Free Clinical Update: Special Edition

This clinical update focuses on Buvidal® (CAM2038), the new prolonged-release subcutaneous buprenorphine injection for opioid use disorder, developed by Camurus.

The purpose of this update is not to summarise the pharmacological properties of Buvidal®, nor to explain in detail how it works. For this the summary of product characteristics can be consulted (see links below). Instead this update evaluates the evidence base for Buvidal®. Three studies are summarised with individual commentary on the results of each study. A wider discussion then follows about the clinical implications of this exciting new technology.

Buvidal 64/96/128 mg prolonged-release solution for injection
Buvidal 8/16/24/32 mg prolonged-release solution for injection

This clinical update has been funded by an educational grant from Camurus.

Effect of buprenorphine weekly depot (CAM2038) and hydromorphone blockade in individuals with opioid use disorder: A randomized clinical trial.


This multisite, double-blind, randomised clinical trial evaluated the ability of the CAM2038 weekly buprenorphine depot injection to block euphorigenic opioid effects and suppress opioid withdrawal. 47 adults with moderate-severe opioid use disorder (OUD) received intramuscular hydromorphone (0, 6mg or 18mg) injections during a 3-day test session and were then randomised to either CAM2038 weekly 24mg (n=22) or 32mg (n=25).

At 4 subsequent 3-day test-sessions participants received further hydromorphone injections and then rated their subjective liking of the drug, and desire to use, using visual analogue scales. Opioid withdrawal symptoms were also assessed using the clinical opioid withdrawal scale. The study was conducted in an inpatient setting and lasted 3 weeks. Patients received a total of 2 CAM2038 weekly injections.

The authors found that both weekly CAM2038 doses produced a rapid rise in plasma buprenorphine levels with maximum concentration at around 24 hours. CAM2038 had a 4-5 day half-life and approximately 50% accumulation of trough concentration from first to second dose. CAM2038 was safely tolerated, suppressed withdrawal symptoms, and produced immediate and sustained opioid blockade.

Commentary:

This phase 2 study effectively demonstrates two key functions of the weekly injectable buprenorphine product CAM2038 – it is able to block the euphorigenic opioid effects of
hydromorphone, and it prevents opioid withdrawal symptoms in patients with opioid dependence.

Pharmacokinetic data revealed that dose-dependent plasma concentrations of buprenorphine with accumulation across successive injections were observed, and authors suggest steady state may be achieved after 4 CAM2038 weekly injections. This is important for patients to understand, so that they have clear expectations of treatment with injectable buprenorphine.

Importantly, this study found that patients did not require induction and stabilisation with sublingual (SL) buprenorphine before initiating treatment. Some patients in the community struggle to adhere to SL buprenorphine during the induction phase, either because of the requirement to be in a state of withdrawal before administering the first dose, or due to the need to attend services and the pharmacy for supervised dosing and titration at the beginning of treatment. The authors speculate that the pharmacokinetic profile of CAM2038, where plasma levels gradually rise to maximum concentration over approximately 24 hours, may mimic the induction procedure of SL buprenorphine, where small doses are typically given incrementally over the first day. So, potentially, injectable buprenorphine is a more suitable treatment option for patients who struggle with the initiation procedure of sublingual preparations. The authors also found no evidence of CAM2038 precipitating withdrawal, even after a protocol deviation where 5 participants received their first injections before exhibiting mild withdrawal symptoms as rated using the clinical opioid withdrawal scale (COWS).

One major benefit of CAM2038 over SL buprenorphine is the reduced risk of diversion, misuse and non-adherence. This may have particular relevance in custodial settings where this is a major concern. Administration of Buvidal® is currently restricted to healthcare professionals, which should also eliminate the need to store medication at home, thereby reducing the risk of accidental administration by children or opioid-naïve adults.

There were no severe adverse events (AEs) thought to be related to CAM2038 in this study, though several side effects were reported. 81% of participants experienced 1 or more AE, the most common being constipation (19%), injection-site pain (11%) and erythema (9%), headache (9%), and nausea (9%). The majority of these are known side effects of buprenorphine. Those unique to CAM2038 are the injection-site related effects, though most of these were rated as mild severity. It is important that patients are aware of potential side effects so they can make informed decisions about their care. Some patients may find injections and needles triggering, and may have had negative experiences when receiving injections from healthcare professionals. We must ensure we are able to have conversations with patients about the specific risks and benefits of this new medication, and service providers must empower their staff to do this by ensuring appropriate training is provided.

