20 September 2018
EMA/693347/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Buvidal

International non-proprietary name: buprenorphine

Procedure No. EMEA/H/C/004651/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
ANOVA	Analysis of variance
AUC	Area under the plasma concentration-time curve
AUCss	AUC during a dosing interval at steady state
BA	Bioavailability
BMI	Body mass index
BPN	Buprenorphine
BPN/NX	Buprenorphine/naloxone
CAM2038 q1w	Buvidal weekly formulation
CAM2038 q4w	Buvidal monthly formulation
CEP	Certificate of Suitability of the European Pharmacopoeia
CDF	Cumulative distribution function
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COWS	Clinical Opiate Withdrawal Scale
CQAs	critical quality attributes
CRU	Clinical research unit
CSR	Clinical study report
Css, max	Maximum plasma concentration at steady state
C-SSRS	Columbia-Suicide Severity Rating Scale
Css, trough	Trough plasma concentration at steady state
DAD	Diode Array detector
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
ECG	Electrocardiogram
EMA	European Medicines Agency
Emax	Maximum effect
EOT	End of treatment
EtO	ethylene oxide
EtOH	ethanol
EU	European Union
FC	FluidCrystal®
FDA	Food and Drug Administration
GC	gas chromatography
GDO	glycerol dioleate
HFE	Human Factors Engineering
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation
IM	intramuscular
IR	Immediate-release
ITT	Intent-to-treat
IV	Intravenous
IVR	*in vitro* release
LC	liquid crystal
LS	Least squares
MAT	Medication-assisted treatment
MOR	Mu Opioid Receptor

N/A	Not applicable
NCA	Non-compartmental analysis
NMT	not more than
norBPN	Norbuprenorphine
NX	Naloxone
OOWS	Objective Opioid Withdrawal Scale
PD	Pharmacodynamic(s)
PDE	Permitted daily exposure
PFS	pre-filled syringes
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
QTPP	Quality Target Product Profile
RH	relative humidity
RNS	rigid needle shield
RR	Response rate
SAXD	Small-Angle X-ray Diffraction
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SL	Sublingual
SmPC	Summary of Product Characteristics
SOWS	Subjective Opiate Withdrawal Scale
SPC	soybean phosphatidylcholine
US	United States
USP	United States Pharmacopoeia
UV	ultraviolet spectrometry
VAS	Visual analog scale
WPAI-GH	Work Productivity and Activity Impairment Questionnaire-General Health

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Camurus AB submitted on 27 July 2017 an application for Marketing authorisation to the European Medicines Agency (EMA) for Buprenorphine Camurus AB (later renamed as Buvidal), through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 October 2016. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Treatment of opioid dependence within a framework of medical, social and psychological treatment

Treatment is intended for use in adults and adolescents aged 16 years or over.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC)

The application submitted is composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product Subutex and appropriate non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Subutex, 0.4 mg, 2 mg, 8 mg, sublingual tablet
- Marketing authorisation holder: Indivior UK Limited
- Date of authorisation: 14-05-1999
- Marketing authorisation granted by:
  - Member State (EEA) : Denmark
    - MRP/DCP
- Marketing authorisation number: 19572, 19573, 19574

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Subutex, 0.4 mg, 2 mg, 8 mg, sublingual tablet
- Marketing authorisation holder: Indivior UK Limited
- Date of authorisation: 14-05-1999
- Marketing authorisation granted by:
  - Member State (EEA): Denmark

  - MRP/DCP
- Marketing authorisation numbers: 19572, 19573, 19574

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Subutex, 0.4 mg, 2 mg, 8 mg, sublingual tablet
- Marketing authorisation holder: Indivior UK Limited
- Date of authorisation: 14-05-1999
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom
    - MRP/DCP
  - Marketing authorisation numbers: PL 36699/0001, PL 36699/0002, PL 36699/0003
- Bioavailability study number(s): 2013-004004-19 and 2014-000498-38

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant received Scientific Advice from the CHMP on 22 October 2015. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey Co-Rapporteur: Peter Kiely

The application was received by the EMA on	27 July 2017
The procedure started on	28 September 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 December 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	19 December 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	15 January 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 May 2018
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	03 July 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 July 2018
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	26 July 2018
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	18 August 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	05 September 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Buvidal on	20 September 2018

2. Introduction

2.1. Problem statement

2.1.1. Disease or condition

Buvidal is indicated for treatment of opioid dependence within a framework of medical, social and psychological treatment.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Opioid dependence constitutes a large burden to patients as well as to their families and to the wider society. It is estimated that 33 million people misused opioids globally in 2014. Of these, 17 million people misused opiates (heroin, morphine or opium). Worldwide there were an estimated 207,400 drug-related deaths in 2015, one third of which were due to overdoses. Illicit opioids were responsible for a majority of these deaths, with more than 33,000 deaths reported only in the US in 2015.

There were at least 7585 overdose deaths reported in Europe in 2014 and in over 80% of those, illicit opioids (in particular heroin) were present. This is underpinned by a trend of increasing overdose deaths from methadone and potent synthetic opioids, like fentanyl, as shown by recent statistics from the UK and Scandinavia. This may also be related to poor adherence to current daily medication-assisted treatment (MAT), with continued on-top use of illicit opioids and other drugs, as well as to diversion and misuse of methadone, morphine and BPN-based medication.

Use of injected drugs is a major risk factor for the acquisition and transmission of HIV, and about 5-10% of HIV infections are attributable to injecting drug use worldwide. Transmission of HIV between people who inject drugs is predominantly a result of the sharing of contaminated injecting equipment, but also sexual transmission, both of which are influenced by wider structural and environmental factors such as housing, patterns of drug use and commercial sex work. The prevalence of HCV in drug users is also very high and estimated to be 40-80% in many European countries.

2.1.3. Biologic features - Aetiology and pathogenesis

Opioid dependence is a neurobehavioral disorder characterized by repeated, compulsive seeking, and use of an opioid despite adverse social, psychological, and/or physical consequences (ICD-10).

Biological research indicates that opiate dependence is a chronic relapsing remitting brain disorder that requires long-term treatment.

2.1.4. Clinical presentation, diagnosis

The following are the DSM-5 diagnostic criteria for Opioid Use Disorder:

1	Opioids are often taken in larger amounts or over a longer period than was intended	The presence of at least 2 of these symptoms indicates an Opioid Use Disorder (OUD) The severity of the OUD is defined as: MILD: The presence of 2 to 3 symptoms MODERATE: The presence of 4 to 5 symptoms SEVERE: The presence of 6 or more symptoms
2	There is a persistent desire or unsuccessful efforts to cut down or control opioid use	
3	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects	
4	Craving or a strong desire to use opioids	
5	Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home	
6	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids	
7	Important social, occupational, or recreational activities are given up or reduced because of opioid use	
8	Recurrent opioid use in situations in which it is physically hazardous	
9	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.	
10	Tolerance,* as defined by either of the following: a) Need for markedly increased amounts of opioids to achieve intoxication or desired effect b) Markedly diminished effect with continued use of the same amount of opioid	
11	Withdrawal,* as manifested by either of the following: a) Characteristic opioid withdrawal syndrome b) Same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms	

* Patients who are prescribed opioid medications for analgesia may exhibit these two criteria (withdrawal and tolerance), but would not necessarily be considered to have a substance use disorder.

2.1.5. Management

In Europe, there are an estimated 1.3 million high-risk opioid users and of those, only about 50% (630,000) receive medication-assisted treatment (MAT). Methadone was the first drug to be introduced for MAT in the 1960's when it was discovered that it had stabilizing effects on the addictive behavior and social functioning compared to injected heroin. Methadone also improved the treatment retention rate compared to non-pharmacological treatment and the retention has subsequently been shown to be around 50-70% after 6-12 months in both controlled clinical studies and cohort studies. Furthermore, MAT with methadone has been shown to reduce mortality, illicit use of opioids and risk for infections with blood-borne viruses such as HIV. However, there are major disadvantages with methadone. As a full mu opioid receptor (MOR) agonist, methadone is attractive for diversion and the drug is therefore usually distributed in special programs including medical supervision, and as a daily supervised medication, methadone treatment is resource-intensive. Furthermore, methadone has pronounced negative effects on cognitive function and is associated with a greater risk of causing prolonged QTc intervals and potentially fatal heart arrhythmias compared to BPN. Most importantly, as a full MOR agonist, the drug can lead to overdoses and there is a substantial and increasing number of drug-related deaths in Europe that are related to methadone. Nevertheless, compared to no MAT,

methadone is considered to have a positive benefit-risk balance and it is on the WHO model lists of essential medicines for treatment of opioid dependence.

Currently available treatment options for opioid dependence vary between countries, with the full opioid mu (μ) opioid receptor (MOR) agonist methadone being used in 63%, buprenorphine (BPN)-based medications in 35% and other pharmaceutical drugs in 2% of patients in Europe. Besides methadone and BPN (with or without naloxone [NX]), other medicinal products for medication-assisted treatment (MAT) in Europe are the full MOR agonists slow-release oral morphine and supervised injectable heroin. There are several issues with currently available daily MAT:

☐ Need for daily, often supervised, dosing resulting in inconvenience, stigma and reduced quality of life for patients as well as burdens on the healthcare system

☐ Poor treatment adherence including continued use of illicit opioids and limited retention in treatment

☐ Misuse, abuse, diversion and paediatric exposure

☐ Safety concerns including respiratory depression, overdosing and cardiac events

There is no prolonged release form of buprenorphine available in the EU for the treatment of opioid addiction.

2.2. About the product

Buprenorphine is a well-known substance widely used in the treatment of opioid dependence.

Buvidal products are prolonged-release solutions for injection designed to provide therapeutic levels of BPN that are comparable to those of daily sublingual (SL) BPN, over 1 week (CAM2038 q1w) or 1 month (CAM2038 q4w), following a single SC injection.

Buvidal can be used for individualized therapy across treatment phases; from initiation and stabilization to maintenance treatment in adults and adolescents aged 16 years or over. The depot administration was developed to enhance treatment adherence, avoid diversion, misuse, unintentional paediatric exposure and reduce burdens of daily supervised administration. A primary goal of treatment for opioid dependence is to help patients to reduce or eliminate illicit opioid use as this facilitates achievement of other important goals, including improved physical and mental health, and psychosocial functioning.

2.3. The development programme/compliance with CHMP guidance/scientific advice

Pertinent CHMP Guidelines were followed.

Scientific advice was provided by the CHMP (2015) Procedure No: EMEA/H/SA/3166/1/2015/III. CHMP provided scientific advice on the proposed Phase 3 trial to support an MAA submission including study design, study population, choice of comparator and proposed indication. In agreement with the scientific advice provided by the CHMP, the pivotal randomized, double-blind, double-dummy Phase 3 study (HS-11-421) evaluated the non-inferiority of CAM2038 compared to an existing standard of care sublingual buprenorphine/naloxone (SL BPN/NX) with percentage of urine samples negative for illicit opioids being the primary endpoint.

Scientific advice was also provided by BfArM and the MPA in 2011. At these meetings, advice was received regarding additional need of Chemistry, Manufacturing and Controls (CMC) data and non-clinical data for start of late stage clinical development and for Marketing Authorisation Application (MAA), as well as the clinical

development program. Both agencies supported the strategy to provide a combination of published data on BPN together with own non-clinical and clinical data to prove the efficacy and safety of the CAM2038 q1w product.

2.4. General comments on compliance with GMP, GLP, GCP

The pivotal non clinical studies, including repeat dose and chronic toxicity studies of CAM2038 and FC vehicle as well as the toxicity studies for GDO and NMP were conducted in compliance with Good Laboratory Practice (GLP) regulations. For a majority of the publications cited in the nonclinical section of this submission, the GLP status of the studies was not stated. In some publications, however, the GLP status was stated and is noted when describing the results of a specific publication.

The clinical studies submitted with these applications contain a statement that they were performed in compliance with GCP guidelines.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

This marketing authorisation application for the 2 formulations 50mg/ml and 356mg/ml subcutaneous buprenorphine injection depot is being submitted under Article 10(3) of Directive 2001/83/EC, with Subutex as the reference medicinal product. This product is being submitted under Special medical Prescription in accordance with Article 71 of Directive 2001/83/EC.

The reference product is Subutex sublingual tablets 0.4 mg, 2 mg and 8 mg. The proposed product differs from the reference medicinal product in that there is a change of pharmaceutical form, change in strength and change in route of administration.

The application was supported by quality, non-clinical and clinical data. To establish a bridge to the data of the reference medicinal product, the applicant conducted a comparative bioavailability study with Subutex.

- Accelerated procedure

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. Although the potential benefits of a one-weekly or four-weekly injections as opposed to daily administrations is clear, it was not considered that the proposed medicinal product would provide a major improvement over current therapies.

2.6. Quality aspects

2.6.1. Introduction

The finished product is presented as a prolonged-release solution for injection containing 8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg or 128 mg of buprenorphine as the active substance.

Other ingredients apart from the active substance are:

Buvidal 8 mg, 16 mg, 24 mg, 32 mg strength: soybean phosphatidylcholine, glycerol dioleate and ethanol anhydrous;

Buvidal 64 mg, 96 mg 128 mg strength: soybean phosphatidylcholine, glycerol dioleate and *N*-methylpyrrolidone.

The product is available in a pack containing one pre-filled syringe with stopper, needle, needle shield, safety device and one plunger rod, as described in section 6.5 of the SmPC. The pre-filled syringe is made of Type I glass with fluoropolymer-coated bromobutyl rubber plunger stopper. The needle is a ½-inch, 23 gauge, 12 mm needle and the needle shield is made of styrene butadiene rubber. The pre-filled syringe is assembled in a safety device for post-injection needlestick prevention

2.6.2. Active substance

General information

The chemical name of buprenorphine is (2*S*)-2-[17-(cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy--6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol corresponding to the molecular formula $C_{29}H_{41}NO_4$. It has a relative molecular mass of 467.6 g/mol and the following structure (Figure 1):

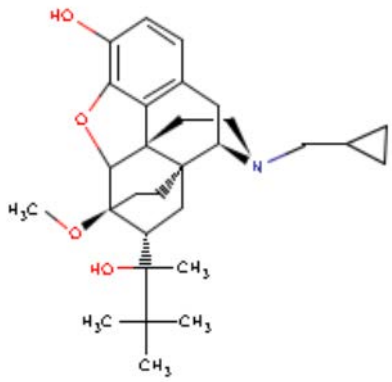


Figure 1. Structure of buprenorphine

Buprenorphine appears as a white or almost white crystalline powder. It is very slightly soluble in water, soluble in methanol and ethanol and dissolves in dilute solutions of acid. Its pKa is 8.31.

There is only one polymorphic form known from literature and observed for buprenorphine.

Buprenorphine is a well-known active substance and it is monographed in the European Pharmacopoeia (monograph number 1180). As there is a monograph of Buprenorphine in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for buprenorphine which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

No information is provided on the elucidation of the structure, which is acceptable in view of the CEP.

According to the CEP, buprenorphine is stored in double polyethylene bags placed in either a cardboard or plastic container.

Specification

Buprenorphine used for Buvidal finished product complies with Ph. Eur. 1180. The specification, Table 1, includes tests and limits for appearance, identification, chromatographic purity, appearance of solution, loss on drying, specific optical rotation and assay base titration. In addition to the compendial requirements and the specification parameters covered by the CEP, the active substance is tested for bacterial endotoxins and microbial quality. With exception of the HPLC-UV methods used for analysis of chromatographic purity, the methods according to the Ph. Eur. buprenorphine monograph are applied. The HPLC-UV methods are covered by the CEP.

Table 1. Specification of buprenorphine active substance.

Specification parameter	Test method	Acceptance Criteria *Finished product manufacturer*
Appearance	Visual inspection	A white or almost white crystalline powder
Identification, IR	Ph. Eur. 2.2.24	Complies with reference spectrum
Chromatographic purity	Ph. Eur. 1180 (*FP manufacturer)* *HPLC-UV (API manufacturer)*	
Individual specified impurities:		
Ph. Eur. Impurity A *N-but-3-enylnorbuprenorphine*		≤ 0.2%
Ph. Eur. Impurity B *Norbuprenorphine*		≤ 0.2%
Ph. Eur. Impurity C *3-O-methyl-N-cyano-nor-buprenorphine*		Not specified
Ph. Eur. Impurity D *3-O-methylbuprenorphine*		Not specified
Ph. Eur. Impurity E *6-O-desmethylbuprenorphine*		Not specified

Ph. Eur. Impurity F *15,16-dehydrobuprenorphine* Ph. Eur Impurity G Ph. Eur. Impurity H Ph. Eur. Impurity J *17,18-dehydrobuprenorphine* Individual unspecified impurities Total impurities		≤ 0.2% ≤ 0.15% ≤ 0.25% ≤ 0.2% ≤ 0.10% ≤ 0.7%
Appearance of solution	Ph. Eur. 1180	Clear and colourless
Loss on drying	Ph. Eur. 1180	≤ 0.5%
Specific optical rotation	Ph. Eur. 1180	-103° to -107° (dried substance)
Assay base titration	Ph. Eur. 1180	98.5% to 101.5%
Bacterial endotoxins	Ph. Eur. 2.6.14	NMT 1.0 E.U./mg
Total aerobic microbial count (TAMC)	Ph. Eur. 2.6.12	NMT 100 CFU/g
Total yeast and moulds count (TYMC)	Ph. Eur. 2.6.12	NMT 100 CFU/g

The particle size distribution has been measured by the active substance manufacturer for information, but is not included in the active substance specification as the finished product is in solution and particle size is not critical. The particle size distribution was measured by laser diffraction technique. Results for representative buprenorphine batches were presented.

Batch analysis results from 4 batches of the active substance have been provided. In addition, a summary of batch analysis results for 6 representative buprenorphine batches by the two active substance manufacturing sites was provided.

Stability

According to the CEP the retest period of the buprenorphine active substance is 48 months if stored in double polyethylene bags placed in either a cardboard or plastic container.

2.6.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a sterile filtered yellowish to yellow clear liquid aseptically filled into pre-sterilized, ready to use, 1 ml long, type I clear glass syringes with grey fluoropolymer coated bromobutyl elastomer, type I, plunger stoppers, and rigid needle shields.

Buvidal finished product is formulated as weekly or monthly depots, both containing the active substance buprenorphine but in different delivery system compositions based on the proprietary FluidCrystal® injection depot technology. The FluidCrystal (FC) injection depot is a lipid-based liquid, with dissolved active substance buprenorphine, that can be injected subcutaneously. When injected into the subcutaneous (SC) or intramuscular (IM) tissue, the FC formulation absorbs interstitial aqueous body fluid and transforms from liquid to highly viscous (>>106 mPas) liquid crystal (LC) (or gel-like) phases *in situ*, which effectively encapsulate the active substance. This results in a slow and consistent release of buprenorphine, which can be controlled for a week or a month depending on the composition.

Different drug product strengths are achieved by different syringe fill volumes. Buvidal for weekly administration contains 50mg/ml buprenorphine and Buvidal for monthly administration contains 356mg/ml buprenorphine. The compositions of each strength of either the weekly or monthly formulation are dose proportional.

The pharmaceutical development of Buvidal was guided by the Quality Target Product Profile (QTPP) presented separately for the weekly (CAM2038 q1w) and the monthly (CAM2038 q4w) formulation.

The composition consists of lipids and co-solvents. The lipids, soybean phosphatidylcholine (SPC) and glycerol dioleate (GDO), are the key excipients for the FC injection depot technology. These lipids are the key structure forming, release controlling components of the finished product.

Polar organic co-solvents, ethanol for CAM2038 q1w and N-methyl-2-pyrrolidone (NMP) for CAM2038 q4w, are used to achieve appropriate product viscosity resulting in adequate manufacturability and injectability and may further aid in achieving appropriate solubility of the active substance in the formulation. The information provided on the solubility of buprenorphine in the individual lipid components and co-solvents is acceptable. The co-solvents are dissipated into the surrounding tissue upon injection of the drug product and are biocompatible (suitable for subcutaneous injection).

The active substance encapsulated in the liquid crystal matrix after injection is released by a combination of simple diffusion and release kinetics due to the biodegradation of the lipid matrix in the SC (or IM) tissue. Clinical and non-clinical assessments of different FC based products have demonstrated similar pharmacokinetics (PK) for IM and SC injection sites, as well as between different SC injection sites. There is no indication during the studies conducted, that rubbing the skin over the depot site would have an adverse impact on the release of the buprenorphine from the depot.

Depending on the ratio between the two lipids, different LC phases are formed with different properties regarding drug release rates. The LC phase is a water-in-oil phase, with an inherent property of absorbing only a certain amount of water up to the swelling limit and thereafter remaining unaltered upon further dilution. The LC phase is robust and stable within a broad temperature range. The LC gel is the *in vivo* functional release matrix and the structure of the gel in aqueous solution and as a function of temperature has been determined *in vitro* by Small-Angle X-ray Diffraction (SAXD) and Nuclear Magnetic Resonance (NMR). Buprenorphine used as

active substance in the CAM2038 q1w and CAM2038 q4w products is in the free base form because of the higher solubility in the drug product lipid matrices compared to the corresponding hydrochloric acid salt. Solubility of buprenorphine in the liquid lipid-based drug product formulation matrix is considered a critical material attribute to achieve the required buprenorphine concentration for the weekly and monthly dose of CAM2038 q1w and CAM2038 q4w, respectively.

The chemical and physical compatibility of the active substance with the excipients (lipid matrix and solvent) was established in early phase R&D stability studies for the respective drug products.

As GDO has no prior use in registered injectable drug products, it is considered a novel excipient for the parenteral route of administration. A risk assessment for use of GDO as a component in products based on the FC injection depot technology was undertaken, which included generation of primary toxicity and toxicokinetic data, as well as reference to relevant toxicity data in the scientific literature. The batch data provides further assurance that aflatoxins and pesticides are not of a critical concern, and justifies these are not included in the specification. In addition a commitment to test one batch of GDO annually for both aflatoxin and pesticides has been made and is included in the dossier. Full information regarding manufacture, characterisation and controls regarding GDO have been presented and are deemed satisfactory.

CAM2038 q1w and CAM2038 q4w formulations of identical composition have been employed throughout Phases 1 - 3 of the clinical development programme. The products used in Phase 3 clinical trials and the product intended for commercial use are presented in pre-filled syringes (PFS), where different strengths, or doses, are achieved by different syringe fill volumes. During the early development phase (Phases 1-2), the CAM2038 formulations were provided in vials, and administered by means of a disposable syringe. The respective drug substance and drug product manufacturing sites used throughout the development were explained. The manufacturing process employed is similar for all sites, and is equivalent for batches used for Phase 3 clinical trials and those intended for commercial manufacture.

The development of the product has been described, the choice of excipients is justified and their functions explained. The development batches are from clinical trial studies and stability studies. These batches were manufactured at a different manufacturing site than the proposed commercial site, however the manufacturing processes are similar and comparative *in vitro* dissolution profiles show that the manufacturing sites are comparable.

The composition of the finished product was guided by performing *in vitro* and *in vivo* PK studies. The critical quality attributes (CQAs) and the related material attributes listed in the respective QTTPs have been evaluated and the criticality of each identified material attribute related to formulation performance was determined and accompanied by a justification and control strategy where required. The following CQAs were identified during the formulation development:

- The weight ratio of SPC/GDO in the formulation.
- Mono-, di, and triglycerides in GDO are known to affect the release controlling properties of the FC injection depot system. These are controlled in the GDO specification.
- Mono- and triglycerides in SPC are known to affect the release controlling properties of the FC injection depot system. These are controlled in the SPC specification.
- The ethanol content in CAM2038 q1w and NMP content in CAM2038 q4w significantly affects the formulation viscosity and hence the injectability and the manufacturability.

The ratio of SPC/GDO was identified as a CQA; it was determined and optimised by *in vitro* release experiments and *in vivo* pharmacokinetic (PK) studies in rat as evaluation tools, respectively. Based on the combined *in vitro* release and multiple *in vivo* rat PK studies, it was concluded that the selected SPC/GDO weight ratio is

appropriate with respect to functional release properties of CAM2038 q1w. For the CAM2038 q4w formulation, the combined *in vitro* and *in vivo* results support a compositionally robust formulation with respect to drug release properties and the selected SPC/GDO weight ratio. Importantly, no observations of burst release (or dose dumping) have been detected for the CAM2038 q4w formulation in any non-clinical studies performed during formulation development. The drug release properties were shown to be robust during shelf-life as evidenced by the absence of change of the *in vitro* release profiles during stability studies as well as *in vivo* rat PK data comparing a freshly prepared formulation with aged formulation stored for 24 months at 25 °C / 60% RH. No significant difference in any PK parameter was observed between the fresh and aged CAM2038 q1w or CAM2038 q4w formulation.

The same composition containing SPC and GDO in the above weight ratios has been used in human PK studies and throughout clinical development and confirmed to possess the desired drug release profile.

The results for the CAM2038 q1w formulation and the corresponding placebo formulation (equivalent SPC/GDO weight ratio) show that the LC gel structure practically does not change within the temperature interval 25 °C to 42 °C, demonstrating good robustness of the *in vivo* functional release matrix at a temperature 5 °C above normal body temperature. Importantly, the LC phases formed by the SPC/GDO lipid mixtures in contact with aqueous media are thermodynamic equilibrium phases and hence, will always form independent of the way the lipid formulation or the lipid formulation/water mixture has been prepared.

A number of solvents and solvent mixtures were evaluated for use as co-solvents in the formulations. Ethanol was found to be the most suitable to achieve the desired viscosity in the weekly formulation whereas NMP was more suitable for the monthly formulation due to the increased drug load required for that formulation. The levels of the co-solvents, EtOH and NMP, have been studied in relation to viscosity, injectability (injection time and force) and *in vitro* release profiles. It was found that, within a broad concentration range, the EtOH or NMP content has no significant effect on the drug release properties whereas it was concluded that their content is a critical material attribute with regard to injectability properties for the respective formulations.

An *in vitro* release (IVR) dissolution method has been developed and the development has been sufficiently described. The dissolution apparatus and operating conditions were selected based on Ph. Eur. 2.9.3. The dissolution medium was selected to enable measuring the dissolution profile, under sink conditions, within an acceptable time-period. Since the dissolution rate of buprenorphine is affected by the pH of the dissolution medium the solubility of buprenorphine in different aqueous media was determined. The QC dissolution medium was selected to obtain a reasonable dissolution rate for the respective target duration (one week and one month), with acceptable discriminating capability. Sampling time points for the QC method were agreed. The conditions for the sample preparation and the proposed QC dissolution test have been described and the controls in place to reduce and minimise the variability of the gel monolith depot geometry and surface area can be accepted. The dissolution method is the basket apparatus (Ph. Eur.) Sampling points are clearly defined.

The discriminatory power of the method was demonstrated by investigating the lipid composition i.e., the weight ratio between the two release controlling excipients, SPC and GDO. It was shown that the differences observed in the release profiles *in vivo* for CAM2038 q1w and CAM2038 q4w made with different SPC/GDO ratios were accurately detected by the IVR method. Therefore, the method is considered to be sufficiently discriminating. Also, the linear relationship between the *in vitro* release data and the human PK study further supports the dissolution method and specification limits.

The finished product manufacturing process is straightforward, comprising only conventional pharmaceutical processing steps, i.e., weighing and dissolving of raw materials, sterile filtration, filling and closing, visual inspection, labelling, assembly in the safety device and secondary packaging. The critical process parameters

were identified. The sterilisation method is sterile filtration. Based on assessments made during product development, a combination of sterile filtration, pre-sterilized containers and aseptic processing for sterilization of CAM2038 q1w and CAM2038 q4w drug products is used. To ascertain the most suitable sterilisation method, the decision tree for sterilisation of non-aqueous liquids, semi-solid or dry powder products was employed as stipulated in the Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container (EMA/CHMP/CVMP/QWP/BWP/850374/2015). A risk assessment on the impact of different sterilisation methods on the assembled CAM2038 drug product was carried out to investigate the effect of each sterilisation process would have on the individual drug product components e.g. formulation, glass barrel, needle shield and plunger stopper. From the assessment, sterile filtration was the only process compatible with CAM2038 drug product. Sterilization at elevated temperatures, i.e., steam and dry-heat sterilization, results in solvent evaporation from the formulation. In addition, steam sterilization is not generally suitable for hygroscopic non-aqueous lipid formulations, and might lead to increased water uptake by the product. Gamma irradiation is known to cause degradation of unsaturated lipids and is therefore unsuitable for the (unsaturated) lipid-based drug product formulation. Gamma irradiation is also known to cause discoloration of the borosilicate-based clear-glass syringes. It was concluded that that the proposed method of sterilization is suitable, it does not compromise the quality, safety and efficacy of the product and thus is considered acceptable.

There had been non-compliance GMP issues at the development manufacturing site and as a result of that, a different site is proposed as the commercial finished product manufacturing site. The risk assessment provided in relation to the development site adequately addressed concerns in view of cross contamination, quality oversight and sterilization procedures, and data integrity in relation to analytical testing and in reporting analytical results. Considering that the finished product is no longer manufactured at the development site and no product will be released from this site, the presented information can be accepted. In addition, the main differences between the commercial and development sites were discussed and none of them have any impact on the CQAs. Furthermore, comparative batch analyses (including *in vitro* dissolution profiles) were presented on 3 full scale batches from the development and commercial site. Based on the presented information, the manufacturing processes are considered similar for all sites and are equivalent for batches used for Phase 3 clinical trials and commercial batches.

The product is provided in single-dose pre-filled sterile syringe (Type I, clear glass), stainless steel staked needle and rubber needle shield and a bromobutyl plunger stopper. The filled syringe is assembled in a safety device for post-injection needlestick prevention. Both the pre-filled syringe, assembled in the safety device and the plunger rod are co-packaged in a secondary pack. The pre-filled syringe (PFS) components include the syringe barrel with staked needle, rigid needle shield (RNS) and plunger stoppers and are delivered pre-sterilised and are ready-to-use. Relevant studies performed to verify the suitability of the container closure including extractables and leachables, moisture ingress, container closure integrity, elemental impurities, safety device functionality, extractable volume, injectability and Human Factors Engineering (HFE) have been presented and are considered satisfactory. Ethanol loss over time has been specifically discussed. The origin of the ethanol loss during storage and potential mitigation measures, have been thoroughly investigated and it is concluded that there is no safety or efficacy concern related to the ethanol loss within a large range. This justification is sufficient as it is not expected that any loss would exceed this margin. In addition, any changes to the container closure system potentially affecting the product quality will be evaluated in terms of ethanol loss and if such changes are warranted they will be introduced through, at minimum, a Type 1B variation application.

The primary packaging has been the same throughout late phase development and clinical Phase 3. The only difference is the needle shield which has been changed to a Datwyler FM 27/0 rubber formulation. The needle

shield type is considered critical because it relates to ethanol loss. The proposed needle shield provides better protection and significantly reduces ethanol loss.

Novel excipient

Glyceryl dioleate

Glyceryl dioleate (GDO) appears as an off-white solid at 15 °C or a colourless to slightly yellow liquid at 25 °C, with the molecular formula $C_{39}H_{72}O_5$ and a molecular weight of 620.99 g/mol. GDO is a mixture of glyceryl-1,2-dioleate and glyceryl-1,3-dioleate and the respective structures are shown in Figure 2.

Glyceryl-1,2-dioleate Glyceryl-1,3-dioleate

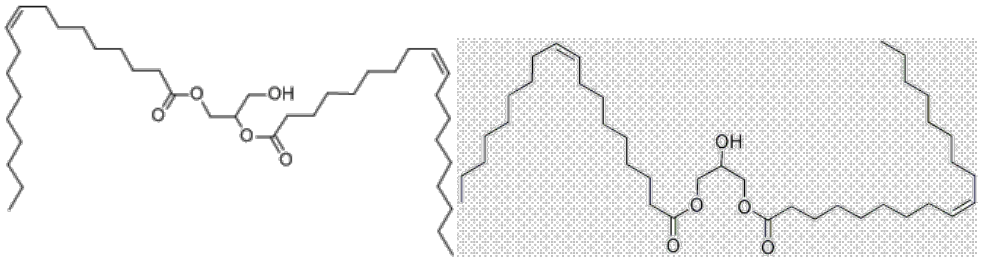


Figure 2. Structure of Glyceryl dioleate

It is derived from the partial esterification of glycerol (also referred to as glycerine) with oleic acid followed by subsequent purification processes including distillation.

The specification for GDO is based on the Ph. Eur. monograph for Glycerol Mono- oleates (01/2008:1430) with the limits being adjusted to account for the chemical differences in the two materials. A comparison table is provided below in below which demonstrates the similarity between the specifications.

The limits applied to the specification for GDO are appropriate for this grade of material and are aligned to those for Glycerol mono-oleates. Additional tests are added to the specification and the limits applied to heavy metals, bio-burden and endotoxins are judged appropriate for the parenteral application. Batch analysis data are presented for three batches of GDO. Batches confirm compliance with all control specifications.

GDO is packaged in conventional lacquer-lined steel drums with non-vented, pre-lacquered steel bungs. The lacquer used for the lining of the steel drums is based on a phenolic resin dissolved in a mixture of organic solvents with a dispersed titanium dioxide pigment. It is stated that the lacquer complies with current US regulations 21 CFR 175.300 (for resinous and polymeric coatings for use as the contact surface of articles for packaging foodstuffs) as well as EU regulation (EC) 1935/2004 (on the use of coatings intended to come into contact with foodstuffs) and EC directive 94/62/EC (Packaging (Essential Requirements) Regulations).

18 months ICH stability data at 25 °C / 60% RH and 30 °C / 65% RH and 9 months at 40 °C / 75% RH has been submitted in support of the claimed retest period. The material is stored in identical packaging to that for the sale and distribution of the finished GDO substance. Stability samples have been tested against the specification and using validated methods that have been provided. All results currently available are within specification and no unexpected trends are observed. These data demonstrate that the proposed retest period of 24 months for GDO is appropriate.

Manufacture of the product and process controls

The manufacturing processes comprise conventional pharmaceutical processing steps, i.e., weighing, dissolving, sterile filtration, filling, closing, visual inspection, labelling, assembly in safety device and secondary packaging. The process and process controls are schematically described in Figure 3.

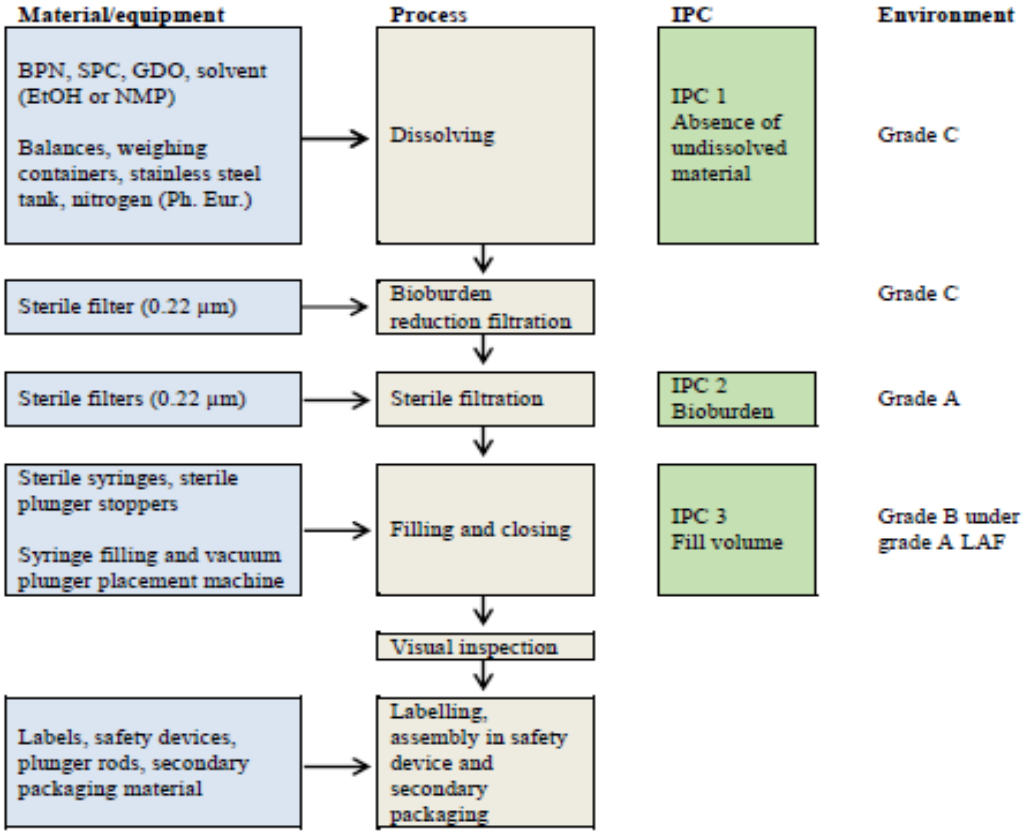


Figure 3: Manufacturing scheme for Buvidal manufacturing processes.

The following process parameters were identified as critical: mixing time, mixing tank tightness, sterile filtration, fill volume and the unit operations are controlled by suitable in-process controls. The manufacturing process is regarded as non-standard because it comprises sterilisation by filtration, therefore validation data on three consecutive full scale batches by the proposed finished product manufacturer have been provided according to the Guideline on process validation for finished products, EMA/CHMP/CVMP/QWP/BWP/70278/2012.

