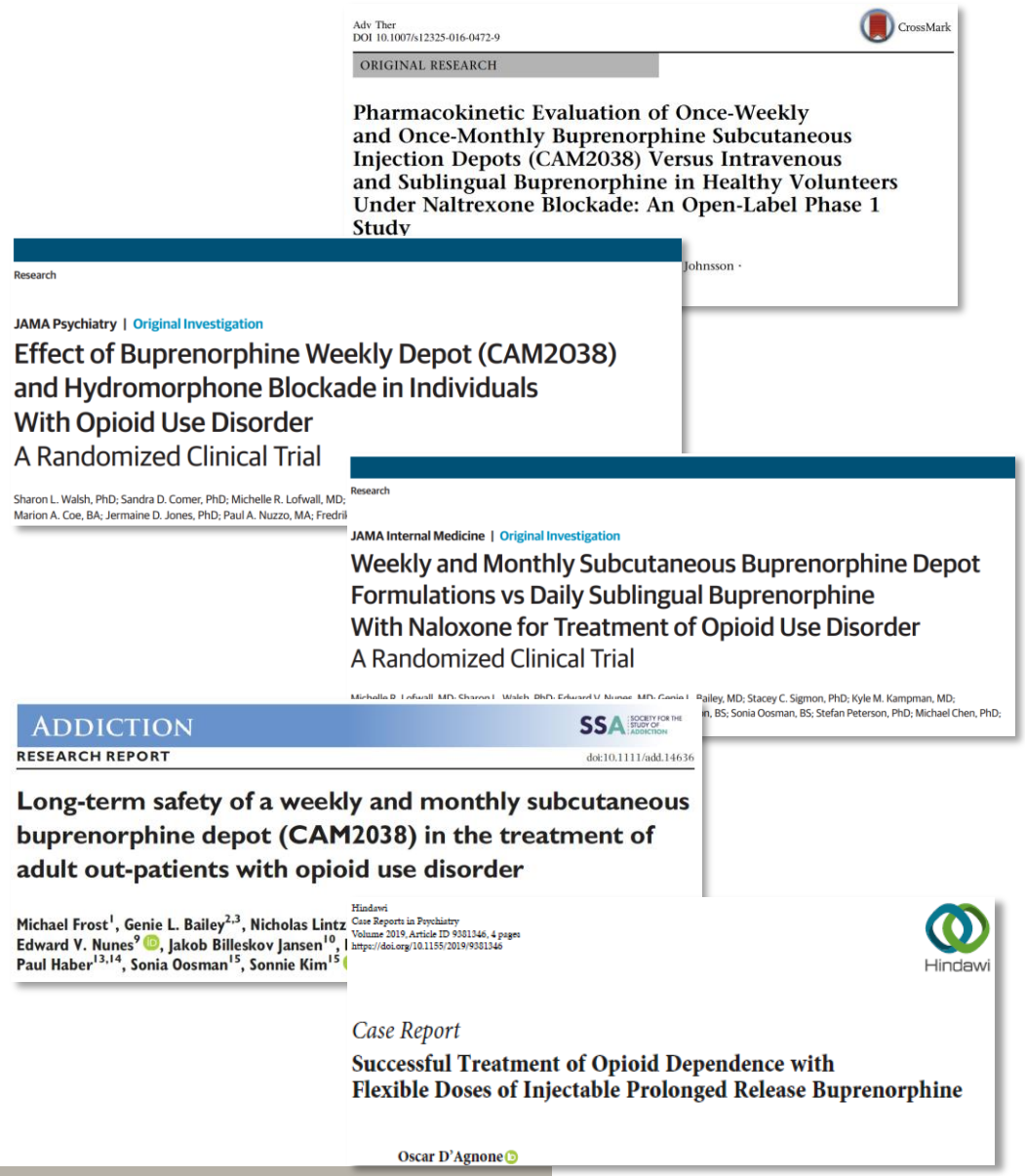
A 24-week, randomised, double-blind, double-dummy study assessing efficacy and safety of CAM2038 versus daily sublingual buprenorphine/naloxone[4]

Phase 3 long-term safety

A 48-week, multinational, open-label study assessing long-term safety and efficacy of CAM2038[5]

Real world evidence

Case reports in clinically relevant scenarios[6]

