23 June 2022
EMA/88938/2023
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal variation assessment report

Buvidal

International non-proprietary name: buprenorphine

Procedure No. EMEA/H/C/004651/II/0017

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	27 Nov 2021	27 Nov 2021	☐
☐	CHMP Rapporteur Assessment Report	21 Jan 2022	26 Jan 2022	☐
☐	CHMP Co-Rapporteur Assessment Report	21 Jan 2022	21 Jan 2022	☐
☐	PRAC Rapporteur Assessment Report	28 Jan 2022	31 Jan 2022	☐
☐	CHMP Co-Rapporteur Critique	02 Feb 2022	02 Feb 2022	☐
☐	PRAC members comments	02 Feb 2022	02 Feb 2022	☐
☐	Updated PRAC Rapporteur Assessment Report	03 Feb 2022	03 Feb 2022	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	10 Feb 2022	10 Feb 2022	☐
☐	CHMP members comments	14 Feb 2022	07 Feb 2022	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 Feb 2022	17 Feb 2022	☐
☐	Request for supplementary information	24 Feb 2022	24 Feb 2022	☐
☐	Submission of responses	22 April 2022	22 April 2022	☐
☐	Re-start of procedure	25 April 2022	25 April 2022	☐
☐	CHMP (Co-)Rapporteur Response Assessment Report	24 May 2022	25 May 2022	☐
☐	PRAC Rapporteur Response Assessment Report	30 May 2022	30 May 2022	☐
☐	PRAC members comments	01 June 2022	01 June 2022	☐
☐	Updated PRAC Rapporteur Response Assessment Report	02 June 2022	02 June 2022	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	10 June 2022	10 June 2022	☐
☐	CHMP members comments	13 June 2022	13 June 2022	☐
☐	Updated CHMP Response Rapporteur(s) (Joint) Assessment Report	16 June 2022	16 June 2022	☐
☒	Request for Supplementary Information	23 June 2022	23 June 2022	☐
☐	MAH submission deadline	28 Feb 2023		☐
☐	Re-Start of procedure	01 Mar 2023		☐
☐	PRAC Rapporteur Assessment Report	06 Mar 2023		
☐	PRAC members comments	08 Mar 2023		☐
☐	Updated PRAC Rapporteur Assessment Report	09 Mar 2023		☐
☐	CHMP Rapporteur Assessment Report	15 Mar 2023		☐
☐	PRAC outcome	16 Mar 2023		☐
☐	CHMP members comments	20 Mar 2023		☐
☐	Updated CHMP Rapporteur Assessment Report	23 Mar 2023		☐

Status of this report and steps taken for the assessment				
☐	Opinion	30 Mar 2023		☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Procedure resources	
Rapporteur:	Peter Kiely
Co-Rapporteur critique	Agnes Gyurasics

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List of abbreviations

AADP Average of the average daily pain
AE Adverse event
API Average pain intensity
AUC Area under the plasma concentration-time curve
AUCss Area under the plasma concentration-time curve at steady state
AWDP Average of the worst daily pain
BMI Body mass index
BPN Buprenorphine
CI Confidence interval
CL Clearance
CLBP Chronic low back pain
CNS Central nervous system
COWS Clinical Opiate Withdrawal Scale
Css,max Maximum concentration at steady state
C-SSRS Columbia-Suicide Severity Rating Scale
Css,trough Trough concentration at steady state
CYP3A4 Cytochrome P450 3A4
DEA US Drug Enforcement Administration
ECG Electrocardiogram
EEW Enriched-enrolment withdrawal
FDA US Food and Drug Administration
GCP Good Clinical Practice
IM Intramuscular
IMP Investigational medicinal product
IR Immediate-release
MAA Marketing authorisation application
MED Morphine equivalent dose
mITT Modified intention-to-treat
MMRM Mixed-model repeated measures
MOR mu-opioid receptor
norBPN Norbuprenorphine
NRS Numerical rating scale
NX Naloxone
OLE Open-label extension
OR Opioid receptor
OUD Opioid use disorder
PGI-I Patient Global Impression of Improvement
PK Pharmacokinetic
q1w Once weekly
q4w Once monthly
QTcF Fredericia corrected QTc
SAE Serious adverse event
SC Subcutaneous
SD Standard deviation
SL Sublingual
SmPC Summary of Product Characteristics
SOWS Subjective Opiate Withdrawal Scale
TEAE Treatment-emergent adverse event
WAAPI Weekly average of the (daily) average pain intensity
WAWPI Weekly average of the (daily) worst pain intensity
WHO World Health Organization
WPAI Work Productivity and Activity Impairment

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Camurus AB submitted to the European Medicines Agency on 10 November 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

To add the new therapeutic indication of treatment of moderate to severe chronic pain in patients with opioid dependence. As a consequence, sections 4.1, 4.2, 4.5, 5.1 and 6.6 of the SmPC and sections 1, 3 and Instruction for use of the PL are updated accordingly. The updated RMP version 2.1 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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 MAH 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.

Derogation(s) of market exclusivity

N/a

Scientific advice

The MAH did not seek scientific advice at the CHMP.

2. Scientific discussion

2.1. Introduction

Buvidal is currently indicated for treatment of opioid dependence within a framework of medical, social and psychological treatment. Treatment is indicated for use in adults and adolescents aged 16 years or over. The Market Authorisation Holder (MAH) proposes to add a new indication of treatment of moderate to severe chronic pain in patients with opioid dependence.

2.1.1. Problem statement

Disease or condition

The most recent classifications define chronic pain as any somatic pain lasting longer than 3 months. Common types of chronic non-cancer pain include low back pain, osteoarthritis, headache, fibromyalgia and neuropathic pain.

State the claimed the therapeutic indication

The proposed indications:

Treatment of moderate to severe chronic pain in patients with opioid dependence.

Epidemiology

Chronic pain is very prevalent and affects over 20% of the European population, with increased presence in females and older individuals.

Among patients with diagnosed opioid dependence receiving pharmacological opioid agonist treatment for addiction, chronic pain is very common with reported prevalence rates in Europe of 33% to 55%. Chronic pain in patients with opioid dependence is often moderate to severe and associated with older age and psychiatric comorbidities, and the most frequently reported pain locations are the lower extremities and the back.

Biologic features Aetiology and pathogenesis

The most recent classifications define chronic pain as any somatic pain lasting longer than 3 months. Common types of chronic non-cancer pain include low back pain, osteoarthritis, headache, fibromyalgia and neuropathic pain. Chronic pain is very prevalent and affects over 20% of the European population, with increased presence in females and older individuals.

Clinical presentation, diagnosis and stage/prognosis

Chronic pain is one of the most frequent reasons to seek medical care and a leading cause of disability and disease burden globally. Chronic pain management is one of the most difficult clinical challenges in medicine today with a high and unmet medical need. Treatment often requires a multimodal, interdisciplinary approach, which might include pharmacotherapy, psychotherapy, integrative treatment and invasive procedures.