Syringe barrels with staked needle and rigid needle shield are delivered by the supplier pre-sterilised by ethylene oxide (EtO) and ready to use. The provided sterilisation validation & re-validation reports conform with harmonised standard EN ISO 11135-1:2007 concerning EtO sterilisation of devices and thus, fulfil the Medical Device Directive ANNEX 1 requirements. The plunger stoppers are also delivered pre-sterilized and ready-to-use. The stoppers are sterilised by steam (autoclave) at 121.1 °C for 60 minutes, in line with the Ph. Eur. requirements and no further information is considered necessary.

The manufacturing process validation is satisfactory and the manufacturing process is considered validated. In conclusion, it has been demonstrated that the manufacturing process is sufficiently robust to provide assurance that finished product of consistent quality, complying with the specification, is produced.

Product specification

The finished product release specifications include appropriate tests and limits for appearance (visual), identification of buprenorphine (HPLC, UV-DAD), assay (HPLC-UV), degradation products (HPLC-UV), water content (Ph. Eur.), ethanol content (GC), viscosity (Ph. Eur.), *in vitro* release (Ph. Eur.), gelling properties (visual), uniformity of dosage forms (Ph. Eur.), fill volume (weight control), sub-visible particles (Ph. Eur.), break-loose force (ISO 11040), gliding force (ISO 11040), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and container closure integrity (dye ingression test).

The specification limits were determined based on the mean results of 82 batches (CAM2038q1w) and 47 batches (CAM2038q4w) from development batches and stability batches. The same batches were used in the safety and efficacy studies.

Norbuprenorphine is the main degradation product but is also the main buprenorphine metabolite. According to ICH Q3B(R2), degradation products that are also significant metabolites present in animal and/or human studies are generally considered qualified.

An elemental impurities risk assessment has been performed according to ICH Q3D. The levels of elemental impurities in the finished product are within safe levels, well below 30% of the proposed ICH Q3D PDES. The risk for the patient is considered negligible and no further action to control elemental impurities in the finished product is required.

The finished product is released on the market following traditional finished product release testing. The procedures for analytical methods used were provided. Non-compendial analytical methods were validated according to current ICH guidance. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data from 3 commercial scale batches per strength from the proposed manufacturer was provided. In addition, batch results from 2-5 batches for each strength from the development site have also been presented. All results obtained are within the proposed limits and any out of specification results have been satisfactorily discussed or justified as appropriate.

Stability of the product

Stability data from two commercial scale batches from the proposed manufacturer for the 8 mg and 32 mg strengths and from one batch of the 16 mg and 24 mg of CAM2038 q1w have been presented. Stability data from two commercial scale batches from the proposed manufacturer for the 64 mg and 160 mg (not intended for marketing, but produced during development) strengths and from one batch from the 96 mg and 128 mg of CAM2038 q4w have also been presented. Since Buvidal is available in multiple strengths accomplished by filling different volumes of the same formulation in the same pre-filled syringe, the proposed bracketing approach in terms of number of batches tested per strength is considered acceptable as per the ICH guideline Q1D ‘Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products’.

The stability batches were stored in horizontal position which was argued to be the worst case scenario by risk assessment regarding the syringe orientation. This justification was accepted. Data were generated under long-term conditions (25 °C/60% RH, 30 °C/65% RH) for up to 9 months and under accelerated conditions at (40 °C/75% RH) for up to 6 months according to the ICH guidelines. Stability samples were tested for appearance, assay, degradation products, water content, ethanol content, viscosity, *in vitro* release, sub-visible particles, break-loose force (ISO 11040), gliding force and sterility.

For both formulations, appearance, particulate matter, sterility and container closure integrity complied with the requirements for all strengths and all time points studied. For the buprenorphine assay and *in vitro* release parameters, no discernible trends were observed over time. Water content and the total amount of degradation products showed some increase with storage time and temperature but all levels are within the proposed specification limits. Ethanol content, viscosity, break-loose and gliding force parameters which are all linked and affect the injectability of the product were also within the specifications.

Supportive data from the development manufacturing site have also been presented for seven batches of 8 mg strength, three batches of the 16 mg strength and five batches of the 32 mg strength from the weekly formulation. From the monthly formulation, the supportive data come from four batches of the 64 mg, three batches of the 160 mg and one of the 192 mg strength (not intended for marketing but manufactured during development). Samples were stored for up to 24 months under the long-term condition (25 °C / 60% RH), and 6 months under accelerated conditions (40 °C / 75% RH). The results of the supportive stability studies were consistent with the results of the pivotal stability studies.

A photostability study according to ICH Q1B 'Photostability Testing of New Drug Substances and Products' (November 1996) was performed on two pilot batches of the weekly formulation (8 mg and 32 mg strengths) and two pilot batches of the monthly formulation (64 mg and 192 mg strengths). Parameters tested were appearance, assay, degradation products, viscosity and *in vitro* release. The results of light exposed product in the primary packaging alone, compared to the control samples, showed no or negligible change for all parameters tested except for a slight increase in the specified degradation product norbuprenorphine. It was concluded that the product in the primary packaging and an outer carton representative of commercial secondary packaging, is stable when exposed to light.

The proposed shelf-life is based on the available real-time data of the pivotal stability study (up to 9 months long-term and 6 months accelerated condition) and the statistical evaluation performed. The shelf-life is further supported by the consistency of the stability data from the supportive studies with up to 24 months. In addition the first three production batches will be placed on long term stability studies through the proposed shelf life and on accelerated studies for 6 months.

The proposed shelf-life of 18 months with the precaution "Do not refrigerate or freeze" (SmPC 6.3 and 6.4) has been adequately justified is considered acceptable.

Adventitious agents

None of the excipients used in the manufacture of Buvidal is of human or animal origin

2.6.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The development of the formulation system has been adequately described.

The use of novel excipient glycerol dioleate (GDO) has been justified and sufficient information on the manufacture, control and stability of GDO has been presented in the dossier. The proposed *in vitro* release (IVR) method has been shown to be suitable for the quality control and stability studies of the product. The finished product manufacturing process has been validated. The container closure system is considered suitable for this type of product and its intended use as per the SmPC. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.6.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.6.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

- any future changes in any component of the container closure system that could possibly affect quality of the product, but specifically any change in needle shield type, will have to be investigated in terms of ethanol loss. These changes will have to be introduced by Type IB variation as minimum.

2.7. Non-clinical aspects

2.7.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. In addition, the applicant conducted some safety pharmacology and pharmacokinetics studies. The general toxicology programme consisted of single and repeat dose toxicity studies in the dog and 1 study in the mini-pig. For genotoxicity, carcinogenicity and reproductive and developmental toxicity, bridging studies in the mouse, rat and rabbit were used to cross-refer to the findings described in the Subutex label.

In addition to the studies conducted with the active drug, single dose studies were conducted with the excipients GDO and NMP in rats and rabbits, and repeat dose studies with GDO, NMP and the FluidCrystal® vehicle. Genotoxicity studies were performed with the novel excipient GDO.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

2.7.2. Pharmacology

Pharmacodynamic studies

In vitro and *in vivo* studies have shown that BPN is a partial agonist with high affinity at μ-opioid receptors in the CNS, which are thought to be responsible for the therapeutic effects. However, BPN also has mixed but primarily antagonistic properties with high affinity at κ-receptors and weak affinity at and δ-opioid receptors. As a result of the high affinity partial agonist action of BPN at μ-receptors, commonly abused opiates (full agonists) are unable to displace BPN and therefore do not exert an effect if taken concomitantly. At ORL-1 (nociceptin) receptors BPN is a partial agonist, which is thought to be involved in the ability to treat opioid dependence.

A single study from published literature conducted in multiple species following SC injections of BPN showed that mice, rats, and cats displayed an increase in activity whilst guinea pigs and monkeys exhibited a decrease in activity.

Studies in humans show that a metabolite of BPN, NBPN, is also active at opioid receptors with high affinity for μ- and κ-receptors and lower affinity for δ-receptors. However, NBPN has weak pharmacodynamics activity as it is a substrate for P-glycoprotein (P-gp) and therefore has low CNS permeability.

The secondary pharmacodynamic effects of BPN have been well established in the clinical setting and include CNS and respiratory depression. Considering this and the available information on this provided in the approved Subutex label the absence of secondary pharmacodynamic studies for the proposed formulation is accepted. Potential secondary pharmacology effects of the NMP solvent used in the Q4W formulations included CNS and respiratory depression. Although there is potential overlap of these effects with those seen with BPN use it is accepted that there exists a margin of exposure from the NOAELs compared to the NMP exposure levels seen in patients. Furthermore, these effects are more pronounced when administered via inhalation than SC injection.

Safety pharmacology programme

In vitro studies performed using human embryonic kidney cells and Chinese Hamster ovary cells demonstrated a concentration dependent increase in hERG potassium current inhibition for both BPN and NBPN. In hNav1.5 (sodium) peak and late current, hCav1.2 (L-type) calcium and the hKvLQT1/hminK channels inhibition was seen with both BPN and NBPN, although the safety margins indicate that this is not clinically relevant.

Results from the two 8-week *in vivo* studies conducted in dogs were varied with one showing no effect on QT interval but an increase in heart rate, whilst another showed a decrease in heart rate. Neither of these studies contained control groups and in TK-12-448 heart rate was not measured pre-dose, so it is difficult to accurately draw any conclusions from these studies. In the 18-week study no effects on heart rate or QT interval were seen and the 9-month study showed a decrease in heart rate and a dose related prolongation of the QT interval after the first dose but was not observed thereafter. However, ECGs were not performed regularly throughout the studies so it is difficult to ascertain how long these effects lasted. QT prolongation is a well-known effect of BPN and therefore given the well-established clinical use, is acceptable.

The novel excipient was tested for CNS safety in a modified Irwin test up to a dose of 1000 mg/kg with no behavioural or functional differences noted at any dose for the duration of the study. CNS endpoints were investigated and no significant safety concerns were observed.

2.7.3. Pharmacokinetics

The rat, dog, and mini-pig were chosen as species to evaluate the PK profile. The PK profile in rats and dogs is similar at the dose intervals examined and the metabolism of BPN in the rat and dog are similar to that seen in humans.

In 6 rat studies, it was noted that on examination of the subcutaneous tissue at the site of the injections, that instead of a single depot being reported there were often a number of adjacent located depots. However, in some cases, no depots were found (Study 14-517, 1 rat per group that received mechanical challenge to the injection sites. No discussion has been provided on how the presence of several depots instead of a single depot, may have influenced release of the active substance from the depots and the pharmacokinetic parameters. The Applicant has performed an additional study showing that administration of two separate injections instead of one resulted in a group mean with a higher C_{max} and AUC and a lower T_{max} as would be expected given the larger surface area, however none of the pharmacokinetic parameters from two injection animals were significantly different to those that resulted from a single injection. It was not recorded in the original studies as to whether the injections formed single or multiple depots in dogs.

In studies PK-14-509 and PK-14-517 using CAM2038 q1w and q4w in rats it is stated that at the time points of mechanical challenge at 1 and 6 hours post-dose, that the gelling process of the depot was ongoing and that at 8 and 14 days post-dose the depot was in a completely gelled form. An *in vitro* model has been used to demonstrate that the gelling process begins shortly after contact with water, and the time taken has little effect on the controlled release parameter of the drug product.

Single dose CAM2038 q1w

In rats, there was rapid absorption with BPN concentrations detectable within 30 minutes of administration. Mean peak plasma concentrations were achieved within approximately 0.5-3.76 days, although an initial peak tended to be obtained from 6-24 hours post-dose with a second reached at around 5 days. Exposure of BPN increased approximately proportionally to dose. Half-life increased with increasing doses and volumes which was thought to be likely due to slower degradation of the higher dose volumes of the depot matrix. However, there was a large variability in the estimates of terminal t1/2 and therefore it is difficult to draw conclusions based on these results. . It is accepted that the secondary peak seen on the plasma concentration curves is due to variability in release of BPN from the CAM2038 depot matrix. The peaks are unlikely to be associated with exaggerated pharmacology or toxicity.

BPN was quantifiable in most animals for the entire duration of all studies, therefore the applicant may not have extended the studies sufficiently to accurately capture the time course of the elimination of BPN from CAM2038 q1w.

Bioavailability in rats was estimated at over 100% which is considered unrealistic, this may have resulted from an underestimation of AUC after IV administration or an overestimation of the AUC for the SC formulation.

After mechanical challenges of rubbing or squeezing the injection site, C_{max} and AUC_{inf} were similar to each other, but higher than the control group. The applicant has stated that external manipulation of the injection site had no effect on the release of BPN, although these experimental conditions are not considered to be a worst-case scenario. It is accepted that the depots are not altered substantially following mechanical challenge.

Administration via the IM route in rats resulted in a faster and higher initial exposure however, the overall total exposure was similar for both administration routes.

The effect of storage of CAM2038 q1w was investigated in rats, with PK parameters largely consistent except for T_{max} and $t_{1/2}$ which were faster following administration of the freshly prepared CAM2038 q1w.

In dogs, no single dose studies were conducted with a clinically relevant formulation of CAM2038 q1w, therefore the data is considered to be of limited value. Similar to the rat studies there was rapid initial release of BPN, with mean Tmax values ranging from 15-72 hours (mean values). The applicant states that C_{max} increased proportionally with dose volume and therefore proportionally with depot surface area. However, there was no report of examination of injection sites and therefore it is not known if there was one or multiple depots, so a surface area calculation cannot be made. Total exposure was proportional to dose volume. Half-life increased with increasing doses.

In mini-pigs there no single dose studies conducted with a clinically relevant formulation, therefore the data is considered to be of limited value. T_{max} was achieved in approximately 1 day and $t_{1/2}$ at 2.7 days.

Repeat dose CAM2038 q1w

There was a large amount of variability following repeat-doses of CAM2038 q1w in dogs. C_{max}, $t_{1/2}$ and AUC increased with dose but not proportionally. Tmax was similar for the 15 mg and 30 mg dose groups after the second dose. Accumulation ratios indicated a potential for accumulation in some animals.

Steady state was stated by the applicant to be achieved by day 85 in a 9-month study, however there were only 3 time points taken for PK analysis at day 1, 141 and 225 so it is difficult to elucidate whether this calculation is accurate.

Bioavailability was calculated as 156% in males and 130% in females, which is considered to be unrealistic.

Single dose CAM2038 q4w

Like the CAM2038 q1w formulation a small initial peak was followed by a second larger peak with the CAM2038 q4w formulation. In the PK-14-517 rat study, after mechanical challenge T_{max} (range 4.99-21 days) appeared to become more variable compared to the control group (8.05-14.0 days). Half-life was variable across all groups. C_{max} was similar for the control group and the group that had the injection site squeezed at 1 hour before sampling at 6 hours and 8 days post-dose, while AUC_{inf} was similar for the control, the group that had the injection site rubbed after dosing and the group that was squeezed at 1 hour before sampling at 24 hours and 14 days post-dose. In all but 1 group there were individual animals that had the percentage of AUC estimated by extrapolation of the terminal phase as greater than 20%.

Plasma profile and PK parameters were similar for both stored and fresh CAM2038 q4w.

In dogs, no single dose studies were conducted with a clinically relevant formulation of CAM2038 q4w, therefore the data is considered to be of limited value. There was a large amount of variability between animals with the Cmax ranging from 8.5-75.6 ng/mL, T_{max} 0.2-240 hours, AUC_{inf} 2715-3619 and $t_{1/2}$ 117-367 hours. BPN was detectable at all time points throughout the study indicating that the applicant may not have accurately captured the elimination profile.

Repeat dose CAM2038 q4w

Following repeated doses of CAM2038 q4w there was a high level of variability in plasma concentrations and AUC, however mean systemic exposure increased approximately proportionally with dose.

In the TO-13-489 study, absorption was rapid with BPN quantifiable at the first sampling time of 30 minutes, C_{max} was achieved after the first dose at 4 hours for the 64 mg dose and 5 hours for the 128 mg dose. However, following the 128 mg dose in TO-15-531 the C_{max} was achieved at a mean of 30.4 hours. Mean exposures in

females were greater than in males but this was attributed to data variability rather than differences in absorption or elimination. Accumulation ratios were variable but high.

In TO-15-531 steady state was stated to be achieved on day 85, however the C_{trough} values for the 160 mg and the 192 mg doses appear to be increasing throughout the study. The Applicant has withdrawn the 160 dosefrom the marketing authorisation application, therefore the highest dose available is 128 mg. The accumulation ratio for the 128 mg dose is approximately 1.4 after steady state is reached at around Day 85. It is accepted that there is minimal accumulation for this dose.

Bioavailability was calculated as exceeding 100% in both sexes.

BPN is approximately 96% plasma protein bound, with relatively higher concentrations in the brain than other compartments. Following IV administration BPN is distributed to the skin, muscle, fat, lung, spleen, liver, and kidney, with higher levels observed in the lung, spleen, muscle, and fat compared to blood. No discussion is included on how BPN is distributed following SC administration.

BPN is metabolised by CYP 3A4 to a primary metabolite NBPN. BPN and NBPN undergo enterohepatic circulation after conjugation with glucuronide. Ratios of systemic exposure to NBPN in relation to BPN were calculated in repeat dose studies as 0.7-12%. The metabolic pathway in humans is consistent with that in animals.

The elimination of BPN is bi- or tri-exponential with a long terminal elimination phase of 20-25 hours, due to its highly lipophilic nature and to reabsorption of the conjugated derivative. Elimination of BPN is primarily by biliary excretion of the glucuronide conjugates in the faeces.

Pharmacokinetic interactions may occur when BPN is given concomitantly with agents that affect CYP3A4 activity.

In rats, the plasma concentration of GDO remained relatively constant, and similar to the control group with no notable difference between the endogenous pre-dose and post-dose GDO levels. Exposures were similar across increasing doses and similar to control.

In vitro NMP showed a rapid initial release over 24 hours followed with a slower release resulting in 100% release over 1 week. In rats NMP C_{max} increased with dose but was less than proportional to dose level. AUC increased with dose but was more than proportional to dose level, exposure was higher in females than males. Data from the literature confirm the applicant's findings. The Applicant has demonstrated that there is little difference in exposures in rats following administration from the oral and IV routes. Additionally, exposure to NMP in humans is not significantly different between males and females when administered subcutaneously and therefore the difference in exposure following subcutaneous administration in rats is not clinically relevant.

In rabbits, the T_{max} of NMP was around 1 hour, with $t_{1/2}$ increasing with dose. AUC increased with dose and appeared to be more than proportional to dose level, whilst Cmax increased proportionally to dose level.

2.7.4. Toxicology

Single and repeat dose toxicity

Acute toxicity of CAM2038 q1w and CAM2038 q4w were performed in dogs and minipigs. In dogs, signs of reduced activity, trembling, ataxia, salivation, weight loss, soft faeces and hunched posture were seen in doses up to 192 mg. Swelling and tenderness was observed around injection sites which were associated with cystic spaces with granulomatous inflammation, with macrophages and occasional multinucleated giant cells. Some

spaces contained yellow pigment thought to be the test item. Surrounding the spaces and inflammation were fibrous capsules. In mini-pigs the only clinical sign was weight loss seen at a dose of 20 mg. Injection sites reactions were similar to the dogs, with swelling, SC cystic spaces and fibrosis associated with granulomatous inflammation.

Single dose toxicity was also reviewed for the GDO and NMP excipients. GDO demonstrated low toxicity, limited to injection site reactions. NMP again showed site reactions with mild findings of degeneration and ulceration.

Repeat-dose toxicity of the CAM2038 products was evaluated in 4 studies in Beagle dogs. Animals received fixed doses corresponding to clinically relevant doses of CAM2038 q1w and CAM2038 q4w. In addition, studies were completed to review the toxicity of GDO (rat) and of FluidCrystal (rat, dog, minipig). The safety of NMP was reviewed from evidence from published literature.

In repeat dose studies BPN in both CAM2038 q1w and q4w formulations, has been examined in dogs treated via SC injection for up to 9 months duration.

Treatment with the CAM2038 products resulted in decreased activity, sedation, soft faeces, inappetence and weight loss, salivation, and abnormal gait. Vocalisation and aggressive behaviour were also observed but this occurred largely on dosing days. For the 9-month study a mild heart rate reduction and QT prolongation were observed post-dose on day 1. All are expected clinical signs with BPN. In addition, in this study beginning on Day 169 the dogs required sedation prior to the administration of the q4w formulations, including the vehicle control, to alleviate injection-related discomfort as the dogs noted to have increased vocalisation immediately dose-dosing and aggressive behaviour. This behaviour was only associated with the q4w formulation and was also evident in the vehicle control animals. The data presented by the applicant suggest that the vocalisation and aggressive behaviour was evident from the beginning of this study and was not limited to just the NMP formulation with incidences also occurring in the CAM2038 q1w administered animals. Microscopic examination of the injection sites did not differ between any of the formulations including placebo not containing NMP. Taken together the data presented does not suggest local tolerance issues with the presence of NMP in the formulation.

An increase in neutrophils and a decrease in lymphocytes was seen in one study, with a reduction in white blood cells and neutrophils for males only in another. Vacuolation of the axillary lymph nodes was seen in animals treated for 9 months with the CAM2038 q1w product as well as those treated with placebo CAM2038 q1w and q4w.

Injection site reactions were similar to those seen in the single dose toxicity, with swelling/thickening, erythema and tenderness. Cystic spaces with granulomatous inflammation with macrophages and occasional giant multinucleate cells surrounded by fibrosis were seen in all repeat dose studies. Necrosis was reported occasionally. Recovery of the injection sites was noted as the severity of changes decreased with age of injection site. There were no indications that multiple injections into the same injection site enhanced the inflammatory response from a previous injection.

GDO

Repeat dose studies were performed in rats for up to 26 weeks. Increased white blood cells, neutrophils, and fibrinogen with a decreased percentage of lymphocytes were observed as well as an increased spleen weight in both sexes and at a dose of 1000 mg/kg extramedullary haematopoiesis of the spleen. Inflammatory response in regional lymph nodes was also seen.

Reactions at the injection site were oedema, sores, slight to moderate haemorrhage, ulceration, staining and scabbing. There was cystic granulomatous inflammation with a dose related trend, which was sometimes associated with necrosis.

FluidCrystal®

The FluidCrystal® vehicle has been examined in repeat dose studies in the rat (26 weeks), dog (8 weeks) and mini-pig (4 weeks). In the rat study, there was an increase in white blood cells, neutrophils, lymphocytes and monocytes and fibrinogen concentration. A decrease in plasma protein and a shorter activated partial thromboplastin time, enlarged lymph nodes and extramedullary haematopoiesis. All animals had swelling at the injection site, with rats sometimes having more than 1 swelling at a site. Cystic spaces associated with granulomatous inflammation and fibrosis were common to all animals. Rats showed pigmented macrophages and occasional foamy macrophages. Both rats and dogs showed a trend towards recovery.

NMP

Following oral administration clinical signs were decreases in body weight and hypocellular bone marrow in both sexes, testicular degeneration in males and thymic atrophy in females. An increase in liver weight and hepatic centrilobular hypertrophy were also observed.

Repeated inhalational exposure resulted in an increase in neutrophils and a decrease in lymphocytes. In animals that had died pulmonary oedema and congestion were observed, with haemorrhage, hypoplasia and necrotic haematopoietic cells in the bone marrow. Atrophy and lymphoid cell depletion of the thymus, spleen and lymph nodes was seen in sacrificed animals

The use of the solvent NMP in the Q4W formulation and the safety evaluation made by the applicant is considered acceptable. Although the NMP is rapidly absorbed into the systemic circulation leading to a bolus exposure to high levels of NMP, it is administered once monthly and quickly eliminated ($T_{1/2}$=3h), resulting in intermittent and not continuous exposure or accumulation of NMP. A safety margin exceeding 50 has been calculated for reproductive toxicity endpoints with NMP.

Genotoxicity

The overall conclusion based upon literature was that BPN and the excipient, NMP, were not genotoxic. Studies completed with GDO were negative for genotoxic potential.

Carcinogenicity

No new carcinogenicity studies with BPN were performed. A bridging study was conducted for BPN to enable the applicant to rely on the carcinogenicity data in the Subutex label. Margins of exposure to humans based on exposure to mice and rats are acceptable. Given the extensive clinical use of BPN it is concluded that BPN is not carcinogenic.

Carcinogenicity for DAG, (in support of GDO), SPC and NMP have been reviewed from the published literature, which conclude that there is no added risk for carcinogenicity due to exposure to these additional excipients.

Reproduction toxicity

The ability of BPN to produce reproductive and developmental toxicity is well characterised and described in the reference product. As no additional risk was anticipated when BPN is delivered by injection of the CAM2038 products the applicant has not conducted additional studies.

Literature evidence has been supplied to describe the effects of SPC, GDO (DAG) and NMP on reproductive toxicity. The influence of each excipient is not expected to unduly influence the overall risk for use during pregnancy and breastfeeding over that of BPN. GDO/DAG show some marginal effects in developmental toxicity, although more significant effects are noted for NMP. In rabbits, high dose NMP (540 mg/kg), an increase in post-implantation loss, altered foetal morphology and increased incidences of cardiovascular and skull malformations. At doses of 175 mg/kg and 540 mg/kg there was a reduction in maternal weight gain. Overall the doses required to achieve these effects well exceed that which would be seen during treatment with CAM2038, and would not deviate much from risks already characterised with BPN.

Local tolerance

The reactions at injection sites were similar across species and showed a tendency towards recovery. There appeared to be no difference in reaction between the 2 drug products or the FC vehicle. Repeat injections into the same site did not result in an increase in response.

The reactions were inflammatory in nature and are expected given that a 'foreign body' is being injected subcutaneously.

2.7.5. Ecotoxicity/environmental risk assessment

The applicant submitted an incomplete Phase I assessment with a refined PEC calculation, based on maximum recommended doses of buprenorphine used chronically without tapering. The refined $PEC_{SURFACeWATER}$ was 0.003 µg/L which is below the action limit of 0.01 µg/L. No further assessment in Phase II is required; however a PBT screening should be included as part of Phase I. Information on the log K_{ow} of buprenorphine is recommended to be provided.

2.7.6. Discussion on non-clinical aspects

The presented non-clinical data package was a mixture of bibliographic information for buprenorphine available from the public domain, along with additional studies conducted with the product on safety pharmacology, pharmacokinetics and toxicology.

A brief summary on the pharmacology of buprenorphine was provided from the literature, describing the mixed partial agonist activity at µ-opioid receptors and antagonistic activity at κ- and δ-opioid receptors. The major metabolite norbuprenorphine is also active at opioid receptors but has low CNS permeability as it is a substrate for P-glycoprotein. Secondary pharmacodynamics effect for BPN and NBPN were well characterised.

In vitro and *in vivo* studies were conducted to investigate cardiovascular safety pharmacology with the CAM2038 products showing an expected prolongation of the QT interval commensurate with the known effects of buprenorphine. A modified Irwin test in rats was conducted, with the excipient GDO, which did not highlight any safety concerns.

The pharmacokinetics of buprenorphine are well characterised, however absorption of the CAM2038 products was investigated in studies using rats, dogs, and pigs. In a number of the rat studies multiple adjacent depots were observed, although these are not judged to affect the pharmacokinetics significantly. It was clarified that the length of time taken for a fully gelled matrix to form has limited influence on pharmacokinetics.

There was rapid absorption of buprenorphine with levels detectable at 30 minutes in all animals. The time taken to attain mean peak plasma concentrations were variable, however, there appeared to be an initial peak between 6 and 24 hours, with a second reached at around 5 days in both rats and dogs. Exposure of buprenorphine increased approximately proportionally with dose, and half-life increased with increasing doses. However, there was large variability in terminal half-lives. Exposure to buprenorphine following mechanical challenge was higher than the control group although was of limited significant difference.

The measurements of BPN in rats has been performed with an ELISA method which appears to have overestimated C_{max}, at least in dog plasma, the LC-MS/MS method was determined to be more specific.

Following repeated dosing there was a high level of variability in plasma concentrations and AUC, however mean systemic exposure increased approximately proportionally with dose. Accumulation ratios were variable but high.

The distribution, metabolism and elimination of buprenorphine were described using published literature. Buprenorphine is approximately 96% protein bound, with relatively higher concentrations in the brain than other compartments. It is metabolised by CYP3A4 to a primary metabolite, norbuprenorphine. The metabolic pathway is similar between animals and humans. Elimination has a long terminal elimination phase due to its lipophilic nature and to reabsorption of the conjugated derivative.

Exposure to GDO in rats showed that GDO plasma concentration remained relatively constant with no notable difference between endogenous pre- and post-dose levels. NMP showed a rapid initial release over 24 hours followed by a slower release resulting in 100% over 1 week.

The toxicity of the CAM2038 products was investigated in dogs, with 1 non-GLP study in mini-pigs. The main findings with both CAM2038 q1w and q4w products were the expected signs of buprenorphine, including reduced activity, ataxia and weight loss. At the injection sites swelling and tenderness was observed which were associated with cystic spaces with granulomatous inflammation, with macrophages and occasional multinucleated giant cells. Some spaces contained yellow pigment thought to be the test item. Surrounding the spaces and inflammation were fibrous capsules. In the 9-month study with CAM2038 q1w vacuolation of the lymph nodes was observed.

Studies performed with GDO and the FluidCrystal® vehicle showed similar signs at the injection sites with increases in white blood cells, neutrophils, and fibrinogen with a decreased percentage of lymphocytes were observed. Data from the literature was provided in support of NMP however, the data supplied addressed the oral and inhalational routes of administration. Decrease in body weight, testicular degeneration in males and thymic atrophy in females were noted as well as an increase in liver weight and hepatic centrilobular hypertrophy.

The 9-month repeat dose toxicity study reported that from Day 169 the dogs required sedation prior to the administration of any of the CAM2038 q4w drug products due to increased vocalisation and aggressive behaviour. The data presented by the Applicant suggests that the vocalisation and aggressive behaviour was evident from the beginning of the study and was not limited to just the NMP formulation with incidences also occurring in the CAM2038 q1w administered animals.

Carcinogenicity data from the published literature was provided for DAG in support of GDO, SPC and NMP. There is no added risk for carcinogenicity due to exposure to these additional excipients.

Limits on impurities in the drug substance and product are acceptable.

A refined PEC calculation was provided for buprenorphine using a worst-case scenario based on maximum recommended doses used chronically without tapering showing that the $PEC_{SURFACEWATER}$ is below the action limit of 0.01 µg/L However, it is recommended to provide a complete Phase I ERA post-approval by submitting an experimentally determined log k_{ow}.

2.7.7. Conclusion on the non-clinical aspects

The submitted non-clinical data package is sufficient to support the Marketing Authorisation of Buvidal in the proposed indication.

2.8. Clinical aspects

2.8.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.8.2. Pharmacokinetics

The CAM2038 products q1w and the q4w differ in composition and release rates.

Both products contain the same active entity, BPN, as the authorized SL products Subutex® and Suboxone® but are provided in a new FC formulation for SC injection.

BPN PK following SC injection of CAM2038 has been investigated in 5 clinical studies, whereof 2 studies were conducted in healthy volunteers under naltrexone (NTX) blockage and 3 studies were conducted in patients with opioid dependence.

Five clinical pharmacology studies were conducted to support the proposed dosing of CAM2038, and to support the bridging of clinical pharmacology data from SL BPN (Subutex) to CAM2038. The PK of BPN and norBPN following administration of SC CAM2038 q1w and SC CAM2038 q4w were compared with data obtained after administration of SL BPN (Subutex and Suboxone) and after a single IV injection of BPN (Temgesic) in healthy volunteers under NTX blockage and patients. The PK parameters were estimated using standard NCA methods and are summarized across all studies in Table 9 for BPN and in Table 10 for norBPN.

A population PK model of BPN was developed for evaluation of the influence of covariates on the PK of BPN and for simulations of different treatment schedules with CAM2038 q1w, CAM2038 q4w and SL BPN (Subutex).

Table 9 Summary of PK parameters of BPN based on NCA after SC buttock injections of CAM2038 q1w and CAM2038 q4w and SL administration of Subutex and Suboxone film

Product	Dose (mg) (Study)	Dose No.	Population	C_{max} (ng/mL)	T_{max} [a] (h)	C_{trough} [b] (ng/mL)	AUC_{τ} (ng*h/mL)	AUC_{inf} (ng*h/mL)	C_{av} (ng/mL)	$t_{½}$ (h)	% Fluctuation	R_{ac} (AUC_{τ})
CAM2038 q1w	7.5 (HS-07-307)	1	Patient (n=6)	1.58 (38)	18.0	NC	NC	161 (17)	NA	70.2	NA	NA
	8 (HS-11-426)	1	HV (n=18)	1.71 (36)	23.0	0.304 (26)	131 (24)	166 (20)	NA	70.7 (28)	NA	NA
	15 (HS-07-307)	1	Patient (n=6)	2.75 (18)	24.0	NC	NC	349 (14)	NA	107	NA	NA
	16 (HS-11-426)	1	HV (n=15)	3.08 (49)	23.1	0.611 (25)	241 (28)	335 (13)	NA	96.4 (44)	NA	NA
	16 (HS-13-487)	1	HV (n=15)	3.05 (46)	23.6	0.580 (25)	243 (30)	NC	NA	NC	NA	NA
	16 (HS-13-487)	4[c]	HV (n=15))	4.30 (44)	23.2	0.842 (22)	350 (24)	NA	2.09 (24)	126 (44)	160 (36)	1.44 (25)
	22.5 (HS-07-307)	1	Patient (n=8)	3.67 (34)	24.0	NC	NC	420 (18)	NA	80.5	NA	NA
	24 (HS-13-478)	1	Patient (n=22)	3.64 (39)	24.0	0.822 (25)	304 (30)	NA	NA	NC	NA	NA
	30 (HS-07-307)	1	Patient (n=6)	4.92 (28)	24.0	NC	NC	529 (15)	NA	87.8	NA	NA
	32 (HS-11-426)	1	HV (n=16)	5.27 (45)	22.9	1.13 (24)	431 (25)	638 (12)	NA	112 (45)	NA	NA
	32 (HS-13-478)	1	Patient (n=24)	4.39 (43)	24.0	0.993 (32)	376 (31)	NA	NA	NC	NA	NA
	32 (HS-15-549)	4-7[c]	Patient (n=21)	6.87 (37)	24.0	2.63 (39)	700 (27)	NA	4.17 (27)	NC	95.3 (39)	NA
CAM2038 q4w	64 (HS-13-487)	1	HV (n=17)	3.81 (60)	10.0	0.449 (57)	955 (33)	1360 (33)	NA	447 (52)	NA	NA
	96 (HS-13-487)	1	HV (n=14)	5.47 (56)	10.0	0.538 (28)	1170 (29)	1830 (26)	NA	555 (34)	NA	NA
	128 (HS-13-487)	1	HV (n=16)	6.59 (68)	6.1	0.934 (33)	1580 (44)	2550 (26)	NA	502 (52)	NA	NA
	128 (HS-15-549)	4[c]	Patient (n=16)	11.1 (54)	10.0	2.09 (55)	2610 (42)	NA	3.89 (42)	NC	220 (44)	NC
	160 (HS-15-549)	4[c]	Patient (n=12)	15.4 (52)	24.0	2.66 (61)	3540 (26)	NA	5.27 (26)	NC	237 (80)	NC
	192 (HS-13-487)	1	HV (n=13)	7.54 (58)	4.0	1.26 (36)	1790 (34)	3260 (31)	NA	611 (28)	NA	NA
Subutex	8 (HS-11-426)	1	HV (n=18)	4.32 (32)	1.49	0.249 (38)	17.5 (29)	NC	NA	NC	NA	NA
		7[c]	HV (n=18)	4.74 (29)	1.25	0.606 (46)	27.2 (34)	NA	1.13 (34)	35.8 (35)	373 (16)	NC
	8 (HS-13-487)	1	HV (n=17)	4.35 (41)	1.03	0.259 (35)	18.5 (30)	NC	NA	NC	NA	NA
		7[c]	HV (n=17)	4.74 (36)	1.48	0.677 (52)	29.8 (33)	NA	1.24 (33)	42.5 (34)	338 (30)	1.61 (23)
	16 (HS-11-426)	1	HV (n=15)	6.71 (62)	1.03	0.381 (36)	25.4 (45)	NC	NA	NC	NA	NA
		7[c]	HV (n=15)	6.25 (49)	1.48	0.794 (58)	38.5 (37)	NA	1.60 (37)	38.7 (28)	347 (33)	NC
	16 (HS-13-487)	1	HV (n=15)	5.88 (31)	1.00	0.374 (44)	26.5 (34)	NC	NA	NC	NA	NA
		7[c]	HV (n=15)	6.72 (47)	1.02	1.05 (46)	45.7 (33)	NA	1.90 (33)	42.8 (16)	308 (35)	1.73 (28)
	24 (HS-11-426)	1	HV (n=16)	7.08 (19)	1.03	0.490 (39)	33.1 (25)	NC	NA	NC	NA	NA
		7[c]	HV (n=16)	7.78 (37)	1.01	1.24 (44)	56.3 (29)	NA	2.34 (29)	39.0 (23)	282 (34)	NC
	24 (HS-13-487)	1	HV (n=16)	8.23 (60)	0.83	0.544 (44)	34.8 (34)	NC	NA	NC	NA	NA
		7[c]	HV (n=16)	8.45 (54)	1.04	1.61 (40)	63.9 (34)	NA	2.66 (34)	38.3 (33)	272 (27)	1.84 (28)
Suboxone	8 (HS-15-549)[d]	19[c]	Patient (n=16)	11.1 (61)	1.69	NC	NC	NC	NC	NC	NC	NC