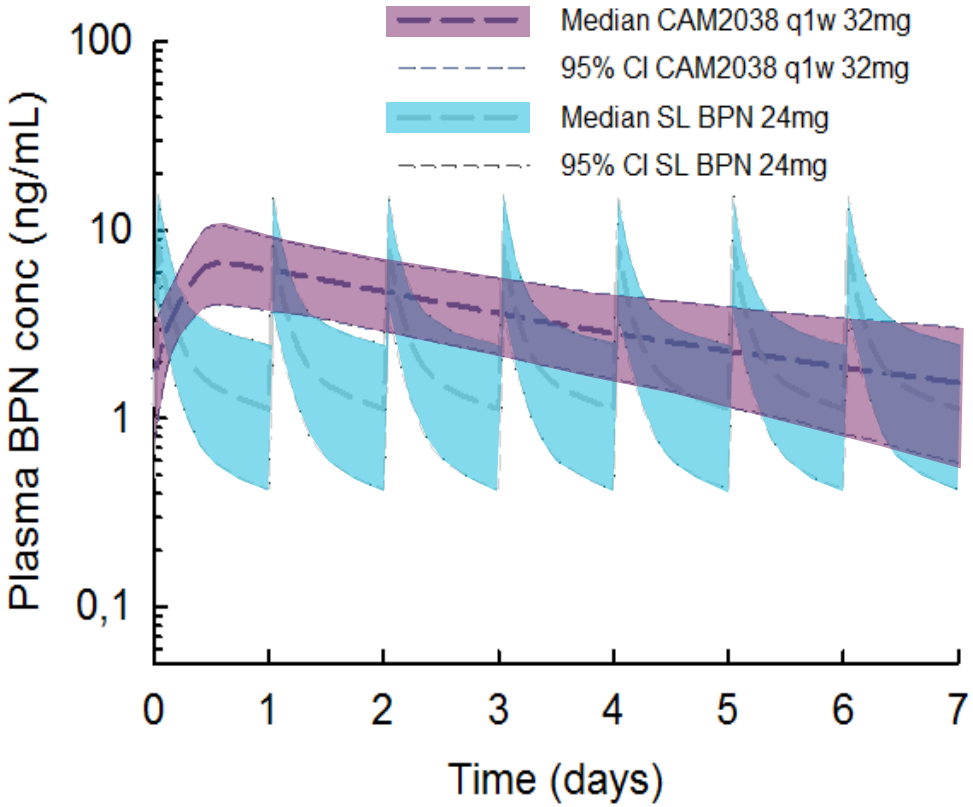


1 Haasen, C, et al, J Subst Abuse Treat. 2017;78:22-29 2 Albayaty M, et al, Adv Ther. 2017 34(2):560-575; 3 Walsh et al, JAMA Psychiatry 2017;74(9):894-902;; 4 Lofwall et al. JAMA Int. Med. 2018;178(6); 764-773; 5 Frost et al, Addiction, 2019;114(8):1416-1426; D'Agnone , Case Reports in Psychiatry 2019 https://doi.org/10.1155/2019/9381346

Steady-state population pharmacokinetics (PK) profile after weekly dosing of Buvidal® (CAM2038)[1,2]

Weekly Buvidal – Daily SL BPN

Population PK analysis and modelling based on data from four clinical studies (n=236)



Dose proportional PK observed for both weekly and monthly Buvidal® formulations

Rapid and sustained blockade of opioid effects observed from first dose[3]

SL, sublingual; BPN, buprenorphine

1 Abstract - Annual conference of the Society for the Study of Addiction- November 2018 https://www.addiction-ssa.org/symposium/presentation/cam-2038-a-new-liquid-lipid-crystal-depot-buprenorphine-a-dose-ranging-suit; 2 Albayaty M, et al. Adv Ther. 2017;34(2):560–575. 3. Walsh SL, et al. JAMA Psychiatry 2017; 74(9): 894-902.

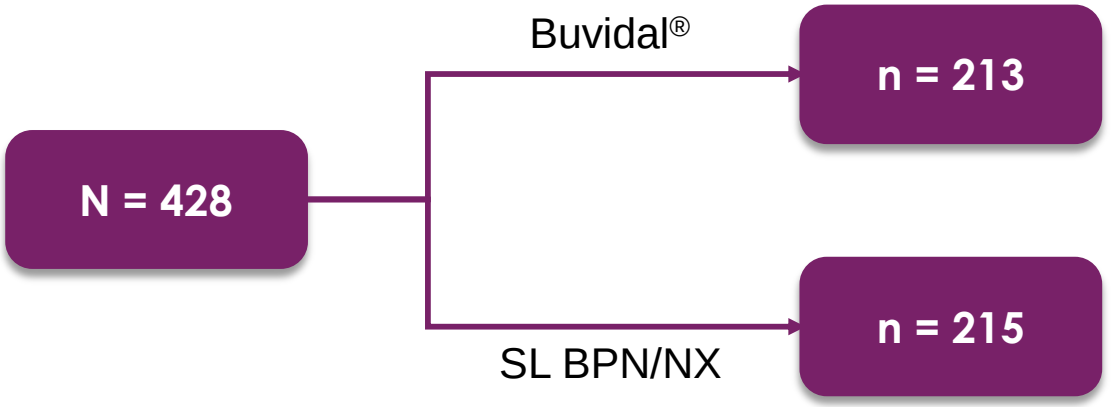
Dose conversion between sublingual buprenorphine and weekly and monthly Buvidal®