Management

There is currently no medicinal product approved for treatment of both chronic pain and opioid dependence. The well-known drug substance buprenorphine (BPN) is, however, widely used both in the treatment of opioid dependence and in the treatment of pain. As a partial mu-opioid receptor (MOR)

agonist, it has been shown to give dose-dependent analgesia with a ceiling effect on respiratory depression. Dose-dependent analgesia has been observed with intramuscular (IM) doses up to 10 mg. The effect of BPN on respiratory depression appears to be lower than that of full MOR agonists, due to a ceiling effect at higher doses. Furthermore, the slow dissociation of BPN from receptors results in a long effect duration and reduces withdrawal symptoms upon discontinuation. BPN has proven effective in patients with chronic cancer and non-cancer pain, with a reduced need for additional oral analgesics and improved quality of life. A large number of studies have also compared the efficacy of BPN with morphine for treatment of acute pain and a systematic review found BPN to be an equally efficacious analgesic agent. BPN is therefore an effective analgesic substance across a broad set of pain conditions. In addition, BPN presents with a lower abuse potential than most opioids indicated for chronic pain management. The US Drug Enforcement Administration (DEA) has classified BPN as a Schedule III substance, one that has a potential for abuse lower than substances in the Schedule I and II categories. Most other opioids indicated for chronic pain management, such as morphine, fentanyl, oxycodone, hydrocodone and hydromorphone, fall into the Schedule II category.

Several treatment goals have been proposed for improved patient therapy, many of which are based on World Health Organization (WHO) recommendations, including providing a stable plasma drug concentration to ensure long-lasting and effective pain relief and an improved quality of life. By using transdermal BPN formulations, such as BPN patches, the rate of drug delivery can be controlled and stable plasma concentrations achieved. However, transdermal administration of BPN results in slow onset and relatively low plasma BPN concentrations, which can result in suboptimal therapeutic effects, and is also associated with adverse skin reactions. Transdermal BPN formulations are not available in all EU countries, as these products have been approved through national and decentralised procedures. Thus, differences between countries regarding Marketing Authorisations of BPN products indicated for chronic pain or pain are not related to the efficacy of the active substance but related to operational and regulatory aspects. Finally, patches may be subject to abuse and diversion, as BPN may be extracted from the patches (including improperly disposed patches) and injected, snorted or otherwise misused.

2.1.2. About the product

CAM2038, approved in the EU under the tradename Buvidal, is a BPN prolonged-release formulation for injection, available for once weekly (q1w) and once monthly (q4w) treatment. Buvidal (buprenorphine) prolonged-release solution for injection is indicated for 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.

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

The Applicant has not sought scientific advice for the development programme for the additional indication "Treatment of moderate to severe chronic pain in patients with opioid dependence."

A pre-submission meeting was held with the Rapporteur on 24 April 2020.

2.1.4. General comments on compliance with GCP

Trial HS-16-555 was conducted in accordance with GCP, but it should be noted that **2 investigational sites were terminated during the trial due to non-compliance with GCP.**

During the course of the study, 2 for-cause study site audits were conducted which resulted in the discontinuation of 2 study site's participation in the clinical study. As such, changes to the study populations were made. The details of the study site audits are summarized in the following sections. Because the 2 sites were terminated early, the data from these sites was not reviewed for accuracy and completeness. Therefore, the data from these 2 sites was excluded in analyses.

Study Site 068

A for-cause audit was performed on 02OCT2017 for Site 068 in response to a quality event.

There were several Critical and Major Observations noted during the audit; the deficiencies noted during the audit were based on a random sampling of data.

The Critical Observations were:

- Subject signatures on revised ICFs could not be confirmed as authentic.
- The data on subject diaries could not be attributed to the subjects themselves.
- Subject eligibility could not be confirmed with provided source documents.

The Major Observations were:

- Source documentation provided was found to be inadequate and/or unreliable.
- There was inadequate accountability and review by site staff of subject diaries.
- There was inadequate reporting and assessment of AEs.
- The site did not have appropriate research staff based on qualification, training and experience.

The above observations led the Sponsor to question the integrity and reliability of the data collected at this site. Following completion of the audit, the site was terminated on 23 October 2017 and FDA was notified on 31 October 2017. Recently, the owner of this site was found guilty in federal court in November 2019 for fraudulently conducting and falsifying data in this study. For these reasons, this data was excluded from the efficacy and primary safety analyses.

Study Site 077

Multiple audits, including a for-cause audit and several quality visits, were conducted by the Sponsor, Medpace (the contract research organization [CRO]) and third-party auditors, due to the Site 077 enrolling a large number of subjects into the study (approximately one third of the total study sample). These audits and quality visits led to several Critical and Major Observations noted below:

The Critical Observations were:

- Not all subjects spoke, read or comprehended English, and as a result, the Informed Consent process and every study visit was conducted in Spanish or through an interpreter/impartial witness. This was not permitted in the protocol and was not documented in the source documentation.
- The study staff were unblinded throughout the entire study. The study staff who administered the investigational product also performed the protocol-required assessments at each visit.
- Source documentation was manually changed, allowing several subjects to meet inclusion and exclusion criteria for the study.
- The medical records at the site were incomplete or missing. As a result, it could not be determined whether the subjects met inclusion criteria to qualify for the study.

The Major Observations were:

- The questionnaires, scales and diaries required to be completed by subjects at each visit could not be attributed to the appropriate subjects.
- There was inadequate accountability for and review of subject diaries by site staff.
- The electronic medical records were not validated and contained numerous inconsistencies.
- The above observations led to uncertainty in the integrity and reliability of the data collected at Site 077. Therefore, the data was not included in the efficacy analysis.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

As the patient population with chronic pain and opioid dependence is part of the patient population for which Buvidal is already approved (opioid dependence), this will not increase the use of buprenorphine.

Therefore, the currently approved ERA is considered valid also for the present application, with no need for additional analyses or studies.

2.2.2. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of buprenorphine.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

Although study HS-16-555 was conducted in accordance with GCP, it should be noted that 2 investigational sites were terminated during their participation in the study due to apparent or implied noncompliance with GCP (see section 5.1.4).

The MAH 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.