Values are geometric mean (geometric CV%); [a] Median; [b] C_{168h} for CAM2038 q1w, C_{28d} for CAM2038 q4w and C_{24h} for Subutex; [c] Steady-state PK parameters; [d] three times a day
AUC_{inf}: AUC extrapolated to infinity; AUC_{τ}: AUC over the dosing interval; BPN: buprenorphine; C_{av}: average concentration during the dosing interval; C_{max}: maximum observed plasma concentration; C_{trough}: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; %Fluctuation: percentage fluctuation of concentration from average concentration; HV: healthy volunteer; NA; not applicable; NC: not calculated; NCA: non-compartmental analysis; R_{ac}: accumulation ratio; SC: subcutaneous; SL: sublingual; $t_{½}$: half-life; T_{max}: time corresponding to occurrence of C_{max}
Source: Table 14.2.3.2.2 in CSR HS-11-426, Table 14.2.3.2.2.in CSR HS-13-487, Table 14.2.1.2.1 in CSR HS-07-307, Table 14.2.4.2 to 14.2.4.5 in CSR HS-15-549 and Table 14.2.12.2a-b in CSR HS-13-478

Table 10 Summary of PK parameters of norBPN based on NCA after SC buttock injections of CAM2038 q1w and CAM2038 q4w and SL administration of Subutex and Suboxone film

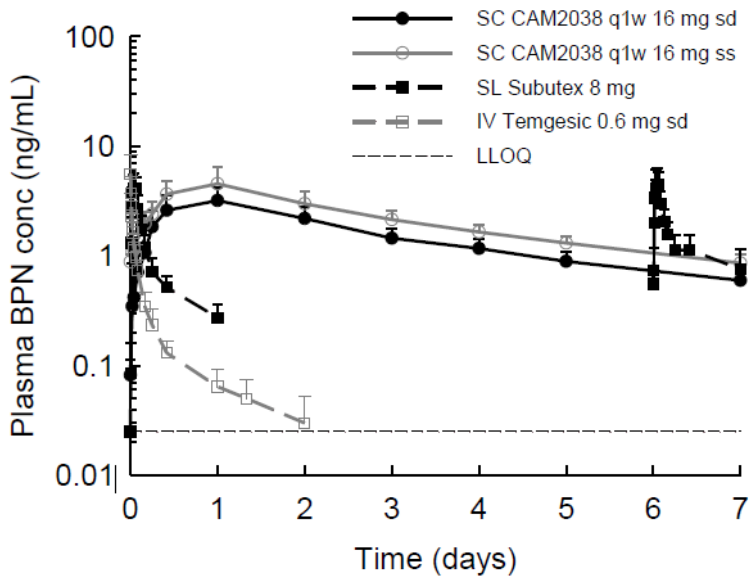
Product	Dose (mg) (Study)	Dose No.	Population	C_{max} (ng/mL)	T_{max} [a] (h)	C_{trough} [b] (ng/mL)	AUC_{τ} (ng*h/mL)	AUC_{inf} (ng*h/mL)	C_{av} (ng/mL)	$t_{½}$ (h)	R_{ac} (AUC_{τ})	Metab ratio C_{max}	Metab ratio AUC_{τ}
CAM2038 q1w	8 (HS-11-426)	1	HV (n=18)	0.359 (51)	84.6	0.147 (54)	39.2 (52)	67.5 (41)	NA	83.6 (34)	NA	NC	NC
	16 (HS-11-426)	1	HV (n=15)	0.649 (51)	71.6	0.309 (45)	71.3 (46)	113 (38)	NA	85.2 (41)	NA	NC	NC
	16 (HS-13-487)	1	HV (n=15)	0.763 (44)	70.7	0.286 (43)	75.9 (57)	NC	NA	NC	NA	NC	NC
	16 (HS-13-487)	4[c]	HV (n=15)	0.921 (55)	72.6	0.416 (41)	108 (49)	NA	0.643 (49)	132 (64)	1.52 (46)	0.242 (41)	0.348 (34)
	24 (HS-13-478)	1	Patient (n=22)	0.770 (51)	72.0	0.454 (45)	88.6 (50)	NC	NA	NC	NC	NC	NC
	32 (HS-11-426)	1	HV (n=16)	0.938 (58)	71.3	0.418 (96)	96.3 (56)	165 (57)	NA	97.1 (33)	NA	NC	NC
	32 (HS-13-478)	1	Patient (n=24)	0.865 (52)	72.0	0.547 (43)	102 (50)	NC	NA	NC	NC	NC	NC
	32 (HS-15-549)	4-7[c]	Patient (n=21)	1.85 (75)	72.0	1.08 (85)	204 (64)	NA	1.22 (64)	NC	NC	0.305 (59)	0.354 (57)
CAM2038 q4w	64 (HS-13-487)	1	HV (n=17)	0.792 (41)	74.6	0.136 (65)	256 (35)	359 (32)	NA	346 (56)	NA	0.235 (58)	NC
	96 (HS-13-487)	1	HV (n=14)	1.10 (71)	95.9	0.146 (83)	305 (68)	443 (64)	NA	394 (54)	NA	0.227 (46)	NC
	128 (HS-13-487)	1	HV (n=16)	1.36 (84)	108	0.266 (78)	439 (69)	653 (53)	NA	386 (47)	NA	0.233 (50)	NC
	128 (HS-15-549)	4[c]	Patient (n=16)	2.14 (123)	84.1	0.835 (201)	795 (131)	NA	1.18 (131)	NC	NC	0.219 (79)	0.344 (79)
	160 (HS-15-549)	4[c]	Patient (n=12)	4.61 (55)	121	1.78 (159)	1590 (55)	NA	2.37 (55)	NC	NC	0.339 (73)	0.532 (50)
	192 (HS-13-487)	1	HV (n=13)	1.62 (58)	73.7	0.390 (54)	555 (55)	895 (47)	NA	432 (34)	NA	0.243 (54)	NC
Subutex	8 (HS-11-426)	1	HV (n=18)	1.61 (37)	1.50	0.578 (34)	15.3 (34)	NC	NA	NC	NA	NC	NC
		7[c]	HV (n=18)	3.35 (36)	1.49	1.81 (47)	47.0 (42)	NA	1.96 (42)	34.8 (23)	NC	NC	NC
	8 (HS-13-487)	1	HV (n=17)	1.46 (59)	1.50	0.515 (46)	14.3 (42)	NC	NA	NC	NA	NC	NC
		7[c]	HV (n=17)	3.03 (34)	1.50	1.52 (47)	42.6 (35)	NA	1.77 (35)	35.7 (38)	2.97 (27)	0.721 (39)	1.62 (39)
	16 (HS-11-426)	1	HV (n=15)	3.90 (41)	0.72	1.10 (45)	31.1 (38)	NC	NA	NC	NA	NC	NC
		7[c]	HV (n=15)	5.41 (80)	1.45	2.90 (80)	74.3 (77)	NA	3.10 (77)	35.4 (35)	NC	NC	NC
	16 (HS-13-487)	1	HV (n=15)	3.96 (49)	1.00	1.10 (63)	34.1 (38)	NC	NA	NC	NA	NC	NC
		7[c]	HV (n=15)	7.04 (66)	0.70	3.81 (54)	105 (51)	NA	4.36 (51)	33.5 (21)	3.07 (38)	1.19 (34)	2.59 (35)
	24 (HS-11-426)	1	HV (n=16)	4.26 (40)	1.24	1.46 (32)	39.9 (30)	NC	NA	NC	NA	NC	NC
		7[c]	HV (n=16)	8.02 (43)	1.08	3.82 (53)	106 (49)	NA	4.43 (49)	35.1 (31)	NC	NC	NC
	24 (HS-13-487)	1	HV (n=16)	4.96 (55)	0.67	1.47 (43)	42.3 (47)	NC	NA	NC	NA	NC	NC
		7[c]	HV (n=16)	9.29 (48)	1.48	4.11 (156)	139 (47)	NA	5.81 (47)	33.5 (33)	3.29 (32)	1.24 (48)	2.46 (45)
Suboxone	8 (HS-15-549)[d]	19[c]	Patient (n=16)	7.92 (76)	1.78	NC	NC	NC	NC	NC	NC	NC	NC

Values are geometric mean (geometric CV%); [a] Median; [b] C_{168h} for CAM2038 q1w, C_{28d} for CAM2038 q4w and C_{24h} for Subutex; [c] Steady-state PK parameters [d] three times a day
AUC_{inf}: AUC extrapolated to infinity; AUC_{τ}: AUC over the dosing interval; C_{av}: average concentration during the dosing interval; C_{max}: maximum observed plasma concentration; C_{trough}: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; HV: healthy volunteer; NA; not applicable; NC: not calculated; NCA: non-compartmental analysis; norBPN: norbuprenorphine; R_{ac}: accumulation ratio; SC: subcutaneous; SL: sublingual; $t_{½}$: half-life; T_{max}: time corresponding to occurrence of C_{max}
Source: Table 14.2.3.2.2 in CSR HS-11-426, Table 14.2.3.2.2.in CSR HS-13-487, Table 14.2.4.2 to 14.2.4.5 in CSR HS-15-549 and Table 14.2.12.2a-b in CSR HS-13-478

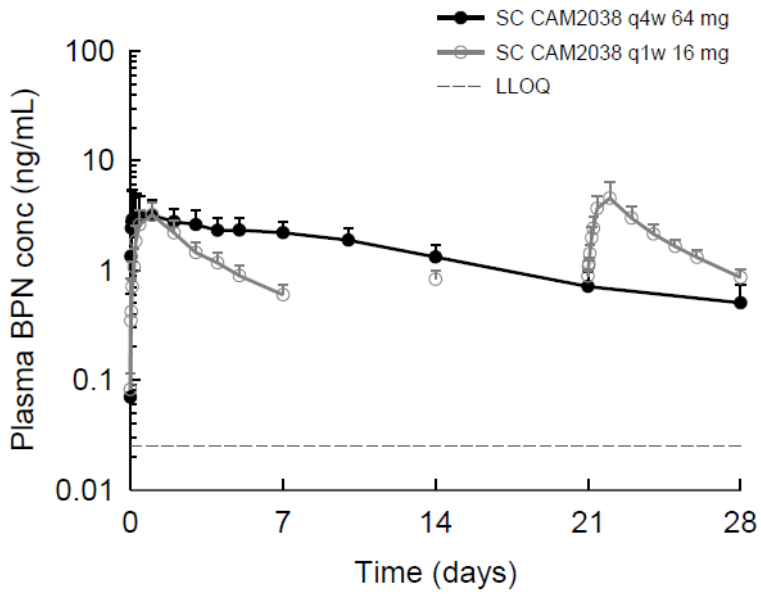
The SL BPN reference product Subutex (UK-sourced, Indivior Ltd) was used as a comparator in the two healthy volunteer studies (HS-11-426 and HS-13-487) to support the hybrid application. The active comparator (SL BPN/NX tablet, Amneal Pharmaceuticals) used in the pivotal Phase 3 study (HS-11-421) was considered appropriate and comparable to the UK sourced reference product (Subutex, Indivior Ltd) used in the PK studies in healthy volunteers (HS-11-426 and HS-13-487).

Overall, the absolute BA of BPN was estimated between 163% and 172% after single SC administration of 8, 16 and 32 mg CAM2038 q1w and was between 151% and 165% after administration of CAM2038 q4w. For SL Subutex, the absolute BA of BPN was 27-29% (8 mg), 20-22% (16 mg) and 19-21% (24 mg). Thus, the BA of BPN was approximately 6 to 9 times higher for CAM2038 q1w and CAM2038 q4w than for Subutex at comparable BPN exposure levels. These absolute BA values were based on plasma sampling up to 24 hours after IV BPN administration. Extending the plasma sampling to 48 hours after IV administration resulted in lower absolute BA of 130% for 96 mg CAM2038 q4w and 114% for 192 mg CAM2038 q4w.

Mean BPN plasma concentration-time profiles after single IV injection of 0.6 mg Temgesic, single and repeated daily SL doses of 8 mg Subutex and weekly SC injections of 16 mg CAM2038 q1w and after single SC injection of 64 mg CAM2038 q4w and 4 repeated weekly SC injections of 16 mg CAM2038 q1w are shown in the Figures below.



Plasma concentration-time profile of BPN after single IV injection of 0.6 mg Temgesic, single and repeated daily SL doses of 8 mg Subutex and weekly SC injections of 16 mg CAM2038 q1w in study HS-13-487



Plasma concentration-time profile of BPN after single and repeated weekly SC injections of 16 mg CAM2038 q1w and single SC injection of 64 mg CAM2038 q4w in study HS-13-487

CYP 3A4 is the main clearance pathway of buprenorphine therefore interactions with inhibitors or inducers are a concern and may differ depending on the dose route. UGT1A1 also appears to be a major clearance pathway thus inhibitors of this enzyme may affect the systemic exposure of BPN.

Drug-drug interactions are expected between buprenorphine and potent inhibitor of CYP3A4 resulting in increased Cmax and AUC of BPN and norBPN. The PBPK model used to investigate the possible effect of CYP 3A4 inhibitors and inducers on the exposure of buprenorphine following subcutaneous dosing is not adequate to support any dose adjustment or recommendation about the DDI in the SmPC. CYP3A4 inhibitors may inhibit the metabolism of buprenorphine resulting in increased Cmax and AUC of BPN and norBPN.

CYP3A4 inducers may induce the metabolism of buprenorphine resulting in decreased BPN levels. At the expected plasma concentrations inhibition of P450 enzymes or drug transporters is not expected.

The posology and transitions from daily doses of SL BPN to initial weekly doses of CAM2038 q1w or monthly doses of CAM2038 q4w were based on the results of the clinical PK studies and the population PK analysis (refer to the Section 3.3.2 for further details).

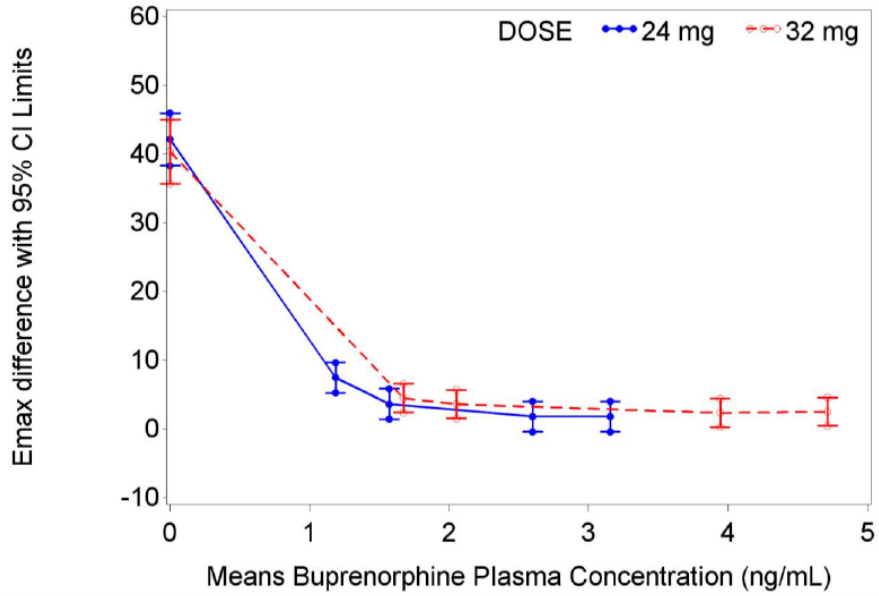
The population PK model was used to extrapolate the PK data in subjects over 16 years of age. Some differences may be observed by comparing the data predicted in this population with the results observed in adults in the clinical study HS-13-487. Particularly, after treatment with 16 mg q1w, lower Cmax (ca. 40% and 30% for male and female, respectively) and AUC (ca. 26% and 22% for male and female, respectively) are predicted in 16 years old patients compared with adult. Steady-state data are not available for 64 mg CAM2038 q4w. Lower $C_{ss,max}$ and $AUC_{ss,\tau}$ were predicted following repeated monthly administration of 64 mg CAM2038 q4w to 16-year-old males and females compared to observed C_{max} and predicted $AUC_{ss,\tau}$ following a single dose to adults.

2.8.3. Pharmacodynamics

The relationship between BNP plasma concentrations and blockade of the subjective opioid effects of hydromorphone has been explored in patients with moderate or severe opioid use disorder after 2 administrations of SC CAM2038 q1w 24 mg and 32 mg to guide target concentrations.

CAM2038 q1w was associated with a gradual increase in mean plasma BPN concentrations following the first (Day 0) and second (Day 7) administration of CAM2038 q1w 24 mg and 32 mg with peak concentrations observed at approximately 24 hours post-dose. BPN plasma concentrations following the first (Day 0) dose gradually decreased with the lowest values observed at 168 hours post-dose, prior to administration of the second (Day 7) dose. Plasma concentrations following the second administration of CAM2038 q1w were higher than those observed following the first dose of CAM2038 q1w, which is likely related to BPN concentrations present at the time of the second injection. Peak and overall exposure to BPN was higher in the CAM2038 q1w 32 mg treatment group compared with the CAM2038 q1w 24 mg group.

In literature, modelling studies have suggested that a BPN plasma concentration from 2 to 3 ng/mL (translated to ≥ 70% μ-opioid receptor occupancy) is needed to produce significant opioid blockade. (Greenwald 2014; Nasser 2014; Nasser 2016). Although plasma concentrations may be useful predictors for blockade, the variability observed in HS-13-478 suggests that a few individuals may experience partial blockade also at high BPN concentrations > 2 ng/mL. However, most patients demonstrated complete opioid blockade for a BPN plasma concentration of 1.2 ng/mL, reached approximately within 4 hours after the 24 mg CAM2038 injections.



Mean BPN concentration vs least square mean estimates of treatment difference (18 mg hydromorphone vs placebo) for Drug-Liking VAS Emax in study HS-13-478 Values are mean (95% CI)

The bridging of doses between SL BPN, CAM2038 q1w and CAM2038 q4w (Table below), are justified by comparable BPN steady-state exposure obtained by simulations using the population PK model.

Proposed switches from daily doses of SL BPN to initial weekly doses of CAM2038 q1w or monthly doses of CAM2038 q4w

Dose of daily SL BPN	Dose of weekly CAM2038 q1w	Dose of monthly CAM2038 q4w
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

BPN: Buprenorphine; SL: sublingual

The comparison of Cmax and Ctrough values for steady-state administrations of SL BPN with the respective values (Cmax and Ctrough) for the initial dose of CAM2038 q1w (a) and CAM2038 q4w(b) are shown below.

Simulated BPN PK parameters following switch from steady-state dosing of SL BPN to the first dose of CAM2038 q1w

Switch from SL BPN	PK parameters at steady state		Switch to CAM2038 q1w	PK parameters after the first dose	
Dose (mg)	C_{max} (ng/mL)	C_{trough} (ng/mL)	Dose (mg)	C_{max} (ng/mL)	C_{trough} (ng/mL)
2	1.7[a]	0.23	8	1.48 (32)	0.271 (39)
6	3.3[a]	0.46		1.68 (31)	0.294 (41)
8	3.92 (37)	0.540 (46)	16	3.01 (31)	0.540 (39)
10	4.7[a]	0.63		3.10 (31)	0.564 (38)
12	5.15 (38)	0.714 (45)	24	4.41 (31)	0.811 (40)
16	6.09 (36)	0.852 (45)		4.58 (33)	0.840 (41)
18	6.6[a]	0.90	32	5.95 (33)	1.09 (38)
24	7.94 (38)	1.10 (47)		5.91 (32)	1.10 (39)

Values are geometric mean (geometric CV%)
BPN: buprenorphine; C_{max}: maximum plasma concentration; C_{peak}: maximum peak concentration; C_{trough}: concentration before the next actual or intended dose; PK: pharmacokinetic; SL: sublingual
[a] BPN C_{peak}

Following Cmax, the BPN plasma concentrations declined slowly for CAM2038 q1w, supporting weekly dosing and monthly dosing for CAM2038 q4w. Similar or higher simulated Ctrough values were shown following the first dose of CAM2038 q1w compared to steady-state dosing of SL BPN for the lowest doses in the dose intervals of 2 to 6 mg, 8 to 10 mg, 12 to 16 mg and 18 to 24 mg**.** At the highest doses of SL BPN in the dose intervals, the simulated Ctrough values after the first dose of CAM2038 q1w were lower or equal to the Ctrough values at steady state for corresponding SL BPN doses, which may indicate a need for an additional 8 mg CAM2038 q1w dose during the first week of treatment with CAM2038 q1w.

Geometric means of simulated Cmax and concentration before the next dose (Ctrough) for the steady-state administrations of SL BPN and the switch to the initial dose of CAM2038 q4w are presented in the table below.

Simulated BPN PK parameters following switch from steady-state dosing of SL BPN to the first dose of CAM2038 q4w

Switch from SL BPN	PK parameters at steady state		Switch to CAM2038 q4w	PK parameters after the first dose	
Dose (mg)	C_{max} (ng/mL)	C_{trough} (ng/mL)	Dose (mg)	C_{max} (ng/mL)	C_{trough} (ng/mL)
8	3.92 (37)	0.540 (46)	64	3.23 (47)	0.581 (27)
10	4.7[a]	0.63		3.33 (47)	0.573 (28)
12	5.15 (38)	0.714 (45)	96	4.93 (49)	0.883 (29)
16	6.09 (36)	0.852 (45)		4.89 (47)	0.871 (29)
18	6.6[a]	0.90	128	6.47 (48)	1.16 (29)
24	7.94 (38)	1.10 (47)		6.61 (47)	1.17 (29)

Values are geometric mean (geometric CV%)
BPN: buprenorphine; C_{max}: maximum plasma concentration; C_{peak}: maximum peak concentration; C_{trough}: concentration before the next actual or intended dose; PK: pharmacokinetic; SL: sublingual
[a] BPN C_{peak}

For all switches (except 10 mg SL BPN) from steady-state dosing of SL BPN to the first dose of CAM2038 q4w, similar or higher Ctrough values were shown for CAM2038 q4w compared to Ctrough at steady state for SL BPN.

Geometric means of simulated Cmax and concentration before the next dose (Ctrough) for the steady-state administrations of CAM2038 q1w and the switch to the initial dose of CAM2038 q4w are presented in the table below

Simulated BPN PK parameters following transfer from steady-state dosing of CAM2038 q1w to the first dose of CAM2038 q4w

Transfer from CAM2038 q1w	PK parameters at steady state		Transfer to CAM2038 q4w	PK parameters after the first dose	
Dose (mg)	C_{max} (ng/mL)	C_{trough} (ng/mL)	Dose (mg)	C_{max} (ng/mL)	C_{trough} (ng/mL)
16	3.38 (24)	0.780 (45)	64	3.62 (46)	0.626 (29)
24	4.97 (25)	1.18 (45)	96	5.25 (45)	0.921 (29)
32	6.75 (24)	1.55 (43)	128	7.32 (44)	1.23 (31)

Values are geometric mean (geometric CV%)
BPN: buprenorphine; C_{max}: maximum plasma concentration; C_{trough}: concentration before the next actual or intended dose; PK: pharmacokinetic
Source: Table 9 in Report REP-2-CAM-2038-PMX-1 and Table 3 in Report REP-1-CAM-2038-PMX-2

For the transfers from steady-state dosing of CAM2038 q1w to the first dose of CAM2038 q4w, the simulated Ctrough values for CAM2038 q4w were slightly lower than for CAM2038 q1w. Therefore, patients may need to be monitored more closely following transitions.

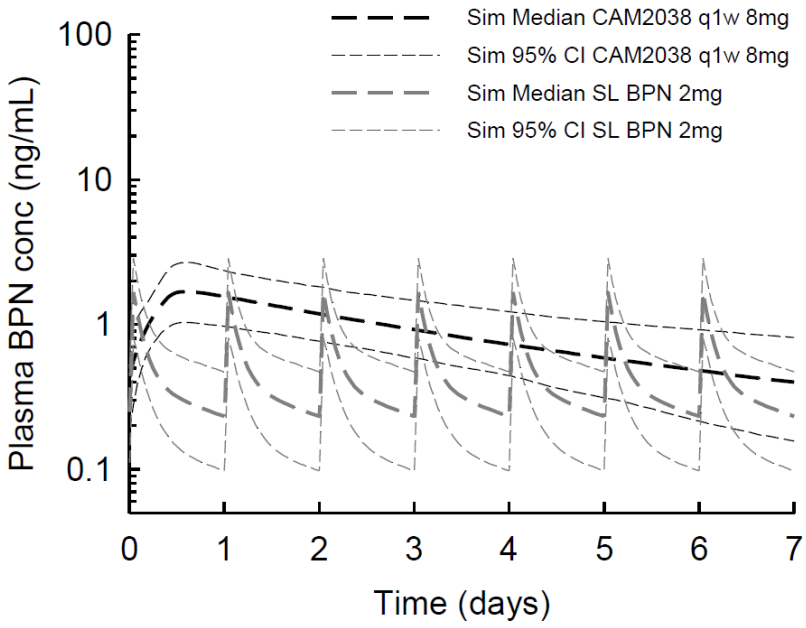
The ability to block the subjective drug-liking response to intramuscular (IM) hydromorphone was investigated in patients with opioid dependence (CSR HS-13-478). Complete blockade of the subjective drug-liking response

was estimated at BPN plasma concentrations above 0.4 ng/mL by population PK/PD modelling. Except for the switch from steady-state dosing of 2 to 6 mg SL BPN to the first dose of 8 mg CAM2038 q1w, all simulated Ctrough values were higher than 0.4 ng/mL after the switches from SL BPN to CAM2038 q1w or CAM2038 q4w and after the transfers from CAM2038 q1w to CAM2038 q4w. Thus, complete blockade of the subjective drug-liking response is maintained throughout the treatment period already after the first dose of 16, 24 or 32 mg CAM2038 q1w or 64, 96 or 128 mg CAM2038 q4w after transitions from previous treatments.

Additional simulations were provided on request.

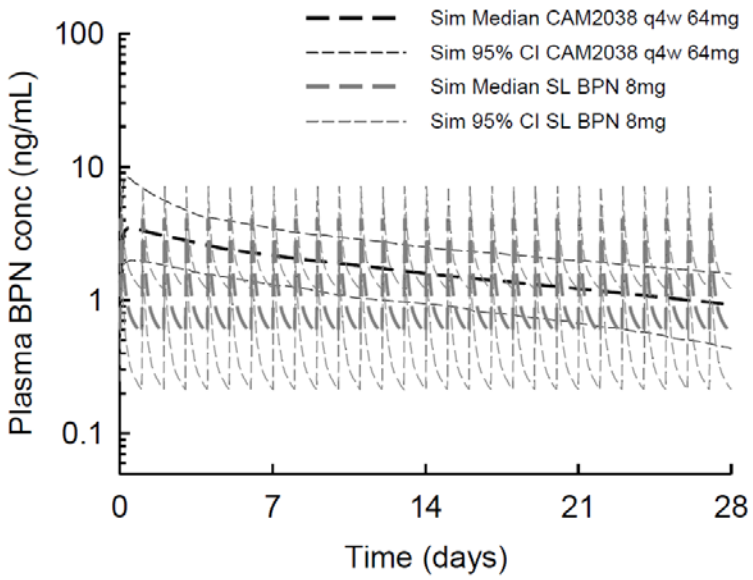
- Bridge between 2 mg SL BPN and 8 mg CAM2038 q1

Simulated steady-state plasma concentration-time profiles of BPN, based on population PK analysis, after weekly SC injection of 8 mg CAM2038 q1w and daily administration of 2 mg SL BPN



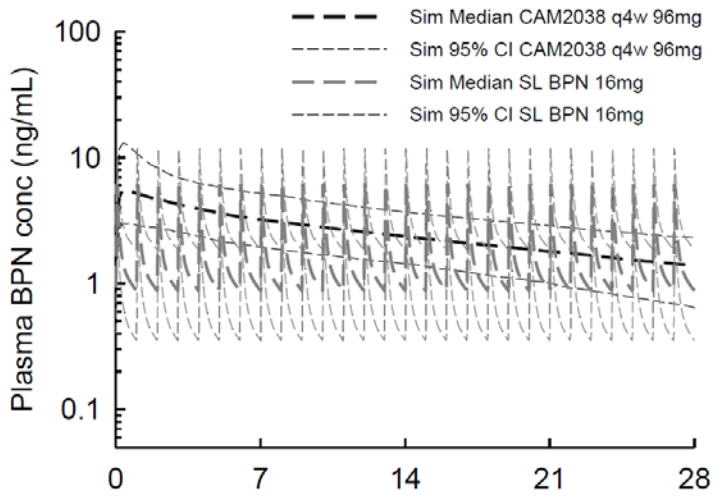
- Bridge for 8 mg SL BPN to 16 mg CAM2038 q1w, ridge for 16 mg SL BPN to 24 mg CAM2038 q1w, ridge for 24 mg SL BPN to 32 mg CAM2038 q1w (provided during the original application)
- Bridge for 8 mg SL BPN to 64 mg CAM2038 q4w

Simulated steady-state plasma concentration-time profiles of BPN, based on population PK analysis, after monthly SC injection of 64 mg CAM2038 q4w and daily administration of 8 mg SL BPN



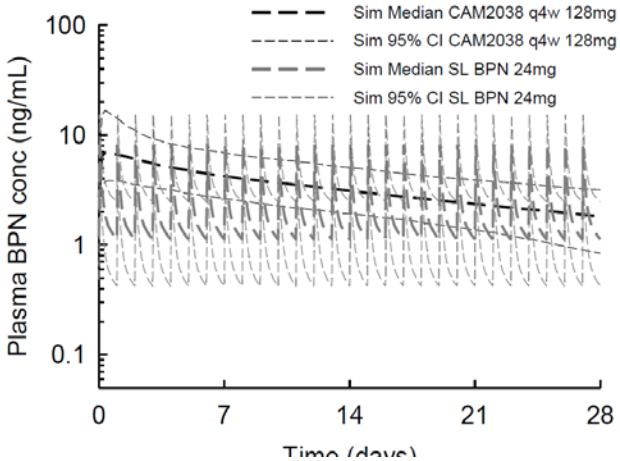
- Bridge for 16 mg SL BPN to 96 mg CAM2038 q4w

Simulated steady-state plasma concentration-time profiles of BPN, based on population PK analysis, after monthly SC injection of 96 mg CAM2038 q4w and daily administration of 16 mg SL BPN



- Bridge for 24 mg SL BPN to 128 mg CAM2038 q4w

Simulated steady-state plasma concentration-time profiles of BPN, based on population PK analysis, after monthly SC injection of 128 mg CAM2038 q4w and daily administration of 24 mg SL BPN



PK/PD relationships between BPN plasma concentrations and measured QT intervals corrected for heart rate using the Fridericia's correction (QTcF) were evaluated for 128 mg CAM2038 q4w. BPN exposure and ECG measurements were performed at 18 to 22 occasions, including 3 occasions around Cmax (at 6, 10 and 24 hour) after the fourth dose, for each subject. The provide data suggests that the absolute QTcF interval prolongation was below the 500 ms threshold and the increase in QTcF from baseline was less than 60 ms for all subjects and measurements. Overall, it appears that no trends were observed in either absolute QTcF interval or change in QTcF from baseline with increasing concentration of BPN at steady-state dosing of 128 mg CAM2038 q4w. Moreover it appears that no ECG-related adverse events (AEs) have been reported in patients related CAM2038 q4w administration.

Opioid dependence has been associated with misuse of gabapentin and pregabalin and the applicant points out that concomitant prescription of BPN or methadone and pregabalin was associated with a higher rate of overdose deaths.

2.8.4. Discussion on clinical pharmacology

On the whole, the PK of CAM2038 q1w could be considered sufficiently characterized in healthy volunteers and patients. Given the proportionality of composition of the different strengths, similar dissolution profiles and linearity, a strength biowaiver for the not fully evaluated doses could potentially be applied to the other strengths.

For CAM2038 q4w, the applicant has withdrawn the 160mg strength as the pharmacokinetic profile for this strength is not currently sufficiently characterised. There is an adequate understanding of the PK of the remaining dose levels. There are several issues to be considered regarding the interaction of buprenorphine with inhibitors or inducers of the CYP 3A4 and inhibitors of UGT1A that are the main clearance pathways of buprenorphine.

Drug-drug interactions are expected between buprenorphine and potent inhibitor of CYP3A4 resulting in increased Cmax and AUC of BPN and norBPN. A PBPK model has been used to investigate the possible effect of CYP 3A4 inhibitors and inducers on the exposure of buprenorphine following subcutaneous dosing. However, the

model appears to contradict some of the conclusions on the general PK properties and is not adequate to support any dose adjustment or recommendation about the DDI in the SmPC.

The posology and transitions from daily doses of SL BPN to initial weekly doses of CAM2038 q1w or monthly doses of CAM2038 q4w were based on the clinical PK studies and the population PK analysis of these data.

The applicant explored the relationship between BNP plasma concentrations and blockade of the subjective opioid effects of hydromorphone in patients with moderate or severe opioid use disorder after 2 administrations of SC CAM2038 q1w 24 mg and 32 mg. This data is important to understand the exposure of the current products in terms of efficacy.

The evaluation of the relationship between PK and PD suggested that concentrations ~1.2 ng/mL, which were reached as early as 4 hours after the first administration of both CAM2038 q1w doses, were sufficient to block the subjective effects of hydromorphone. Higher plasma BPN concentrations were not associated with appreciable increases in blockade in the different treatment groups.

In respect to transfers from SL BPN to weekly injections similar or higher simulated Ctrough values were shown following the first dose of CAM2038 q1w compared to steady-state dosing of SL BPN for the lowest doses in the dose intervals of 2 to 6 mg, 8 to 10 mg, 12 to 16 mg and 18 to 24 mg. On the other hand at the highest doses of SL BPN in the dose intervals, the simulated Ctrough values after the first dose of CAM2038 q1w were lower or equal to the Ctrough values at steady state for corresponding SL BPN doses. This may indicate that those patients are more likely to require additional 8 mg dose.

In respect to transfer from SL BPN to monthly injections for all switches (except 10 mg SL BPN) from steady-state dosing of SL BPN to the first dose of CAM2038 q4w, similar or higher Ctrough values were shown for CAM2038 q4w compared to Ctrough at steady state for SL BPN.

In respect to transfer from weekly to monthly injections for the transfers from steady-state dosing of CAM2038 q1w to the first dose of CAM2038 q4w, the simulated Ctrough values for CAM2038 q4w were slightly lower than for CAM2038 q1w for all dose levels.

2.8.5. Conclusions on clinical pharmacology

The submitted data package supports Marketing Authorisation of Buvidal from clinical pharmacology perspective.

2.8.6. Clinical efficacy

Dose-response studies and main clinical studies

Patients not currently taking BPN maintenance treatment

The starting dose is supported by the results from the HS-13-478, HS-11-421 and HS-14-499 studies. The starting dose for patients not currently receiving BPN maintenance treatment in HS-11-421 and HS-14-499 was 16 mg of weekly CAM2038 and all patients received one titration dose of 8 mg during Week 1 up to a total of 24 mg CAM2038 q1w.

As in clinical practice, dose adjustments (increases in case of withdrawal effects or cravings or decreases for tolerability reasons) were allowed during the Phase 3 studies at scheduled study visits. In the HS-11-421 study,

50.2% of patients reached a maximum dose of 24 mg CAM2038 q1w and 39.9% were titrated double-blinded to a dose of 32 mg of CAM2038 q1w, resulting in effective withdrawal suppression and non-inferior efficacy compared with SL BPN/NX, where 109 patients (50.7 %) reached a corresponding daily dose of 16 mg and 90 patients (41.9 %) were titrated up to 24 mg/day SL BPN/NX.

In the HS-14-499 study, 26 of the 37 new-to-treatment patients (70.3%) reached a maximum dose of 24 mg CAM2038 q1w, and 4 patients (10.8%) received a maximum of 32 mg of CAM2038 q1w during the treatment period.

Furthermore, study HS-13-478 showed that 24 mg CAM2038 q1w provided rapid and sustained blockade of opioid effects and suppression of withdrawal from the first dose and was well tolerated by patients with opioid dependence.

Thus, the approved posology is supported by substantial clinical evidence, including PK, PD, efficacy, safety and tolerability from studies HS-13-478, HS-11-421 and HS-14-499.

Transitioning from Sublingual Buprenorphine to CAM2038

Patients treated with SL BPN may be transitioned directly to weekly or monthly CAM2038.

The transition criteria are based on the results of the clinical PK studies (HS-11-426, HS-13-487, HS-13-478 and HS-15-549) and the population PK analysis of these data. The aim is to achieve appropriate BPN exposures during initiation as well as comparable BPN PK exposure on transfer between SL BPN, CAM2038 q1w and CAM2038 q4w treatments, and to provide sustained efficacy, safety and tolerability in treatment of opioid dependence, as demonstrated in the Phase 3 studies HS-11-421 and HS-14-499. The dose conversion is based on single-dose and steady-state BPN systemic exposure data after repeated daily administration of SL BPN and CAM2038 in studies HS-11-426, HS-13-487, HS-13-478 and HS-15-549 as well as population PK modelling and simulation of data from these studies.

Maintenance Treatment with CAM2038

Patients may be switched from weekly to monthly dosing or from monthly to weekly dosing of CAM2038 (Table below).

The transitioning between weekly and monthly dosing of CAM2038 is supported by PK and population PK modelling, as well as studies HS-11-421 and HS-14-499. Study HS-11-421 included a fixed transition from weekly to monthly treatment with CAM2038 after the initial 12 weeks of treatment. Dose conversions were made based on previous PK and PD study results. The transition between weekly and monthly CAM2038 was smooth, without any out-of-trend observations in any of the PD (withdrawal and cravings), efficacy (illicit opioid use) or safety and tolerability outcomes, or indications of loss of efficacy compared with the SL BPN/NX comparator group. Furthermore, the highest weekly (Phase 1) and monthly (Phase 2) individual doses reached in this flexible dose study were fully consistent with the pre-defined dose conversions between the weekly and monthly products. Moreover, the use of supplemental 8 mg CAM2038 q1w was limited, with fewer patients requiring supplemental doses in the CAM2038 arm compared to the SL BPN/NX arm.