Dose of daily SL BPN*	Dose of Buvidal® weekly	Dose of Buvidal® monthly
2–6 mg	8 mg	–
8–10 mg	16 mg	64 mg
12–16 mg	24 mg	96 mg
18–24 mg	32 mg	128 mg

*The dose of buprenorphine in mg can differ between sublingual products, which needs to be considered on a product-by-product basis

Phase 3 randomised double blind 24-week study of efficacy of Buvidal® vs SL BPN/NX[1]

- Double-blind, double-dummy
- SC depot BPN (Buvidal®) versus SL BPN/NX
- Treatment-seeking adults with moderate-to-severe opioid use disorder
- Flexible dosing according to patient needs and clinical judgement

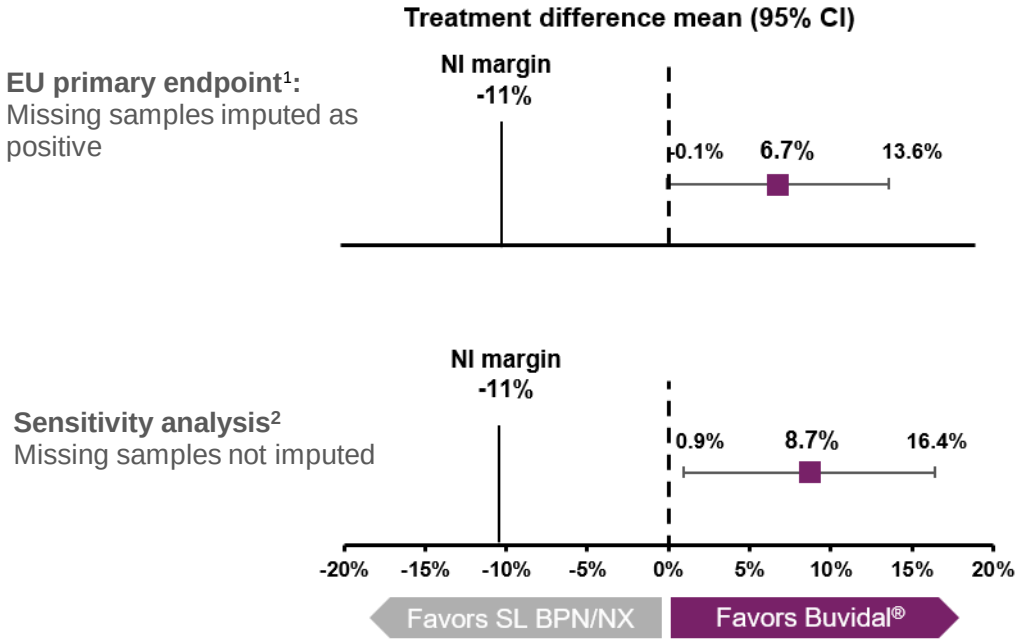


BPN, buprenorphine; SL, sublingual; BPN/NX, buprenorphine/naloxone

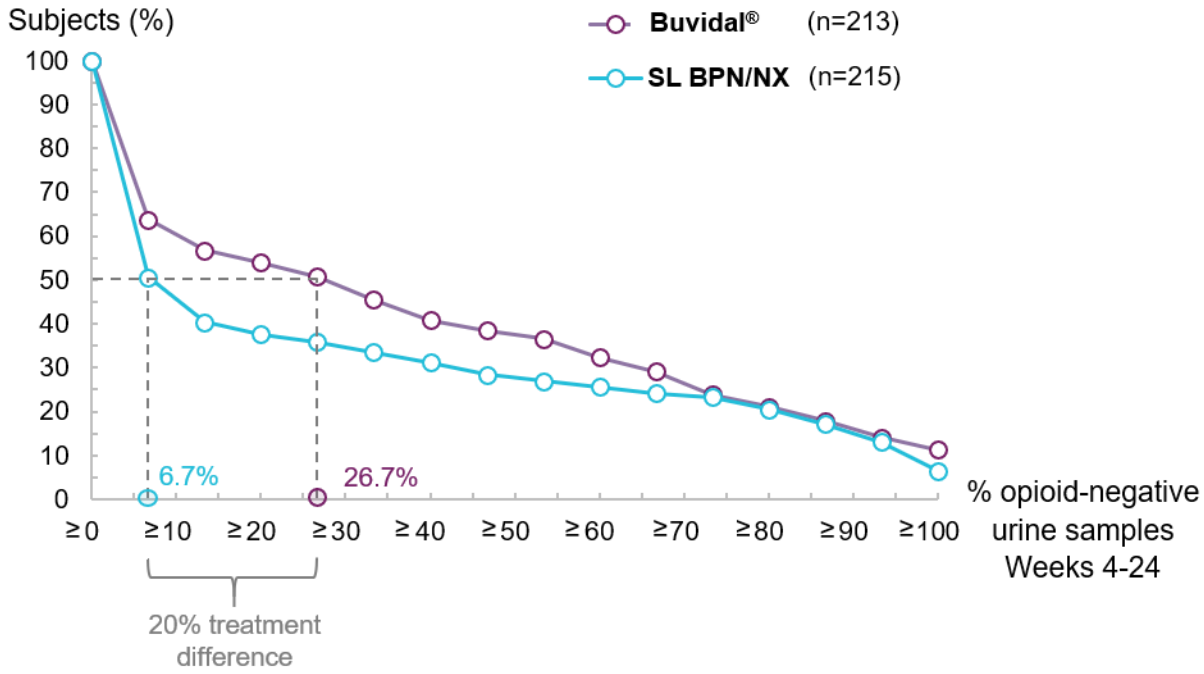
1 Lofwall M R, et al. JAMA Internal Medicine. 2018;178(6); 764-773