Table 1*: Tabular overview of clinical studies*

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK, efficacy and safety	[HS-15-549]	Module 5.3.3.2	Primary objective: - To evaluate the steady state PK of BPN and norBPN following repeated SC administration of CAM2038 q1w at 4 different injection sites in patients with opioid use disorder and chronic pain. - To evaluate steady state PK of BPN and norBPN following repeated SC administration of CAM2038 q4w with the buttock as the injection site. Secondary objectives: - To evaluate the safety and tolerability of CAM2038 q1w and CAM2038 q4w. - To assess relative BA of BPN at steady state following repeated SC administration of 160 mg CAM2038 q4w compared with repeated SL administration of 24 mg BPN/NX. Exploratory objectives: - To evaluate maintenance of treatment efficacy when transferring opioid-dependent patients from SL BPN/NX to CAM2038 q1w and q4w as determined by urine toxicology. - To evaluate subject-rated worst daily pain and average daily pain using an 11-point NRS following repeated SC administration of CAM2038 q1w and CAM2038 q4w.	Phase 2, open-label, partially randomized, multi-center, repeated-dose study Control: Group 1: NA Group 2: NA Group 3: Daily doses of 24 mg SL BPN/NX (Suboxone) for 7 days	Group 1: 3 weekly SC injections of 32 mg CAM2038 q1w in the buttock followed by 4 weekly SC injections of 32 mg CAM2038 q1w in the buttock (reference), abdomen, thigh, and back of upper arm with injection site sequence allocated in a randomized, cross-over design. Group 2: 4 monthly SC injections of 128 mg CAM2038 q4w in the buttock. Groups 1 and 2: Open-label safety extension period including 6 additional weekly SC injections of 32 mg CAM2038 q1w in the buttock, abdomen, thigh and back of upper arm. Group 3: Daily doses of 24 mg SL BPN/NX (Suboxone) for 7 days followed by 4 monthly SC doses of 160 mg CAM2038 q4w in the buttock.	Exposed Group 1: n=28 Exposed Group 2: n=20 Exposed Group 3: n=17 Completed treatment period: Group 1: n=23 Group 2: n=16 Group 3: n=12 Completed open label safety extension period: Group 1: n=14 Group 2: n=12	Adult patients with moderate to severe opioid use disorder (based on DSM-V criteria) and with a history of moderate to severe chronic non-cancer pain. Patients being treated with SL BPN or SL BPN/NX at screening.	CAM2038: Group 1: 7-13 weeks Group 2: 16-22 weeks Group 3: 16 weeks	Completed Full CSR
Efficacy, safety and PK	[HS-16-555]	Module 5.3.5.1	Double-Blind Phase: Primary objective: - To evaluate the efficacy of CAM2038 q1w and CAM2038 q4w compared to placebo on API scores, as measured on the	Phase 3, randomized, double-blind, placebo-controlled, enriched-enrollment withdrawal, repeated-	Titration period, applicable for both the double-blind phase and the open-label safety extension phase:	468 patients entered the titration period of the double-blind phase	Opioid-experienced patients with moderate to severe CLBP (or moderate to severe chronic	52 weeks	Completed Full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
			NRS-11 in patients currently taking daily opioids for moderate to severe CLBP Secondary objectives: - To evaluate change from baseline in the weekly average of (daily) worst pain intensity scores at Week 12 of the double-blind treatment period based on the NRS-11 in subjects who were currently taking daily opioids for moderate to severe CLBP - To evaluate the safety and tolerability of treatment with CAM2038 q1w and CAM2038 q4w in subjects who were currently taking daily opioids for moderate to severe CLBP Open-Label Safety Extension Phase: Primary objective: - To evaluate the safety and tolerability of treatment with CAM2038 q1w and CAM2038 q4w for at least 52 weeks in patients with moderate to severe chronic pain requiring daily treatment with opioids Secondary objectives: - To evaluate the steady-state PK of BPN for CAM2038 q1w and CAM2038 q4w in subjects with moderate to severe chronic pain requiring daily treatment with opioids. - To evaluate the efficacy and safety of CAM2038 q1w and CAM2038 q4w administration for at least 52 weeks in the treatment of subjects with moderate to severe chronic pain requiring daily treatment with opioids	dose, multi-center trial with an open-label safety extension phase Control: Placebo SC injections during the double-blind treatment period of the double-blind phase (patients were randomized in a 1:1 ratio to receive CAM2038 or placebo)	IM injection of 0.30 mg Buprenex® (test dose), followed by 4, 8, 12, 16, 24 or 32 mg SC CAM2038 q1w, for up to 10 weeks until a stable dose was reached. Double-blind treatment period: 4, 8 or 12 mg SC CAM2038 q1w, 64, 96 or 128 mg SC CAM2038 q4w or SC placebo q1w or q4w for 12 weeks. Open-label extension treatment period: 4, 8 or 12 mg SC CAM2038 q1w or 64, 96 or 128 mg SC CAM2038 q4w for up to 52 weeks of total exposure. CAM2038 (or placebo) were given in the buttock, upper thigh, abdomen or back of the upper arm.	222 patients were randomized to CAM2038 (n=112) or placebo (n=110) in the double-blind treatment period 132 patients were exposed to CAM2038 in the open-label safety extension phase (57 rollover patients from the double-blind phase and 75 de novo patients)	pain in the open-label safety extension phase)		

API: average pain intensity; BA: bioavailability; BPN: buprenorphine; BPN/NX: buprenorphine/naloxone; CDF: cumulative distribution function; CHMP: Committee for Medicinal Products for Human Use; CLBP: chronic low back pain; CSR: clinical study report; DSM-V: Diagnostic and Statistical Manual of Mental Disorders – 5th Edition; EMA: European Medicines Agency; EU: European Union; FDA: Food and Drug Administration; ICD-10: International Statistical Classification of Diseases and Related Health Problems – 10th Edition; IM: intramuscular; IV: intravenous; NA: not applicable; norBPN: norbuprenorphine; NRS: numerical rating scale; PD: pharmacodynamic; PK: pharmacokinetic; SAP: statistical analysis plan; SC: subcutaneous; SL: sublingual; SOC: standard of care; VAS: visual analog scale

2.3.2. Pharmacokinetics

The clinical development programme for CAM2038 in patients with chronic pain consisted of 2 clinical trials: one Phase 3 trial (HS-16-555) and one Phase 2 trial (HS-15-549). Blood samples for PK evaluation were collected in both trials.

The results from HS-15-549, which investigated the steady-state PK for 32 mg CAM2038 q1w injected in the buttock, abdomen, thigh and back of upper arm, and the steady-state PK for 128 mg CAM2038 q4w in patents with moderate to severe opioid use disorder (OUD) and with moderate to severe chronic non-cancer pain, were evaluated as part of the initial MAA. HS-15-549 also included a 160-mg CAM2038 q4w treatment arm. The results from that treatment arm were further evaluated as part of an extension application to the initial MAA.

Trial HS-16-555

Trial HS-16-555 was a Phase 3, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of CAM2038 q1w and CAM2038 q4w in patients on daily opioid treatment for moderate to severe chronic low back pain (CLBP). Sparse plasma samples were collected during the open-label extension (OLE) phase, with the objective to evaluate the steady-state PK of BPN for CAM2038 q1w and CAM2038 q4w in patients with chronic pain.

During the treatment period of the OLE phase, doses of 4, 8 or 12 mg CAM2038 q1w or 64, 96 or 128 mg CAM2038 q4w were injected in the buttock, abdomen, thigh, or upper arm. Blood samples for analysis of BPN and norBPN were collected at the 4-month visit of the OLE treatment period, from patients providing additional consent for sampling. Blood samples were collected prior to administration and at approximately 2, 6, and 24 hours as well as 3, 7, 14 and 28 days after the 4-month CAM2038 administration. PK parameters of BPN and norBPN were calculated using non-compartmental analysis methods. In addition, for patients treated with CAM2038 q4w, individual predictions and descriptive statistics of area under the plasma concentration-time curve at steady state (AUCss), maximum concentration at steady state (Css,max) and trough concentration at steady state (Css,trough) of BPN were derived using a previously developed population PK model.