Furthermore, study HS-14-499 allowed investigators flexibility to transition from weekly to monthly CAM2038 dosing in accordance with the same dose conversion schedule, without observations of reduced efficacy or tolerability across the study.

HS-11-421 - Phase III, Randomized, Double-Blind, Active-Controlled, Parallel Group, Multi-center Trial Assessing the Efficacy and Safety of a Once-Weekly and

Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients with Opioid Use Disorder

Methods

The study was designed to evaluate the non-inferiority of CAM2038 compared to an existing standard of care (SL BPN/NX) in initiation and maintenance treatment with BPN. The study involved 4 phases: Screening (3 weeks), Phase 1 (12 treatment weeks), Phase 2 (12 treatment weeks), and Follow-up (4 weeks). The use of suboxone as control is acceptable as the naloxone component doesn't interfere with the pharmacodynamic properties of buprenorphine and is added to deter from misuse of the tablets.

Patients

Main inclusion criteria

1. Male and female subjects 18-65 years of age (inclusive)
2. Primary diagnosis of moderate or severe opioid use disorder (Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition [DSM-V]) were eligible for study participation.
3. Voluntarily sought treatment for opioid use disorder.
4. Had not received medication-assisted treatment for opioid use disorder within 60 days prior to randomization.
5. Considered by the investigator to be a good candidate for BPN treatment, based on medical and psychosocial history.

Main exclusion criteria

Subjects were excluded from the study if they had e.g.:

1. Current diagnosis of Acquired Immune Deficiency Syndrome (AIDS).
2. Current diagnosis of chronic pain requiring opioids for treatment
3. A DSM-V diagnosis of moderate to severe substance use disorder other than opioids, caffeine, or nicotine, which was primary or co-primary
4. Active signs or symptoms of hepatitis and requiring treatment

Treatments

Test product

CAM2038 q1w: BPN FluidCrystal® SC injection depot for once weekly administration (50 mg/mL) at doses of 8, 16, 24 and 32 mg (BPN base) (0.16, 0.32, 0.48 or 0.64 mL SC injection).

CAM2038 q4w: BPN FluidCrystal SC injection depot for once monthly administration (356 mg/mL) at doses of 64, 96, 128 or 160 mg (BPN base) (0.18, 0.27, 0.36 or 0.45 mL SC injection).

Reference product

The reference therapy was SL BPN/NX tablets plus placebo injections. Subjects received sublingual BPN/NX tablets at 16 or 24 mg/day (up to 32 mg/day during Phase 2).

Objectives

The primary objective of the study was to demonstrate non-inferiority of the CAM2038 buprenorphine (BPN) treatment arm as compared to the sublingual (SL) BPN/naloxone (NX) treatment arm in treating adult outpatients with opioid use disorder in terms of urine samples negative for illicit opioids. Due to differences in analyses requested by the US Food and Drug Administration (FDA) and by the Committee for Medicinal Products for Human Use at the European Medicines Agency (EMA), two statistical analysis plans (SAPs) were prepared: one for FDA submission and one for EMA submission. In the FDA SAP, the primary objective was the same as in the protocol, i.e., to demonstrate non-inferiority of the CAM2038 treatment arm as compared to the SL BPN/NX arm as measured by the primary efficacy measure of response rate (RR). In the EMA SAP, the primary objective was to demonstrate noninferiority of the CAM2038 treatment arm as compared to the SL BPN/NX arm as measured by the primary efficacy measure of percentage urine sample negative for illicit opioids.

The secondary objectives were:

- To evaluate the efficacy of CAM2038 compared to SL BPN/NX as measured by the cumulative distribution function (CDF) of percentage urine samples negative for illicit opioids (supported by self-reported opioid use results for the FDA analyses) between Weeks 5 and 25.
- To evaluate the efficacy of CAM2038 compared to SL BPN/NX in adult outpatients with opioid use disorder, as measured by time to sustained abstinence from illicit opioid use.
- To evaluate the efficacy of CAM2038 compared to SL BPN/NX in adult outpatients with opioid use disorder, as measured by retention rate.
- To evaluate the efficacy of CAM2038 compared to SL BPN/NX in adult outpatients with opioid use disorder, as measured by the exploratory efficacy measures.
- To evaluate the safety of CAM2038 in adult outpatients with opioid use disorder.

Outcomes/endpoints

The primary efficacy endpoint for EMA was the percentage of urine samples negative for illicit opioids based on the 18 urine samples obtained during the post-induction period (between Week 2 and Week 25). (This endpoint was added as a primary endpoint for EMA in Protocol Amendment 5).

In this analysis, if urine toxicology samples were missing, for example, due to missing scheduled visit, early discontinuation of the study, or subject's refusal to provide the samples (scheduled or random samples), the results were imputed as positive.

Efficacy evaluation was based on illicit opioid use (as measured through urine toxicology and self-reporting); retention rate (percent of subjects remaining in study); desire and need to use; use of other illicit drugs; withdrawal; need for supplemental SL BPN/NX; and need for supplemental counseling. The primary efficacy variable (for the FDA) was RR, based on urine toxicology results for illicit opioids.

The primary efficacy variable (for EMA) was the percent negative urine samples, based on the 18 urine samples obtained during the post-induction period (between Week 2 and Week 25).

The primary efficacy variable (for the FDA) was RR, based on urine toxicology results for illicit opioids.

To be a responder for Phase 1 (the final responder definition was outlined in Protocol Amendment 4), the subject had to have no evidence of illicit opioids use at Week 13 and no evidence of illicit opioids use for at least two out of the three weeks from Week 10 to Week 12.

To be a responder for Phase 2, the subject had to have no evidence of illicit opioids use at Month 6 (last illicit opioids use assessment in Month 6 or Week 25) and no evidence of illicit opioids use in five out of the six illicit opioids use assessments in Phase 2. To be a responder for the study, the subject must have been a responder for both Phases 1 and 2. Evidence of illicit opioid use was defined as a positive urine toxicology result or a self-reported illicit opioid use.

The primary efficacy analysis was based on the ITT population.

The clinical objective of the study, to demonstrate non-inferiority of the CAM2038 BPN treatment arm as compared to the SL BPN/NX treatment arm in treating adult outpatients with opioid use disorder, was tested using RR. The proportion of responders was calculated in both treatment arms.

Secondary efficacy variables

- Cumulative Distribution Function of Percent Samples That Were Negative for Illicit Opioids for Weeks 5 to 25
- Retention Rate
- Time to Sustained Abstinence of Opioid Use

Sample size

The choice of non-inferiority margin for the variable percent negative urine was based on the outcome of the Rosenthal study (Rosenthal, 2013) where a comparison was evaluated over 24 weeks between SL BPN/NX (n=119) and placebo (n=54) for the outcome variable percent negative urine samples. The reported values from the ANOVA was 35.1% for SL BPN/NX and 14.4% for placebo (difference = 20.7%, P = 0.81). This translates to an approximate 95% CI for the difference of (11.5%, 29.9%). The power calculation was based on the lower limit of this CI representing a level of effect that can be viewed as clinically relevant, and can represent a hypothetical placebo arm in this study.

Randomisation

Randomization was used to avoid bias in the assignment of subjects to treatments, to increase the likelihood that known and unknown subject attributes (e.g., demographics, baseline characteristics) were evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Subjects who provided written informed consent were assigned a unique number in the Screening process. This number was used to identify the subject throughout the study.

Subjects who met the eligibility criteria during the re-check on Day 1 and who tolerated the 4 mg test dose were randomized to one of the two treatment groups in a 1:1 ratio (Group 1: Daily SL BPN/NX plus SC placebo injections or Group 2: CAM2038 [q1w and q4w] SC injections plus SL placebo tablets). Due to the size of the study, it was expected that subjects would be balanced for various other baseline factors, including age.

Once any subject number or randomization number was assigned, it could not be reassigned to any other subject. This study used central randomization, through an Interactive Web Response System managed by DSG, Inc.

Blinding (masking)

In order to reduce the potential for bias in the study, treatment group assignments were double-blinded. The subject, investigational site personnel, sponsor, and sponsor designees directly involved in the conduct and/or monitoring of this study were not aware of the treatment group assignments.

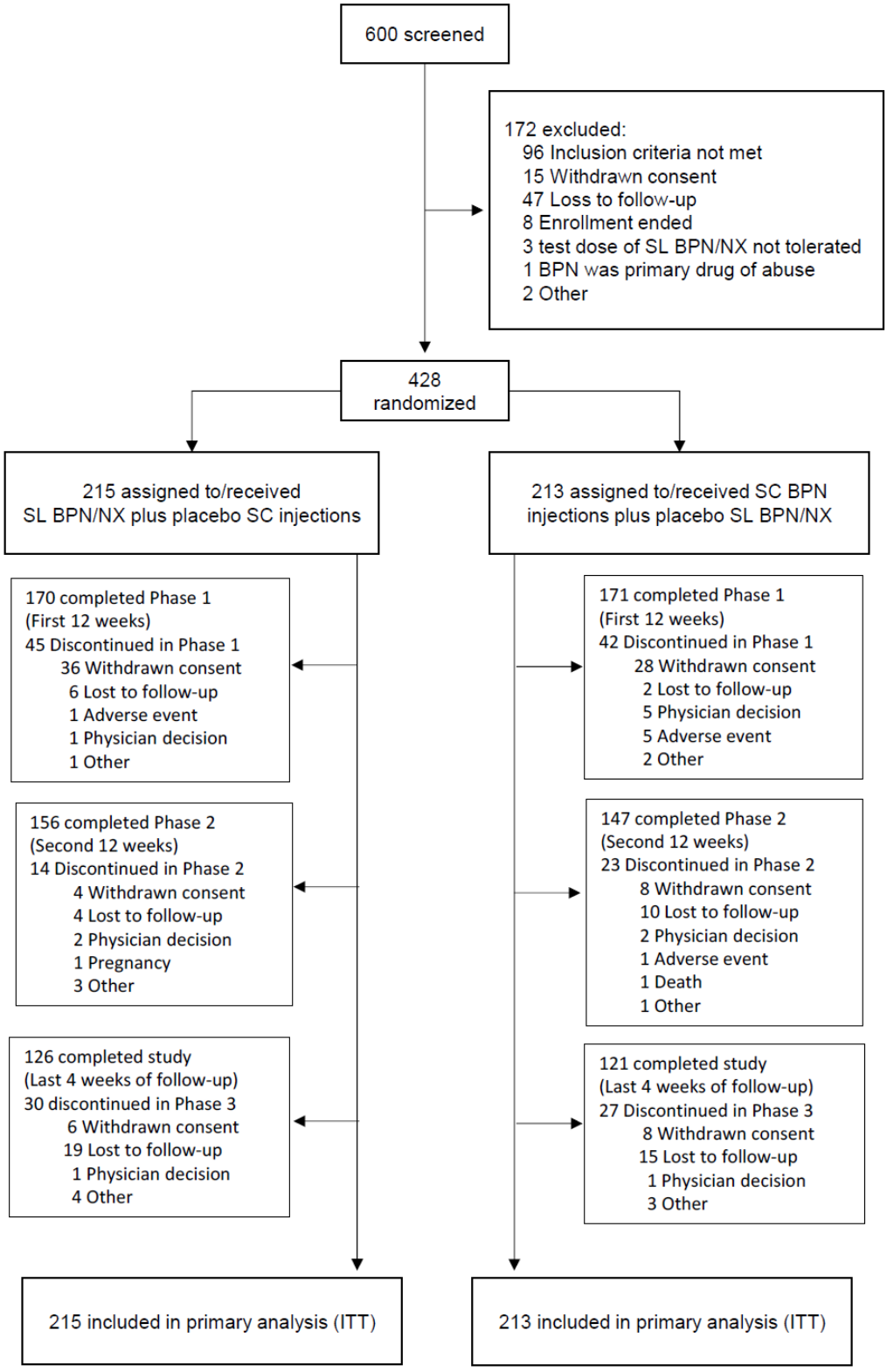
SL BPN/NX tablets used during the study had a nearly matching placebo. Due to minor potential differences between active and placebo SL tablets, subjects were told that clinical supplies of SL BPN/NX were specifically developed for this study and may look or taste different than commercially available products that they may have been treated with previously.

Statistical methods

The primary efficacy endpoint was the percentage of urine samples negative for illicit opioids based on the 18 urine samples obtained during the post-induction period (between Week 2 and Week 25). This variable was analysed via an analysis of variance (ANOVA) model with treatment effects. The difference between the two treatments in percent negative urine samples was obtained from this model and the two-sided 95% CI for the treatment difference was presented.

Results

Participant flow



Recruitment

This study was performed in the US at 36 sites by 36 investigators. Subjects were randomized at 35 sites; one study site did not randomize any subjects.

Study Initiation Date (first subject randomized): 29 December 2015

Study Completion Date (last subject completed): 19 October 2016

Conduct of the study

The secondary and exploratory efficacy endpoints were modified in Protocol Amendments.

Changes made would mainly influence the analysis of the data collected and would not impact on the data per se. The changes made to the SAPs were based on advice received from the CHMP.

Baseline data

Table 11: Demographics (safety population)

Category	SL BPN/NX N=215	CAM2038 N=213	Total N=428
Age (years)			
Mean (SD)	38.0 (10.89)	38.7 (11.17)	38.4 (11.02)
Min, max	18.0 - 65.0	19.0 - 65.0	18.0 - 65.0
Sex, n (%)			
Male	142 (66.0)	121 (56.8)	263 (61.4)
Female	73 (34.0)	92 (43.2)	165 (38.6)
Race, n (%)			
White	164 (76.3)	159 (74.6)	323 (75.5)
Black or African American	48 (22.3)	47 (22.1)	95 (22.2)
Asian	0 (0.0)	1 (0.5)	1 (0.2)
American Indian or Alaska native	1 (0.5)	2 (0.9)	3 (0.7)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.5)	1 (0.2)
Other	2 (0.9)	3 (1.4)	5 (1.2)
Ethnicity, n (%)			
Hispanic or Latino	24 (11.2)	25 (11.7)	49 (11.4)
Not Hispanic or Latino	191 (88.8)	188 (88.3)	379 (88.6)
BMI (kg/m^2)			
Mean (SD)	26.2 (5.55)	25.6 (5.03)	25.9 (5.30)
Min, max	15.8 - 53.2	14.9 - 42.8	14.9 - 53.2

Abbreviations: BMI, body mass index; SD, standard deviation; SL BPN/NX, sublingual buprenorphine/naloxone
Source: Table 14.1.2

A majority (70.8%) of subjects had previously used heroin as the primary opioid of abuse, and approximately half (52.3%) of the subjects used injection as the route of administering opioids (Table below). Positive screening results for amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, and phencyclidine were similar between treatment groups.

Table 12: Opioid use history (safety population)

Category	SL BPN/NX N=215 n (%)	CAM2038 N=213 n (%)	Total N=428 n (%)
Primary opioid of use at initiation			
Heroin	151 (70.2)	152 (71.4)	303 (70.8)
Prescription opioid pain reliever	64 (29.8)	61 (28.6)	125 (29.2)
Route of illicit opioid			
Injection	110 (51.2)	114 (53.5)	224 (52.3)
Non-injection	105 (48.8)	99 (46.5)	204 (47.7)
Positive screening result for:			
Amphetamines	32 (14.9)	38 (18.0)	
Barbiturates	1 (0.5)	3 (1.4)	
Benzodiazepine	35 (16.3)	30 (14.2)	
Cocaine	53 (24.7)	53 (25.1)	
Marijuana	64 (29.8)	57 (27.0)	
Phencyclidine	0	2 (0.9)	

Abbreviations: SL BPN/NX, sublingual buprenorphine/naloxone
Source: Table 14.1.5, Table 14.2.13 EMA, and Table 14.2.14 FDA

Post Hoc Analysis: Other Baseline Characteristics - Most subjects (93.7% overall) had opioid-positive urine samples (supported by subjects' self-reports of opioid use) at Day 1. A majority of subjects (71.0%) had a history of using non-opioid substances, and approximately one-fourth (25.9%) of subjects had a history of fentanyl use. Fentanyl use was slightly higher (29.1%) among subjects in the CAM2038 treatment group compared with the SL BPN/NX treatment group (22.8%).

Table 13: post-hoc - Other Baseline Characteristics - ITT Population

		SL BPN (N=215)	CAM2038 (N=213)	TOTAL (N=428)
At least one other substance use (non-opioid)		149 (69.3%)	155 (72.8%)	304 (71.0%)
Fentanyl use		49 (22.8%)	62 (29.1%)	111 (25.9%)
Hepatitis at study entry	Any Hepatitis	54 (25.1%)	50 (23.5%)	104 (24.3%)
	Hepatitis	3 (1.4%)	1 (0.5%)	4 (0.9%)
	Hepatitis B	2 (0.9%)	2 (0.9%)	4 (0.9%)
	Hepatitis C	50 (23.3%)	49 (23.0%)	99 (23.1%)
Urine Positive for Opioid Use	SCREENING	200 (93.0%)	193 (90.6%)	393 (91.8%)
	PHASE 1 DAY 1	188 (87.4%)	187 (87.8%)	375 (87.6%)
Urine Positive for Opioid Use Supported by Self-report	SCREENING	209 (97.2%)	204 (95.8%)	413 (96.5%)
	PHASE 1 DAY 1	203 (94.4%)	198 (93.0%)	401 (93.7%)

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Psychosocial and Medical History

73 (17.1%) subjects did not have a high school education; 161 (37.6%) had a GED/high school diploma; 146 (34.1%) had received some college or certificate program education; 40 (9.3%) subjects had a 2-year or 4-year college degree; and 7 (1.6%) subjects had a graduate degree. The majority of subjects were unemployed (236 subjects; 55.1%) whereas 148 subjects (34.6%) were employed either full time or part time. The majority of subjects were single (228 subjects; 53.3%), renters (218 subjects; 50.9%), and had been arrested in the past (274 subjects; 64.0%).

Psychosocial history results were comparable between the two treatment groups.

A majority (97.4%) of subjects had medical history available. Overall, the most common medical conditions at study entry were in the SOCs of Psychiatric Disorders (86.9%), followed by Infections and Infestations (38.3%) and Surgical and Medical Procedures (35.3%).

No subject had a medical history of HIV or AIDS.

The majority of subjects were single (228 subjects; 53.3%), renters (218 subjects; 50.9%), and had been arrested in the past (274 subjects; 64.0%).

Post Hoc Analysis: Hepatitis at Study Entry - Approximately one-fourth (25.9%) of subjects had any self-reported history of hepatitis, most of whom had a history of hepatitis C (23.1%).

Prior and concomitant medication

A total of 54 (12.6%) subjects took at least one medication before study entry; the most common class of prior medications was nonsteroidal anti-inflammatory and antirheumatic products (2.8%). No subjects had prior use of strong CYP inducers or inhibitors. The use of prior medications was generally comparable between the two treatment groups.

Table 14: Prior medications – opioids

WHO DRUG ATC CLASS	DRUG NAME	SL BPN (N=215)	CAM2038 (N=213)	TOTAL (N=428)
AT LEAST ONE MEDICATIONS		26 (12.1%)	28 (13.1%)	54 (12.6%)

OPIOIDS		2 (0.9%)	5 (2.3%)	7 (1.6%)
	HYDROCODONE	0 (0.0%)	1 (0.5%)	1 (0.2%)
	MEPERIDINE	1 (0.5%)	0 (0.0%)	1 (0.2%)
	MORPHINE	0 (0.0%)	1 (0.5%)	1 (0.2%)

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BRAEBURN, CAM2038 14.1.6.1 FINAL

OPIOIDS	OPIOIDS	0 (0.0%)	3 (1.4%)	3 (0.7%)
	TRAMADOL	1 (0.5%)	2 (0.9%)	3 (0.7%)

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BRAEBURN, CAM2038 14.1.6.1 FINAL

A total of 54 (12.6%) subjects took at least one medication before study entry.

A majority of subjects (67.1%) took at least one concomitant medication during the study. Overall, the most common class of concomitant medications was opioids (22.2%), followed by nonsteroidal anti-inflammatory and antirheumatic products (14.5%) (Table below). The use of concomitant medications was generally comparable between the treatment groups.

Thirty-five subjects took CYP3A4 inhibitors during the study (after randomization). Of these, 11 were in the CAM2038 treatment group and 24 were in the SL BPN/NX treatment group.

Table 15: Concomitant Medications Taken by ≥ 10% of All Subjects by WHO Drug ATC Class (Safety Population)

WHO Drug ATC Class	SL BPN/NX N=215 n (%)	CAM2038 N=213 n (%)	Total N=428 n (%)
Opioids	54 (25.1)	41 (19.2)	95 (22.2)
Anti-inflammatory and antirheumatic products, non-steroids	29 (13.5)	33 (15.5)	62 (14.5)
Antidepressants	30 (14.0)	29 (13.6)	59 (13.8)
Other analgesics and antipyretics	24 (11.2)	30 (14.1)	54 (12.6)

Abbreviations: ATC, anatomical therapeutic chemical; SL BPN/NX, sublingual buprenorphine/naloxone; WHO, World Health Organization
Source: Table 14.1.6.2

Table 16: Concomitant medications – 2

WHO DRUG ATC CLASS	DRUG NAME	SL BPN (N=215)	CAM2038 (N=213)	TOTAL (N=428)
AT LEAST ONE MEDICATIONS		142 (66.0%)	145 (68.1%)	287 (67.1%)
OPIOIDS		54 (25.1%)	41 (19.2%)	95 (22.2%)
	BUPRENORPHINE	9 (4.2%)	6 (2.8%)	15 (3.5%)
	BUPRENORPHINE HYDROCHLORIDE	2 (0.9%)	2 (0.9%)	4 (0.9%)

SOURCE: 16.2.9; TABLE: T010901B.LIS; RUN: 09JAN2017 19:55
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BRAEBURN, CAM2038 14.1.6.2 FINAL

OPIOIDS	HYDROCODONE	1 (0.5%)	1 (0.5%)	2 (0.5%)
	HYDROMORPHONE HYDROCHLORIDE	1 (0.5%)	0 (0.0%)	1 (0.2%)
	METHADONE	0 (0.0%)	1 (0.5%)	1 (0.2%)
	MORPHINE	2 (0.9%)	1 (0.5%)	3 (0.7%)
	MORPHINE SULFATE	0 (0.0%)	1 (0.5%)	1 (0.2%)
	OPIOIDS	41 (19.1%)	27 (12.7%)	68 (15.9%)
	OXYCODONE	2 (0.9%)	0 (0.0%)	2 (0.5%)
	OXYCODONE HYDROCHLORIDE	0 (0.0%)	1 (0.5%)	1 (0.2%)
	TRAMADOL	4 (1.9%)	1 (0.5%)	5 (1.2%)
	TRAMADOL HYDROCHLORIDE	0 (0.0%)	1 (0.5%)	1 (0.2%)

Numbers analysed

Approximately 380 subjects (190 subjects per arm) were planned for study participation. A total of 428 subjects were randomized into the study (215, SL BPN/NX; 213, CAM2038). All subjects were included in the safety, intent-to-treat (ITT), modified ITT (mITT), and per-protocol (PP) populations.

Outcomes and estimation

Primary efficacy variables

1. **EU primary endpoint**

Table 17: Primary Efficacy Variable for EMA: Percentage of Urine Samples Negative for Illicit Opioids (Without Subjects' Self-reported Opioid Use) (Imputed Data, ITT Population)

	SL BPN/NX N=215	CAM2038 N=213	Difference (%)[a] (95% CI)	P-value[b]
N	215	213		
Mean (SD)	28.4 (36.46)	35.1 (36.00)		
Median	5.6	22.2		
Min, max	0.0 - 100.0	0.0 - 100.0		
LS mean (SE)[c]	28.4 (2.47)	35.1 (2.48)	6.7	<0.001
95% CI[c]	23.5 - 33.3	30.3 - 40.0	-0.1 - 13.6	

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; ITT, intent to treat; LS, least squares; SD, standard deviation; SE, standard error; SL BPN/NX, sublingual buprenorphine/naloxone

[a] Difference = CAM2038 – SL BPN/NX.

[b] The p-value was for non-inferiority with the margin of -11%.

[c] The LS mean and 95% CI were based on the ANOVA model including the treatment effect.

Source: Table 14.2.1.1-EMA

Table 18: Post Hoc Analysis: Primary Efficacy Variable for EMA: Percentage of Urine Samples Negative for Illicit Opioids (Without Subjects' Self-reported Opioid Use) (Without Imputed Data for Missing Samples, ITT Population)

	SL BPN/NX N=215	CAM2038 N=213	Difference (%) (95% CI)	P-value
N	201	197		
Mean (SD)	35.9 (40.47)	44.6 (38.10)		
Median	12.5	41.2		
Min, max	0.0 - 100.0	0.0 - 100.0		
LS mean (SE)	35.9 (2.77)	44.6 (2.80)	8.7	0.028[a]
95% CI	30.4 – 41.4	39.1 – 50.1	0.9 – 16.4	

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; ITT, intent to treat; LS, least squares; SD, standard deviation; SE, standard error; SL BPN/NX, sublingual buprenorphine/naloxone

[a] The p-value was for superiority.

Source: Post hoc Table 3

Post-hoc analyses

Subjects without other drugs of abuse at Screening (52 in the CAM2038 group and 60 in the SL BPN/NX group) and after the first two weeks of treatment (Weeks 4 – 25), including subjects' self-reported opioid use, the LS mean (95% CI) was 45.7 % (35.1 – 56.3) in the SL BPN/NX group and 57.5% (46.1 – 68.9) in the CAM2038 group. The difference between treatment groups was 11.8 % (CAM2038 – SL BPN/NX) with a 95% CI of -3.8 - 27.4 (P = 0.136).

A total of 11 subjects discontinued study medication but continued scheduled visits and completed the study, including Follow-up. Post hoc sensitivity analyses were conducted taking these 11 subjects into consideration. The first set of post hoc analyses included the percentage of urine samples that were negative for illicit opioids, excluding the 11 subjects who discontinued study drug but completed the study. In the analysis that included subjects' self-reported opioid use, the treatment difference was 7.2 % favouring CAM2038 (95% CI: 0.3 – 14.1; P = 0.041). In the analysis that did not include subjects' self-reported opioid use, the treatment difference was 7.1 favouring CAM2038 (95% CI: 0.1 – 14.1; P = 0.046).

Percentage of urine samples that were negative for illicit opioids, performed with imputation of all urine samples that were positive after study drug discontinuation. In the analysis that included subjects' self-reported opioid use, the treatment difference was 6.9 % favouring CAM2038 (95% CI: 0.1 – 13.7; P = 0.047). In the analysis that did not include subjects' self-reported opioid use, the treatment difference was 6.8 favouring CAM2038 (95% CI: -0.1 – 13.7; P = 0.053).

Route of administration of illicit opioids (injected or not injected) – analysis of percentage of urine samples that were negative for illicit opioids without self-reported opioid use. Among subjects who injected opioids (114 in the CAM2038 group and 110 in the SL BPN/NX group), the treatment difference was 13.6 favouring CAM2038 (95% CI: 5.3 – 21.9) without self-reports; p= 0.001. Among **subjects who did not inject opioids (99 in the CAM2038 group and 105 in the SL BPN/NX group), the treatment difference was 0.00 (95% CI: -10.7 – 10.8); p= 0.998.** The test of interaction was significant (P = 0.048), with a stronger effect seen among subjects who injected opioids. Similar results were seen when the analysis was repeated with subjects' self-reported opioid use (test for interaction: P = 0.040).

A similar post hoc sensitivity analysis was performed to assess percentage of urine samples that were negative for illicit opioids by the primary opioid of use at initiation (heroin or prescription opioids); the analysis did not include subjects' self-reported opioid use. Among subjects who used heroin (152 in the CAM2038 group and 151

in the SL BPN/NX group), the treatment difference was 14.8 favouring CAM2038 (95% CI: 8.0 – 21.7); p<0.001. **Among subjects who used prescription opioids (61 in the CAM2038 group and 64 in the SL BPN/NX group), the treatment difference was -11.6 (favouring SL BPN/NX) (95% CI: -24.6 – 1.5); p=0.082**. The test of interaction was significant (P < 0.001), with a stronger effect seen among subjects who used heroin. Similar results were seen when the analysis was repeated with subjects' self-reported opioid use (test for interaction: P < 0.001).

Average maximum doses of SL BPN/NX (i.e. after titration) were 19 mg/day in Phase 1 and 20 mg/day in Phase 2, i.e. known therapeutic doses. For CAM2038, the average maximum doses were 26 mg/week (3.7 mg/day) in Phase 1 and 110 mg/month (3.9 mg/day) in Phase 2.

In the HS-11-421 study, 50.2% of patients reached a maximum dose of 24 mg CAM2038 q1w and 39.9% were titrated double-blinded to a dose of 32 mg of CAM2038 q1w, resulting in effective withdrawal suppression and non-inferior efficacy compared with SL BPN/NX, where 109 patients (50.7 %) reached a corresponding daily dose of 16 mg and 90 patients (41.9 %) were titrated up to 24 mg/day SL BPN/NX.

Exploratory analysis of the EU primary endpoint

In both phases of the study, the CAM2038 group demonstrated numerically higher LS means for the percentage of urine samples negative for illicit opioids (Phase 1: 35.8%; Phase 2: 33.9%) compared to the SL BPN/NX group (Phase 1: 29.9%; Phase 2: 25.4%) (Table 19). The treatment difference (95% CI) was 5.9 (-1.3, 13.1) for Phase 1 and 8.5 (1.2, 15.7) for Phase 2. These results indicate that CAM2038 treatment was superior to SL BPN/NX in allowing subjects to avoid opioid use and achieve a higher percentage of negative urine samples in Phase 2 of the study.

Table 19: Exploratory analysis - Percentage of Urine Samples That Were Negative for Illicit Opioids in Phase 1 and 2 (ITT Population)

Phase Statistic	SL BPN/NX N=215	CAM2038 N=213	Difference (%)[a] (95% CI)	P-value[b]
Phase 1				
N	215	213		
Mean (SD)	29.9 (37.94)	35.8 (38.03)		
Median	8.3	25.0		
Min, max	0.0 - 100.0	0.0 - 100.0		
LS mean (SE)[b]	29.9 (2.59)	35.8 (2.60)	5.9	0.110
95% CI[b]	24.8 - 35.0	30.6 - 40.9	-1.3 - 13.1	

Phase Statistic	SL BPN/NX N=215	CAM2038 N=213	Difference (%)[a] (95% CI)	P-value[b]
Phase 2				
N	215	213		
Mean (SD)	25.4 (37.50)	33.9 (38.97)		
Median	0.0	16.7		
Min, max	0.0 - 100.0	0.0 - 100.0		
LS mean (SE)[b]	25.4 (2.61)	33.9 (2.62)	8.5	0.023
95% CI[b]	20.3 - 30.6	28.7 - 39.0	1.2 - 15.7	

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; ITT, intent to treat; LS, least squares; SD, standard deviation; SE, standard error; SL BPN/NX, sublingual buprenorphine/naloxone

[a] Difference = CAM2038 – SL BPN/NX.

[b] The p-value, LS mean, and 95% CI were based on the ANOVA model including the treatment effect.

Source: Table 14.2.6.1-FDA, Table 14.2.6.2-FDA, Table 14.2.5.1-EMA, Table 14.2.5.2-EMA

Secondary efficacy variables

CDF of Percent of Urine Samples Negative for Illicit Opioids

To evaluate the CDF, the percentage of negative urine samples from the 15 samples required was calculated for each subject with missing sample values imputed as positive.

Let p denote the percentage of negative urine samples (PNU). It should be noted that the CDF in this case is the probability of PNU $\leq$ p (a less desirable outcome) and 1-CDF is the probability of PNU > p (a more desirable outcome). Therefore, per the CDF definition, the treatment with a consistently lower CDF value (thus higher 1-CDF) indicates the treatment is more likely to produce a higher PNU.

Superiority of CAM2038 versus SL BPN/NX on the CDF of the proportion of opioid-negative urine samples without self-reports during treatment Weeks 4 to 24 was demonstrated. The median CDF was 26.7% for CAM2038 and 6.7% for SL BPN/NX (p = 0.008).

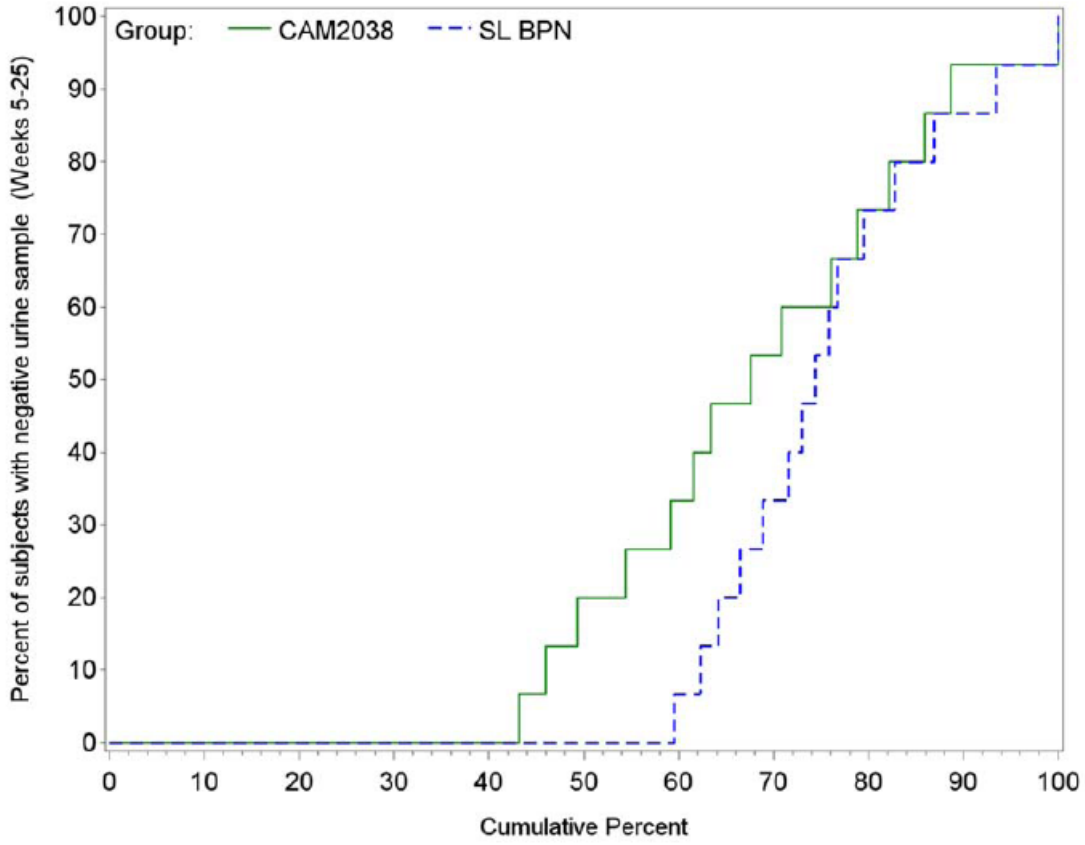
Table 20: Analysis Results for CDF of Percentage of Urine Samples Negative for Illicit Opioids Over Weeks 5-25 (ITT Population)

	With Subjects' Self-reported Opioid Use		Without Subjects' Self-reported Opioid Use	
Statistic	SL BPN/NX N=215	CAM2038 N=213	SL BPN/NX N=215	CAM2038 N=213
N	215	213	215	213
Mean (SD)	26.7 (37.15)	35.1 (37.17)	27.7 (37.40)	35.8 (37.41)
Median	0.0	26.7	6.7	26.7
Min, max	0.0 – 100.0	0.0 – 100.0	0.0 – 100.0	0.0 – 100.0
Wilcoxon rank sums test				
N	215	213	215	213
Sum of scores	42624.0	49182.0	42857.0	48949.0
Expected sum	46117.5	45688.5	46117.5	45688.5
SD of sum	1220.4	1220.4	1227.3	1227.3
Mean score	198.3	230.9	199.3	229.8
Z score (p-value)	2.86 (0.004)	--	2.66 (0.008)	--

Abbreviations: CDF, cumulative distribution function; ITT, intent to treat; SD, standard deviation; SL BPN/NX, sublingual buprenorphine/naloxone

Source: Table 14.2.2.1-FDA, Table 14.2.2.1-EMA

Figure 4: CDF of Percent of Urine Samples Negative for Illicit Opioids Weeks 5 to 25 (ITT Population, Without Subjects' Self-reported Opioid Use)



Abbreviations: CDF, cumulative distribution function; ITT, intent to treat; SL BPN, sublingual buprenorphine/naloxone

Source: Figure 14.1.2-EMA

Similar results were seen when the analysis included patients' self-reported opioid use (p=0.004).