Phase 3 efficacy study primary and key secondary endpoints met[1]

Non-inferiority for mean % urines negative for illicit opioids, p<0.001[1,2]



Superiority for CDF for negative urines weeks 4-24*; median 26.7% vs. 6.7%, p=0.008[1,2]



***Missing samples imputed as positive**

CDF = cumulative distribution function, EMA = European medicines agency, NI = non-inferiority, SL BPN/NX = sublingual buprenorphine/naloxone

1 Lofwall M R, et al, JAMA Internal Medicine. 2018;178(6); 764-773. 2 EPAR December 2018 EMEA/H/C/004651/0000 https://www.ema.europa.eu/documents/assessment-report/buvidal-epar-public-assessment-report_en.pdf

Phase 3 efficacy study adverse events[1]

Safety profile consistent with sublingual BPN/NX, with the exception of mild-to-moderate injection site adverse reactions

Adverse event characteristic ***Trial group, no. (%) of participants***	**SL-BPN/NX** (n = 215)	**Buvidal®** (n = 213)	**All** (N = 428)
Any	119 (55.3%)	128 (60.1%)	247 (57.7%)
Drug-related	64 (29.8%)	70 (32.9%)	134 (31.3%)
Severe	15 (7.0%)	6 (2.8%)	21 (4.9%)
Non-fatal serious	13 (6.0%)	5 (2.3%)	18 (4.2%)
Deaths*	0	1 (0.5%)*	1 (0.2%)
Hospitalisations	12 (5.6%)	3 (1.4%)	15 (3.5%)
Drug overdoses	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			
Injection site reactions	48 (22.3%)	40 (18.8%)	88 (20.6%)
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%)
Urinary tract infection	10 (4.7%)	11 (5.2%)	21 (4.9%)
Insomnia	6 (2.8%)	12 (5.6%)	18 (4.2%)

1 Lofwall M R, et al. *JAMA Internal Medicine. 2018;178(6); 764-773*

*One patient died as a result of being hit by a car. SL, sublingual; BPN/NX, buprenorphine/naloxone

Phase 3 open label long-term (48-week) safety study with flexible dosing regimen[1]

ADDICTION SSA SOCIETY FOR THE STUDY OF ADDICTION

Research Report | Full Access

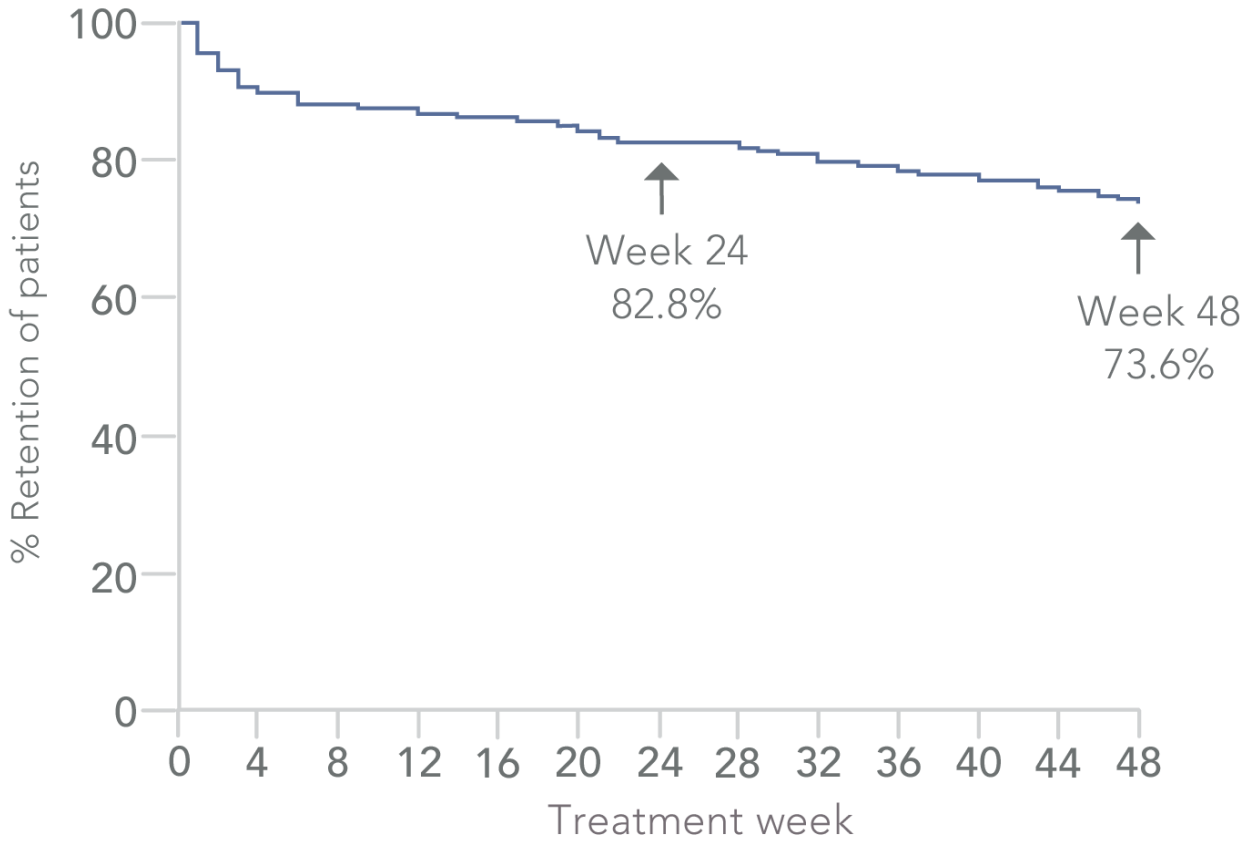
Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult outpatients with opioid use disorder