PK results

PK was evaluated in 46 patients in HS-16-555. One subject received 4 mg, 2 subjects received 8 mg and 1 subject received 12 mg CAM2038 q1w. Four patients received 64 mg, 9 patients received 96 mg and 29 patients received 128 mg CAM2038 q4w. The mean age of the 46 PK patients was 56 years (range: 35 to 80 years) and 48% were men. The mean body weight was 84.9 kg (range: 50.3 to 134.3 kg) and the mean body mass index (BMI) was 28.7 kg/m2 (range: 18.4 to 37.9 kg/m2).

BPN plasma concentrations increased gradually with a peak concentration at approximately 24 hours after administration of 4, 8 and 12 mg CAM2038 q1w, and between 6 and 24 hours after administration of 64, 96 and 128 mg CAM2038 q4w, Figure 1. After the peak, BPN concentrations decreased slowly over time, consistent with the treatment durations for CAM2038 q1w and CAM2038 q4w. Low and stable norBPN plasma concentration-time profiles were observed after steady-state injections of 4, 8 and 12 mg CAM2038 q1w and 64, 96 and 128 mg CAM2038 q4w, Figures 1 and 2. BPN and norBPN Css,trough for CAM2038 q1w and CAM2038 q4w, as well as nor/BPN Css,trough ratios, are summarised in Table 2. High variability is generally noted.

Figure 1:

Mean Concentration-Time Profiles of Buprenorphine by Dose after Administration of CAM2038 (Linear Scale, Steady State)

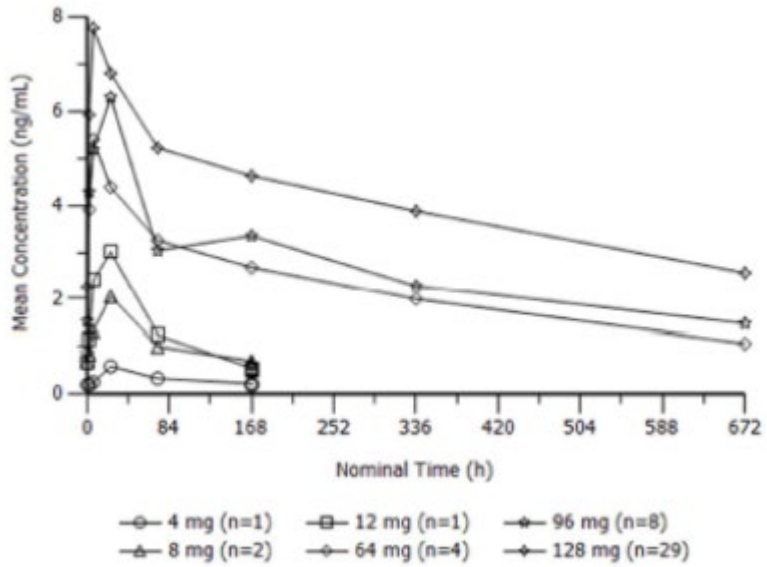


Figure 2

Mean Concentration-Time Profiles of Norbuprenorphine by Dose after Administration of CAM2038 (Linear Scale, Steady State)

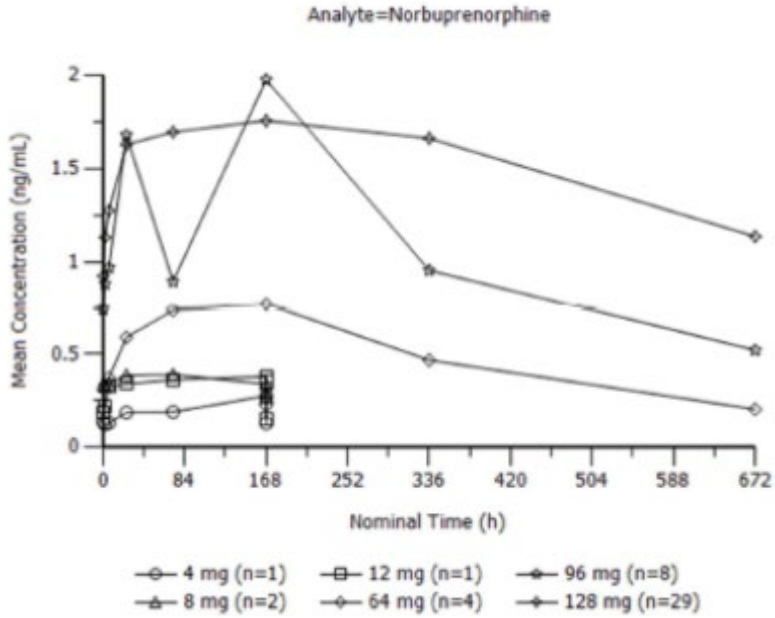


Table 2*:*

Table 2: Buprenorphine and norbuprenorphine trough concentrations at steady state after administration of CAM2038

Dose (mg)	Time (h)	n	Buprenorphine (ng/mL)	Norbuprenorphine (ng/mL)	Norbuprenorphine/ Buprenorphine
4 mg q1w	0	1	0.207 (NC)	0.136 (NC)	0.657 (NC)
	168	1	0.234 (NC)	0.236 (NC)	1.01 (NC)
8 mg q1w	0	2	0.672 (9.38)	0.315 (63.1)	0.468 (75.6)
	168	2	0.657 (7.65)	0.283 (41.1)	0.431 (49.9)
12 mg q1w	0	1	0.688 (NC)	0.183 (NC)	0.266 (NC)
	168	1	0.496 (NC)	0.350 (NC)	0.706 (NC)
64 mg q4w	0	4	0.858 (37.5)	0.165 (91.8)	0.192 (47.5)
	672	4	1.02 (40.3)	0.180 (72.3)	0.177 (32.7)
96 mg q4w	0	8-9	1.46 (22.4)	0.508 (121)	0.325 (120)
	672	7-8	1.43 (18.9)	0.381 (148)	0.238 (121)
128 mg q4w	0	28-29	2.08 (42.3)	0.644 (106)	0.309 (80.0)
	672	25-26	2.41 (39.8)	0.789 (129)	0.320 (88.2)

NC: not calculated; q1w: once weekly; q4w: once monthly
Values are geometric mean (geometric mean coefficient of variation percentage; CV%)
Source: [Table 32, CTR HS-16-555]

Population PK modelling

The aim of the popPK analysis was to derive individual predictions of area under the curve at steady state (AUCss), maximum concentration at steady state (Css,max), and trough concentration at steady state (Css,trough) of buprenorphine (BPN) in subjects treated with CAM2038 q4w in trial HS-16-555, using a previously developed (legacy) popPK model [Report REP-2-CAM-2038-PMX-1, (May 31 2017), Population Pharmacokinetic Analysis of Buprenorphine after CAM2038 Administration in Studies HS-11-426, HS-13-487, HS-13-478, and HS-15-549], and to summarize the PK parameters descriptively.