Table 21: Post-hoc CDF with no grace periodSample weeks 2-25 & with 4 weeks grace period (Sample weeks 6-25 (no self-report) - ITT Population

	SL BPN (N=215)	CAM2038 (N=213)
N	215	213
MEAN (SD)	28.4 (36.46)	35.1 (36.00)
MEDIAN	5.6	22.2
MIN - MAX	0.0 - 100.0	0.0 - 100.0

WILCOXON RANK SUMS TEST

TREATMENT	N	SUM OF SCORES	EXPECTED SUM	STD DEV OF SUM	MEAN SCORE	Z SCORE	P VALUE
SL BPN	215	42970.5	46117.5	1245.1	199.9	2.53	0.011
CAM2038	213	48835.5	45688.5	1245.1	229.3		

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BRAEBURN, CAM2038 Posthoc Table 9 FINAL

	SL BPN (N=215)	CAM2038 (N=213)
N	215	213
MEAN (SD)	27.2 (37.61)	35.9 (37.66)
MEDIAN	0.0	21.4
MIN - MAX	0.0 - 100.0	0.0 - 100.0

WILCOXON RANK SUMS TEST

TREATMENT	N	SUM OF SCORES	EXPECTED SUM	STD DEV OF SUM	MEAN SCORE	Z SCORE	P VALUE
SL BPN	215	42549.5	46117.5	1221.0	197.9	2.92	0.003
CAM2038	213	49256.5	45688.5	1221.0	231.3		

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BRAEBURN, CAM2038 Posthoc Table 11 FINAL

Post hoc sensitivity analyses were conducted to support the results of the prespecified CDF (with subjects' self-reports of opioid use).

Table 22: Post-hoc Comparison of CAM2038 to SL BPN/NX During Grace Period (with Subjects' Self-reports of Opioid Use)

Grace Period (Weeks)	Sample Weeks Included in CDF	Mean % Urine Negative % (SD)		Median % Urine Negative %		*P* value
		SL BPN/NX N=215	CAM2038 N=213	SL BPN/NX N=215	CAM2038 N=213	
0	2-25	27.4 (36.28)	34.2 (35.46)	5.6	22.2	0.006
1	3-25	27.3 (36.76)	34.7 (36.26)	0.0	23.5	0.005
4	6-25	26.2 (37.34)	35.2 (37.35)	0.0	21.4	0.001

Abbreviations: CDF, cumulative distribution function; SD, standard deviation; SL BPN/NX, sublingual buprenorphine/naloxone
Source: Post hoc Table 5, Post hoc Table 6, and Post hoc Table 7

Percentage of Subjects Remaining in the Study (Retention Rate)

Of the 428 participants who were randomized in the study, all received at least one dose of study drug, and 69.0% (147/213) of the CAM2038 and 72.6% (156/215) of the SL BPN/NX patients completed the 24-week treatment period. Including the 4 weeks of study follow-up, 56.8% (121/213) of the CAM2038 and 58.6% (126/215) of the SL BPN/NX patients finished the entire study.

The results in the table below include the 11 subjects who discontinued study treatment but completed the study (7 in the CAM2038 group and 4 in the SL BPN/NX group). The proportion difference between treatment groups was -1.8 (95% CI: -11.2%, 7.6%), and the CAM2038 group achieved non-inferiority in retention rates compared to the SL BPN/NX group (P = 0.006; non-inferiority margin of 15%).

Table 23: Percent of Subjects Remaining in the Study / Retention Rate (ITT Population)

Category	SL BPN/NX N=215	CAM2038 N=213	Proportion Difference[a] (95% CI)	P-value[b] 2-sided
Retained, n (%)	126 (58.6)	121 (56.8)	-1.8 (-11.2, 7.6)	0.006
Not retained, n (%)	89 (41.4)	92 (43.2)	--	--

Abbreviations: CI, confidence interval; ITT, intent to treat; SL BPN/NX, sublingual buprenorphine/naloxone
[a] Proportion difference = CAM2038 – SL BPN/NX.
[b] The p-value was based on the chi square test for non-inferiority with the margin of 15% point.
Source: Table 14.2.4.1-FDA, Table 14.2.3.1-EMA

Post Hoc Analyses: Retention Rate

Among subjects who did not have other drugs of abuse (56 subjects in CAM2038 treatment group; 62 subjects in SL BPN/NX treatment group), the study completion rate (including follow-up) was almost identical between treatment groups (69.6% CAM2038; 69.4% SL BPN/NX).

An additional analysis was performed to assess retention over time. As of Week 25, retention in the SL BPN/NX treatment group was 62.3% compared with 57.7% in the CAM2038 treatment group. Retention by week is presented in Post hoc Table 28.

Table 24: Percentage of subjects remaining in study at EOT (week 25 visit) - finished actual 24 weeks of study (even if missed visits in between) - ITT Population

Remaining in Study at Week 25	SL BPN (N=215)	CAM2038 (N=213)
Yes	134 (62.3%)	123 (57.7%)
No	81 (37.7%)	90 (42.3%)

REMIANING IS STUDY AT WEEK 25 IS DEFINED AS SUBJECTS WITH URINE LAB TEST AT WEEK 25/EOT VISIT AND AT LEAST ONE TEST BETWEEN WEEKS 21 TO 24.

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BRAEBURN, CAM2038 Posthoc Table 13 FINAL

Time to Sustained Abstinence of Opioid Use

The fourth hypothesis, superiority for time to sustained abstinence after 8 weeks of treatment, was not met (p=0.221) and hypothesis testing was stopped.

Table 25: Time to Sustained Abstinence of Opioid Use (ITT Population)

Category	SL BPN/NX N=215	CAM2038 N=213
Subjects with sustained abstinence of opioid use, n (%)	30 (13.95)	39 (18.31)
Subjects without sustained abstinence of opioid use, n (%)	185 (86.05)	174 (81.69)
Survival analysis p-value (log rank)	0.221	–

Abbreviations: ITT, intent to treat; SL BPN/NX, sublingual buprenorphine/naloxone
Source: Table 14.2.3.1-FDA, Table 14.2.4.1-EMA

Ancillary analyses

Improvements were also seen for patients treated with CAM2038 compared with SL BPN/NX for exploratory endpoints of percentage of patients with negative urine samples by time point (overall [by week] and for sampling Weeks 7, 10, 11, 12, 17, and 25), percentage of patients with negative urine samples with self-reports of no illicit opioid use by time point (overall [by week] and for sampling Weeks 7, 9, 10, 11, 12, and 17), and percentage of patients with no self-reported illicit opioid use by time point (sampling Weeks 9, 11, 17, and 21).

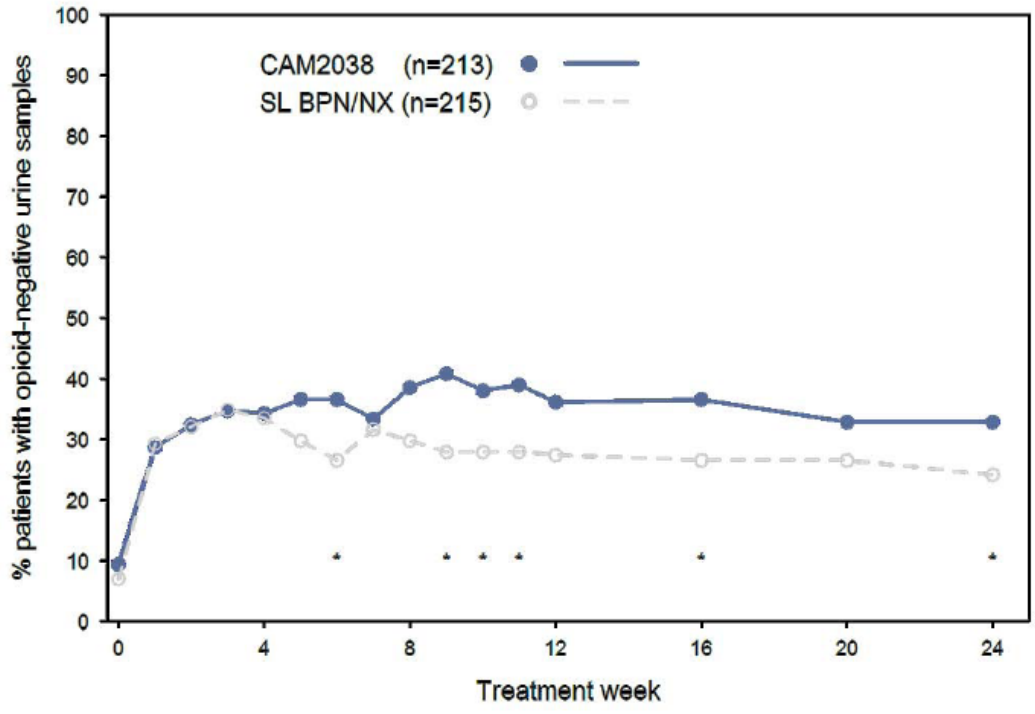
Percentage of Subjects with Negative Urine Samples by timepoint

At Week 25, the percentage of subjects in the CAM2038 group with negative urine samples was 32.9% compared to the SL BPN/NX group (24.2%) with an overall proportion difference overall was 8.4% (95% CI: 1.1%, 15.6%) with the following times points favouring the CAM2038 group over the SL BPN/NX group: Weeks 7, 10, 11, 12, 17, and 25.

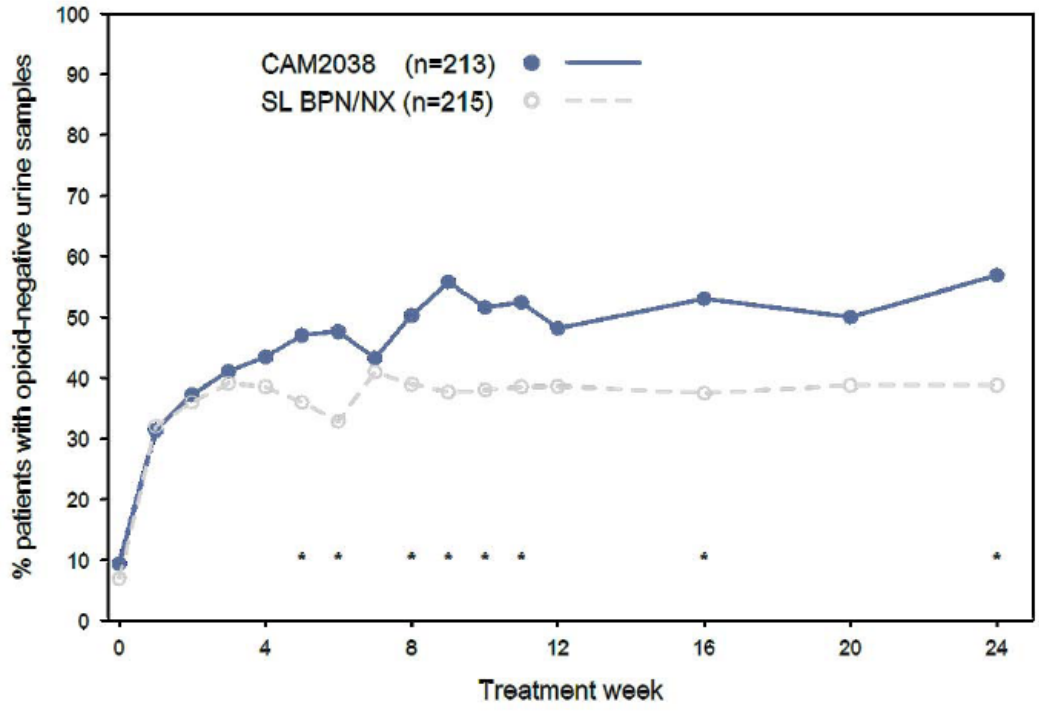
Table 26: Analysis Results for Percent of Subjects with at Least 25% Reduction in Positive Urine Test Performed at Weeks 10-13 Compared to Weeks 2-5 - ITT Population

	SL BPN (N=215)	CAM2038 (N=213)	PROPORTION DIFFERENCE (95% CI) (CAM2038 - SL BPN)	P-VALUE (2-SIDED)&
RESPONDER	30 (14.0%)	53 (24.9%)	10.9% (3.5%, 18.4%)	0.004
NON-RESPONDER	185 (86.0%)	160 (75.1%)		

Figure 5: Study HS-11-421: Urine samples negative for illicit opioids by time point (ITT Population)



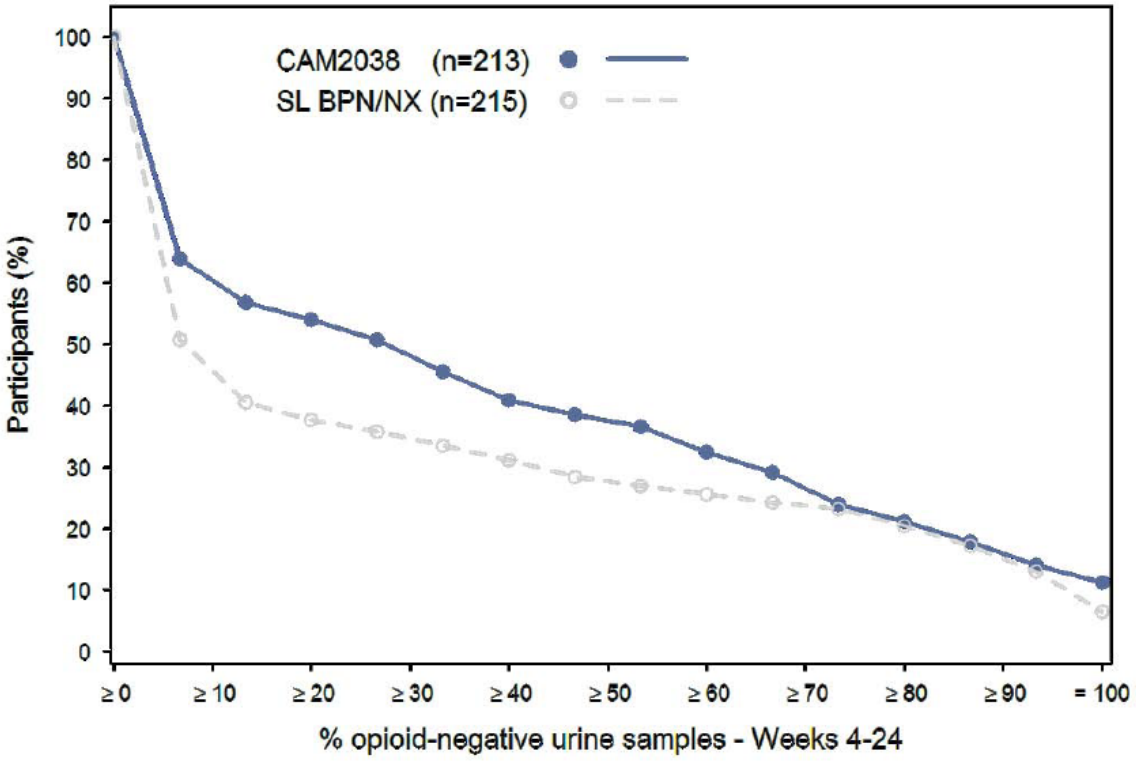
a)



b)

ITT, intent-to-treat; SL BPN/NX, sublingual buprenorphine/naloxone
a) Missing urine samples imputed as positive b) Missing urine samples not imputed
* $p<0.05$ (Chi-square test)
Source: Table 14.2.6.1-EMA and *Post hoc* Table 34 in CSR HS-11-421

Figure 6: Study HS-11-421: CDF of percent of urine samples negative for illicit opioids during treatment Weeks 4 to 24 (without self-reported opioid use) (ITT Population)



CDF, cumulative distribution function; ITT, intent-to-treat; SL BPN/NX, sublingual buprenorphine/naloxone
The CDF is expressed as cumulative percentage of patients with opioid-negative urine samples.
Source: Figure 4 and Figure 14.1.2-EMA in CSR HS-11-421

Cumulative Percentage of Subjects with Negative Urine Samples after Two Months of Treatment by Time Point (from Week 9 to Week 25)

The proportion differences between treatment groups by time point were between - 1.1% (Week 9) and 3.8% (Week 25); no statistical difference was found between treatment groups at any time point between Weeks 9 and 25 or overall for the cumulative percentage

Percentage of subjects with no self-reported illicit opioid use by time point

At all time points measured, a majority of subjects (> 54%) in both groups reported no illicit opioid use. At Week 2, 62.3% of subjects in the SL BPN/NX group and 55.4% of subjects in the CAM2038 group reported no opioid use. Between Weeks 3 and 21, the percentage of subjects with no self-reported illicit opioid use in the SL BPN/NX group was within the range of approximately 55% to 67%; the range for the CAM2038 group was approximately 58% to 76%. By Week 25, these percentages were 70.6% for the SL BPN/NX group and 77.2% for the CAM2038 group, and the difference between treatment groups was not significant at this point (P = 0.225). Based on subjects' self-reporting, the CAM2038 group was favoured (P < 0.05) over the SL BPN/NX group for a greater proportion of subjects with no illicit opioid use at the following time points: Weeks 9, 11, 17, and 21.

Percentage of Subjects Meeting Criteria of Stability

At each weekly visit, starting at Week 5, the subjects were evaluated with regard to the following stability criteria:

• Has the subject been on a stable dose of CAM2038 q1w/Placebo SC injections without any fluctuations in doses for the last 4 weeks?

• Does the subject exhibit minimal subjective and no objective withdrawal symptoms, based on SOWS $\leq$ 7 and COWS < 5?

• Does the subject exhibit diminished desire/need to use, based on VAS scores (defined as at least 50% reduction from baseline in the VAS score)?

• Does the subject exhibit diminished use of illicit opioids, according to the Investigator's discretion?

Percent of subjects meeting criteria of stability by time point (by scheduled post baseline visit) was analyzed using chi square tests, with Week 13 as the primary time point. The percentages for each treatment and between treatment percentage differences were estimated with 95% confidence intervals of the estimated treatment differences. Additionally, for the primary time point (Week 13), sensitivity analysis were performed quantifying the number of subjects with at least 25% reduction in positive urine test performed at Weeks 10-13 compared to Weeks 2-5 (replacing the last question where PI assessed diminished illicit opioid use.

When the percentage of subjects meeting the criteria of stability included the PI assessment, the range demonstrated was within 33% to 54% for the SL BPN/NX group and 31% and 56% for the CAM2038 group. In general, results were similar between treatment groups. The greatest treatment difference (95% CI) observed was at Week 13 (5.3 % [-5.7 %, 16.3 %]) when 50.3 % of subjects in the SL BPN/NX group and 55.6% subjects in the CAM2038 group met the criteria for stability. Yet, when the superiority of CAM2038 to SL BPN/NX was tested with the chi square test, the P value at Week 13, along with the P values at all other time points, did not indicate a difference.

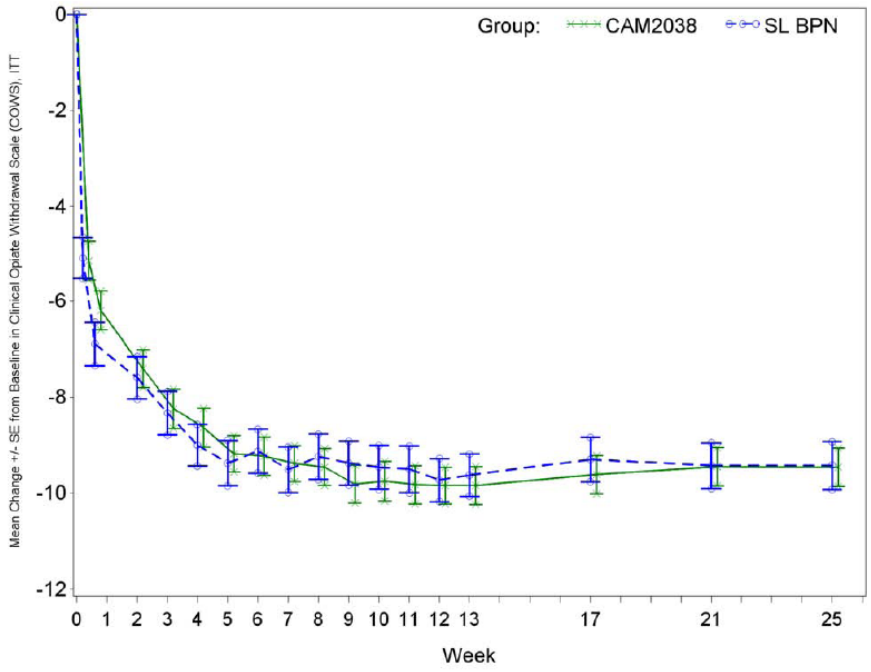
When the analysis did not include PI assessment, the percentages of subjects who met the stability criteria at each time point were approximately 10% to 15% higher. In this analysis, the percentages of subjects who met the stability criteria at Week 13 were 67.7 % for the SL BPX group and 68.8 % for the CAM2038 group. The greatest treatment difference (95% CI) observed was at Week 11 (6.1 % [- 4.4%, 16.5%]) when 62.3 % subjects in the SL BPN/NX group and 68.4 % subjects in the CAM2038 group met the criteria for stability. Similar to the results for the analysis that included PI assessment, CAM2038 did not demonstrate improvement over SL BPN/NX at any time point.

Opioid craving

Mean VAS scores for morning desire/need to use were similar between treatment groups at Week 2 (SL BPN/NX: 33.0; CAM2038: 37.1). For both treatment groups, morning cravings decreased between Week 2 and Week 12 (SL BPN/NX: 15.1; CAM2038: 13.1 at Week 12), then remained relatively consistent until Week 25 (SL BPN/NX: 18.3; CAM2038: 12.8). Overall, morning cravings were generally similar for subjects treated with CAM2038 or SL BPN/NX. With the exception of Week 9 (difference of -6.6 [95% CI -12.3, -0.9] favoring CAM2038; P = 0.024) and Week 10 (difference of -5.8 [95% CI -11.2, -0.5]; P = 0.034), no statistical differences were found between treatment groups.

The mean COWS score at Baseline was 12.2 (mild to moderate withdrawal) for both treatment groups. The mean score for both groups declined rapidly up to Week 5, at which time the mean COWS score was 2.9 for the SL BPN/NX group and 3.0 for the CAM2038 group. These values had a mean change from Baseline of -9.4 for the SL BPN/NX group and -9.2 for the CAM2038 group. Following Week 5, the mean COWS scores were mostly stable and below 3.0. At Week 25, the mean COWS score was 2.8 for both groups, which represented mean changes from Baseline of -9.4 (SL BPN/NX) and -9.5 (CAM2038). The changes from Baseline in COWS scores were similar for subjects treated with CAM2038 or SL BPN/NX (Figure 8), and no statistical difference was found between treatment groups at any time point.

Figure 8: Change from Baseline in Clinical Opiate Withdrawal Scale Over Time (ITT Population)



Abbreviations: ITT, intent to treat; SE, standard error; SL BPN/NX, sublingual buprenorphine/naloxone
Source: Figure 14.1.6

The mean SOWS score at Baseline was 30.6 for the SL BPN/NX group and 31.5 for the CAM2038 group (severe withdrawal for both groups). These values had a mean change from Baseline of -23.1 for the SL BPN/NX group and -22.7 for the CAM2038 group. Following Week 5, the mean SOWS scores were mostly stable. At Week 25, the mean SOWS score was 6.3 for the SL BPN/NX group and 7.3 for the CAM2038 group, which represented mean changes from Baseline of -24.2 for both groups. The changes from Baseline in SOWS scores were similar for subjects treated with CAM2038 or SL BPN/NX; no statistical differences were found between treatment groups at any time point.

Percentage of Subjects Without Evidence of Using Other Drugs of Abuse by Time Point

There was no statistical difference between study groups for the use of barbiturates, amphetamine, phencyclidine or marijuana at any time point.

Evidence for the use of barbiturates was low at Screening (0.5% SL BPN/NX and 1.4% CAM2038) and remained low throughout the study (SL BPN/NX: 0.7% at Week 25, range 0.0% [Weeks 3, 4, 5, 10, 11, 12, 13, and 21] to 2.3% [Week 7]; CAM2038: 2.4% at Week 25, range 0.0% [Day 1 and Weeks 2, 3, 4, 8, 10, 11, 12, 13, and 17] to 2.4% [Week 25]).

Evidence for the use of phencyclidine was very low at Screening (0.0% SL BPN/NX and 0.9% CAM2038) and was generally low throughout the study (SL BPN/NX: 1.5% at Week 25, range 0.0% [Screening] to 2.0% [Week 17]; CAM2038: 4.1% at Week 25, range 0.6% [Weeks 9 and 12] to 4.1% [Week 25]).

Evidence for the use of marijuana was approximately 28% at Screening (29.8% SL BPN/NX and 27.0% CAM2038) and was generally stable throughout the study (SL BPN/NX: 29.9% at Week 25, range 27.7% [Week 8] to 37.0% [Week 3]; CAM2038: 30.9% at Week 25, range 26.8% [Week 8] to 33.8% [Week 13]).

Evidence for the use of amphetamines was approximately 15% at Screening (14.9% SL BPN/NX and 18.0% CAM2038) and was generally stable throughout the study (SL BPN/NX: 14.2% at Week 25, range 10.9% [Week 12] to 16.4% [Week 17]; CAM2038: 17.9% at Week 25, range 13.5% [Week 7] to 18.6% [Week 21]).

Evidence for the use of cocaine was approximately 25% at Screening (24.7% SL BPN/NX and 25.1% CAM2038) and increased slightly during the study (SL BPN/NX: 29.9% at Week 25, range 24.7% [Screening] to 37.8% [Week 12]; CAM2038: 30.1% at Week 25, range 25.1% [Screening] to 32.9% [Week 6]).

The use of benzodiazepines was approximately 15% at Screening (16.3% SL BPN/NX and 14.2% CAM2038) and increased slightly during the study (SL BPN/NX: 21.6% at Week 25, range 9.6% [Week 8] to 21.6% [Week 25]; CAM2038: 20.3% at Week 25, range 13.3% [Week 4] to 21.4% [Week 21]). The proportion differences ranged from -11.2% at Week 21 to 2.3% at Week 5. With the exception of Week 10 (proportion difference of -7.9% [95% CI: -15.5%, -0.3%]; P = 0.044) and Week 21 (proportion difference of -11.2% [95% CI: -19.5%, -2.8%]; P = 0.010), there were no statistical differences between treatment groups.

Illicit use by gender

A post hoc analysis was performed by ma for the percentage of urine samples that were negative for illicit opioids (with subjects' self-reports of opioid use). For women, the difference between treatment groups was 6.6 (CAM2038 – SL BPN/NX) with a 95% CI of -5.0 - 18.3 (Post hoc Table 14). For men, the difference between treatment groups was 5.9 (CAM2038 – SL BPN/NX) with a 95% CI of -2.5 – 14.3. An ANOVA test of treatment by gender interaction found no difference between men and women for this endpoint (P = 0.919). Results were similar when subjects' self-reports of opioid use were not included (P = 0.863)

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27: Summary of efficacy for trial HS-11-421

Title: A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel Group, Multi-center Trial Assessing the Efficacy and Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients with Opioid Use Disorder	
Study identifier	HS-11-421

Design	Phase 3, double-blind, double-dummy, active-controlled, parallel-group multi-center study, designed to evaluate the non-inferiority of CAM2038 compared to an existing standard of care (SL BPN/NX) in initiation and maintenance treatment with BPN. The study involved 4 phases: Screening (3 weeks), Phase 1 (12 treatment weeks), Phase 2 (12 treatment weeks), and Follow-up (4 weeks).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks (last visit) not applicable 1 month
Hypothesis	Non-inferiority – Hierarchical testing		
Treatments groups	Control (SL BPN/NX)		SL BPN/NX and placebo SC injections. 24 weeks, 215 randomized
	Test (CAM2038)		CAM2038 injections and SL BPN/NX placebo. 24 weeks, 213 randomized
Endpoints and definitions	Primary endpoint	% urine samples negative for illicit opioids based on the 18 urine samples obtained during the post-induction period (between Week 2 and Week 25)	EMA endpoint Imputed and non-imputed data for non-inferior analysis. Population for non-imputed data was not defined.
	Secondary 1:	Cumulative Distribution Function of Percent Samples That Were Negative for Illicit Opioids for Weeks 5 to 25	CDF of % of Negative Urinary Samples (NUS) for illicit opioid. Data without self-report are included here
	Secondary 2:	Retention Rate	Retention to end of study seems to have been used for the original analysis.
	Secondary 3:	Time to Sustained Abstinence of Opioid Use	Reported as % with sustained abstinence

Database lock	Not given		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	CAM2038	SL BPN/NX
	Number of subjects	213	215
	% NUS week 2-25 ***Imputed data*** (LS mean)	35.1%	28.4%
	SE	2.48	2.47
	% NUS week 2-25 ***No imputation*** (LS mean)	44.6%	35.9%
	SE	2.80	2.77
	CDF of NUS without self-report (sum of scores)	26.7	6.7
	N/A	N/A	N/A
	Retention rate (%)	56.8%	58.6%
	N/A	-	-
	Time to abstinence (reported as % with sustained abstinence)	18.31%	13.95%
	N/A	N/A	N/A
Effect estimate per comparison	Primary **% NUS week 2-25** ***Imputed data***	Comparison groups	CAM2038 vs. SL BPN/NX
		Estimated treatment difference	6.7%
		95% CI	-0.1%, 13.6%
	Primary endpoint: **% NUS week 2-25** ***No imputation***	Comparison groups	CAM2038 vs. SL BPN/NX
		Estimated treatment difference	8.7
		95% CI	0.9 – 16.4

	Secondary 1: **CDF without self-report**	Comparison groups	CAM2038 vs. SL BPN/NX
		Z score	2.66
		P-value	0.008
	Secondary 2: **Retention rate**	Comparison groups	CAM2038 vs. SL BPN/NX
		Estimated treatment difference	-1.8
		95% CI	-11.2%, 7.6%
	Secondary 3: **Time to abstinence**	Comparison groups	CAM2038 vs. SL BPN/NX
		Estimated treatment difference	Not reported
		95% CI	Not reported
		P-value (log-rank)	0.221

Analysis performed across trials (pooled analyses AND meta-analysis)

Table 28: Comparison and analyses of patient populations and exposure data across studies providing pharmacodynamic and/or efficacy data

	HS-07-307	HS-13-478	HS-15-549	HS-11-421	HS-14-499
Population	Patients with opioid dependence on stable maintenance treatment with SL BPN for ≥6 months	Patients with moderate to severe opioid dependence stabilized on IR morphine	Patients with moderate to severe opioid dependence and a history of moderate to severe chronic non-cancer pain; treated with SL BPN at screening	Untreated patients with moderate to severe opioid dependence	Patients with moderate to severe opioid dependence taking SL BPN (or BPN/NX) or actively seeking BPN treatment before enrollment
Duration of Treatment	1 Week	2 Weeks	Group 1: 7-13 Weeks Group 2: 16-22 Weeks Group 3:17 Weeks	24 Weeks	48 Weeks
Total No: of Patients Exposed/Completed the Study	42[a]/0	47/46	65/50[b]	428 (215 SL BPN/NX and 213 CAM2038)/ 247 (121 SL BPN/NX and 126 (CAM2038)	227/157[c]
No: of Patients Discontinued or Dropped out	42[d] (100%)	1 (2.1%)	15 (23.1%)	181 (42.3%) SL BPN/NX: 89 (41.4%) CAM2038: 92 (43.2%)	70 (30.8%) Patients receiving SL BPN at entry: 58 (30.5%) New to BPN treatment: 12 (32.4%)
Reasons for Discontinuation	Intake of rescue medication Protocol violation Development of exclusion criteria	AE unrelated to the study drug	Withdrawal by patient Lost to follow-up Non-compliance Study terminated by the Sponsor	Withdrawal by patient Lost to follow-up Other Physician's decision AE Pregnancy Death	Withdrawal by patient Lost to follow-up Lack of Efficacy (only in patients receiving SL BPN at entry) Physician's decision AE Other Pregnancy

AE, adverse event; BPN, buprenorphine; BPN/NX, buprenorphine/naloxone, IR, immediate-release; SL, sublingual
[a] Of whom 1 patient was treated in 2 different dose cohorts and is counted twice; henceforth N=42 for this study
[b] 50 patients completed the HS-15-549 study in Groups 1, 2 and 3. 51 patients completed the Treatment Periods in Groups 1, 2 and 3 and 26 patients completed the Open-Label Extension Period in Groups 1 and 2.
[c] 156 patients completed 48 weeks of treatment and 157 patients completed the study.
[d] All patients discontinued study HS-07-307 since they were only treated with 1 weekly dose of CAM2038 q1w and the study duration was 35 days.
Source: CSRs of HS-07-307/Table 4, HS-13-478/Table 6, HS-15-549/Table 7, HS-11-421/Table 14.1.1.1, HS-11-421/Table 14.1.1.2, HS-14-499/Table 14.1.1.1 and HS-14-499/Table 14.1.1.2.1

Table 29: Comparison and analyses of demographic characteristics across studies

	HS-07-307[a] (N = 42)	HS-13-478 (N = 47)	HS-15-549 (N = 65)	HS-11-421		HS-14-499 N = 227	Total CAM2038 N=594
				CAM2038 (N = 213)	SL BPN/NX (N = 215)		
Age (years)							
Mean (SD)	39.7 (7.6)	35.8 (9.1)	45.3 (11.4)	38.7 (11.2)	38.0 (10.9)	41.4 (9.6)	40.3 (10.5)
Median	40.5	36.0	46.0	36.0	36.0	40.0	39.0
Min; Max	22; 52	18; 54	24; 65	19; 65	18; 65	24; 66	18; 66
Sex, n (%)							
Female	11 (26.2%)	12 (25.5%)	27 (41.5%)	92 (43.2%)	73 (34.0%)	84 (37.0%)	226 (38.0%)
Male	31 (73.8%)	35 (74.5%)	38 (58.5%)	121 (56.8%)	142 (66.0%)	143 (63.0%)	368 (62.0%)
Race, n (%)							
Others	0	1 (2.1%)	1 (1.5%)	7 (3.3%)	3 (1.4%)	4 (1.8%)	13 (2.2%)
Asian	0	0	0	0	0	0	0
Black or African American	0	24 (51.1%)	4 (6.2%)	47 (22.1%)	48 (22.3%)	20 (8.8%)	95 (16.0%)
White	42 (100.0%)	22 (46.8%)	60 (92.3%)	159 (74.6%)	164 (76.3%)	203 (89.4%)	486 (81.8%)
Ethnicity, n (%)							
Hispanic or Latino	0	1 (2.1%)	1 (1.5%)	25 (11.7%)	24 (11.2%)	4 (1.8%)	31 (5.2%)
Not Hispanic or Latino	0	46 (97.9%)	64 (98.5%)	188 (88.3%)	191 (88.8%)	222 (97.8%)	520 (87.5%)
Unknown	0	0	0	0	0	1 (0.4%)	1 (0.2%)
Weight (kg)							
Mean (SD)	74.6 (18.0)	75.9 (14.0)	81.0 (16.7)	76.0 (17.5)	78.3 (19.0)	79.4 (19.7)	77.8 (18.1)
Median	71.1	73.4	79.8	73.6	76.7	77.3	75.8
Min; Max	49; 140	53; 110	53; 127	42; 141	36; 177	45; 173	42; 173
BMI (kg/m^2)							
Mean (SD)	24.3 (4.8)	24.8 (4.2)	26.9 (4.0)	25.6 (5.0)	26.2 (5.6)	26.5 (5.8)	25.9 (5.2)
Median	23.3	24.3	26.8	24.8	25.3	25.5	25.1
Min; Max	17; 40	17; 34	20; 35	15; 43	16; 53	17; 50	14.9; 50.4

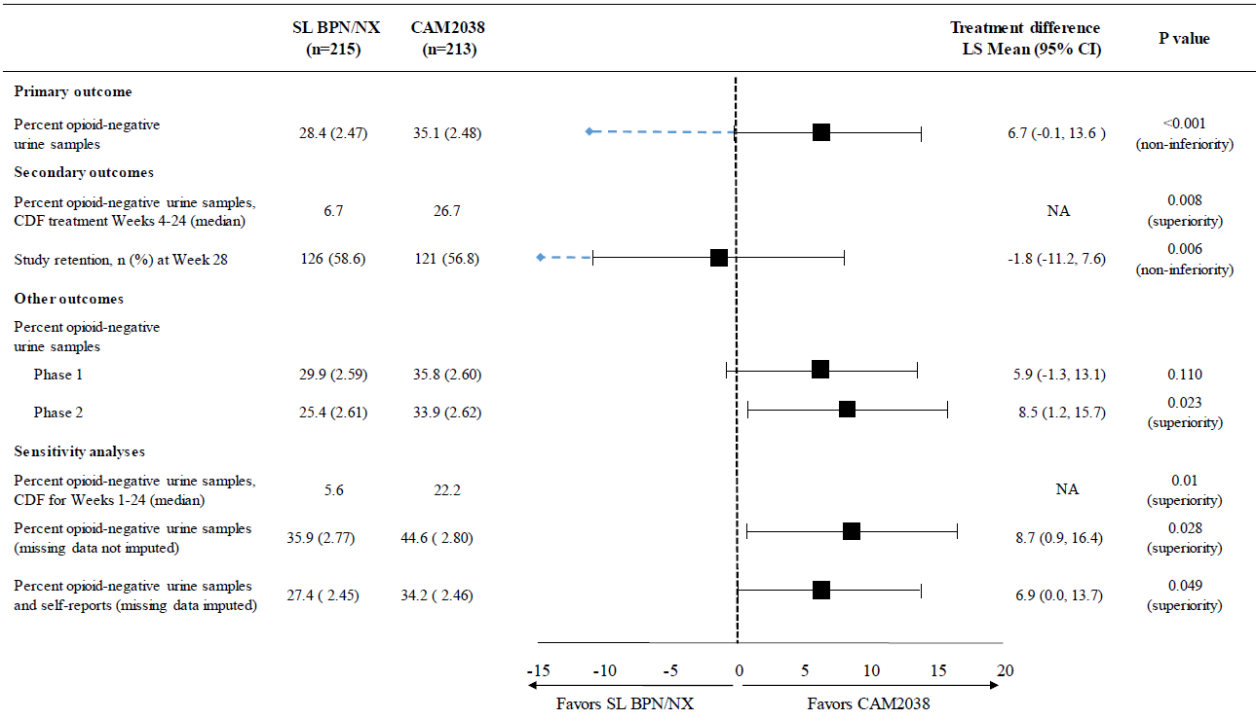
BMI, body mass index; Max, maximum; Min, minimum; SD, standard deviation; SL BPN/NX, sublingual buprenorphine/naloxone
[a] Ethnicity was not collected for HS-07-307 study
Source: Table 3.5.1 in Module 5.3.5.3, Table 3.4.1 in Module 5.3.5.3

Table 30: Overview of assessments of interest for evaluation of efficacy (and pharmacodynamics), by study

Study	Variables of relevance for efficacy and pharmacodynamic assessment
HS-07-307	COWS, SOWS and time from CAM2038 dosing until first dosing of rescue medication
HS-13-478	COWS, OOWS, VAS for 'Drug Liking', 'High', 'Any Drug Effects', 'Good Drug Effects', 'Bad Drug Effects', 'Alertness/Drowsiness' and 'Desire to Use opioids'
HS-15-549	COWS, SOWS, urine toxicology and pain assessments
HS-11-421	Urine toxicology, retention in study, sustained abstinence of opioid use, VAS for 'Desire to Use', VAS for 'Need to Use', COWS, SOWS, supplemental BPN and self-reported illicit use
HS-14-499	Urine toxicology for illicit opioids, self-reported illicit opioid use, retention in treatment and study, COWS, SOWS, VAS for 'Desire to Use' and VAS for 'Need to Use'

COWS: Clinical Opiate Withdrawal Scale; OOWS: Objective Opioid Withdrawal Scale; SOWS: Subjective Opiate Withdrawal Scale; VAS: visual analog scale
Source: CSR HS-07-307, CSR HS-15-549, CSR HS-13-478, CSR HS-11-421 and CSR HS-14-499

Figure 9: Study HS-11-421: Clinical outcomes of non-inferiority and superiority analyses



Values are LS Mean (SE) unless otherwise stated
Blue dashed line shows the non-inferiority margin
Source: Table 14.2.1.1-EMA, Table 14.2.2.1-EMA, Table 14.2.3.1-EMA, Table 14.2.5.1-EMA, Table 14.2.5.2-EMA, *Post hoc* Table 3, *Post hoc* Table 9 and *Post hoc* Table 32 in CSR HS-11-421

Supportive studies

Study HS-14-

It is an open-label multicenter study evaluating the long-term safety of a q1w and q4w CAM2038 in adult outpatients with opioid use disorder. It differs from HS-11-421 in that the main objective of this 48 weeks open-label study was long-term safety but it included efficacy parameters such as urine toxicology screening for opioids and other drugs of abuse; self-reported illicit drug use; measures of withdrawal (Subjective Opiate Withdrawal Scale [SOWS] and Clinical Opiate Withdrawal Scale [COWS]); measures of craving (desire and need to use); quality of life questionnaires; subject satisfaction; and unscheduled visits, medication, and counselling.