The absence of a control group is a limitation of this study, as is the relatively small sample size. The study participants may also not be entirely representative of the target treatment population. Participants were aged 18-55 and, as is often the case with research trials, relatively healthy. The use of CAM2038 in older populations, those with comorbidity, and patients with polysubstance use, needs further study. Interestingly, the participants were specifically not seeking treatment for OUD. Patients who were treatment-seeking were excluded and instead referred to services.

Although it was not within the scope of this study, it would be interesting to explore whether or not there were any significant differences in characteristics and demographics between treatment-seeking and non-treatment-seeking individuals.
naloxone for treatment of opioid use disorder: A randomized clinical trial.


This double-blind, double-dummy, randomised clinical trial aimed to determine whether or not weekly and monthly subcutaneous buprenorphine (SC-BPN) preparations were non-inferior to daily sublingual buprenorphine with naloxone (SL-BPN/NX) for the treatment of OUD. 428 treatment-seeking participants with moderate-to-severe OUD were recruited at 35 outpatient sites in the United States.

Participants were randomised to one of two groups: daily SL placebo and weekly (first 12 weeks) and monthly (last 12 weeks) SC-BPN, or daily SL-BPN/NX with matched weekly and monthly placebo injections. Physicians were also able to provide individualised dose titration during the second 12 weeks with the availability of supplemental 8mg injections, though few patients require these.

Having no evidence of illicit opioid use for at least 8 of 10 pre-specified points during weeks 9 to 24. The mean proportion of opioid-negative urine samples evaluated by a cumulative distribution function (CDF) was an a priori secondary outcome. The study duration was 24 weeks.

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. 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. The CDF for the SC-BPN group (26.7%) was statistically superior to the CDF for the SL-BPN/NX group. Mild to moderate injection site-related AEs were reported in 48 participants (22.3%) in the SL-BPN/NX group and 40 (18.8%) in the SC-BPN group. Similar study retention was observed in both groups.

The authors concluded that depot buprenorphine is efficacious and may have advantages compared to SL-BPN. Depot buprenorphine did not result in an inferior likelihood of having opioid-negative urine test results, or being a responder, and produced superior results on the CDF of no illicit opioid use.

Commentary:

This pivotal phase 3 study effectively demonstrated that subcutaneous depot buprenorphine is non-inferior to sublingual buprenorphine. The superiority of SC-BPN on the CDF of negative urine samples meant that participants receiving SC-BPN produced higher rates of opioid-negative urine samples as the study progressed, and effectively used less illicit opioids. This finding is consistent with another study on the buprenorphine implant and is not entirely surprising given that adherence to treatment is achieved based on a single weekly or monthly dose, compared to daily dosing of SL-BPN/NX. For patients taking a daily medication the demands on the individual to adhere to treatment are higher as they are presented with a daily choice about adherence. A weekly or monthly injection removes this demand, though some may see this loss of autonomy as restrictive. Clinicians must ensure that the use of depot buprenorphine is not punitive and that restrictions imposed on the basis of safety and efficacy are decided upon collaboratively with capicitous patients.

The relatively low percentage of opioid-negative urine samples and low responder rate with both buprenorphine preparations in this study reminds us that we must have realistic expectations of any new technology and not assume that a new buprenorphine preparation is going to completely change the landscape of opioid treatment. Opioid substitution therapy (OST) is an important and widely used component of harm reduction, and buprenorphine is one of the best treatment options we currently have available. With that in mind, prolonged-release SC-BPN presents several potential advantages over sublingual preparations for use in various patient populations.
Depot buprenorphine may be particularly useful in prison populations. The authors note that one heroin overdose occurred in the SL-BPN/NX group when a participant was jailed, did not have access to study medication, and on release used heroin to treat withdrawal symptoms and overdosed. We know that opioid-dependent individuals released from prison are at high risk of dying from an opioid overdose, often due to loss of opioid tolerance and non-engagement with treatment services. If prisoners were instead maintained on long-acting subcutaneous buprenorphine, tolerance to opioids would be maintained, and individuals would be less likely to discontinue their opioid substitution therapy specifically due to an inability to present at community substance misuse services on the day of release. Methadone is currently the first-line treatment for OUD offered in prisons. Buprenorphine is not commonly prescribed in prisons due to the risks of diversion and misuse, and the difficulty of supervising administration, which can take several minutes. Subcutaneous buprenorphine administered by a healthcare professional would present two main benefits over both sublingual buprenorphine and methadone; it would eliminate the risk of diversion and misuse, and it would reduce the pressure on patients and community services to see patients for assessment and prescribing on the day of release.

Likewise, transitions between care settings, such as community to hospital, may be less fraught if patients are prescribed long-acting subcutaneous buprenorphine, rather than oral or sublingual OST. Discontinuation of medical care in hospital due to poor management of opioid withdrawal, and delays in confirming community methadone or buprenorphine prescriptions, is not uncommon.