A total of 325 observations of BPN concentrations in 42 subjects treated with CAM2038 q4w in trial HS-16-555 were included in this analysis. A summary of the number of subjects and number of BPN concentrations, and of baseline covariates for the subjects included in the analysis data set for the final population PK model of BPN are presented in Table 3, Table 4 and Table 5, respectively.

Table 3: Number of individuals with observations and number of BPN observations in the analysis data set

Dose	Number of subjects	Number of BPN observations
64 mg	4	32
96 mg	9	65
128 mg	29	228
All	42	325

BPN: buprenorphine

Table 4: *Baseline continuous covariate statistics for the* analysis data set

Covariate		
Age (years)	min median max	38.0 56.0 81.0
	mean (SD)	56.9 (9.92)
	N	42
Body weight (kg)	min median max	50.3 80.2 128
	mean (SD)	82.3 (19.0)
	N	42

SD: standard deviation. Values are rounded to three significant digits.

Table 5: *Categorical covariate statistics for the analysis data set*

Covariate			
Sex	Male	N	19
		Percent (%)	45
	Female	N	23
		Percent (%)	55
Race	American Indian or Alaska Native	N	1
		Percent (%)	2
	White	N	41
		Percent (%)	98

Legacy PK model

The legacy popPK model was a three-compartment disposition model with first-order elimination from the central compartment. The absorption of SC CAM2038 q4w was described by two parallel absorption pathways with first order absorption. The absorption of SC CAM2038 q1w was described by a model with the same structure as for CAM2038 q4w, but with a zero-order input to one of the absorption compartments. The legacy model also included parameters for the absorption after sublingual (SL) administration. However, in the current study, no SL doses were administered.

Covariates included age and body weight on CL, sex and population on Fq1w1, and of opioid dependent patients (compared to healthy volunteers) on Vc. The latter covariate effect indicated that patients with OUD had a larger Vc than healthy subjects. This effect was tentatively explained by peripheral compartments already being loaded with BPN in patients with OUD who were pre-exposed to BPN in contrast to healthy subjects. In addition, the fraction of dose going into the faster of the 2 absorption pathways for CAM2038 q1w was higher in patients than in healthy subjects. Together, these differences may result in somewhat lower maximum concentration, and higher Css,trough (for CAM2038 q1w) in patients than in healthy subjects. However, the overall BPN exposure (area under the plasma concentration-time curve [AUC]) is similar in patients and healthy subjects.

The subjects in the current analysis were opioid experienced pain patients rather than patients with OUD. However, both groups had been treated with opioids prior to enrolment in the trials. Therefore, the covariate was included as if the subjects in the current trial were similar to the opioid dependent patients.

External evaluation

An external evaluation of the legacy PK model for BPN was performed by simulating BPN concentrations using the legacy PK model and the design, dosing, and subject characteristics from trial HS-16-555, and comparing to the observed concentrations. As shown in Figures 3 and 4, the legacy PK model could adequately predict the BPN concentrations in trial HS-16-555. Therefore, no further refinements of the model were considered necessary.

Figure 3*:*

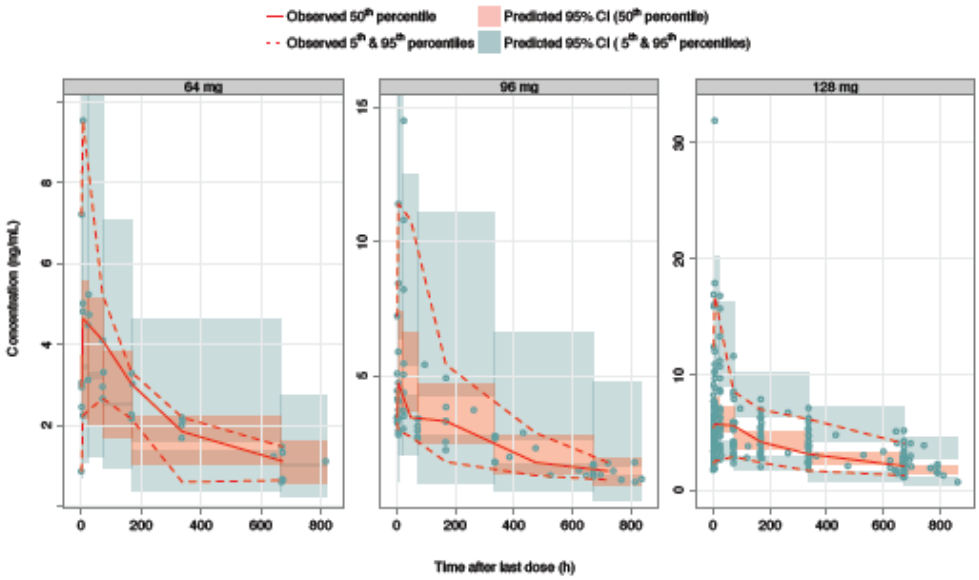


Figure 6: External evaluation of the legacy PK model on data from trial HS-16-555, on a linear scale, stratified by dose. The red lines are the medians, 5th, and 95th percentiles based on the observed data. The shaded areas are 95% confidence intervals for medians, 5th, and 95th percentiles based on the simulated data. Circles are the observations.

Figure 4*:*

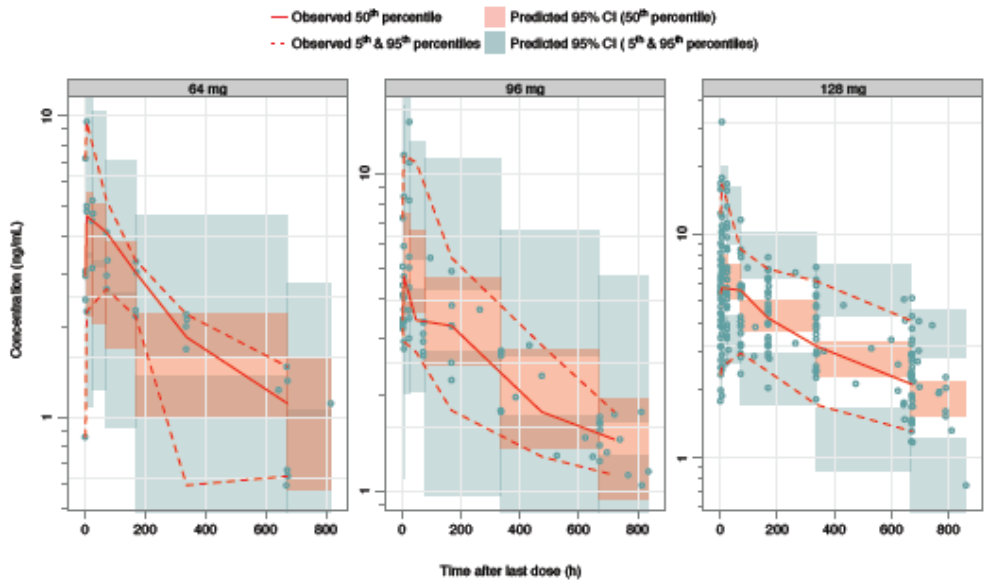


Figure 7: External evaluation of the legacy PK model on data from trial HS-16-555, on a semi-logarithmic scale, stratified by dose. The red lines are the medians, 5th, and 95th percentiles based on the observed data. The shaded areas are 95% confidence intervals for medians, 5th, and 95th percentiles based on the simulated data. Circles are the observations.