Patients recruited in this study were taking sublingual buprenorphine or were actively seeking BPN treatment before enrolment. At any visit, the investigator could transition patients from q1w to q4w.

This study is further discussed in the discussion on clinical efficacy below.

Study HS-07-307

Study HS-07-307 was a Phase 1/2, single-center, single-blind, single dose, dose-escalation, parallel-group, a first-time-in-man study investigating tolerability, PK, and pharmacodynamics (PD) of 4 different doses of CAM2038 q1w in patients with opioid dependence.

The study enrolled 41 patients (of whom 1 was included in 2 dose cohorts and is counted twice; N=42), who were on stable maintenance treatment with Subutex for ≥ 6 months and on a daily dose of 6 to 24 mg for ≥ 2 weeks before screening.

The *primary objectives* were to evaluate the systemic and local tolerability and the PK profile of BPN of 4 different single doses of CAM2038 q1w when delivered via SC buttock injection. The secondary objectives were to assess the PK profile of norbuprenorphine (norBPN) and the PD profile of BPN. Withdrawal symptoms were evaluated by Subjective Opiate Withdrawal Scale (SOWS), Clinical Opiate Withdrawal Scale (COWS), and time from the CAM2038 dosing until dosing with rescue medication.

The *PK data* from this study are discussed in the PK section of this report. The PD variables are limited and do not contradict previous findings but more importantly the formulation for this study is not the final one and the results are no further discussed.

Phase 2 supportive study HS-13-478

HS-13-478 was a Phase 2, multiple-dose opioid challenge study assessing blockade of subjective opioid effects of CAM2038 q1w in patients with moderate or severe opioid use disorder, who were physically dependent on IV or insufflated opioids, had self-reported opioid-use of a minimum of 21 days in the 30 days prior to screening and had positive urine drug screen for opioids at screening or check-in.

The primary endpoint was the maximum rating on the visual analog scale (VAS) for 'Drug Liking' on a 100 mm bipolar scale (50 mm being neutral response and 100 mm being highest), study HS-13-478. This study is further described in the PD section of this report and provides evidence of opioid blockage with CAM2038 although the absence of dose relationship has not been justified considering the use of 32mg BPN in study HS-11-421.

Phase 2 Supportive Study HS-15-549

Phase 2, open-label, partially randomized, multi-center, 3-treatment group study that evaluated the steady-state PK of BPN and norBPN in opioid-dependent patients with a history of chronic non-cancer pain following multiple weekly SC administrations of CAM2038 at different injection sites or multiple monthly SC administrations of CAM2038 in the buttock.

Patients had a current diagnosis of moderate to severe opioid dependence (based on DSM-5 or past medical history of opioid dependence) and with a history of moderate to severe chronic non-cancer pain. Patients had to be taking a daily dose of 24 mg SL BPN "Subutex equivalent" for at least 30 days prior to screening.

The *primary objectives* were to evaluate the steady-state PK of BPN and norBPN following repeated SC administration of CAM2038 q1w at different injection sites (buttock, abdomen, thigh and back of upper arm) and to evaluate steady-state PK of BPN and norBPN following repeated SC administration of CAM2038 q4w with the buttock as the injection site.

This was a phase 2 open label study investigating steady state PK following multiple injections of SC CAM2038. weekly injections of 32mg CAM2038 or four 128mg or 160 mg monthly CAM2038. PK data are further described in the PK section of this report.

Duration of treatment was short (maximum 3 months and one week) with the main objective being to study the steady state profile of q1w and q4w CAM2038. Results of urine tests and craving do not contradict that of the other studies.

2.8.7. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study was a phase 3 randomised, double-blind, active-controlled, parallel group, multi-centre study designed to evaluate the non-inferiority of CAM2038 compared to an existing standard of care (SL BPN/NX) in initiation and maintenance treatment with Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038). The study involved 4 phases: Screening (3 weeks), Phase 1 (12 treatment weeks), Phase 2 (12 treatment weeks), and Follow-up (4 weeks). The use of SL BPN/NX is acceptable.

Subjects were on average white (75.5%) males (61.4%) of 38.4 years of age with a mean BMI of 25.9 kg/m2. They were heroin users in 70.8% of cases (prescription opioid pain reliver in 29.2% of cases). Concomitant use of other narcotic anaesthetics, benzodiazepines, phenothiazines, other tranquilizers, or other central nervous system (CNS) depressants (including alcohol and sedative/hypnotics) was minimized during the pivotal study. If these sedatives were required during the study, the medical monitor was consulted. However, opioids were prescribed during the study for pain and tooth problems and this was seen more in the control group. The lower end of the 95% CI from the analysis of the primary endpoint in the ITT population is -0.1 and the applicant clarified in the response to another question that the ITT and the PP protocol were identical therefore it is concluded that such concomitant medication demonstrates the need for additional treatment in the control group.

A majority (70.8%) of subjects had previously used heroin as the primary opioid of abuse, and approximately half (52.3%) of the subjects used injection as the route of administering opioids. They also had positive screening results for a number of other substances of abuse, e.g. marijuana (approx. 28%, cocaine (approx. 25%), benzodiazepine (approx. 15%) and amphetamines (approx. 16%). A total of 91.8% of subjects had opioid-positive urine samples at screening down to 87.6% on Day 1 with similar numbers between groups.

All patients received an open-label dose of active 4mg of BPN on Day 1 to test tolerability. Then patients received either active or matching placebo as follow:

- an additional 4 mg SL BPN/NX (SL placebo in the CAM2038 group) was given on Day 1 with 0.32 mL SC placebo CAM2038 (16mg SC CAM2038 q1w in the CAM2038 group)

- 16 mg SL BPN/NX on Days 2 and 3 (SL placebo in the CAM2038 group)

- 16 mg SL BPN/NX and an SC injection of 0.16 mL placebo CAM2038 on Day 4 (16 mg SL placebo and 8 mg SC CAM2038 q1w in the CAM2038 group)

- and 16 to 24 mg SL BPN/NX with an optional 8mg SC injection of 16 mL of placebo CAM2038 on Days 5 to 7 (16 to 24 mg SL placebo with an optional SC injection of 8 mg of CAM2038 q1w in the CAM2038 group).

On the first day of Week 2 (i.e., Day 8), subjects received a CAM2038 SC injection (24 mg or 32 mg CAM2038 q1w, or 0.48 mL or 0.64 mL CAM2038 placebo), based on total dose given by end of Week 1/Day 7. Subjects were also provided with one-week take-home SL BPN/NX / placebo (16 mg or 24 mg SL BPN/NX / placebo), based on total daily dose established at end of Week 1/Day 7.

In Phase 2, subjects continued to receive the daily dose of SL BPN/NX or SL placebo that they received at the end of Phase 1. Based on their CAM2038 q1w (or SC placebo) dose at the end of Phase 1, subjects were transitioned to a corresponding dose of CAM2038 q4w or placebo SC injection in Phase 2. Dosage adjustment was allowed during at the monthly visits, up to a maximum of 32 mg SL BPN/NX (or placebo) and up to 160 mg CAM2038

q4w (or placebo). The dose of 160mg has now been withdrawn by the applicant as this dose was not used by a sufficient number of subjects and its PK profile was not fully characterised. In study HS-11-421 1 supplemental dose q1w 8mg was allowed with q4w (2d phase) monthly; in study HS-14-499 supplemental q1w 8mg was allowed with both q1w and q4w (1 a week and up to 40mg weekly if on q1w and 2 per week if q4w). A maximum of 2 supplemental doses were given weekly in the open-label study but only one dose per month could be given in the pivotal study. Considering there are no PK data for more than one supplemental dose a week on a regular basis the wording of the SmPC for supplemental doses should be as follows: "A maximum of one supplemental Buvidal 8 mg dose may be administered at an unscheduled visit between regular weekly or monthly doses, based on individual patient's temporary needs. The maximum dose per week for patients who are on weekly Buvidal treatment is 32 mg with an additional 8 mg dose. The maximum dose per month for patients who are on monthly Buvidal treatment is 128 mg with an additional 8 mg dose.

The use of Suboxone as control is acceptable as the naloxone component doesn't interfere with the pharmacodynamic properties of buprenorphine and is added to deter from misuse of the tablets. The test dose was followed by a dose escalation (starting dose of 16 mg CAM2038 q1w supplemented with another 8mg CAM2038 injection on Day 4 and also potentially between days 5 and 7). Also, patients were transitioned to q4w only after they had received q1w for 12 weeks. In the long-term safety and efficacy study HS-14-499 patients were transitioned to q4w only after a week of q1w at the earliest. The SmPC contains a recommendation for a test dose of SL BPN to be applied in patients who are new to buprenorphine.

In phase 2 the maximum dose of buprenorphine from SL BPN/NX tablets was 32mg. The primary efficacy endpoint for EMA was the percentage of urine samples negative for illicit opioids based on the 18 urine samples obtained during the post-induction period (between Week 2 and Week 25). This variable was analysed via an analysis of variance (ANOVA) model with treatment effects. The difference between the two treatments in percent negative urine samples was obtained from this model and the two-sided 95% CI for the treatment difference was presented. In this analysis, if urine toxicology samples were missing, the results were imputed as positive. An analysis of non-inferiority in the primary efficacy variable between the two treatment arms was performed using a margin of 11% points. Non-inferiority was concluded if the two-sided 95% confidence interval (CI) for the difference between the percentage negative urine samples (Active-Control) was above -11%. Testing was done using hierarchical order.

The applicant has provided a definition for the ITT and per protocol populations. All patients were included in the PP population since no major protocol deviation was reported in this study.

The applicant has performed two post-hoc analyses using post-hoc defined per protocol populations. One PP population excludes patients with major violations relating to exposure and the second excludes the foregoing population along with those who missed two or more consecutive urine toxicology screens. In both PP populations non-inferiority was demonstrated. It would appear that major protocol violations were not well defined before database lock. However, the two post-hoc analyses presented are acceptable.

The non-inferiority margin for the primary endpoint is accepted, also considering that p-values are far from the 5% limit and that superiority has been shown for some endpoints.

Efficacy data and additional analyses

These applications are for depot injections of buprenorphine for the treatment of opioid addiction in adults. Buprenorphine is currently available as sublingual tablets with or without naloxone; these tablets can be delivered daily but also for a number of days. The products are to be administered by healthcare professionals

and are meant to improve treatment adherence, improve convenience and decrease the risk of misuse and accidental absorption by e.g. children.

Supportive studies looking at PK data and various PD variables support the possibility to bridge the efficacy and safety of SL buprenorphine to CAM2038 in the sought indication.

Non-inferiority to SL BPN/NX was demonstrated in the pivotal study HS-11-421 for the primary endpoint of proportion of negative urine samples between Week 2 and Week 25 when the proposed products as administered sequentially over 12 weeks each (q1w then q4w). 35.1% in the CAM2038 had a negative urine test by the end of the treatment period compared to only 28.4% in the control group (ITT population). The difference between treatment groups is of 6.7% (95% CI: -0.1-13.6) with the lower end of the 95% CI close to 0 and well above - 11%. The same analysis without imputed data provides a 8.7% difference between treatments with a 95% CI of 0.9-16.4.

Treatment effect favours CAM2038 in patients using heroin at entry with a treatment difference of 13.6 % (95% CI: 5.3 – 21.9). But among subjects who did not inject opioids, the treatment difference was 0.00 (95% CI: -10.7 – 10.8); p= 0.998. The test of interaction was significant (P = 0.048), with a stronger effect seen among subjects who injected opioids.

With regards to primary opioid of use at initiation, treatment effect favours CAM2038 in patients taking heroin (treatment difference of 14.8%, 95% CI: 95% CI: 8.0 – 21.7). But the treatment effect is clearly in favour of SL BPN in patients taking prescription opioids with a treatment difference of -11.6 % (95% CI: -24.6 – 1.5), i.e. non-inferiority was not demonstrated

When looking at data obtained for period 1 and period 2, the difference between test and control group at the end of phase 1 in the ITT population is 5.9 % (95% CI: -1.3-13.1) and in phase 2 it is 8.5 % (95% CI: 1.2 - 15.7). Therefore, non-inferiority can be inferred for both q1w and q4w, with additional superiority for the q4w only.

The overall median cumulative percent urine samples negative for illicit opioids over treatment Weeks 4-24 was 26.7% for CAM2038 vs 6.7% for SL BPN/NX. Also, treatment CAM2038 favoured for retention in the study (treatment difference -1.8, 95% CI: -11.2 – 7.6) and time to abstinence (p value = 0.221).

The efficacy of CAM2038 is supported by the results from study HS-14-499 where the percent of negative urine tests increased from 0.0 % at baseline to 63.0% overall after 48 weeks. In stable patients who were receiving SL BPN at entry, the percentage of negative urine samples increased from 78.8% at baseline to 84.0% at Week 48. Study retention was high with 68.4% of patients receiving all doses over the 48-week treatment period, higher that with study HS-11-421. Cravings and withdrawal outcomes also improved over the treatment period and patients generally reported high treatment satisfaction, including also comparison to pre-study treatment with daily SL BPN/NX.

2.8.8. Conclusions on clinical efficacy

The efficacy data submitted in support of this application supports authorisation of Buvidal in the proposed indication.

2.8.9. Clinical safety

The safety of BPN is supported by clinical studies enrolling patients with opioid dependence (n=3,214) using the reference product Subutex SL tablet or Suboxone (SL BPN/NX tablet/film) at doses within the range used in the treatment of opioid dependence, i.e. 4 to 24 mg daily. The relative BA of BPN for CAM2038 q1w vs SL BPN (Subutex) was evaluated in studies HS-11-426 and HS-13-487 in part as a bridge to the established Subutex safety dataset. CAM2038 provided plasma levels of BPN comparable to those of daily SL BPN, supporting the use of Subutex as reference product.

The pharmacological class effects of opioids are known, with nausea, constipation, headache, insomnia and withdrawal symptoms (e.g. hyperhidrosis, tremor, pain) being the most common adverse reactions of BPN. BPN may as other opioids cause respiratory depression, central nervous system (CNS) depression and dependence. Furthermore, opioids may cause orthostatic hypotension but have also been shown to increase pressure, e.g. elevate intracholedochal or cerebrospinal fluid (CSF) pressure, and the latter may also cause seizures.

Opioids may also cause miosis, changes in the level of consciousness, changes in the perception of pain and prolonged QTc intervals. CAM2038 will as a BPN-containing opioid exhibit the same class effects and the general warning for the reference product is applicable to CAM2038.

Buprenorphine as an active substance in the proposed indication is well known. The proposed product, unlike any other currently marketed buprenorphine product, is a depot injection and its main differences compared to the known safety properties of buprenorphine stem from its pharmacokinetics. A depot injection is likely to provide more stable blood levels of the active substance and it is not possible to remove it from the body in case of an overdose. It is also conceivable that the tolerance and dependence properties are different compared to the immediate release formulations.

Patient exposure

A total of 729 subjects were exposed to CAM2038 in the clinical program. Two of the 7 clinical studies included a total of 135 healthy volunteers exposed to CAM2038. The 5 clinical studies conducted in patients with opioid dependence included different subpopulations: patients on stable maintenance treatment with SL BPN for ≥ 6 months (HS-07-307; N=42), patients who had a history of moderate to severe chronic non-cancer pain and were treated with SL BPN or SL BPN/NX at screening (HS-15-549; N=65), patients stabilized on IR morphine (HS-13-478; challenge study; N=47), untreated outpatients (HS-11-421; CAM2038: N=213; SL BPN/NX + SC placebo injections of CAM2038: N=215) and patients who were taking SL BPN or SL BPN/NX, or were actively seeking BPN treatment before enrolment (HS-14-499; CAM2038: N=227).

The 729 subjects received in total 8693 injections (mean: 11.9 injections per subject) of CAM2038 corresponding to 270.8 subject-exposure-years. Across regimens, 604 subjects received CAM2038 q1w and 408 subjects received CAM2038 q4w. Many patients received both CAM2038 q1w and CAM2038 q1w since flexible, individualized dosing was applied in the Phase 3 studies, i.e. patients could switch between the regimens and between different dose levels (per protocol in HS-11-421 and per Investigators' judgement in HS-14-499, i.e. based on patient's stability). 132 patients were exposed to CAM2038 over 48 weeks, of whom 42 patients received CAM2038 q1w over the entire 48-week period, 45 patients received CAM2038 q4w over the entire 48-week period and the remaining patients were transitioned between CAM2038 q1w and CAM2038 q4w, or vice versa, over 48 weeks of treatment in study HS-14-499. Only 7 patients who were exposed to weekly doses for at least 48 weeks and 22 patients were exposed to any dose in the q4w regimen for 48 weeks never changed dose.

Across all studies, the mean age was 39.5 years (range: 18 to 66 years) and 61.0% of the subjects were men. Most subjects were 'White' (78.1%) or 'Black or African American' (16.5%). Subjects of different BMI categories were exposed to CAM2038, 2.5% of the subjects were underweight (BMI <18.5 kg/m2), 81.2% had a BMI of 18.5- <30 kg/m2 and 16.3% were obese (BMI of ≥ 30 kg/m2). The mean BMI was 25.6 kg/m2 (range: 15 to 50 kg/m2). A majority of the patients had concomitant diseases and concomitant medications at study enrolment, but subjects with renal or hepatic impairment were excluded (see respective CSR for criteria). Concomitant hepatitis was common (128 patients receiving CAM2038 had hepatitis reported as ongoing at study entry).

The development programme included healthy volunteers, patients with opioid dependence, and patients with pain. There were two products involved: the weekly injection (q1w) and the monthly injection (q4w). Some of the participants received single dose, while others received multiple doses of various lengths. Despite listing all exposures per study, the applicant initially failed to summarise this data to a format usable for assessment of safety. For the purposes of understanding the short and long-term safety, the data describing the extent of exposure has been presented in response to the initial list of questions outlining how many patients with target indication received each of the two versions of the product and for how long. This has been compared with the overall exposure.

Adverse events

Common AEs in Phase 1 Naltrexone Blockade Studies in Healthy Volunteers

Safety was investigated in healthy volunteers under NTX blockage, i.e. the number of reported AEs also included AEs occurring after daily exposure to NTX throughout treatment with all 3 investigated IMPs (SL BPN [Subutex] and IV BPN [Temgesic] and CAM2038), which may have influenced the number and severity of reported AEs.

128 (94.8%) of the 135 healthy volunteers who received at least one dose of CAM2038 had at least one AE. The most common AEs after administration of CAM2038 were dizziness (58.5% of subjects), nausea (57.8%), headache (33.3%), vomiting (33.3%) and somnolence (25.2%), all of which were also common for SL BPN and IV BPN and are known class effects of opioids.

The number of AEs per subject-exposure-year was consistently higher for these AEs after SL BPN than after CAM2038 q1w or CAM2038 q4w.

Ten subjects experienced a total of 11 injection site AEs, all of which were mild and transient.

The number of AEs per subject-exposure-year increased with increasing dose of CAM2038 q1w, from 52.2 after 8 mg to 94.7 after 32 mg, while no clear trend was observed after CAM2038 q4w. As for CAM2038 q1w, the number of AEs per subject-exposure-year increased with increasing dose of SL BPN, from 111.6 (8 mg) to 198.6 (24 mg).

A majority of the AEs reported after CAM2038 were assessed as related to the IMP and 91.9% of subjects receiving CAM2038 experienced at least one adverse drug reaction (ADR).

703 of the 884 AEs (79.5%) occurring within 30 days of CAM2038 were of mild intensity, 175 AEs (19.8%) were moderate and 6 AEs (0.7%) were severe. The AEs of severe intensity were ADRs that resolved during the study and are known class effects of opioids.

Two SAEs were reported by 2 subjects receiving 192 mg CAM2038 q4w. One SAE of withdrawal reaction of moderate intensity, which started after 35 days, lasted until the next day and was assessed as possibly related

to both CAM2038 q4w and NTX. The event was classified as serious due to hospitalization and was reported as a suspected unexpected serious adverse reaction (SUSAR), despite being a well-known class effect of opioids.

The safety record of the products in this group of patients is of limited value in understanding the safety of the products in the target population, apart from the study of the local reactions. Buprenorphine is a substance of well-known clinical properties and unless adverse events are related to the excipients or the method of administration, they would be primarily connected to the high plasma levels acting on opioid receptors. In healthy subjects, presumably, there would be up or down regulation of opioid receptors and in these studies they would be protected by naltrexone, so the safety record seen in these studies is really only relevant to the clinical situation in those studies, and not particularly to the clinical situation in which the products are proposed to be used.

Common AEs in the Single-dose, Dose Escalation Study (HS-07-307) and the Opioid Challenge Study (HS-13-478)

Based on the design of studies HS-07-307 and HS-13-478, these studies were not included in any of the pools for analysis of common non-serious AEs presented by the applicant.

Study HS-07-307 was carried out with a different formulation and it is agreed that the safety records from this study would not be relevant for the safety of the proposed products.

However, study HS-13-478 is similar to the clinical situations that may be encountered in use of products. It is also conducted in the appropriate target population. The safety record from this study has been presented in response to the initial list of questions.

Common Adverse Events in Phase 3 Studies

Summary of AEs in Phase 3 Studies

In total, 271 patients (61.6%) receiving CAM2038 in the Phase 3 studies reported 1240 AEs and 119 patients (55.3%) receiving SL BPN/NX reported 562 AEs. The mean number of AEs per subject-exposure-year was 5.1 for patients receiving CAM2038 and 7.3 for patients receiving SL BPN/NX. The mean number of AEs per injection was 0.16 for patients receiving CAM2038 and 0.20 for patients receiving SL BPN/NX.

130 patients (29.5%) receiving CAM2038 reported 443 ADRs and 64 patients (29.8%) receiving SL BPN/NX reported 193 ADRs. The mean number of ADRs per subject-exposure-year was 1.8 for patients receiving CAM2038 and 2.5 for patients receiving SL BPN/NX.

Overall, 49.5% of the patients receiving CAM2038 reported 866 AEs of mild intensity, 32.5% reported 343 AEs of moderate intensity and 4.8% reported 31 AEs of severe intensity. The percentages of mild, moderate and severe AEs were similar between the treatments.

87.3% of the AEs in patients receiving CAM2038 resolved, 11.9% did not resolve during the study, 0.4% resolved with sequelae and 1 AE (0.1%) resulted in death. The outcome was unknown for 0.2% of the AEs.

In total, 17 patients (3.9%) receiving CAM2038 reported 20 SAEs and 13 patients (6.0%) receiving SL BPN reported 18 SAEs. The percentage of patients with at least one AE leading to withdrawal of treatment was 2.3% for patients receiving CAM2038 and 1.4% for patients receiving SL BPN.

Although the numbers presented here do not reflect the entire population involved in the clinical development programme, this subset allows for a comparison between those receiving the treatment and those on other treatments.

As a general conclusion, it can be said that the numbers of AEs and their characteristics were comparable between those receiving CAM2038 and those receiving other treatments.

AEs by Regimen and Dose in Phase 3 Studies

The percentage of patients with at least one AE was 49.5% for CAM2038 q1w and 43.7% for CAM2038 q4w. The mean number of AEs per subject-exposure-year was higher for CAM2038 q1w (6.8) than for CAM2038 q4w (3.3), which may be explained by a visit frequency bias (patients receiving CAM2038 q1w once weekly had more frequent visits and had AEs collected more often than patients receiving CAM2038 q4w once monthly).

The percentage of patients with at least one ADR was 24.6% for CAM2038 q1w and 14.6% for CAM2038 q4w. The mean number of ADRs per subject-expose year was 2.7 for CAM2038 q1w and 0.9 for CAM2038 q4w.

The percentage of patients with at least one severe AE was 2.2% for CAM2038 q1w and 4.5% for CAM2038 q4w.

The percentage of patients with at least one AE leading to withdrawal was 2.2% for CAM2038 q1w and 0.3% for CAM2038 q4w.

Table below summarizes AEs by regimen in the Phase 3 studies.

With increasing dose of CAM2038 q1w, there were trends of increasing percentage of patients with at least one AE, increasing number of AEs per subject-exposure-year, increasing number of ADRs per subject-exposure-year and increasing percentage of patients with at least one AE of severe intensity. For CAM2038 q4w (64 mg, 96 mg, 128 mg, and 160 mg), the AE profile was more similar across dose levels.

Table 31: Overall summary of AEs by regimen in Phase 3 studies (CAM2038 safety population)

Category		CAM2038 q1w (N=402)	CAM2038 q4w (N=309)
No. of subject with at least one AE		199 (49.5%)	135 (43.7%)
No. of subject with at least one related AE		99 (24.6%)	45 (14.6%)
Severity No. of subjects (%)	Mild	159 (39.6%)	106 (34.3%)
	Moderate	100 (24.9%)	58 (18.8%)
	Severe	9 (2.2%)	14 (4.5%)
Outcome No. of subjects (%)	Recovered/resolved	180 (44.8%)	125 (40.5%)
	Not recovered/not resolved	54 (13.4%)	38 (12.3%)
	Recovered/resolved with sequelae	3 (0.7%)	2 (0.6%)
	Fatal	0	1 (0.3%)
	Unknown	3 (0.7%)	0
No. of subject with at least one SAE		5 (1.2%)	12 (3.9%)
No. of subject with at least one AE leading to withdrawal		9 (2.2%)	1 (0.3%)
No. of deaths		0	1 (0.3%)

Although a death was recorded in the q4w subgroup and the number of patients in q1w was larger, it can still be seen that the related events occur more frequently in q1w group. Considering that there were no predefined criteria for comparison of the groups the difference can be regarded as being on the border of clinical significance, but it cannot be disregarded. It is also of potential significance that the dose played higher role in the frequency of the reported events for q1w than in q4w.

Nature of AEs in Phase 3 Studies

The most commonly reported AEs in the Phase 3 studies included injection site pain (overall 12.3% of patients receiving CAM2038), injection site swelling (8.2%), headache (7.7%), injection site erythema (7.5%), and nausea (7.0%). Table below shows AEs reported by at least 5% of the patients in the Phase 3 studies. The incidences and rates of these AEs were similar between the treatments in study HS-11-421.

When looking at the 5 most commonly reported AEs by regimen (injection site pain, injection site swelling, headache, injection site erythema and nausea), the rates of these were higher for CAM2038 q1w than for CAM2038 q4w, which may be explained by a visit frequency bias (patients receiving CAM2038 q1w once weekly had more frequent visits and had AEs collected more often than patients receiving CAM2038 q4w once monthly), Table below.

Across dose levels, there was a trend of increasing injection site pain with increasing dose of both CAM2038 q1w and CAM2038 q4w. A trend of increasing injection site swelling with increasing dose was observed for CAM2038 q1w but not for CAM2038 q4w. Increases in injection site AEs with increasing dose, in applicant's opinion, are likely to be driven by larger injection volumes at higher dose levels (the highest dose volume was slightly higher for q1w than q4w).

It is difficult to draw any firm conclusion regarding dose relationships for individual PTs, however, the highest percentage of patients with nausea was observed at 160 mg CAM2038 q4w (9.7% of patients).

Table 32: AEs by study, treatment group and PT (incidence of ≥ 5%) in Phase 3 studies (safety population)

Preferred Term	HS-11-421		HS-14-499	Total
	CAM2038 (N=213)	SL BPN (N=215)	CAM2038 (N=227)	CAM2038 (N=440)
	n (%)	n (%)	n (%)	n (%)
Injection site pain	19 (8.9%)	17 (7.9%)	35 (15.4%)	54 (12.3%)
Injection site swelling	9 (4.2%)	6 (2.8%)	27 (11.9%)	36 (8.2%)
Headache	16 (7.5%)	17 (7.9%)	18 (7.9%)	34 (7.7%)
Injection site erythema	12 (5.6%)	12 (5.6%)	21 (9.3%)	33 (7.5%)
Nausea	15 (7.0%)	17 (7.9%)	16 (7.0%)	31 (7.0%)
Urinary tract infection	11 (5.2%)	10 (4.7%)	12 (5.3%)	23 (5.2%)
Constipation	16 (7.5%)	16 (7.4%)	6 (2.6%)	22 (5.0%)
Nasopharyngitis	4 (1.9%)	2 (0.9%)	18 (7.9%)	22 (5.0%)

Table 33: AEs by regimen, dose and PT (incidence of ≥ 5%) in Phase 3 studies (CAM2038 safety population)

Preferred Term	CAM2038 q1w (N=402)	CAM2038 q4w (N=309)
	n (%)	n (%)
Injection site pain	38 (9.5%)	20 (6.5%)
Injection site swelling	27 (6.7%)	10 (3.2%)
Headache	25 (6.2%)	11 (3.6%)
Injection site erythema	25 (6.2%)	9 (2.9%)
Nausea	20 (5.0%)	12 (3.9%)
Urinary tract infection	12 (3.0%)	12 (3.9%)
Constipation	19 (4.7%)	3 (1.0%)
Nasopharyngitis	17 (4.2%)	6 (1.9%)

The comparison between the treatments clearly indicates the importance of the local injection site reactions for the safety of the products. While opioid related adverse events appear very similar across the treatment groups, the ones relating to the injections do not. The injection site safety should be regarded as event of special interest.

It is also a curious finding that those on the open label product in HS-14-499 had somewhat lower frequencies of constipation than those in the oral treatment. While the numbers are too low to make reliable generalisations, the finding could be regarded as potentially important safety advantage.

Intensity of AEs in Phase 3 Studies

Overall, 49.5% of the patients receiving CAM2038 reported 866 AEs of mild intensity, 32.5% reported 343 AEs of moderate intensity and 4.8% reported 31 AEs of severe intensity. The percentages of mild, moderate and severe AEs were similar between the treatments.

The most common PTs of severe intensity in patients receiving CAM2038 were road traffic accident, seizure and urinary tract infection, which were reported by 2 patients (0.5%) each.

There was a trend of increasing rate of AEs of severe intensity with increasing dose of CAM2038 q1w, while no such trend was observed for CAM2038 q4w. However, the total number of patients with AEs of severe intensity was low (9 in total for CAM2038 q1w and 14 in total for CAM2038 qw).

No important differences between the frequencies of severe adverse events can be deduced from these numbers.

Relationship to IMP in Phase 3 Studies

130 patients (29.5%) receiving CAM2038 reported 443 ADRs and 64 patients (29.8%) receiving SL BPN/NX reported 193 ADRs. The mean number of ADRs per subject-exposure-year was 1.8 for patients receiving CAM2038 and 2.5 for patients receiving SL BPN/NX.

The most commonly reported ADRs in patients receiving CAM2038 in the Phase 3 studies were injection site pain (overall 12.3% of patients receiving CAM2038), injection site swelling (8.0%), injection site erythema (7.0%) and injection site pruritus (4.3%). The 3 most commonly reported non-injection site-related ADRs were constipation (overall 3.6% of patients receiving CAM2038), nausea (3.4%) and headache (3.0%). Table below shows ADRs reported by at least 1% of the patients receiving CAM2038 in the Phase 3 studies.

As for AEs overall, the percentage of patients with any ADRs was higher for CAM2038 q1w (24.6%) than for CAM2038 q4w (14.6%), which may be explained by a visit frequency bias (patients receiving CAM2038 q1w had more frequent visits and had AEs collected more often than patients receiving CAM2038 q4w).

An increase in the rate of ADRs with dose was observed both for CAM2038 q1w and CAM2038 q4w.

Few ADRs (4 in total) were of severe intensity, whereof 1 in the CAM2038 group (injection site pain) and 3 in the SL BPN/NX group (increased ALT, increased gamma-glutamyltransferase [γ-GT] and decreased libido), Table below. The one patient with an ADR of severe intensity in the CAM2038 group had a single event of severe injection site pain, which resolved the same day.

One patient receiving CAM2038 was hospitalized with an SAE of vomiting 3 days after randomization and the first dose of IMP. The patient had a medical history of acid reflux (ongoing at Screening) had complained of nausea already before randomization and had induced vomiting to relieve heartburn on Day 1 of treatment. Further examination during the hospitalization revealed an ulcer, an oesophageal rupture and dehydration, all classified as non-serious AE and all likely associated with the acid reflux and the vomiting. The ADR resolved, but the patient withdrew from treatment.

One patient receiving CAM2038 had 'weight decrease' of mild intensity considered by the investigator as treatment related. The event was not resolved by end of the study. The patient weighed 67.1 kg (BMI: 23.9kg/m2) at Screening, and 56.8 kg (BMI 20.2kg/m2) at end of treatment 6 months later. No other patients in the Phase 3 studies had an event of 'weight decrease' reported as treatment related.

One patient receiving CAM2038 had 'lipase increase' at the Week 25 visit (end of treatment), considered by the investigator as treatment related. The event resolved after 9 days. Except for the Week 25 visit, the patient had normal levels of lipase at all study visits. No other patients in the Phase 3 studies had an event of 'lipase increase' reported as treatment related.

One patient receiving CAM2038 had cellulitis considered by the investigator as treatment related. The event was mild and resolved after 16 days. The event was not an injection site reaction. No other patients in the Phase 3 studies had an event of non-injection site cellulitis reported as treatment related.

Table 34: Treatment-related AEs reported by at least 1% of the patients by study, treatment group and PT in Phase 3 studies (safety population)

Preferred Term	HS-11-421		HS-14-499	TOTAL
	CAM2038 (N=213)	SL BPN (N=215)	CAM2038 (N=227)	CAM2038 (N=440)
	n (%)	n (%)	n (%)	n (%)
Injection site pain	19 (8.9%)	16 (7.4%)	35 (15.4%)	54 (12.3%)
Injection site swelling	9 (4.2%)	6 (2.8%)	26 (11.5%)	35 (8.0%)
Injection site erythema	10 (4.7%)	12 (5.6%)	21 (9.3%)	31 (7.0%)
Injection site pruritus	13 (6.1%)	12 (5.6%)	6 (2.6%)	19 (4.3%)
Constipation	13 (6.1%)	12 (5.6%)	3 (1.3%)	16 (3.6%)
Nausea	9 (4.2%)	3 (1.4%)	6 (2.6%)	15 (3.4%)
Headache	8 (3.8%)	5 (2.3%)	5 (2.2%)	13 (3.0%)
Insomnia	5 (2.3%)	2 (0.9%)	2 (0.9%)	7 (1.6%)
Vomiting	3 (1.4%)	2 (0.9%)	4 (1.8%)	7 (1.6%)
Fatigue	0	2 (0.9%)	6 (2.6%)	6 (1.4%)
Injection site mass	3 (1.4%)	1 (0.5%)	3 (1.3%)	6 (1.4%)
Injection site reaction	6 (2.8%)	6 (2.8%)	0	6 (1.4%)
Injection site induration	4 (1.9%)	6 (2.8%)	1 (0.4%)	5 (1.1%)

Table 35: Treatment-related AEs of severe intensity by study, treatment group and PT in Phase 3 studies (safety population)

Preferred Term	HS-11-421		HS-14-499	TOTAL
	CAM2038 (N=213)	SL BPN (N=215)	CAM2038 (N=227)	CAM2038 (N=440)
	n (%)	n (%)	n (%)	n (%)
Injection site pain	0	0	1 (0.4%)	1 (0.2%)
Alanine aminotransferase increased	0	1 (0.5%)	0	0
Gamma-glutamyltransferase increased	0	1 (0.5%)	0	0
Libido decreased	0	1 0.5%)	0	0

The numbers are relatively small for reliable conclusions, but the trend does appear that injection site events are associated and more frequent in the CAM2038 groups. There is also a trend indicating the higher frequency of these problems with q1w product. While potentially explainable by the higher frequency of visits and injections, this nevertheless amounts to the potential inferiority in safety of the q1w product. If the rate of local events per injection was the same for q1w and q4w, this would still amount to real difference in frequencies per period of time in treatment. However, the importance of this difference is relatively small.