Michael Frost, Genie L. Bailey, Nicholas Lintzeris, John Strang, Adrian Dunlop, Edward V. Nunes, Jakob Billeskov Jansen, Lars Chemnitz Frey, Bernd Weber, Paul Haber, Sonia Oosman ... See all authors

First published: 23 April 2019 | https://doi-org.ezproxy.newcastle.edu.au/10.1111/add.14636

Frost et al Addiction 2019

- Open label 48-week safety study
- 26 centres: Europe, USA, Australia
- N=227: 190 transferred from SL BPN, 37 new to BPN
- Injection site reactions (mild-moderate) 20%
  - Pain, swelling, erythema

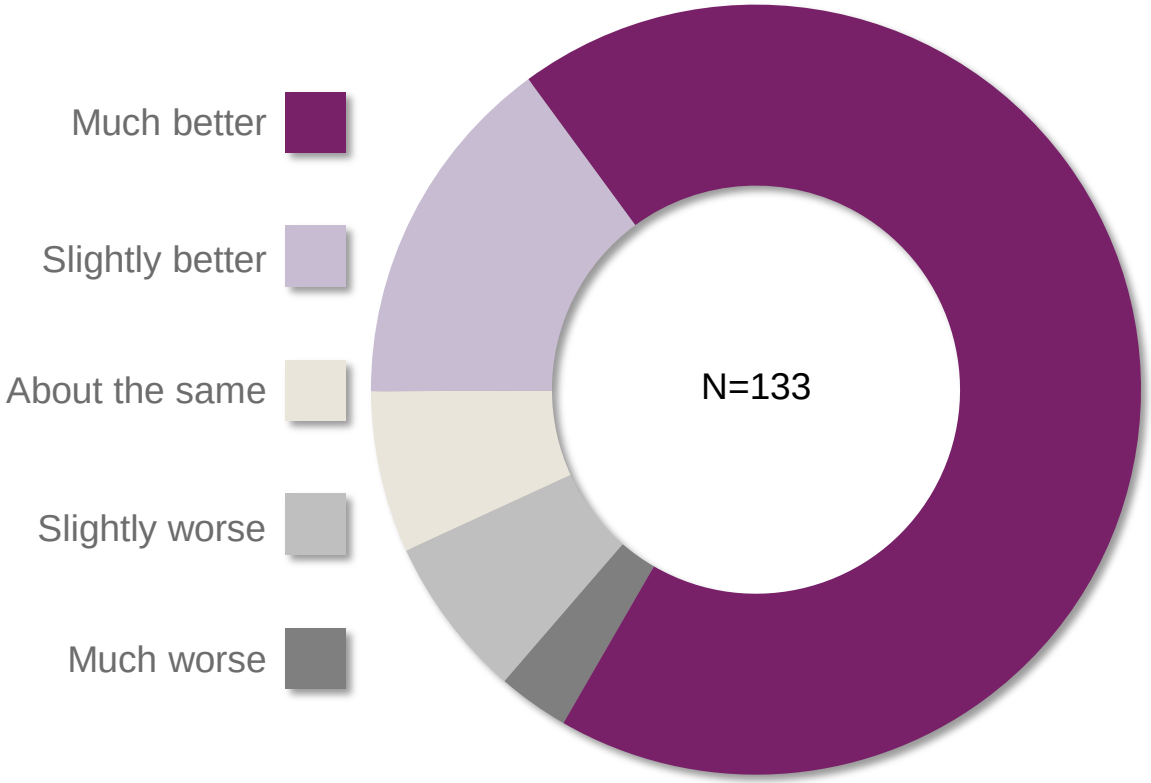


SL, sublingual; BPN, buprenorphine

1 Frost M, et al. Addiction. 2019

Phase 3 long-term safety study patient satisfaction[1]