Individual parameter estimates

Empirical Bayes estimates (EBE) of primary PK parameters were estimated for all subjects based on the legacy model, the individual covariates and the individual plasma concentration measurements of BPN in trial HS-16-555. The secondary PK parameters Css,max, Css,trough, and AUCss were derived through simulations using the individual EBEs. A summary of the model-predicted PK parameters of BPN for 64, 96 and 128 mg CAM2038 q4w is presented by dose in Table 6. The predicted BPN Css,trough values were in agreement with the observed data in Trial HS-16-555 (see Table 2, PK results above).

Table 6: Summary statistics for the individual estimates of the secondary PK parameters (C_{ss}, max, C_{ss}, trough, and AUC_{ss}).

Dose		$C_{ss,max}$ (ng/mL)	$C_{ss,trough}$ (ng/mL)	AUC_{ss} (ng · h/mL)
64 mg	mean	5.84	0.904	1350
	median	5.05	1.01	1410
	geometric mean	5.33	0.707	1290
	min	3.12	0.191	862
	max	10.2	1.41	1700
	sd	3.02	0.566	419
	geometric cv%	51.7	116	34.1
96 mg	mean	5.89	1.54	1950
	median	5.05	1.56	1990
	geometric mean	5.45	1.53	1930
	min	2.79	1.21	1500
	max	10.0	1.97	2410
	sd	2.49	0.217	300
	geometric cv%	43.1	14.0	15.9
128 mg	mean	7.80	2.23	2650
	median	6.98	2.31	2650
	geometric mean	7.14	2.11	2550
	min	3.00	0.535	1160
	max	21.5	3.72	4600
	sd	3.76	0.693	738
	geometric cv%	43.2	38.7	29.8

AUC_{ss}: area under the curve at steady state, $C_{ss,max}$: maximum concentration at steady state, $C_{ss,trough}$: trough concentration at steady state, cv: coefficient of variation, sd: standard deviation. Values are rounded to three significant digits.

Effects of age on drug exposure

In trial HS-16-555, the population of opioid-experienced patients with moderate to severe chronic pain had a higher average age than the patients in the trials in the initial MAA. Therefore, potential effects of age on drug exposure were addressed.

In the legacy pop PK model of BPN for CAM2038 in healthy subjects and in patients with OUD, age was found to be a predictor of BPN clearance, with a decrease in clearance and, thus, an increase in AUC being associated with increasing age. The age range of subjects included in the initial MAA was 18 to 65 years (median 35 years) and the difference in clearance within this range was 26%. This difference was not regarded as clinically relevant, particularly since patients with opioid dependence will be titrated to the optimal dose of CAM2038 products.

In trial HS-16-555, the age of subjects sampled for PK ranged from 35 to 80 years (median 56 years), with 8 patients above 65 years. The legacy model, based on the trials of the initial MAA, appeared to accurately predict exposure parameters in the older patient population of trial HS-16-555 using the algorithm for CL dependent of age. Based on this algorithm, clearance in an 80 year old subject would be 29% lower than in an 18 year old subject and only 5% lower than in a 65 year old subject. As such, this difference is not considered to be clinically relevant given the titration to an optimal dose for each individual patient with opioid dependence and chronic pain. Furthermore, as illustrated in Figure 5, the effect of age on resulting Css, trough appears to be limited.

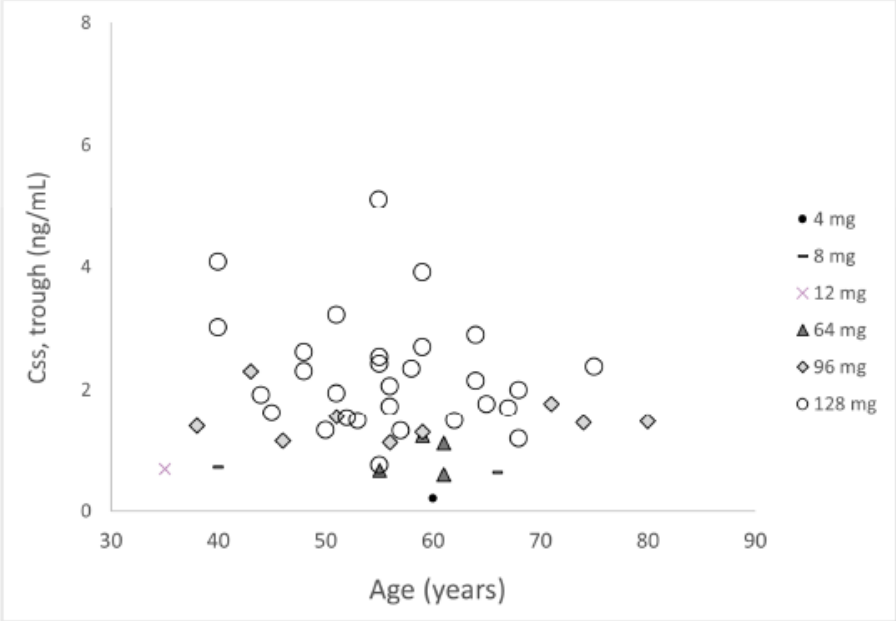


Figure 5: **Individual $C_{ss,trough}$ values after administration of CAM2038 versus age by dose (PK population)**

$C_{ss,trough}$: trough concentration at steady state
Source: [CTR HS-16-555]

2.3.3. Pharmacodynamics

N/a

2.3.4. PK/PD modelling

N/a

2.3.5. Discussion on clinical pharmacology

Two clinical trials, one Phase 3 trial (HS-16-555) and one Phase 2 trial (HS-15-549), were pertinent for the present variation application for CAM2038 in patients with chronic pain. Trial HS-15-549 was assessed in previous applications. Therefore, only the PK of Trial HS-16-555 were presented and assessed.

The population PK analysis is deemed acceptable. Despite some overestimation of variability particularly at lower dose levels, likely due to the small sample sizes, the VPCs showed that the previously developed (legacy) model could describe the data from trial HS-16-555 adequately without needing further refinements. This supports the assumption that patients with opioid use disorder patients and opioid-experienced pain patients are pharmacokinetically similar. Individual predictions of BPN Cmax, Cmin and AUC at steady state in patients with chronic pain were derived as planned.

It is agreed that the marginal reduction in clearance of BPN in elderly patients (>65 years) is not of clinical relevance since the dose is titrated to optimal levels in each individual patient. The update to Section 4.2 of the SmPC (Special populations - elderly), which now states that "No dosage adjustment is required in elderly patients ≥65 years of age", is acceptable.

2.3.6. Conclusions on clinical pharmacology

In terms of clinical pharmacology there are no notable issues. As such, no major objections or other concerns are raised.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response studies have been carried out for the new sought indication.