Common Adverse Events in Multiple-dose Open-Label Studies (HS-15-549, HS-14-499) in Patients with Opioid Dependence

AEs in the multiple-dose, open-label studies followed the same trends as in the Phase 3 studies, which to a large extent is explained by study HS-14-499 being included in both these pools. (HS-14-499 contributed with 227 of the 292 patients included in the multiple-dose, open-label studies).

176 patients (60.3%) reported 838 AEs, corresponding to 4.5 AEs per subject-exposure-year.

The 5 most commonly reported AEs in the multiple-dose, open-label studies were injection site pain (12.0% of patients), injection site swelling (10.3%), injection site erythema (8.2%), nausea: (7.2%) and headache (6.8%).

16 patients (5.5%) reported any AE of severe intensity. Seizure and urinary tract infection (each reported by 2 patients [0.7%]) were the only AEs of severe intensity reported by more than 1 patient.

AEs of severe intensity was reported by 2.6% of patients receiving CAM2038 q1w and 5.9% of patients receiving CAM2038 q4w.

69 patients (23.6%) reported any ADR. The most commonly reported ADRs in the multiple dose, open-label studies were injection site pain (12.0% of patients), injection site swelling (9.9%), injection site erythema (8.2%), fatigue (2.4%) and headache (2.1%).

Focusing on the open label phase 3 studies does not reveal any trends different form the overall phase 3 pool. It is interesting that the injection site side events are more frequent in the phase 3 OL study HS-14-499 then in the phase 2 HS-15-549 study.

Subjects could transition between weekly and monthly dosing regimens and vice versa. In the open label study the majority of subjects (65.6%,) had no transition between treatment regimens during the study; 33% of subjects (75/227) had a transition from weekly to monthly and 25.6% (58/227) had transition from monthly to weekly regimens. The safety of switching between regimens has been further discussed following the initial list of questions. A cumulative overview of safety data for subjects (those who were receiving BPN and those who

were new to BPN) who transitioned from weekly to monthly and monthly to weekly regimens across the two phase 3 studies has been presented and the observed differences were not seen as clinically relevant.

In the phase 3 open label study overall rates of AEs (both injection site reactions and non-injection site reactions) were higher in subjects who were receiving BPN at entry compared to those who were new to BPN in the open label study. The reason for this large discrepancy between these two populations was further discussed by the applicant and no clinically relevant trends were identified.

40% of subjects in the long-term safety study required booster doses of 8mg CAM2038. The safety profile for subjects who received or didn't receive booster doses has been summarised following the initial list of questions. The impact of these additional dose of CAM2038 on the safety profile has been discussed and found to be of no clinical importance.

Injection site findings by treatment dose/regimen and anatomic location, injection site rotation and whether there are particular injection sites that are better for weekly versus monthly injections has been discussed by the applicant following the initial list of questions. The applicant has amended the SmPC to give instructions for choosing the injection site for monthly and weekly injections and about reinjecting.

There were 7 cases of injection site ulceration across all studies. Five subjects in Study HS-11-421 (3, SL BPN/NX; 2, CAM2038) had an injection site ulcer (3, mild; 2, moderate). Two cases of injection site ulcer were also reported at higher doses (96 mg and 128 mg in the Q4w regimen) in the open label studies. The 5 subjects in the pivotal trial with an injection site ulcer were enrolled at the same site. The ulcerative injection site reactions were all attributed to inappropriate injection technique by a single individual at the study site. Further discussion on the cases of ulceration including further information on the inappropriate technique has been presented by the applicant. The appropriate instructions have been provided in the product information about the safe administration technique.

Severe and Serious Adverse Events and Deaths

Non-serious Adverse Events of Severe Intensity across Studies in Patients with Opioid Dependence (HS-07-307, HS-13-478, HS-15-549, HS-11-421, HS-14-499)

Across studies in patients with opioid dependence, 31 patients (5.2%) receiving CAM2038 and 8 patients (3.7%) receiving SL BPN/NX reported any non-serious AEs of severe intensity.

Four PTs of non-serious AEs of severe intensity were reported by more than 1 patient receiving CAM2038: drug withdrawal syndrome (2.2%), headache (0.8%), migraine (0.3%) and urinary tract infection (0.3%). The number of non-serious AEs of severe intensity per subject-exposure-year was higher in patients receiving CAM2038 q1w (0.44) than in patients receiving CAM2038 q4w (0.06).

Non-serious ADRs of severe intensity were reported by 2 patients (0.3%) receiving CAM2038, who reported a total of 3 such ADRs (injection site pain, migraine and nausea) and 2 patients (0.9%) receiving SL BPN/NX, who also reported a total of 3 such ADRs (increased ALT, increased γ-GT and decreased libido).

The numbers presented here are too small for any reliable generalisations, although the number of non-serious AEs of severe intensity per subject-exposure-year was higher in q1w group than in q4w (0.44 vs 0.06) which conforms to the overall trend of q1w being of inferior safety profile compared to q4w.

Serious Adverse Events in Healthy Volunteers

Two healthy volunteers who had received CAM2038 experienced an SAE, both of which were assessed as related to the IMP, however, both occurred more than 30 days after the last dose of CAM2038.

The products are not intended for administration to healthy individuals. The applicant's handling and assessment of the reports of these two serious adverse events can be accepted, despite the fact that the onset of withdrawal symptoms at day 35 may well be linked to the discontinuation of the product.

Serious Adverse Events across All Studies

Across all studies, 17 subjects (2.3%) receiving CAM2038 experienced a total of 20 SAEs and 13 subjects (6.0%) receiving SL BPN/NX experienced a total of 18 SAEs.

The number of SAEs was 0.07 per subject-exposure-year in subjects receiving CAM2038.

Two SAEs were reported by more than 1 subject receiving CAM2038: road traffic accident and seizure (each reported by 2 subjects [0.3%]). The percentage of subjects with any SAE was 0.8% for CAM2038 q1w and 2.9% for subjects receiving CAM2038 q4w.

For CAM2038 q1w, the highest number of subjects with any SAE was observed at the highest dose level (32 mg; 3 subjects), while for CAM2038 q4w, the highest number of subjects with any SAE was observed at the lowest dose level (64 mg; 5 subjects). However, it is difficult to draw any conclusions regarding dose relationship due to the low number of SAEs.

There was 1 treatment-related SAEs (vomiting) occurring within 30 days after the last dose of CAM2038. This SAE occurred in a subject receiving 16 mg CAM2038 q1w.

Most of the SAEs were of severe intensity with 11 subjects (1.5%) receiving CAM2038 reporting 13 SAEs of severe intensity.

Most SAEs (15 of 20) resolved during the study, 2 SAEs did not resolve during the study, 2 SAEs resolved with sequelae and 1 SAE was fatal (described below).

The overall SAE counts for the q1w and q4w do not follow the trends that q4w is safer although there seem to be a dose relationship with q1w. The numbers are, however, too low to make any reliable generalisations. It is not clear if the road traffic accident was the same case that resulted in death, or a separate incident.

Deaths

No deaths occurred in studies in the healthy volunteer studies (HS-11-426, HS-13-487) in the dose escalation study (HS-07-307), in the multiple-dose opioid challenge study (HS-13-478) or in the multiple-dose, open-label studies (HS-15-549 or HS-14-499).

One death occurred in the CAM2038 group in study HS-11-421. The cause of death was a road traffic incident, which was assessed by the Investigator as unlikely related to the IMP.

One case of death reported in the summary of safety in the dossier is related to a road traffic accident. The investigator has marked the event as unrelated, but the proposed SmPC bears the warring that buprenorphine can cause drowsiness and interfere with ability to drive and operate machinery. The proposed products are of different pharmacokinetic profile to the available oral buprenorphine products, which potentially can provide constant higher levels of buprenorphine in blood. This is especially a problem during the dose adjustment. The possible role of buprenorphine in this case of death cannot be entirely ruled out. The applicant was asked to

discuss and consider including special warnings about driving and use of machinery during the period of dose adjustment in product literature.

Other Significant Adverse Events across All Studies (Healthy Volunteer Studies and Studies in Patients with Opioid Dependence)

Across all studies, 12 subjects (1.6%) receiving CAM2038 had any AE resulting in withdrawal from treatment (CAM2038 q1w: 1.8%; CAM2038 q4w: 0.2%). These were mainly injection site AEs and gastrointestinal events. AEs resulting in withdrawal from treatment reported by more than 1 subject included injection site pain and injection site swelling (3 subjects each), injection site erythema, injection site pruritus and injection site reaction (2 subjects each) and vomiting (2 subjects).

Across all studies, 8 subjects (1.1%) receiving CAM2038 had any ADR resulting in withdrawal from treatment. These included injection site pain and injection site swelling (3 subjects each), injection site erythema, injection site pruritus, injection site reaction and vomiting (2 subjects each), and nausea, oedema peripheral and oesophageal rupture (1 subject each).

Table 36: AEs leading to treatment withdrawal by regimen, dose and PT across all studies (safety population)

Preferred Term	CAM2038 q1w (N=604)	CAM2038 q4w (N=408)	TOTAL CAM2038 (N=729)
	n (%)	n (%)	n (%)
Any AE leading to drug withdrawal	11 (1.8%)	1 (0.2%)	12 (1.6%)
Injection site pain	2 (0.3%)	1 (0.2%)	3 (0.4%)
Injection site swelling	3 (0.5%)	0	3 (0.4%)
Injection site erythema	2 (0.3%)	0	2 (0.3%)
Injection site pruritus	2 (0.3%)	0	2 (0.3%)
Injection site reaction	2 (0.3%)	0	2 (0.3%)
Vomiting	2 (0.3%)	0	2 (0.3%)
Dehydration	1 (0.2%)	0	1 (0.1%)
Facial bones fracture	1 (0.2%)	0	1 (0.1%)
Intervertebral disc injury	1 (0.2%)	0	1 (0.1%)
Lower limb fracture	1 (0.2%)	0	1 (0.1%)
Multiple injuries	1 (0.2%)	0	1 (0.1%)
Nausea	1 (0.2%)	0	1 (0.1%)
Non-cardiac chest pain	1 (0.2%)	0	1 (0.1%)
Oedema peripheral	1 (0.2%)	0	1 (0.1%)
Oesophageal rupture	1 (0.2%)	0	1 (0.1%)
Pharyngeal injury	1 (0.2%)	0	1 (0.1%)
Road traffic accident	1 (0.2%)	0	1 (0.1%)
Sedation	1 (0.2%)	0	1 (0.1%)
Skull fractured base	1 (0.2%)	0	1 (0.1%)
Spinal fracture	1 (0.2%)	0	1 (0.1%)
Ulcer	1 (0.2%)	0	1 (0.1%)
Upper limb fracture	1 (0.2%)	0	1 (0.1%)
Ventricular extrasystoles	1 (0.2%)	0	1 (0.1%)

Source: Extracted from Table 7.3.1 in Module 5.3.5.3

From the data above, the safety areas of interest appear to be local injection site reactions, which is expected. In addition, gastrointestinal side-effects were a prominent finding in the studies. This too is expected. Furthermore, the injuries appear to be of importance, which is possibly related to the effects of the active substance on the CNS.

Severe drug withdrawal syndrome was experienced by 2.2% of subjects with opioid dependence. The source of these reports is unclear. In study HS-07-307 –the most frequent TEAE observed for 40 patients (95.2%) overall was drug withdrawal syndrome. This was expected due to the study design with a study duration exceeding the target effect duration of CAM2038-G. However, none of these cases were reported as severe in the CSR. These cases of severe drug withdrawal syndrome have been further discussed and clarified following the initial list of questions.

Of particular interest was to find out if the GI side effects and locomotor injuries were any more frequent in patients treated with the products. Considering the changed PK profile, the more constant levels of buprenorphine might have been responsible for different overall reactions, e.g. due to different circadian influence etc. This issue has been clarified following the initial list of questions. No new risks with CAM2038 compared to oral buprenorphine are identified.

Laboratory findings

The shift tables of clinical haematology data showed that the most frequently observed shifts from a normal baseline value to a low or high value at EOS in patients receiving CAM2038 were (% of patients):

• shift from normal to low in haemoglobin (CAM2038: 7.8%; SL BPN/NX: 10.5%)

• shift from normal to low in erythrocyte mean corpuscular haemoglobin concentration (CAM2038: 6.0%; SL BPN/NX: 7.1%)

• shift from normal to low in erythrocytes (CAM2038: 5.1%; SL BPN/NX: 4.8%)

These changes were similar between the treatments and may result from frequent blood sampling in the clinical study.

The shift tables of clinical chemistry data showed that the most frequently observed shifts from a normal baseline value to a low or high value at EOS in patients receiving CAM2038 were (% of patients):

• shift from normal to high in glucose (CAM2038: 10.5%; SL BPN/NX: 14.0%)

• shift from normal to high in creatine kinase (CAM2038: 8.7%; SL BPN/NX: 6.5%)

• shift from normal to high in cholesterol (CAM2038: 8.5%; SL BPN/NX: 6.5%)

When looking specifically into increases in liver enzymes, the shift tables showed similar percentages of patients between the treatments (% of patients):

• shift from normal to high in ALT (CAM2038: 5.6%; SL BPN/NX: 4.2%)

• shift from normal to high in albumin (CAM2038: 0.5%; SL BPN/NX: 0.0%)

• shift from normal to high in alkaline phosphatase (CAM2038: 2.5%; SL BPN/NX: 3.7%)

• shift from normal to high in AST (CAM2038: 6.0%; SL BPN/NX: 4.2%)

• shift from normal to high in bilirubin (CAM2038: 1.3%; SL BPN/NX: 0.5%)

• shift from normal to high in γ-GT (CAM2038: 3.1%; SL BPN/NX: 5.1%)

Only 1 subject (in the SL BPN/NX group in study HS-11-421) in the pooled studies had ALT and AST values >3 × ULN associated with total bilirubin > 2 × ULN. This subject did not meet the criteria for Hy's law because the subject had hepatitis C reported as ongoing at time of entry.

The shift tables of clinical coagulation laboratory showed that 10.9% of the patients in both groups had a shift from normal to high in prothrombin international normalized ratio (INR).

Prothrombin time was not measured in study HS-11-421 and data on this parameter is therefore not available for SL BPN/NX. In patients receiving CAM2038, 6.4% of patients had a shift from normal to low, 3.6% of patients had a shift from normal to high and 2.7% had a shift from low to high.

The percentages of patients with changes in laboratory values (clinical hematology, clinical chemistry and clinical coagulations) were similar between CAM2038 and SL BPN/NX.

Changes in laboratory values as reported were similar between the treatment groups. However, Shift from normal to high for INR values following treatment with buprenorphine is noted. The clinical significance of increases in INR has been further discussed following the initial list of questions. No additional concerns were identified.

Adverse Events of Special Interest

The following potential AESIs were specified by the Sponsor based on the labelling of the reference product and taking the different route of administration into account:

☐ Allergic reactions

☐ Central nervous system (CNS) depression

☐ Device failure

☐ Drug abuse or dependence

☐ Drug withdrawal

☐ Elevated CSF pressure

☐ Elevated intracholedochal pressure

☐ Gastrointestinal disorders

☐ Hepatic disorders

☐ Medication errors including Overdose

☐ Orthostatic hypotension

☐ Psychiatric disorders

☐ QT prolongation

☐ Reproductive or neonatal disorders

☐ Respiratory depression

☐ Severe injection site reactions

The incidence rate of the pre-defined potential AESIs was similar between CAM2038 and SL BPN/NX in the randomized, double-blind, double-dummy study HS-11-421, except for the AESI "Drug abuse and dependence", which was more common in the SL BPN/NX group (p=0.03). No AEs were reported within this AESI in the CAM2038 group in HS-11-421, while 'Accidental overdose' (4 patients; heroin [3] and clonazepam [1]), 'Intentional overdose' (1 patient; doxepin, prazosin, and venlafaxine) and 'Substance-induced mood disorder' (1 patient) were reported in the SL BPN/NX group.

Based on pooled data from the Phase 3 studies, 10.2% of patients receiving CAM2038 and 8.8% of patients receiving SL BPN/NX had any treatment-related potential AESI. These were mainly within the pre-defined SMQs for 'Gastrointestinal disorders' and 'Psychiatric disorders', all of which were known class effects of opioids. Five patients (1.1%) receiving CAM2038 had 5 serious events of potential AESIs and 4 patients (1.9%) receiving SL BPN/NX had 8 serious events of potential AESIs. In the CAM2038 group, 1 serious potential AESI (vomiting) was assessed as possibly treatment-related. Withdrawals from treatment due to any potential AESI were few and included 4 patients (0.9%) receiving CAM2038 (1 AE of sedation, 2 AEs of vomiting, 1 AE of nausea and 1 AE of non-cardiac chest pain) and 1 patient (0.5%) receiving SL BPN/NX (1 AE of drug withdrawal syndrome). No AEs of adrenal cortical insufficiency/Addison's disease, device failure, elevated CSF or elevated intracholedochal pressure, miosis, orthostatic hypotension or pain perception changes were reported.

The listed adverse events of special interest are based on the well-known safety of the active substance. The main difference between known oral formulations and the proposed product is in their pharmacokinetics and the possibility of local injection site reactions. There were also substantial number of injuries recorded in the development programme which are not sufficiently analysed and may need to be added to the list of events of special interest.

Suicidality

In the Phase 3 studies, 14 (3.2%) CAM2038-treated patients had any type of suicidal ideation at least once after Day 1; 14 (3.2%) had wished to be dead; 5 (1.1%) had non-specific active suicidal thoughts; and 3 (0.7%) had active suicidal ideation with any method without intent to act. Two (0.5%) patients had any type of suicidal behaviour at least once after Day 1, characterized as non-suicidal, self-injurious behaviour. No CAM2038-treated patients had an actual suicide attempt on study. No appreciable differences in C-SSRS results were observed between CAM2038 and SL BPN/NX in study HS-11-421.

Cardiac safety

QT prolongation is a known class effect of opioids. However, analyses of PK/PD relationships showed that CAM2038 was not associated with significant QTc interval prolongation. The QTcF profiles of CAM2038 were well aligned with those observed for Subutex and Temgesic in the same subjects at similar ranges of BPN plasma concentrations.

The 12-lead ECG results showed that no healthy volunteers had any QTcF observation $\geq$ 480 ms at any post-baseline visit or an increase in QTcF of $\geq$ 60 ms from baseline at any time-point.

Across all Studies in Patients with Opioid Dependence there was an increase from 1.8% at baseline to 2.6% at EOS in the number of subjects with a QTcF interval of 450 ms or longer. Only 1 patient (0.2%) (study HS-11-421) had a QTcF ≥500 ms at end of study. At end of study 3 (0.6%) patients (2, study HS-11-421; 1, study HS-14-499) had a change from baseline in QTcF ≥60 ms. Across all studies in subjects with opiod dependence thirteen (13) ECG related AEs were reported including 2 patients who reported QRS complex abnormal and electrocardiogram QT prolonged (this patient was withdrawn from the study) and ventricular tachycardia. No of these AEs were assessed as being related to study drug.

The applicant has further discussed the potential for QT-prolongation with sc administration of CAM2038. The narratives for the 13 ECG related AES were presented for review. Appropriate warnings including a warning regarding the potential additive effect of CAM2038 if co-administered with other medications that prolong the QT interval have been included in section 4.4 of the SmPC by the applicant.

In HS-11-421, 1 patient in each treatment group had a QTcF ≥ 500 ms at a post-baseline evaluation; both were isolated occurrences and none was reported in association with any cardiac-related AEs. One patient in HS-14-499 had a change from Baseline in QTcF of ≥ 60 ms at end of study. Similar results were observed for QTcB.

In HS-11-421, 2 patients receiving CAM2038 and 3 patients receiving SL BPN/NX (not further described) had a clinically significant ECG abnormality reported as an AE. Clinically significant ECG abnormalities reported as AEs in CAM2038-treated patients across all studies included:

☐ HS-15-549: 1 patient had a moderate paroxysmal atrial fibrillation (not related).

☐ HS-13-478: 2 patients had mild ventricular tachycardia (possibly related), 1 patient had moderate ventricular extrasystoles (unrelated) and 1 patient had mild abnormal ECG STT segment (unrelated).

☐ HS-11-421: 2 patients had mild atrial fibrillation and moderate abnormal ECG (not related).

☐ HS-14-499: 1 patient had abnormal ECG QRS complex and prolonged QT, both of moderate intensity (not related), 1 patient had mild myocardial ischaemia (not related) and 1 patient had severe ventricular tachycardia (SAE; not related).

The cardiac safety of the products, can generally be regarded as similar to that of oral preparations.

Local injection site reactions – spontaneous reporting

Across all studies, 118 subjects (16.2%) receiving CAM2038 reported a total of 385 unsolicited injection site AEs. The mean number of injection site AEs per injection was low (0.04) and the mean number of injection site AEs per subject-exposure-year was 1.4. In line with most injection site AEs by nature being treatment-related, 109 subjects (15.0%) had any injection site ADR.

The most commonly reported injection site AEs were injection site pain (9.3% of subjects), injection site erythema (5.5%) and injection site swelling (5.5%). A majority of the injection site AEs were of mild (78.7%) or moderate (21.0%) intensity. One injection site AE (0.3%), a transient event of injection site pain, was of severe intensity.

The percentage of subjects with any injection site AE was 14.6% for CAM2038 q1w and 9.3% for CAM2038 q4w. There was a trend of increasing number of injection site AEs with increasing dose for both CAM2038 q1w (from 2.7% at 8 mg to 18.3% at 32 mg) and CAM2038 q4w (from 4.5% at 64 mg to 11.1% at 160 mg). Overall, the percentage of subjects reporting any unsolicited injection site AE increased with increasing volume, from 2.9% after injection volumes of <0.27 mL to 13.7% after injection volumes of 0.45-0.64 mL. The increase in number of injection site AEs with increasing dose within the respective regimen (i.e. CAM2038 q1w and CAM2038 q4w) is, to a large extent, likely to result from the larger injection volume at higher dose levels.

The highest rate of injection site AEs was observed after the first 5 injections and then decreased with increasing number of injections the subjects received. This might be due to reporting bias (higher awareness of AEs after the first doses), visit frequency bias (more frequent visits and thereby opportunities to report AEs in the beginning of the long-term studies) or that subjects not tolerating the treatment are more likely to drop out from studies. However, the latter is less likely since the number of withdrawals due to injection site AEs was low.

The vast majority (98.4%) of the injection site AEs resolved, 1.4% did not resolve during the study and 1 (0.3%) was resolved with sequelae. Five subjects (0.7%) receiving CAM2038 withdrew from treatment due to any injection site AE. No injection site AEs were serious.

Spontaneously reported injection site reactions were high. Around 15% of all patients reported such events. They were mostly mild, but in some cases there were more intense. There is a difference between spontaneous reports of injection site adverse reactions for q1w and q4w: 14.6% vs 9.3%. The volume of injected fluid, expectedly, influenced the likelihood of a reaction. To clarify the possible influence of formulations on the likelihood of local adverse reaction, considering that the products are given repeatedly, following the initial list of questions, the applicant has presented the percentage of reactions per injection. They were comparable between the formulations.

Local injection site reactions – active investigation

There was no collection of solicited injection site reactions in the healthy volunteer studies or study HS-07-307.

To further investigate solicited injection site reactions based on assessment forms, the following analyses were conducted using pooled data from studies HS-13-478, HS-15-549, HS-11-421, and HS-14-499:

- ☐ Summary of injection site reactions at any visit by study; injection number; and injection location
- ☐ Worst injection site reaction at any visit by study; injection number; and injection location.

These analyses were conducted using all available data reported on the assessment forms for each study; Ns used in the analyses are based on patients with available data.

Overall, 63/487 (12.9%) patients reported 99 occurrences of injection site pain; 70/552 (12.7%) had 189 occurrences of erythema/redness; 53/552 (9.6%) had 99 occurrences of swelling/oedema; 27/487 (5.5%) had 60 occurrences of itching; 48/440 (10.9%) had 88 occurrences of tenderness; and 1/440 (0.2%) patient had a single occurrence of discharge. For each of these injection site signs/symptoms, reactions were mostly reported in the buttocks. This finding is likely a result of study 499, in which all injections were administered in the buttock (per protocol). Other injection site signs/symptoms were reported in the abdomen, arm, and thigh, but with much less frequency.

All worst cases of injection site related erythema/redness and swelling/oedema were mild or moderate in severity based on the local tolerability assessment. Across all reported injection site related pain scores, individual pain scores ranged from 1 to 10 (with higher scores indicative of greater pain) and the majority of scores were $\leq$ 7.

The numbers of local adverse reactions actively collected were also high. It is not clear how they compare with the numbers seen in spontaneous reporting.

Safety in special populations

Gender

In patients with opioid dependence, a higher percentage of CAM2038-treated women than men had at least one AE (women: 69.9% [158/226]; men: 61.4% [226/368]). This pattern was not observed for the incidence of unsolicited injection site AEs (18.1% [41/226] vs 18.2% [67/368]) or drug-related, unsolicited injection site AEs (16.8% [38/226] vs 16.6% [61/368]).

The mean number of AEs per patient-exposure-years after administration of CAM2038 was 9.6 in men and 7.7 in women.

The 2 most commonly reported PTs in women were nausea (12.8%) and urinary tract infection (11.9%); both occurred at a lower incidence in men (<5%). The incidence of headache was slightly lower in females (7.1%) than in males (11.4%), as was the incidence of injection site pain (8.4% vs 12.0%). A slightly higher percentage of CAM2038-treated women than men had injection site erythema (9.3%, vs 5.2%, males). The 1 severe unsolicited injection site AE occurred in a female patient.

The reported differences in safety of products between men and woman are minor. The significance of increased frequency of nausea and urinary tract infection between men and women is unclear. This was queried and important differenced compared to the reference product were seen.

Age

No appreciable differences were observed among the age subgroups.

One of 4 patients ≥ 65 years of age had an AE. The numbers of elderly exposed in the programme is insufficient to allow any conclusions on safety of the products in this age group.

There does not seem to be any number of patients younger than 18 involved in the development programme. A question about extrapolation of available data to these two populations was raised. The product information reflects the lack of information on the safety in elderly and paediatric populations.

Race

A higher percentage of CAM2038-treated 'White' patients than 'Black or African American' patients had at least one AE (66.9% [325/486] vs 49.5% [47/95]) or drug-related AE (32.5% [158/486] vs 17.9% [17/95]). A similar pattern was observed for the incidence of unsolicited injection site AEs (18.9% [92/486] vs 10.5% [10/95]) and drug-related, unsolicited injection site AEs (17.9% [87/486] vs 7.4% [7/95]). The mean number of AEs per patient exposure- years after administration of CAM2038 was 9.9 in 'Whites' and 2.1 in 'Black or African Americans'; the mean number of unsolicited injection site AEs per patient-exposure years was 1.5 and 0.42, respectively.

Thirty-nine (8.0%) 'White' patients had a severe AE; none of the 'Black or African American' patients had a severe event. The 2 most commonly reported PTs in 'White' patients were injection site pain (11.7%) and headache (11.3%); both occurred at a lower incidence in 'Black or African American' patients (≤ 5.3%).

Racial differences in safety have been recorded. The findings are inconclusive. The dossier does not discuss how the populations involved in the studies relate to the target European populations. This has been queried and sufficient information provided in the response.

Renal Disease

Early PK studies with IV BPN showed similar clearance in patients with normal and impaired renal function, as well as similar dose-corrected plasma concentrations of BPN (Hand 1990).

BPN has in a review been concluded to be a safe choice for pain treatment of patients with reduced renal function, chronic renal insufficiency and hemodialysis (Böger 2006). Less has been published on the use of BPN in opioid-dependent patients with renal insufficiency and a literature search resulted in only 6 articles, among which one fulfilled inclusion and exclusion criteria to be assessed as directly relevant for providing information on benefit-risk for patients with opioid dependence undergoing BPN treatment. In addition, one other relevant article was found and included in the literature set after the medical expert review.

One case report described an opioid-dependent patient with HCV developing acute hepatic and renal failure during BPN treatment, which resolved after suspension of the drug (Zuin 2009).

The observed renal effect was most likely secondary to liver toxicity, possibly caused by direct mitochondrial toxicity. A similar case report has been published in a French patient with acute hepatitis and renal failure related to intranasal BPN misuse (Eiden 2013).

In summary, in accordance with the label of the reference product and the proposed label for CAM2038, modification of the BPN dose is not generally required for patients with renal impairment (Subutex Label). Caution is recommended when dosing patients with severe renal impairment (creatinine clearance <30 mL/min), which may require dose adjustment.

It is not expected that renal safety issues additional to those recognised with oral preparations will be seen due the formulation specific properties of the proposed products.

Hepatic Disease

A literature search of hepatic insufficiency and BPN resulted in 19 publications since 2007. Of those, 6 fulfilled inclusion and exclusion criteria to be assessed as directly relevant for providing information on benefit-risk for patients with opioid dependence undergoing MAT with BPN. In addition, 5 other relevant articles were found and included in the literature set.

A number of case reports have been published of acute hepatic failure in patients with opioid dependence treated with, or misusing or abusing BPN (French 2015; Eiden 2013; Zuin 2009; Peyrière 2009). In particular, IV misuse appears to increase the risk of liver toxicity following BPN exposure.

These case reports motivated a number of large prospective studies of the effects of BPN on liver health in patients undergoing MAT for opioid dependence. A large randomized controlled trial (CTN-0027) of 340 patients randomized to BPN who completed at least 24 weeks of treatment and provided at least 4 post-baseline transaminase specimens demonstrated no evidence of liver damage (Saxon 2013). Similar results were observed in a German prospective observational follow- up study of with 181 BPN/NX-treated patients completing 12-month assessments, with 1-2% of patients having discrete elevations of liver enzymes and no patient meeting the criteria for drug-induced liver injury (Soyka 2014b). Furthermore, no increased hepatotoxicity in BPN maintained patients compared to patients undergoing short detoxification with BPN was observed in a large 52-week randomized trial of over 1000 patients in China and Thailand (Lucas 2014).

Three cohort studies examined the risk of hepatic insufficiency in opioid-dependent patients with HCV and/or HIV infection treated long-term with BPN (Tetrault 2016; Fareed 2014; Petry 2000). These publications found a higher risk of transaminase elevations in BPN-treated patients with co-infection of HCV and/or HIV, but no cases were considered to be clinically significant hepatic failure. Neither did a small study of BPN treatment in 4 patients with acute HCV and elevated liver transaminases find any signs of development of hepatic failure (Bruce 2007).

A recent study examined PK of SL BPN/NX in patients with variable degrees of hepatic impairment (Child-Pugh classes A-C), in HCV-infected patients and healthy volunteers (Nasser 2015). The study found that severe and moderate hepatic impairment significantly increased exposure of naloxone and to a lesser extent of BPN. The combination product should therefore not be used in patients with hepatic impairment. This is in line with the indication for the reference product where BPN is contraindicated in patients with severe hepatic insufficiency and should be used with caution in patients with moderate impairment (Subutex Label).

The restrictions in use for those with liver impairment are necessary. Since the proposed products are depot injections and it is not possible to withdraw them once injected section 4.4 of the SmPC has been revised to reflect the fact that the products are depot injections and any measures to minimise the risks should be taken before administration.

Pregnancy

Seven pregnancies were reported within the CAM2038 clinical program:

Four pregnancies were reported during study HS-11-421 (CSR HS-11-421):

☐ Subject No. 102-024 (CAM2038) became pregnant and lost the foetus to spontaneous abortion (reported as an SAE); no action was taken with IMP, and the subject completed the study. The investigator considered the event to be not related to the IMP.

☐ Subject No.105-006 (SL BPN/NX) became pregnant and discontinued the study due to the pregnancy. The subject declined any follow-up regarding her pregnancy; outcome of the pregnancy is unknown.

☐ Subject No. 115-006 (CAM2038) became pregnant during the study and elected to terminate the pregnancy. The subject chose to stop the IMP due to the pregnancy. The subject's last injection of CAM2038 was administered on 05-May-2016. The subject completed the study on 14-Oct-2016.

☐ Subject No. 133-009 (CAM2038) became pregnant during the study. The subject's partner (Subject No. 133-010), was also a study participant (CAM2038). The couple elected to terminate the pregnancy. No action was taken with the IMP, and both subjects completed the study.

Three pregnancies were reported during study HS-14-499:

☐ Subject No. 90-04-026 (CAM2038) had an elective abortion.

☐ Subject No. 90-06-026 (CAM2038) had an elective abortion.

☐ Subject No. 90-11-001 gave birth to a female infant who experienced an SAE of withdrawal symptoms. The subject had her last menstrual period on Day 77 and received her last dose of 128 mg CAM2038 q4w on Day 85. On Day 113, she had a positive urine pregnancy test and pregnancy was estimated to be 5 weeks gestation. On the same day, she was transitioned to standard of care consisting of 16 mg SL BPN daily dosing and her dose was tapered to 12 mg.

She elected to withdraw from study medication. The Investigator assessed the event of infant withdrawal symptoms to be moderate in intensity and not related to the IMP or procedure (the subject had withdrawn from the study more than 230 days prior to the delivery and was taking prescribed Subutex during pregnancy and at the time of delivery). For further details, see the narrative located in the CSR (CSR HS-14-499).

No studies have been conducted with CAM2038 in pregnant animals. To justify the reliance of the developmental and reproductive toxicity data described in the Subutex Label, bridging toxicokinetic studies were completed with BPN in pregnant rats and rabbits and in non-pregnant rats, and adequate margins of exposure for humans based on the exposure observed in pregnant rats and rabbits and the non-pregnant rat were shown.

Animal studies demonstrated that low doses of BPN during pregnancy and lactation lead to changes in biochemistry and protein changes (Belcheva1998), but these changes were transient and diminished a few days after birth (postnatal day 7) (Belcheva 1994). Effects on offspring behaviour and neuroanatomy was observed following exposure of BPN (Robinson 2001), The effects could be explained by parental behaviour (i.e. pup

retrieval, grooming and hovering/crouching over the pups), being impaired during the prenatal or postnatal period (Barron 1997) (reviewed by Farid 2008).

The following articles were found after a literature search on BPN and pregnancy or lactation and included after medical expert review. As reviewed by Goodman, opioid dependence during pregnancy is associated with serious adverse outcomes for the mother, the foetus, and the newborn (Goodman 2011). Use of opioids have been associated with numerous obstetrical complications including intrauterine growth restriction, placental abruption, preterm delivery, oligohydramnios, stillbirth, and maternal death (Stover 2015). Pregnant, opiate-dependent women experience a 6-fold increase in maternal obstetric complications such as third trimester bleeding, and foetal complications such as low birth weight, toxaemia, malpresentation, puerperal morbidity, foetal distress and meconium aspiration (Minozzi 2013). Neonatal complications include narcotic withdrawal, postnatal growth deficiency, microcephaly, neurobehavioral problems, increased neonatal mortality and a 74-fold increase in sudden infant death syndrome (Minozzi 2013). Intravenous drug use places pregnant women at additional risk from blood-borne disease, endocarditis, needle-site abscesses, and deep vein thrombosis (Goodman 2011).

Publications on PK of BPN in pregnant women suggest that upward dose adjustments may be needed with advancing gestation (Kacinko 2009; Concheiro 2011; Bastian 2017). On the other hand, BPN (Minozzi 2013) as well as methadone and heroin are known to cross the placenta (Serra 2016) and affect placenta as well as foetus.

A PK study by Concheiro 2010 showed statistically significant correlations between mean maternal daily dose of BPN and placenta BPN-glucuronide, as well as for norBPN-glucuronide concentrations and time to onset as well as duration of neonatal abstinence syndrome). In addition, norBPN/norBPN-glucuronide ratio correlated with and maximum NAS score, and newborn length. In another PK study by Kacinko 2008, free and total BPN and norBPN, nicotine, opiates, cocaine, benzodiazepines, and metabolites were quantified in meconium from 10 infants born to women who had received BPN during pregnancy. Neither cumulative nor total third-trimester maternal BPN dose predicted meconium concentrations or neonatal outcomes.

However, total BPN meconium concentrations and BPN/norBPN ratios were significantly related to NAS scores >4. Furthermore, as free BPN concentration and percentage free BPN increased, head circumference decreased. Time of last drug use and frequency of use during the third trimester were important factors associated with drug-positive meconium specimens (Kacinko 2008).

A prospective observational cohort study (Chavan 2017) followed pregnant women receiving BPN for MAT of opioid use disorders. Data on NAS was available for 55 patients. The incidence of NAS was 34.5% (n=19). The occurrence of NAS was not related to the BPN dose used for MAT.

A registry study (Wurst 2016) investigated adverse birth outcomes observed with BPN or methadone treatment compared to the general population. Pregnant women and their corresponding births during 2005-2011 were identified in the Swedish Medical Birth Register.