If patients requiring acute medical care no longer have the additional concern of developing opioid withdrawal symptoms due to missing OST doses when they are admitted to hospital, they may be more likely to adhere to medical treatment in hospital. This of course is beneficial to patients and treatment providers.

One limitation of this study is that SC-BPN was compared with a sublingual buprenorphine /naloxone preparation, rather than buprenorphine alone. In the UK buprenorphine is far more commonly prescribed than buprenorphine /naloxone. Whilst it is unlikely that comparing SC-BPN with sublingual buprenorphine (SL-BPN) alone, rather than SC-BPN/NX, would produce dramatically different results, there is a paucity of evidence on the differences and similarities between different sublingual buprenorphine formulations. It therefore remains to be seen whether or not these results are entirely applicable to patients in the UK who would otherwise be prescribed SL-BPN, rather than SL-BPN/NX.

Injection site-related AEs occurred in both groups, and at a slightly lower rate in the active SC-BPN group. Whilst complications arising from injecting drugs are common, patient acceptability of treatment-related injecting site AEs should be explored in future qualitative studies. The most common injection site reaction was transient pain, an expected effect of many injectable medications. Future studies should evaluate the impact of repeated dosing of SC-BPN over time. For now, clinicians should ensure that injection administration sites are clearly documented and injection sites are rotated.

Unlike the first study discussed above, participants in this study were aged 18-65 years, which is slightly more representative of the target treatment population. However, like the study above, patients with renal or hepatic impairment, and pregnant patients, were excluded. Real-world patients, particularly those with polysubstance misuse and associated comorbidities, often have renal or hepatic impairment and many are prescribed concomitant medications that may interact with buprenorphine. Prescribers will have to carefully consider the risks of prescribing SC-BPN to these complex patients.
buprenorphine (CAM2038) in adult outpatients with opioid use disorder.


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This phase 3 open-label study aimed to demonstrate the safety and tolerability of CAM2038 once weekly (q1w) and once monthly (q4w). Adult outpatients (n=227) with OUD were enrolled across 26 sites in the United States, UK, Europe, and Australia, and received at least one dose of CAM2038. Subjects were either seeking buprenorphine treatment or already receiving sublingual buprenorphine (SL-BPN) or buprenorphine with naloxone (SL-BPN/NX). Those already receiving SL-BPN or SL-BPN/NX had the option of transferring to q1w or q4w, whereas those not prescribed OST commenced CAM2038 q1w. A pre-specified dose conversion schedule was used to guide initiation doses, and dose adjustments were available using supplemental 8mg injections of CAM2038 q1w.

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156 subjects (68.7%) were exposed to CAM2038 for the full 48 weeks. Subjects receiving SL-BPN at entry had a high percentage of negative urine samples from month 1 to month 12 (72.8% to 78.3%). Subjects who were new to BPN treatment had a low percentage of negative urine samples at month 1 (2.7%) and generally increased through month 12 (48.3%; range 2.7% to 48.3%). Withdrawal symptoms were low at baseline and reduced throughout the study, as did cravings. Other drug use was low and remained generally stable throughout the study.

The authors concluded that, with the exception of injection site treatment emergent adverse events (TEAEs), the long-term safety profile of CAM2038 was generally consistent with the known safety profile of SL-BPN. Injection site TEAEs were generally mild-moderate in severity, and rarely led to study discontinuation. Patient satisfaction surveys at 6 and 12 months revealed a majority of the 133 respondents who converted from SL-BPN felt CAM2038 was “much better” than previous treatment (68.4%), while only 3% described CAM2038 as “much worse”.

Commentary:

Although the majority of subjects were receiving SL-BPN at entry (n=190), 37 subjects were new to buprenorphine treatment. This study again demonstrated that patients did not need to be inducted using SL-BPN before commencing CAM2038. Of note is that a large proportion of participants (42.6%) who were receiving SL-BPN at entry had abused prescription opioids, whereas 51.1% used heroin as their primary drug of use. This suggests that CAM2038 may have clinical applications in diverse populations, and not solely in patients dependent on heroin. Future studies evaluating the use of CAM2038 in patients dependent on prescribed opioids would help to determine its efficacy in this specific population.

The fact that those subjects already prescribed SL-BPN at commencement had a much higher percentage of negative urine samples compared to subjects who were new to BPN treatment, is not entirely unexpected, and suggests that the SL-BPN subjects had a period of stability prior to study commencement. Despite this those subjects new to treatment showed marked improvement and the findings suggest that the SL-BPN patients remained stable or improved with CAM2038 treatment.