2.4.2. Main study

The Applicant has submitted one study in support of the sought indication "Treatment of moderate to severe chronic pain in patients with opioid dependence". The study was conducted at approximately 82 sites in the USA.

Study title

CSR HS-16-555. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Enriched-Enrollment Withdrawal, Multicenter Study to Evaluate the Efficacy and Safety of a Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Subjects with Moderate to Severe Chronic Low Back Pain Currently Treated with Daily Opioids

Methods

Study design

The study was a randomised placebo controlled, enriched enrolment withdrawal study in a study population already receiving opiate treatment for chronic low back pain. The study also had an open label extension phase which allowed for the recruitment of new patients with a history of chronic pain as well as low back pain.

The double blind phase of the study included a Screening Period (up to 2 weeks), a Transition Period (up to 2 weeks), an Open-Label Titration Period (up to 10 weeks), a Double-Blind Treatment Period including a Final Study Visit (12 weeks), and a Follow-up Period (4 weeks). The overall duration of participation for the Double-Blind Phase was up to 30 weeks, from the Screening Period through to the Follow-up Period. An overview of the study design is provided in Figure 6.

Transition period (up to 2 weeks duration)

Following the Screening Period and confirmation of eligibility, subjects entered a Transition Period of up to 2 weeks, during which their current opioid doses were down-titrated by approximately 25% per day to:

- ≤80 mg/day MED (for subjects whose opioid dose at screening was ≥80 mg/day MED);

or

- ≤40 mg/day MED (for subjects whose opioid dose at screening was between 40 to 79 mg/day MED).

Following the down titration, subjects were transitioned to morphine IR for at least 2 days before entering the Open-Label Titration Period, as follows:

- 15 mg 4 times daily (QID) for subjects whose screening MED was ≥80 mg/day; or
- 15 mg 3 times daily (TID) for subjects whose screening MED was 40 to 79 mg/day.

Subjects who were taking BPN at screening did not transition to morphine IR but were required to refrain from taking BPN for 12 to 24 hours as a washout prior to starting the Open-Label Titration Period with CAM2038.

Open label titration period (10 weeks duration)

The goal of the Open-Label Titration Period was to achieve a stable dose of CAM2038 q1w that produced analgesia by the end of the 10-week period.

On Day 1 of the Open-Label Titration Period, subjects returned to the clinic after a washout period of at least 12 hours from their last morphine IR dose, or 12 to 24 hours from their last BPN dose. Subjects who reported to the clinic with chronic low back pain (CLBP) of ≥5 on an average pain intensity (API) scale over the previous 24 hours and who had a Clinical Opioid Withdrawal Scale (COWS) score of ≥5 received a BPN test dose (Buprenex 0.30 mg intramuscular injection) at the clinical site. After the BPN test dose, subjects were assessed for any changes in QTcF (Fridericia's corrected QTc) and opioid withdrawal. Subjects who tolerated the BPN test dose (did not show a >30 ms increase in QTcF within 1 hour of BPN test dose administration, and a COWS score of <5 within 15 minutes of BPN test dose administration) received the first dose of CAM2038 q1w. The CAM2038 q1w dose was administered within 4 hours (+30 minutes) of the BPN test dose (4 mg CAM2038 for subjects whose screening morphine equivalent dose (MED) was 40-79 mg/day and 8 mg CAM2038 for subjects whose screening MED was ≥80 mg/day).

During the first week of the Open-Label Titration Period, subjects who experienced significant pain could have received an additional 4 mg (for subjects whose screening MED was 40 to 79 mg/day) or 8 mg supplemental dose of CAM2038 (for subjects whose screening MED was ≥80 mg/day) on Days 3, 4 or 5 (the supplemental dose could have been administered on Days 4, 5, or 6, if the subject was enrolled prior to Amendment 6 [22FEB2017]) at the discretion of the Investigator. Thereafter, dose adjustments were made by increasing or decreasing the dose level of CAM2038 q1w at the scheduled weekly visits (doses of 4, 8, 12, 16, 24, or 32 mg per week). Subjects who required doses >32 mg/week were discontinued from the study.

Hydrocodone/acetaminophen 5 mg/325 mg every 4 to 6 hours (q4-6h) as needed (prn), up to 15 mg/975 mg/day (3 tablets) for subjects whose screening opioid doses were between 40 and 79 mg/day MED or 30 mg/1950 mg/day (6 tablets) for subjects whose screening opioid doses were ≥80 mg/day MED was permitted as a rescue.

Double blind treatment period

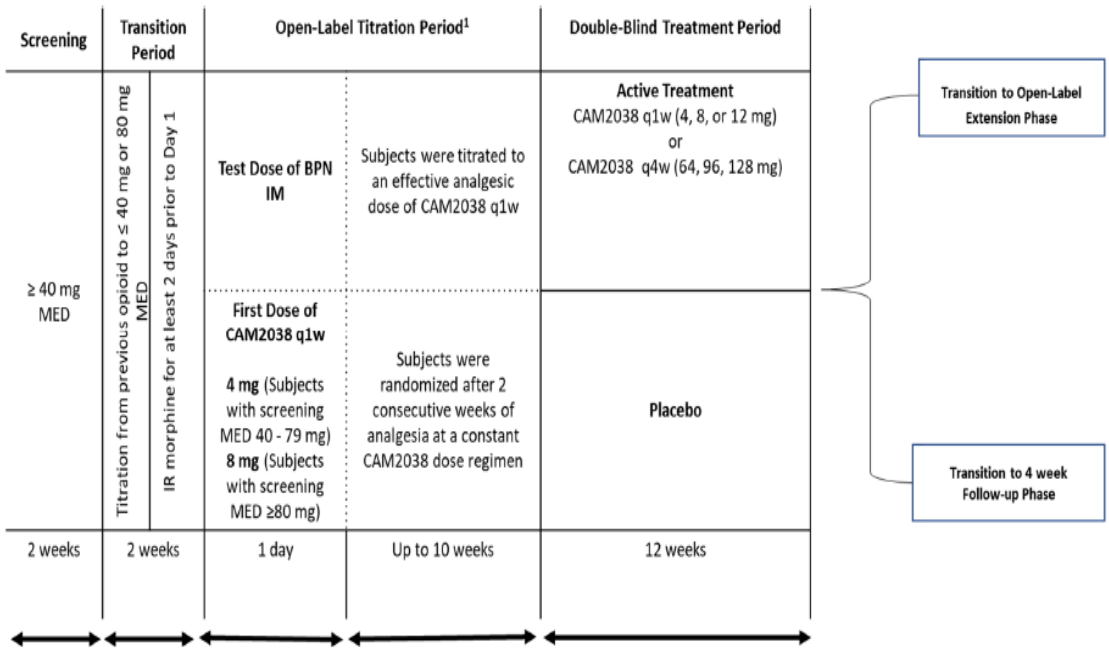
At the end of the titration period Subjects who were stabilized and responded to their CAM2038 q1w doses (4, 8, 12, 16, 24, or 32 mg/week) at the end of the Open-Label Titration Period and who fulfilled the pre-defined randomization criteria were randomized to 1 of 2 treatment groups in the 12-week Double-Blind Treatment Period:

- Group 1: CAM2038 q1w or CAM2038 q4w SC injections
- Group 2: Placebo q1w or placebo q4w SC injections

During the Double-Blind Treatment Period, all subjects who received 4, 8 or 12 mg CAM2038 q1w at the end of the Open-Label Titration Period were randomized to continue their respective CAM2038 q1w dosing of 4, 8, or 12 mg CAM2038, or to receive matching placebo q1w, for a total treatment duration of 12 weeks. Subjects who received 16, 24, or 32 mg CAM2038 q1w at the end of the Open-Label Titration Period were randomized to receive 64, 96, or 128 mg CAM2038 q4w, respectively, or to receive matching placebo q4w, for a total treatment duration of 12 weeks.