746,257 pregnancies among 538,178 women resulted in 746,485 live births. No stillbirths or neonatal/infant deaths occurred among the 194 women treated with BPN or methadone. NAS developed in 23.3% of infants born to mothers treated with BPN and in 38.5% of infants born to mothers treated with methadone. The frequency of the selected adverse birth outcomes assessed in women treated with BPN as compared to the general population was not significantly different. In addition, a retrospective cohort study investigated whether infant gender influences the course of NAS following exposure to BPN during pregnancy. Maternal and infant data were collected for 46 male and 44 female infants born to women enrolled in a BPN treatment program. Male

infants experienced more severe NAS with a higher mean peak NAS score (10.04 vs. 7.98, p=0.028) and were more likely to require pharmacologic treatment for NAS (39.1% vs. 11.4%, p=0.005) (O'Connor 2013).

A Cochrane review (Minozzi 2013) found 4 studies with 271 pregnant women. Three compared methadone with BPN and one methadone with oral slow-release morphine. The drop-out rate from treatment was lower in the methadone group than in the BPN group (RR: 0.64, 95% CI: 0.41 to 1.01). The birth weight was higher in the BPN group in two studies, while a third study reported that there was no statistically significant difference. No significant difference between methadone and BPN was found for APGAR. The number of newborns treated for NAS did not differ significantly between groups. Only one study compared methadone- with BPN-reported side effects. For the mother, there was no statistically significant difference; for the newborns there were significantly fewer serious side effects in the BPN group. The authors conclude that while methadone seems superior in terms of retaining patients in treatment, BPN seems to lead to less severe NAS, but there is still a need for randomised controlled studies of adequate sample size comparing different maintenance treatments.

In summary, there are not sufficient adequate data from the use of BPN in pregnant women and BPN should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus (Subutex Label).

There were few pregnancies recorded during the development programme. The additional information has been supplied from the published literature. It is agreed that important additional safety issues will not be seen due the formulation specific properties of the products. The precautions applicable to the oral formulations should be sufficient for the proposed products.

Lactation

No data on exposure to CAM2038 are available for lactating women (one woman receiving SL BPN/NX in study HS-11-421 had a baby but declined to be contacted and one woman receiving CAM2038 in study HS-14-499 had a baby but stopped IMP >230 days before birth).

BPN appears to transfer to human milk through diffusion, and the ratio of BPN concentration in breast milk to maternal serum (milk/plasma ratio) is approximately 1 (Goodman 2011). Levels in breast milk fluctuate with duration of time after maternal BPN dose. Because of the limited bioavailability of BPN orally, the amount of drug actually absorbed by the breastfed infant is assumed to be one-fifth to one-tenth of the dose present in breast milk. Because newborns who have been exposed to BPN in utero are habituated to much higher transplacental doses of BPN, limited exposure from breastfeeding is unlikely to cause adverse effects in those children. Low levels of BPN in breast milk are also unlikely to alleviate neonatal abstinence. Although symptoms consistent with NAS have been reported in infants after abrupt discontinuation of breastfeeding by mothers taking methadone, this phenomenon has not been observed in breastfed infants of mothers taking BPN.

One study has investigated the transfer of BPN and its main active metabolite, nor BPN, into human milk in 7 lactating women as well as the drug dose and effects in 6 exposed infants (Lindemalm et al. 2009). BPN and norBPN were found in low levels in the infants' urine and the authors conclude that the data support the use of BPN during breastfeeding and recommend that infants should be monitored closely.

The proposed SmPC initially advised discontinuation of breast-feeding while on treatment with the proposed products. Following further consideration this has been downgraded to a warning.

Immunological events

No immunological events were reported in the dossier.

Safety related to drug-drug interactions and other interactions

Smoking

There are no published studies indicating that smoking affects the outcome of BPN treatment of opioid dependence. However, smoking as a use disorder is exceptionally common in the opioid dependent population, and for instance, 88-95% of pregnant women receiving MAT smoke cigarettes (reviewed in Akerman 2015). There is a medical need for smoking cessation in particular in this subgroup of patients with opioid dependence and a number of studies have therefore focused on this (reviewed in Akerman 2015).

Alcohol

Alcohol use is very common among patients with opioid dependence and is potentially associated with significant morbidity and mortality, primarily as there is a risk for an additive effect on respiratory depression (reviewed in Nolan 2016). Another review indicated that up to one third of patients with opioid dependence has a dual diagnosis of alcohol use disorder, which might be a long-term risk factor for worse clinical outcome and can cause poor physical and mental health, including liver disorders, noncompliance, social deterioration and increased mortality risk (Soyka 2015).

In the label of the reference product and the proposed label for CAM2038, BPN should not be taken together with alcohol and is contraindicated in patients with concomitant acute alcoholism or delirium tremens (Subutex Label).

The restrictions on use of alcohol during the treatment are acceptable.

Benzodiazepines

A literature search of drug interactions and BPN resulted in 71 publications since 2007. Of those 24 fulfilled inclusion and exclusion criteria to be assessed as directly relevant for providing information on benefit-risk for patients with opioid dependence undergoing MAT with BPN. In addition, 3 other relevant articles were found and included in the literature set after medical expert review.

Benzodiazepines have not been reported to influence BPN exposure or PK profile and the drug interaction at therapeutic doses appears to be a PD response in exacerbation of primarily the effects on sedation and depression of the respiratory and central nervous system (reviewed in Lintzeris 2010). Benzodiazepine use is very common in patients with opioid dependence and is thought to contribute to a large part of the fatal overdoses with BPN (reviewed in Jones 2012).

Although there is a warning for concomitant benzodiazepine use in the label of the reference product (Subutex Label) as well as for other opioid agonists used for MAT, co-prescriptions appear to be common and contributing to the mortality in this patient population indicating a need for further education about the risks of respiratory depression with concomitant use of these medications (Abrahamsson 2017). There is a warning against concomitant use of benzodiazepines in the proposed label of CAM2038.

The restrictions on use of benzodiazepines during the treatment are acceptable.

CYP3A4 Inducers or Inhibitors

BPN is a substrate of CYP3A4 and inhibitors of this enzyme (e.g. protease inhibitors like ritonavir, nelfinavir or indinavir, or azole antifungals such as ketoconazole and itraconazole, or macrolide antibiotics) might therefore increase BPN plasma concentrations, while CYP3A4 inducers (e.g. phenobarbital, carbamazepine, phenytoin or rifampicin) might decrease BPN plasma concentrations. In the label of the reference product, these drug-drug

interactions are mentioned and Subutex should be used cautiously together with these medications (Subutex Label).

PK modelling after co-administration of the strong CYP3A4 inhibitor ketoconazole was predicted to increase the exposure by 35% for CAM2038 q1w and by 34% CAM2038 q4w. Also, the strong CYP3A4 inducer rifampicin was predicted to decrease the exposure by 26% for both CAM2038 q1w and CAM2038 q4w. These results suggest a lack of clinically meaningful drug-drug interactions when CAM2038 is co-administered with CYP3A4 inhibitor or inducer (Liu published manuscript).

The appropriate warnings regarding the use of CYP3A4 have been included in the SmPC. Buprenorphine is a substrate of CYP3A4. The potential for interactions is well described. Due to lack of first-pass effect for CAM2038, the magnitude of drug interaction with a CYP 3A4 inhibitor or inducer may be less for CAM2038 in comparison to SL buprenorphine products. The applicant has discussed the impact of switching between SL BPN and SC CAM2083 and transitioning between weekly and monthly CAM2083 in subjects who are being treated with CYP3A4 inducers or inhibitors in their responses to the initial list of questions.

Cocaine

The literature safety search on drug-drug interactions with BPN identified two articles examining the effect of cocaine use on BPN plasma exposure in patients with opioid dependence. One study in patients treated with BPN/NX did not find any effect of cocaine on BPN plasma exposure (Tetrault 2015), while the other study indicates that cocaine use might lower BPN plasma concentrations (McCance-Katz 2010).

Codeine

The literature safety search on drug-drug interactions with BPN identified one article examining the effect of codeine on BPN exposure without finding any clinically relevant effect on PK (Gelston 2012).

Product information does not contain sufficient warnings against the concomitant abuse of drugs. The applicant should review the PI and include appropriate warnings in both the SmPC and the PIL.

Drug Interactions with Antiviral Drugs

The majority of the articles identified in the literature safety search examine interactions between BPN and antiviral medications, mainly for treatment of HIV or HCV.

Studies of the 3 direct-acting (3D) antiviral regimen containing ombitasvir, paritaprevir, ritonavir and dasabuvir, with and without ribavirin did not identify any clinically relevant effects on PK of BPN (King 2017; Menon 2015).

Studies of boceprevir (Hulskotte 2015), faldaprevir (Joseph 2015), daclatasvir (Garimella 2015), elvitegravir/cobicistat (Bruce 2013b), raltegravir (Bruce 2013c), telaprevir (Luo 2012), darunavir-ritonavir (Gruber 2012; Sekar 2011), fosamprenavir-ritonavir (Gruber 2012), atazanavir (Vergara-Rodriguez 2011), lopinavir-ritonavir (Bruce 2010), didanosine, lamivudine, and tenofovir (Baker 2010), nevirapine (McCance-Katz 2010), efavirenz, delavirdine, nelfinavir and ritonavir (Moody 2009) did not identify any clinically relevant effects on BPN PK at therapeutic doses.

One study has found that treatment with rifampin, but not rifabutin, might require a higher BPN dose (McCance-Katz 2011).

Two studies have found that tipranavir/ritonavir might require higher BPN doses (Bruce 2011; Bruce 2009).

One study has found that BPN treatment might influence the plasma concentrations of opinavirritonavir (Moody 2009). Another study has reported that atazanavir or atazanavir/ritonavir may influence BPN PK and that a decreased BPN dose might be required (McCance-Katz 2007).

Monoamine Oxidase Inhibitors

The UK Subutex label states that the product should be taken cautiously together with monoamine oxidase inhibitors (MAOI) due to a possible exacerbation of the effects of opioids, based on experience with morphine. In the literature, there is one case report of a case of serotonergic syndrome triggered by BPN/NX for opioid dependence (Isenberg 2008).

Overdose, Dependence, Withdrawal and Abuse

Overdose

An overdose of BPN causes a typical opioid toxidrome of miosis, respiratory depression, sedation, and hypotension (Milne 2009). Compared with the full mu-opioid agonist methadone, the partial-agonist properties of BPN with a potential “ceiling effect” on respiratory depression in many patients has obvious benefits for tolerability as well as for accidental or intentional overdose. The mortality due to overdoses with BPN is consequently lower than for methadone for patients retained in treatment (Marteau 2015; Kimber 2015).

Several studies have shown that almost all cases of SL BPN overdosing have been reported to involve concomitant intake of benzodiazepines (Lintzeris 2010; Jones 2012).

Compared to current standard treatment, the administration of SC CAM2038 by health care professionals in combination with the prolonged BPN release with less fluctuations and more stable BPN levels as well as a rapid and sustained blockade of the effects of exogenously administered opioids are expected to protect patients from illicit opioid use and potentially result in fewer occurrences of opioid overdoses.

Withdrawal

Symptoms of drug withdrawal (e.g. insomnia, headache, nausea, hyperhidrosis, tremor and pain) constitute a known pharmacological class effect of opioids after suboptimal dosing and patients should therefore be monitored for these symptoms to limit the risk of relapse (Subutex Label).

For BPN, as a partial opioid receptor agonist, there is a risk of precipitating withdrawal during the initiation of the treatment, and to avoid this, inductions should be undertaken when objective signs and symptoms of mild to moderate withdrawal are evident (Subutex Label). There have been no literature reports on withdrawal changing the risk profile since approval of the reference product.

BPN has been used for treatment of opioid withdrawal (reviewed in Gowing 2017). This is not the proposed indication for CAM2038 or the reference product Subutex, therefore, the literature on this off-label use is not described here. There are nevertheless no safety signals affecting the benefit-risk profile of the reference product based on the use of BPN in treatment of opioid withdrawal.

Rebound has not been specifically studied with CAM2038 and no relevant literature on rebound has been identified.

Abuse

Current self-administered opioid substitution regimens are associated with several issues including e.g. misuse and abuse. In the EQUATOR survey, 25% of the respondents who had misused their opioid maintenance

pharmacotherapy (Fischer 2012). Oral BPN misuse has been reported through crushing of the tablets followed by IV injection (Soyka 2013; Alho 2015; Uosukainen 2013). The addition of NX to BPN to deter parenteral misuse did not abolish diversion and the combination product is also misused (Alho 2015; Larance 2016).

A large number of studies report substantial diversion of prescribed methadone and BPN (Yokell 2011; Lofwall 2014; Launonen 2015; Reimer 2016). The exact prevalence of diversion is difficult to assess but surveys indicate that diversion over a period of 1 month in certain settings might be over 10% (Bleckwenn 2016) or even over 20% (Johnson 2015).

In summary, BPN is subject to misuse, abuse and diversion, similar to other opioids, legal or illicit. However, as administration of CAM2038 is restricted to healthcare professionals, there is no potential for intentional misuse, abuse or diversion.

The information provided in the dossier is sufficient. The issue of particular concern is the misuse of prescribed psychotropic medicines and drugs of abuse during the treatment. The warnings regarding this are not sufficient in the product literature at the moment, and this will need to be addressed. The appropriate RMP measures are also necessary to address these concerns.

Administration of CAM2038 is restricted to healthcare professionals. However, the condition of drug dispensing should be defined by national authorities. The risk of abuse, diversion and the potential for subsequent misuse of a prefilled syringe (i.e. intravenous injection of CAM2038) has been further discussed by the applicant. To limit the potential for diversion CAM2083 should be dispensed directly to the healthcare provider for administration by the healthcare provider to the patient. There was no evidence of attempts to extract CAM2038 following injection. A warning regarding the potential for diversion, misuse and abuse has been included in section 4.4 of the SmPC.

Long Term Safety

The primary objective of study HS-14-499 was to demonstrate the safety and tolerability of CAM2038 in 48-week BPN treatment in adult outpatients with opioid use disorder.

In this study, the Full Exposure Safety Population was defined as all patients who completed scheduled visits for Week 48 and received their last injection (N=156). Mean duration of exposure to IMP was 48.1 (SD: 0.37) weeks (range: 46.9-49.9 weeks).

In the Full Exposure Safety Population, 103 (66.0%) patients experienced at least 1 AE; 30 (19.2%) had at least 1 injection site AE and 96 (61.5%) had at least 1 non-injection site AE. 42 (26.9%) patients had at least 1 ADR (19.2%, injection site AE; 11.5%, non-injection site AE). 12 (7.7%) patients had at least 1 severe AE; all of the severe AEs were non-injection site events.

Nine (5.8%) patients in the Full Exposure Safety Population experienced at least 1 SAE; none were related to the IMP or occurred at the injection site. Eight (5.1%) patients were hospitalised.

None of the patients in the Full Exposure Safety Population withdrew from treatment due to an AE; 4 were lost to follow-up.

Overall AE incidence in the Full Exposure Safety population was higher in patients who were receiving SL BPN/NX at entry (74.2%) compared to patients who were new to BPN treatment (28.6%), as was the incidence of injection site AEs (22.7% vs 3.6%) and non-injection site AEs (68.8% vs 28.6%). The incidence of severe AEs

was higher in patients who were receiving SL BPN/NX at entry (8.6% vs 3.6%), as was the incidence of SAEs (6.3% vs 3.6%).

In the Full Exposure Safety population, the most common (≥ 5%) AEs were injection site pain (14.7%), injection site swelling (12.8%), nasopharyngitis (10.3%), nausea (9.6%), injection site erythema (9.0%), headache (7.7%), vomiting (7.7%), urinary tract infection (5.8%), diarrhoea (5.1%), migraine (5.1%), pain in extremity (5.1%), and hypertension (5.1%).

Twelve (7.7%) patients had at least 1 severe AE, all of which were non-injection site events.

In the Full Exposure population, 4 (1.8%) patients had at least 1 laboratory-related TEAE. None of the laboratory AEs were serious, severe in intensity, or related to IMP, and no laboratory AEs led to discontinuation of IMP. None of the patients met the criteria for Hy's Law.

In the Full Exposure population, 2 patients had an ECG-related AE: mild myocardial ischaemia (1 patient) and severe ventricular tachycardia (1 patient). None of the ECG-related AEs were related to the IMP. None of the vital signs or C-SSRS results indicated any clinically meaningful concerns.

In the Full Exposure population, 2 pregnancies occurred during the study; outcome was reported as elective abortion (2 patients).

In conclusion, with the exception of injection site AEs, the long-term safety profile observed with CAM2038 was consistent with the known systemic safety profile of BPN. No unexpected AEs were observed. All injection site AEs associated with CAM2038, except one, were mild to moderate in intensity and rarely led to discontinuation of IMP.

The long term open label study lasted 48 instead of 52 weeks, which is closer to 11 rather than 12 months. This does not conform to the ICH requirements for investigation of long term safety.

2.8.10. Discussion on clinical safety

The safety specification of CAM2038 as presented in the dossier is based on the established safety profile of BPN (including Subutex as reference product) and the safety profile observed in the clinical studies.

Safety of the products is similar to the safety of oral buprenorphine products with the exception of injection site reactions, which were frequent. In that respect the safety of the products can be regarded as inferior to the safety of oral buprenorphine products.

From the provided information, it appears that the safety of q1w is somewhat inferior to safety of q4w. This is primarily since q1w requires higher number of injections than q4w for the same period of time. Some other adverse reactions also appear in dose related manner with q1w and not with q4w, especially constipation. None of these differences constitutes a major concern.

Overall exposure to CAM2038 in terms of numbers treated and duration of exposure up to 48 weeks is limited across the various dosing levels of both the q1w and q4w regimens; this is reflected in the SmPC.

The products have not been investigated in those 16 to 18 years of age and those older than 66.

The safety record gives only a limited amount of data on direct comparison of the safety of the proposed products to that of the licensed oral buprenorphine products. It is not possible to establish from the reported safety record if the relatively constant exposure to buprenorphine provided by CAM2038 introduces safety related issues compared to the known profile of the oral products, other than local injection site reactions.

2.8.11. Conclusions on clinical safety

The safety of Buvidal in the proposed indication has been sufficiently demonstrated.

2.9. Risk Management Plan

Safety Concerns

Table 37: - Summary of Safety concerns

Important identified risks	Injection site reactions Use in patients with severe respiratory insufficiency Use in patients with severe hepatic impairment Use in patients with acute alcoholism or delirium tremens Abuse and misuse Withdrawal reactions in opioid-dependent patients Concomitant use of other medications (Cytochrome P 3A4 [CYP3A4] inhibitors; benzodiazepines; other central nervous system depressants; and monoamine oxidase inhibitors [MAOI]) Overdose
Important potential risks	Intravascular injection Medication error Use in patients with various disease states (renal impairment; head injuries; increased intracranial pressure; hypotension; prostatic hypertrophy; and urethral stenosis) Concomitant use of gabapentinoids
Missing information	Use in pregnancy

Pharmacovigilance plan

N/A

Risk minimisation measures

Table 38: - Summary of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Injection site reactions	Routine risk minimisation measures: *SmPC section 6.6 and PL Instructions for use* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with severe respiratory insufficiency	Routine risk minimisation measures: *SmPC sections 4.3 and 4.4* *PL sections 2 and 4* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with severe hepatic impairment	Routine risk minimisation measures: *SmPC sections 4.3 and 4.4* *PL section 2* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with acute alcoholism or delirium tremens	Routine risk minimisation measures: *SmPC sections 4.3 and 4.5* *PL section 2* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Abuse and misuse	Routine risk minimisation measures: *SmPC sections 4.2 and 4.4* Legal status: *The product is being submitted under*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	special medical prescription in accordance with Article 71 of Directive 2001/83/EC. Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Withdrawal reactions in opioid-dependent patients	Routine risk minimisation measures: *SmPC section4.4* *PL section 2* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Concomitant use of other medications (Cytochrome P 3A4 [CYP3A4] inhibitors; benzodiazepines; other central nervous system depressants; and monoamine oxidase inhibitors [MAOI])	Routine risk minimisation measures: *SmPC sections 4.4 and 4.5* *PL section 2* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Overdose	Routine risk minimisation measures: *SmPC sections 4.4, 4.5 and 4.9* *PL sections 2 and 4* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Intravascular injection	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, and 6.6* *PL Instructions for use* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Medication error	Routine risk minimisation measures: *SmPC sections 4.2 and 4.4*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL section 3 Other routine risk minimisation measures beyond the Product Information: The product is intended to be administered by healthcare professionals only. The secondary packaging for weekly and monthly products will be in different colours. In addition, the different doses will be differentiated by different colours on the secondary packaging. Additional risk minimisation measures: None	detection: None Additional pharmacovigilance activities: None
Use in patients with various disease states (renal impairment; head injuries; increased intracranial pressure; hypotension; prostatic hypertrophy; and urethral stenosis)	Routine risk minimisation measures: *SmPC sections 4.2 and 4.4* *PL section 2* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Concomitant use of gabapentinoids	Routine risk minimisation measures: *SmPC sections 4.4 and 4.5* *PL section 2* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in pregnancy	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.10. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

There were at least 7585 overdose deaths reported in Europe in 2014 and in over 80% of those, illicit opioids (in particular heroin) were present. This is underpinned by a trend of increasing overdose deaths from methadone and potent synthetic opioids, like fentanyl, as shown by recent statistics from the UK and Scandinavia. This may also be related to poor adherence to current daily MAT, with continued on-top use of illicit opioids and other drugs, as well as to diversion and misuse of methadone, morphine and BPN-based medication.

Use of injected drugs is a major risk factor for the acquisition and transmission of HIV, and about 5-10% of HIV infections are attributable to injecting drug use worldwide. Transmission of HIV between people who inject drugs is predominantly a result of the sharing of contaminated injecting equipment, but also sexual transmission, both

of which are influenced by wider structural and environmental factors such as housing, patterns of drug use and commercial sex work. The prevalence of HCV in drug users is also very high and estimated to be 40-80% in many European countries.

4.1.2. Available therapies and unmet medical need

Currently available treatment options for opioid dependence vary between countries, with the full opioid mu (μ) opioid receptor (MOR) agonist methadone being used in 63%, buprenorphine (BPN)-based medications in 35% and other pharmaceutical drugs in 2% of patients in Europe. Besides methadone and BPN (with or without naloxone [NX]), other medicinal products for medication-assisted treatment (MAT) in Europe are the full MOR agonists slow-release oral morphine and supervised injectable heroin. There are several issues with currently available daily MAT:

• Need for daily, often supervised, dosing resulting in inconvenience, stigma and reduced quality of life for patients as well as burdens on the healthcare system

• Poor treatment adherence including continued use of illicit opioids and limited retention in treatment

• Misuse, abuse, diversion and paediatric exposure

• Safety concerns including respiratory depression, overdosing and cardiac events

Several of these shortcomings are likely to contribute to health problems, the social burden on the patient, their relatives and the society, as well as criminality.

There is no prolonged release form of buprenorphine available in the EU for the treatment of opioid addiction.

4.1.3. Main clinical studies

Study HS-11-421, the pivotal study, was a phase 3 randomised, double-blind, active-controlled, parallel group, multi-centre study designed to evaluate the non-inferiority of CAM2038 compared to an existing standard of care (SL BPN/NX) in initiation and maintenance treatment with Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038). The study involved 4 phases: Screening (3 weeks), Phase 1 (12 treatment weeks), Phase 2 (12 treatment weeks), and Follow-up (4 weeks).

Male and female subjects 18-75 years of age were recruited on the basis of primary diagnosis of moderate or severe opioid use disorder (DSM-5, that includes 11 symptoms, with moderate disorder if 4-5 symptoms) or severe disorder if > 6 symptoms). Also, subjects were excluded from the study if they had received medication-assisted treatment for opioid use disorder within 60 days prior to randomisation.

This study was conducted in the US only. Approximately 380 subjects (190 subjects per arm) were planned for study participation. A total of 428 subjects were randomized into the study (215, SL BPN/NX; 213, CAM2038).

Following Screening and confirmation of eligibility, patients were randomized to one of two treatment groups in a 1:1 ratio:

- Group 1: SL BPN/NX tablets + placebo SC injections
- Group 2: CAM2038 SC injections + SL placebo tablets

Randomized patients underwent initiation of BPN treatment with either SL BPN/NX or SC CAM2038 q1w and participated in weekly visits for 12 weeks (Phase 1). All patients received an open-label dose of active 4mg of BPN on Day 1 to test tolerability. Then patients received either active or matching placebo as follow:

- an additional 4 mg SL BPN/NX (SL placebo in the CAM2038 group) was given on Day 1 with 0.32 mL SC placebo CAM2038 (16mg SC CAM2038 q1w in the CAM2038 group)

- 16 mg SL BPN/NX on Days 2 and 3 (SL placebo in the CAM2038 group)

- 16 mg SL BPN/NX and an SC injection of 0.16 mL placebo CAM2038 on Day 4 (16 mg SL placebo and 8 mg SC CAM2038 q1w in the CAM2038 group)

- and 16 to 24 mg SL BPN/NX with an optional SC injection of 16 mL of placebo CAM2038 on Days 5 to 7 (16 to 24 mg SL placebo with an optional SC injection of 8 mg of CAM2038 q1w in the CAM2038 group).

On the first day of Week 2 (i.e., Day 8), subjects received a CAM2038 SC injection (24 mg or 32 mg CAM2038 q1w, or 0.48 mL or 0.64 mL CAM2038 placebo), based on total dose given by end of Week 1/Day 7. Subjects were also provided with one-week take-home SL BPN/NX / placebo (16 mg or 24 mg SL BPN/NX / placebo), based on total daily dose established at end of Week 1/Day 7.

After Week 12, patients were transitioned to Phase 2 with monthly visits. During Phase 2, patients in Group 1 continued treatment with monthly dispensing of daily SL BPN/NX and monthly placebo SC injections, and patients in Group 2 (receiving CAM2038 q1w) were transferred to monthly injections of CAM2038 q4w and monthly dispensing of daily SL placebo. Patients participated in 6 visits during the 12 weeks of Phase 2; 3 scheduled monthly visits and 3 random urine toxicology visits. At each visit, efficacy and safety outcome measures were assessed.

Data for the efficacy study are supported by **study HS-14-499,** An Open-Label Multicenter Study Assessing the Long-Term Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injection Depot of Buprenorphine (CAM2038) in Adult Outpatients with Opioid Use Disorder. The subject population was the same as for the pivotal study, male or female of 18-65 years of age with moderate to severe opioid use disorder but this time subjects seeking treatment *as well as subjects already on SL BPN* were included. This study was conducted in the US and in centre in Europe.

Subjects received CAM2038 treatment for up to 12 months (48 weeks) during the study:

• For subjects who were not receiving SL BPN or SL BPN/NX at entry, treatment was initiated with a single CAM2038 q1w 16 mg SC injection (following a 4 mg SL BPN/NX test dose); additional dose adjustments were allowed up to maximum weekly dose of 40 mg (the maximum weekly dose was increased from 32 to 40 mg in Protocol Amendment 2).

• Subjects who were receiving SL BPN or SL BPN/NX at entry transitioned to CAM2038 q1w or q4w SC injections according to their current dose of SL BPN or SL BPN/NX. Subjects were advised not to take their ordinary SL BPN (or BPN/NX) tablet(s) on Day 1 (i.e., the last dose of SL BPN [or BPN/NX] was taken on the day before dosing with CAM2038 q1w or CAM2038 q4w).

Subjects transitioned to CAM2038 q1w could return to the clinic for additional titration with CAM2038 q1w (8 mg SC supplemental injections), as needed, up to a maximum weekly dose of 40 mg per week. At any visit, the investigator could transition patients from q1w to q4w.

265 subjects were screened for the study, and 228 subjects were enrolled. One subject refused to be dosed and withdrew consent prior to receiving the first dose of CAM2038, and 227 subjects received at least one dose of

CAM2038. Of these, 190 subjects were receiving SL BPN (either SL BPN or SL BPN/NX) at entry and 37 were new to BPN treatment.

PD variables evaluated in the phase 2 studies concur with the results from the two studies mentioned above.

4.2. Favourable effects

This application is made under article 10.3 of the Directive 2001/83/EC, amended with reference to Subutex. These new depot formulations would allow to increase the choice of administration of buprenorphine for the treatment of opioid addition in adults with a weekly and monthly injection.

Therefore, the pivotal study is study HS-11-421, a phase 3, double-blind, active-controlled parallel-group with Suboxone as comparator, which is acceptable.

The non-inferiority study HS-11-421 is pivotal as it is a randomised double-blind comparison to the Suboxone. The primary endpoint prespecified in the SAP for these applications is the percentage of urine samples negative for illicit opioids based on the 18 urine samples obtained during the post-induction period. 35.1% in the CAM2038 had a negative urine test by the end of the treatment period compared to only 28.4% in the control group (ITT population). The difference between treatment groups is of 6.7% (95% CI: -0.1-13.6) with the lower end of the 95% CI close to 0 and well above - 11%. The same analysis without imputed data provides a 8.7% difference between treatments with a 95% CI of 0.9-16.4. Treatment difference also favoured CAM2038 when looking at:

- presence or not of other drugs of abuse at baseline

- injection of opioids

- heroin use at initiation

There was no effect of gender on the primary endpoint. Non-inferiority to Suboxone was demonstrated for CAM2038 and also for CAM2038 q4w, with additional statistical superiority for the q4w only.

For CDF of percentage of urine samples negative over weeks 5-25 i.e. with grace period, without subjects' self-reported opioid use, the median CDF was 26.7% for CAM2038 and 6.7% for SL BPN/NX with a treatment difference of 20% (p = 0.008).

Retention rate - Including the 4 weeks of study follow-up, 56.8% (121/213) of the CAM2038 and 58.6% (126/215) of the SL BPN/NX patients finished the entire study; the proportion difference between treatment groups was -1.8 (95% CI: -11.2%, 7.6%), and the CAM2038 group achieved non-inferiority in retention rates compared to the SL BPN/NX group (P = 0.006; non-inferiority margin of 15%).

Time to Sustained Abstinence of Opioid Use - 18.31% (39/213) in the CAM2038 group and 13.95% (30/215) of the SL BPN/NX patients had sustained abstinence of opioid use, with no statistical difference between the two groups (survival analysis p-value=0.221, log-rank).

Desire/need to use and withdrawal symptoms decreased with time and no difference was seen between groups. There was no statistical difference between study groups for the use of barbiturates, amphetamine, phencyclidine or marijuana at any time point.

At Week 25, the percentage of subjects in the CAM2038 group with negative urine samples was 32.9% compared to the SL BPN/NX group (24.2%) with an overall proportion difference overall was 8.4% (95% CI:

1.1%, 15.6%) with the following times points favouring the CAM2038 group over the SL BPN/NX group: Weeks 7, 10, 11, 12, 17, and 25.

This is supported by the results of the long-term open-label safety and efficacy study HS-14-499. In patients who were receiving SL BPN at entry, the percentage of negative urine samples increased from 78.8% at baseline to 84.0% at Week 48 (similar results were obtained with self-reports).

In patients who were new to BPN treatment (of whom 100% reported heroin use at screening), the percentage urine samples negative for illicit opioids increased from 0.0% at baseline to 63.0% at Week 48.

Positive results are found in the phase 2 supportive studies.

4.3. Uncertainties and limitations about favourable effects

The applicant has withdrawn the 160mg strength and conversion tables are available for patients not already taking SL BPN and for patients on maintenance SL BPN for a dose up to 24mg.

A test dose is requested in the product information for patients not already receiving SL BPN.

No specific dosing recommendation is required for patients with moderate OUD, patients totally new to BPN treatment and patients with OUD related to pain relievers.

Further advice is given in the product information for concurrent pain relief or the possibility to extract the CAM2038 depot once injected.

4.4. Unfavourable effects

The safety profile of the active substance is relatively well known. The applicant is not proposing that any of the known unfavourable effects of buprenorphine would be improved by the use of their products.

A total of 132 patients were exposed to CAM2038 over 48 weeks. 42 patients received CAM2038 q1w over the entire 48-week period, 45 patients received CAM2038 q4w over the entire 48-week period and the remaining patients were transitioned between CAM2038 q1w and CAM2038 q4w, or vice versa, over 48 weeks of treatment in study HS-14-499.

Only 7 patients were exposed to weekly doses for at least 48 weeks and 22 patients were exposed to any dose in the q4w regimen for 48 weeks never changed dose. The ICH guideline on extent of population exposure recommends 100 patients exposed for a minimum of one-year at dosage levels intended for clinical use to support long term safety. Although this criterion is met in terms of overall exposure, exposure in terms of numbers treated and duration of exposure up to 48 weeks is limited across the various dosing levels of both the q1w and q4w regimens. Subjects were allowed to switch between the regimens and between different dose levels. Supplemental SC injections of CAM2038 q1w 8 mg were also permitted at the discretion of the Investigator.

Due to method of administration, the main recognised safety issue for the proposed products relates to injection site reactions.

Across all studies, 118 subjects (16.2%) receiving CAM2038 reported a total of 385 unsolicited injection site AEs. The mean number of injection site AEs per injection was low (0.04) and the mean number of injection site AEs per subject-exposure-year was 1.4. In line with most injection site AEs by nature being treatment-related, 109 subjects (15.0%) had any injection site ADR.

The most commonly reported injection site AEs were injection site pain (9.3% of subjects), injection site erythema (5.5%) and injection site swelling (5.5%). A majority of the injection site AEs were of mild (78.7%) or moderate (21.0%) intensity. One injection site AE (0.3%), a transient event of injection site pain, was of severe intensity.

The percentage of subjects with any injection site AE was 14.6% for CAM2038 q1w and 9.3% for CAM2038 q4w. There was a trend of increasing number of injection site AEs with increasing dose for both CAM2038 q1w (from 2.7% at 8 mg to 18.3% at 32 mg) and CAM2038 q4w (from 4.5% at 64 mg to 11.1% at 160 mg). Overall, the percentage of subjects reporting any unsolicited injection site AE increased with increasing volume, from 2.9% after injection volumes of <0.27 mL to 13.7% after injection volumes of 0.45-0.64 mL. The increase in number of injection site AEs with increasing dose within the respective regimen (i.e. CAM2038 q1w and CAM2038 q4w) is, to a large extent, likely to result from the larger injection volume at higher dose levels.

The highest rate of injection site AEs was observed after the first 5 injections and then decreased with increasing number of injections the subjects received.

Overall, 63/487 (12.9%) patients reported 99 occurrences of injection site pain; 70/552 (12.7%) had 189 occurrences of erythema/redness; 53/552 (9.6%) had 99 occurrences of swelling/edema; 27/487 (5.5%) had 60 occurrences of itching; 48/440 (10.9%) had 88 occurrences of tenderness; and 1/440 (0.2%) patient had a single occurrence of discharge.

The two formulations q1w and q4w have somewhat different safety profiles but this difference is not regarded to be of clinical importance.

4.5. Uncertainties and limitations about unfavourable effects

There is limited exposure to all doses over the longer term.

There is no data on safety in those older than 66 and those younger than 18.

There is no substantial data on safety in pregnancy and lactation.

4.6. Effects Table

Table 39. Effects Table for X 8/16/24/32/64/96/128/160 mg prolonged release solution for injection in the treatment of opioid addition in adults

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
% NUS	Negative urine sample Week2 to Week25 – imputed data	%	35.1	28.4	Maximum dose in the control group not accepted	N/A
% NUS	Negative urine sample Week2 to Week25 – No imputation	%	44.6	35.9	Also, imputation method not described	N/A

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
CDF	Cumulated Distribution Function Week5 to Week25	% (median)	36.7	6.7	Supported by CDF Week 2 to Week25	N/A
Retention rate	Retention in study	%	56.8	58.6	Retention to treatment slightly lower	N/A
Opioid abstinence	Time to sustained abstinence	%	18.31	13.95		N/A
Unfavourable Effects						
Adverse event	Injection site pain	%	9.3	-	N/A	N/A
Adverse event	Injection site erythema	%	5.5	-	N/A	N/A
Adverse event	Injection site swelling	%	5.5	-	N/A	N/A

Abbreviations: CDF: Cumulated Distribution Function; NUS: Negative Urine Sample
Notes:

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Buprenorphine for the treatment of opioid addiction is only currently available as sublingual tablets in Europe. It is agreed that additional treatment options would be beneficial for this condition.

Non-inferiority to SL BPN/NX has been demonstrated in the pivotal study. The need for a test dose with SL BPN has been added to the product information documents and additional changes were proposed. No dose adjustment is required for special groups such as patients with moderate OUD and patients naïve to BPN treatment.

From a safety point of view, it is accepted that injection reactions are to be expected. Safety data is absent for children and the elderly. Exposure particularly at the higher doses for both the weekly and monthly regimen is limited. This product is intended as a maintenance therapy with indefinite duration of treatment. The long-term safety with this new formulation at the doses proposed by the applicant has not been sufficiently evaluated and a warning is found in the SmPC.

4.7.2. Balance of benefits and risks

It is understood that opioid addiction is a major concern and that additional treatment options which could be helpful if increased adherence to treatment and decreased misuse and abuse is demonstrated.

The addition of these products will allow HCP and patients to rely also on weekly or monthly buprenorphine depots for the treatment of opioid dependence.

4.8. Conclusions

The overall B/R of Buvidal prolonged release solution for injection is positive.

5. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Buvidal is favourable in the following indication:

Treatment of opioid dependence within a framework of medical, social and psychological treatment. Treatment is intended for use in adults and adolescents aged 16 years or over.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to special and restricted medical prescription

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.