This study showed that CAM2038 was well tolerated and the safety profile was generally consistent with that of SL-BPN. There were no deaths, no drug-related serious AEs, and no unexpected AEs during the study. 20.3% of the overall safety population (those who received at least 1 CAM2038 injection) experienced at least 1 injection-related TEAE, the most common being injection site pain (15.4%), swelling (11.9%), and erythema (9.3%). Most were mild to moderate in intensity. One subject had a severe injection-site TEAE of CAM2038 was also evaluated using several parameters; urine toxicology, withdrawal symptoms, and cravings.

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(pain) which resolved the same day with no changes to the study drug. Two subjects had a single occurrence of injection site ulcer, both of which resolved spontaneously. These findings are similar to those in the studies above. Qualitative feedback from patients is needed to ascertain patient perceptions of injection-related side effects, and to evaluate whether or not this affects adherence to CAM2038.

The patient satisfaction results in this study are very encouraging and reveal that the majority of participants surveyed preferred CAM2038 to their previous SL-BPN treatment. A qualitative component to research is valuable as it allows us to explore whether or not the treatment priorities of clinicians are in line with those of patients.

Future research should focus on patient satisfaction of CAM2038, specifically in comparison with other available treatment options.

A total of 96 (42.3%) subjects received supplemental doses of CAM2038 during the study, though the vast majority of these (n=91) were receiving SL-BPN at entry. This is important to consider as supplemental dosing may require additional clinic visits and therefore be associated with increased costs in practice. More information and guidance is needed around the timing of supplemental dosing and conversion between SL-BPN and SC-BPN, though I suspect conversion will vary from individual to individual. If a patient is requiring supplemental dosing during the early stages of conversion to injectable buprenorphine it may be prudent to incorporate the additional dose into the standard weekly or monthly dose, if possible. For example a patient on 24mg of SC-BPN requiring a supplemental dose of 8mg would receive a 32mg dose at the next weekly interval. This may prove more difficult for patients on monthly dosing, depending on the number of supplemental doses required throughout the month, and for patients requiring larger than licensed doses. One must also consider the fact that steady state exposure is reached at the fourth weekly or monthly dose. This should be made clear to patients so that supplemental dosing is not overused in the early stages of treatment when patients simply need more time for buprenorphine to reach steady state exposure.

The authors identify several limitations to this study. Some outcomes were collected by self-report to clinicians, so may not be entirely reliable, there was no control group, and broader quality of life outcomes were not collected. However, as an open label safety study there were few exclusion criteria and the screen failure rate was relatively low. Hopefully if prescribing of CAM2038 becomes commonplace longitudinal studies with a focus on treatment retention, psychosocial and quality of life outcomes, and adverse events can be conducted in naturalistic settings, to plug the gaps in the current evidence base.

Discussion:

Much of the research and discussion surrounding this new technology has rightly focused on the safety, efficacy, and initiation of subcutaneous buprenorphine. This is all very sensible and necessary, but consideration also needs to be given to patients who wish to detoxify from long-acting subcutaneous buprenorphine. Traditionally, detoxification from sublingual buprenorphine is done by incrementally reducing the daily dose over a period of days, weeks, or months in a community or inpatient setting. Patients who detox in an inpatient setting generally complete this process over a period of 7-21 days, depending on the starting dose. The trajectory of withdrawal is well documented and can be anticipated, and adjunct pharmacological therapies are often given to manage symptoms. Professionals and patients must now consider what the most appropriate way of detoxing from long-acting formulations is. What are the objective and subjective trajectories of withdrawal symptoms in patients who cease taking weekly or monthly buprenorphine injections? How does length of treatment effect the rate at which buprenorphine leaves the system? Is it necessary to gradually reduce the dose of SC-BPN or can a patient abruptly stop taking their dose? These are questions that have not yet been answered in the literature.

Patients will inevitably lose some autonomy when taking long-acting buprenorphine. An individual taking sublingual buprenorphine can decide to simply stop taking their daily medication (however unwise this decision may be) and after 5 elimination half-lives (24-37
hours = 5-8 days) the plasma concentration will be close to zero. With a half-life of 4-5 days, weekly SC-BPN could take around 4 weeks for plasma concentrations to reduce to zero. Monthly SC-BPN has an even longer half-life of 19-25 days, resulting in a substantially prolonged elimination after discontinuation. Further research into the discontinuation of SC-BPN must be done so that safe, evidence-based, patient-centred detoxification protocols can be created. It might be that a detox (as we know it) is not necessary for patients taking SC-BPN, but it is important that this is studied so that patients and professionals can make collaborative evidence-based treatment decisions.