"Please evaluate your overall experience with the study medication compared to your previously prescribed SL BPN treatment"



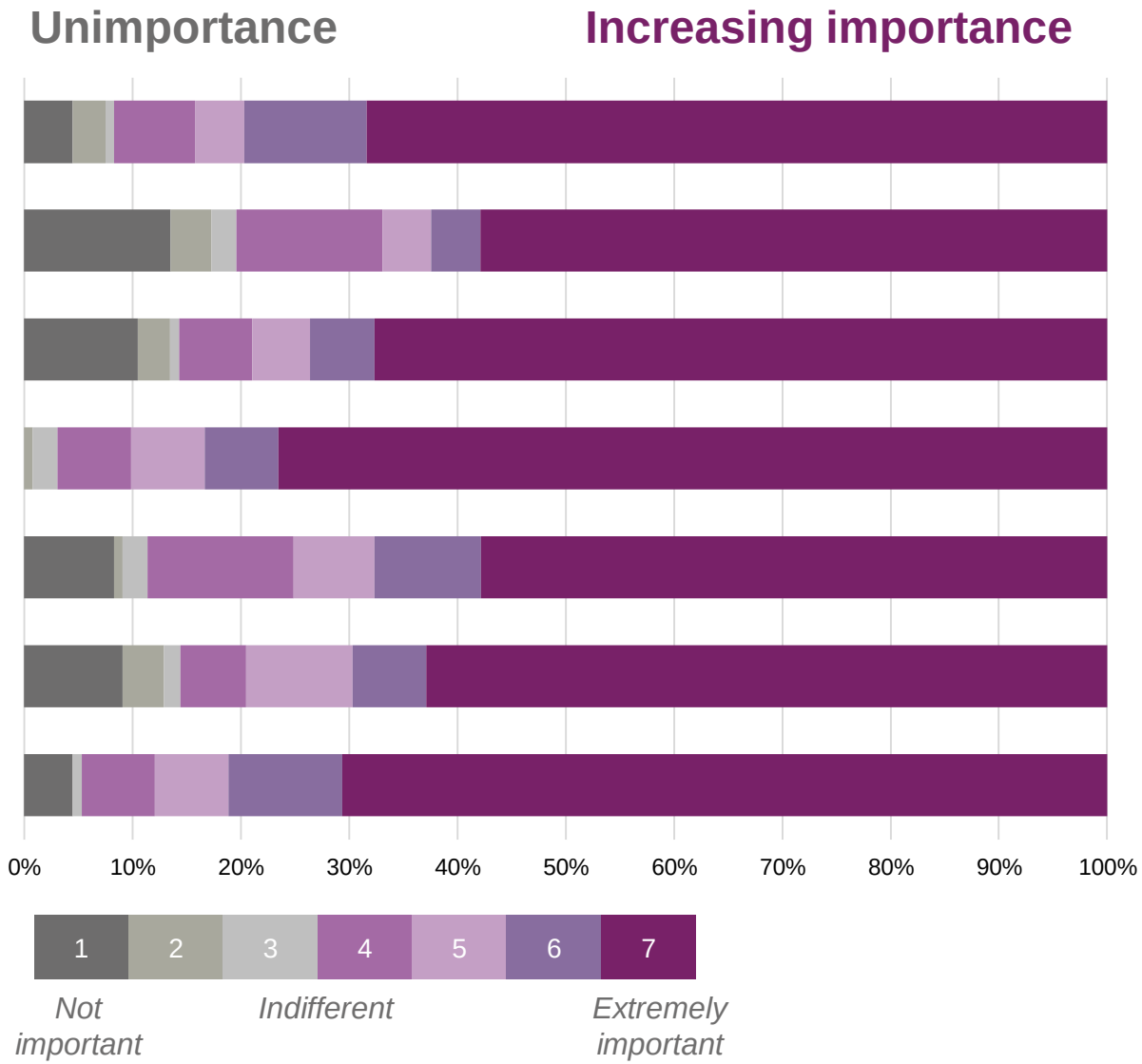
83% SLIGHTLY OR MUCH BETTER

SL, sublingual; BPN, buprenorphine

1 Frost M, et al. Addiction. 2019

Phase 3 long-term safety study patient satisfaction[1]

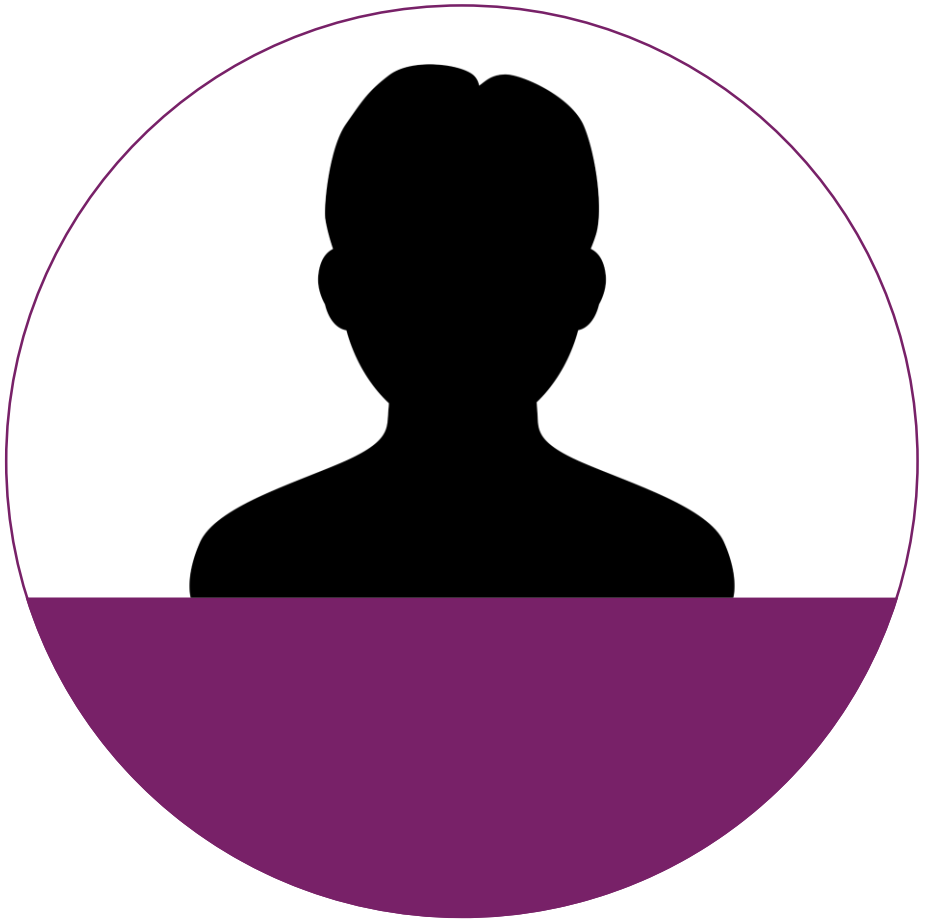
- ✓ **Spares regular visits to the pharmacy (n=133)**
- ✓ Prevents others access to my medication (n=133)
- ✓ Prevents accidental exposure children/pets (n=133)
- ✓ **Not require daily medication (n=133)**
- ✓ Improves my privacy as a patient (n=133)
- ✓ Helps me not miss or skip medication dose (n=132)
- ✓ **Allowed to travel with no medication (n=133)**



SL, sublingual; BPN, buprenorphine

1 Frost M, et al. Addiction. 2019

Case Study (1)