Thought must also be given to patients who wish to attend rehabilitation programs. Typically, residential rehab facilities require patients to have detoxed from OST prior to admission and they must be able to produce opioid-negative urine samples. We must consider at what point patients should be admitted to rehab after taking their last SC-BPN dose.

There is no denying that a healthcare-administered depot injection has several safety benefits compared to SL-BPN. There is no risk of paediatric exposure, as medication would not be stored in the home, and there is a reduced risk of diversion and misuse. Attending a clinic once a week or once a month is also likely to be more convenient for most patients than attending a pharmacy on a daily basis. Daily visits for supervised consumption of medication can also be stigmatising and demoralising, and difficult to adhere to if you have other commitments such as childcare or employment.

There are also some indirect cost benefits to Buvidal® as the cost of supervised administration at a pharmacy would no longer be an issue. However, if more patients are prescribed Buvidal®, substance misuse services may need more qualified nursing staff to administer the injections, which may create additional costs. Services will need to be able to equip staff with the necessary skills to respond to the needs of the patient group as treatment options expand. Service redesign and reallocation of clinical resources is likely to be necessary – a real challenge in times of economic austerity.

One potential risk of SC-BPN is intravenous administration. Buvidal® forms a gel once it makes contact with body fluids, which facilitates its prolonged-release action. If administered intravenously there is a risk of occlusion and death. Whilst there were no reports of intravenous administration in any of the above trials, it remains a risk, which reinforces the need for proper training for healthcare professionals to avoid misadministration.

Clinicians must be careful that the availability of a monthly buprenorphine injection does not lead to less frequent interaction with patients and a reduction in psychosocial interventions. The collection of an OST prescription can be an incentive for attendance at a substance misuse service appointment. Services will need to ensure they maintain engagement with patients, rather than simply transforming into injectable buprenorphine clinics. It is vital that patient feedback is sought and the use of injectable buprenorphine is audited so that we are delivering the services our patients need.

Little information is given about participants’ use of alcohol in the three studies, though one suspects that as eligibility criteria excluded patients with liver dysfunction those with alcohol use disorders were unlikely to be included. With high rates of polysubstance use observed in real-world populations, including comorbid alcohol dependence, clinicians will have to make balanced decisions about the use of Buvidal® in these patients.

An argument could be made that a patient actively dependent on alcohol may find it more difficult to adhere to daily medication, so long-acting OST may be beneficial. However, the safety of long-acting buprenorphine has not been sufficiently examined in patients with alcohol dependence, so professionals must proceed with caution.

None of the studies in this update looked at the use of long-acting buprenorphine in patients requiring opioid analgesia, for example in hospital following trauma. Currently, the typical practice in acute care for patients prescribed SL-BPN for OUD but requiring additional analgesia is to continue the buprenorphine and use higher doses of full agonist opioid analgesia. Alternatively, buprenorphine is discontinued and patients receive full agonist opioid medications to treat both their pain and withdrawal. This second option would be far more difficult if someone is being maintained on long-acting subcutaneous buprenorphine, due to
the comparably long half-life. Further research is needed in this area to see how full opioid agonists interact with long-acting subcutaneous buprenorphine, specifically when used for analgesia.

Finally, it must be noted that the three studies discussed in this update were industry-sponsored. All results must therefore be considered within this context. Further non industry-funded studies are required to replicate results and to strengthen the evidence base.

Take-home messages:

- Weekly and monthly Buvidal® is an efficacious new treatment option for opioid use disorders, with a small but impressive evidence base.

- The availability of Buvidal® increases patient choice in an area where treatment options are not particularly plentiful.

- Buvidal® has bioavailability 6 to 8 times higher than that of sublingual buprenorphine, with a single 24mg weekly injection or 96mg monthly injection delivering a similar exposure to 16mg/day of sublingual buprenorphine hydrochloride.

- There is a lower risk of diversion, misuse, and paediatric exposure with a healthcare professional-administered injection compared to sublingual buprenorphine.

- The safety profile of Buvidal® is comparable to sublingual buprenorphine, with the addition of mild-moderate injection site reactions (most commonly transient pain).

- Injectable long-acting buprenorphine may improve adherence to buprenorphine.

- Substance misuse service redesign and allocation of clinical resources will need to be considered and any changes to service delivery should be made in consultation with relevant stakeholders.

- Services must invest in staff to ensure the workforce is equipped to safely meet the needs of patients.

- More qualitative research is needed on patient perception and acceptability of injectable buprenorphine.

- Further studies are required to support these findings and to demonstrate effectiveness of Buvidal® in clinical practice.

Conflict of interest disclosures:

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