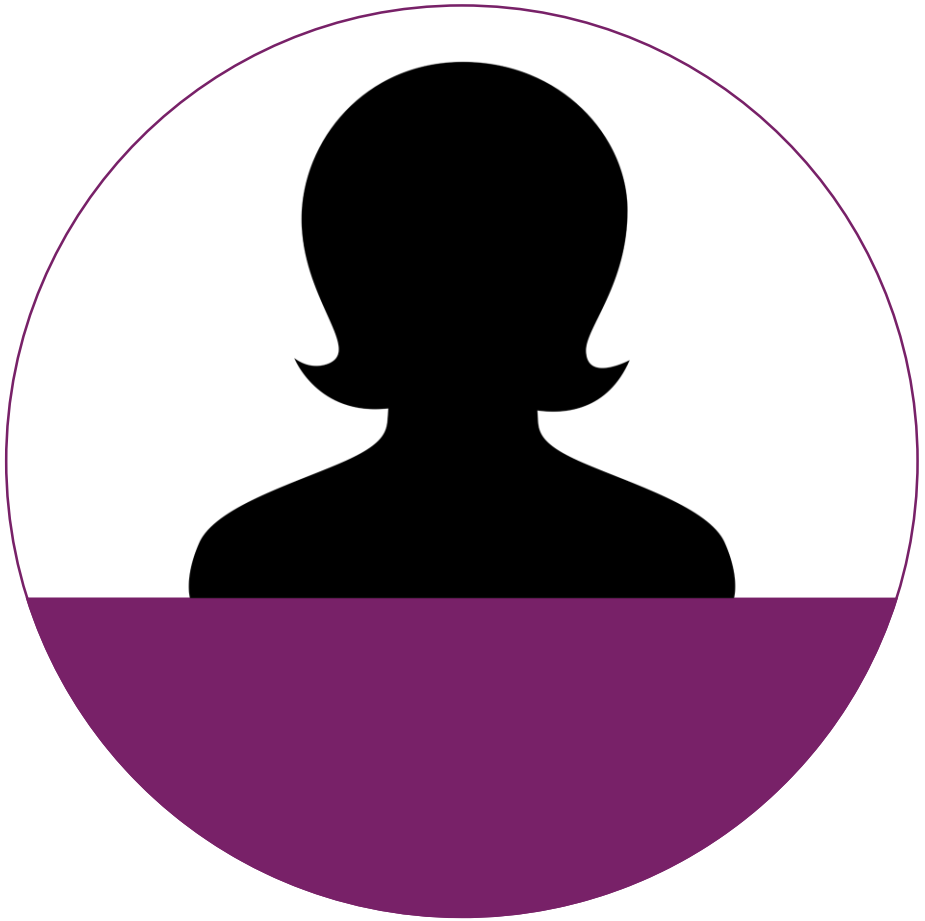
52 year old, male

- >20 years opioid use, intermittent injected heroin use
- No MH problems
- Married with 2 children, living with family
- Employed in senior management role
- Initial treatment plan based on supervised SL BPN

MH, mental health; SL, sublingual; BPN, buprenorphine

D'Agnone , Case Reports in Psychiatry 2019 https://doi.org/10.1155/2019/9381346

Case Study (2)



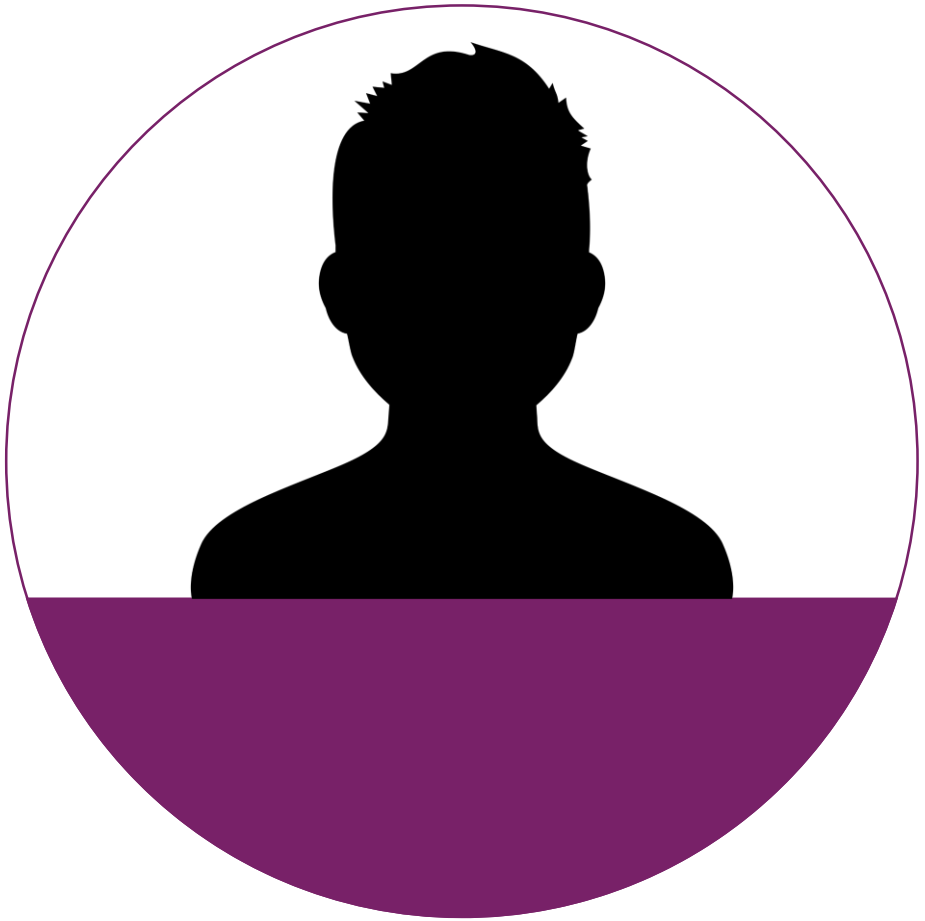
56 year old, female

- >20 years use on and off, heroin smoker
- Support from friends
- Committed to treatment
- Poor compliance, has relapsed before
- Initial treatment plan based on oral methadone
- Started to smoke heroin daily in addition to prescribed methadone

ODT, opioid dependence therapy

D'Agnone , Case Reports in Psychiatry 2019 https://doi.org/10.1155/2019/9381346

Case Study (3)



48 year old, male

- >20 years on and off use, IV heroin user
- No MH issues
- Strong family support
- Employed full-time
- Committed to treatment
- Positive results with buprenophine ODT previously
- Beginning new treatment episode

IV, intravenous; MH, mental health; ODT, opioid dependence therapy

D'Agnone , Case Reports in Psychiatry 2019 https://doi.org/10.1155/2019/9381346