Rescue medication, hydrocodone/acetaminophen 5/325 mg q4-6h, prn, was allowed during the Double-Blind Treatment Period as described for the Open-Label Titration Period. Whenever subjects took rescue medication, they were to record their pain intensity "at that moment" prior to taking rescue medication in their electronic diaries. However, there were certain geographical areas where there were connectivity issues reported with the electronic diaries. As a result, sites were permitted to utilize a paper diary in situations where consistent connection issues were observed.

Figure 6*:* **Overview of Study Design – Double-Blind Phase**



[1]One supplemental dose was allowed on Days 3 to 5 after the first CAM2038 4 or 8 mg injection. If a supplemental dose was taken, the next dose on Week 2 was 8 or 12 mg, otherwise the next dose was to stay at 8 mg. Titration was performed weekly up to 10 weeks. The Final Study Visit was completed 1 week after the last CAM2038 q1w dose for q1w subjects and 4 weeks after the last CAM2038 q4w dose for q4w subjects. The Follow-up Period was 4 weeks after the final study visit. IM=intramuscular; IR=immediate release; MED=morphine equivalent dose; q1w=once weekly; q4w=once monthly; R=randomization.

Figure 7*:* **Overview of Open-Label Safety Extension Phase for Rollover Subjects Continuing from the Double-Blind Treatment Period**

<table>
<tr><td>Screening</td><td colspan="5">Double-Blind Phase</td><td colspan="3">Open-Label Safety Extension Phase (Up to 52 weeks total exposure)</td></tr>
<tr><td></td><td colspan="2">Transition Period</td><td colspan="2">Open-Label Titration Period[1]</td><td>Double-Blind Treatment Period</td><td>Titration Period</td><td>Open-Label Enrollment Period</td><td>Follow-up Period</td></tr>
<tr><td rowspan="2">≥40 mg MED</td><td rowspan="2">Titration from previous opioid to ≤ 40 mg or 80 mg MED</td><td rowspan="2">IR morphine for at least 2 days prior to Day 1</td><td>Test Dose of BPN IM</td><td>Subjects were titrated to an effective analgesic dose of CAM2038 q1w</td><td>Active CAM2038 q1w or q4w</td><td rowspan="2">Treatment with CAM2038 for at least 1 week</td><td rowspan="2">Active treatment CAM2038 q1w and CAM2038 q4w</td><td rowspan="2">For Concomitant Medications and AEs</td></tr>
<tr><td>First dose of CAM2038 q1w

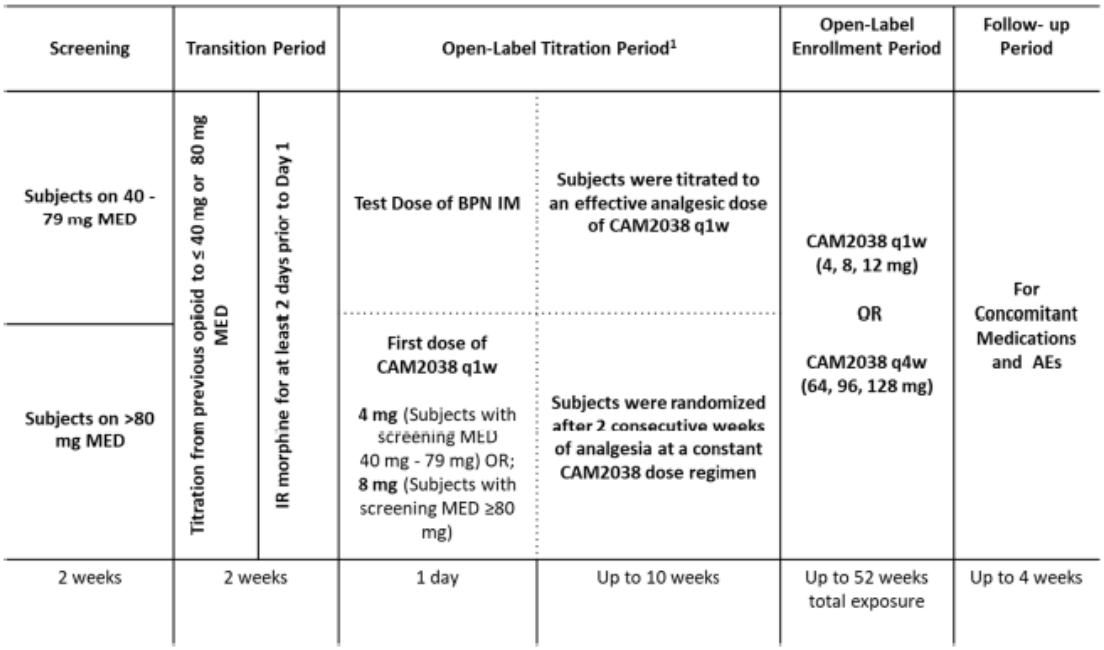
4 mg (Subjects with screening MED 40 mg - 79 mg)
8 mg (Subjects with screening MED ≥80 mg)</td><td>Subjects may be randomized after 2 consecutive weeks of analgesia at a constant CAM2038 dose regimen</td><td>Placebo</td></tr>
<tr><td>2 weeks</td><td colspan="2">2 weeks</td><td>1 day</td><td>Up to 10 weeks</td><td>12 weeks</td><td>1 week</td><td>Up to 36 weeks</td><td>Up to 4 weeks</td></tr>
</table>

IM=intramuscular; IR=Immediate release; MED=morphine equivalent dose; q1w=once weekly; q4w=once monthly; R=randomization.

Note: Figure 2 represents entire participation of rollover subjects who continued on from the Double-Blind Treatment Period of the study into the Open-Label Safety Extension Phase. Subjects were not required to participate in the Double-Blind Follow-Up Period and could proceed directly into the Open-Label Safety Extension Phase. A maximum gap of 28 days was allowed between the end of the Double-Blind Phase and the start of the Open-Label Safety Extension Phase. Subjects who started treatment in the Open-Label Safety Extension Phase more than 28 days after the Double-Blind Phase were considered to be de novo.

[1]One supplemental dose with 4 or 8 mg CAM2038 q1w was permitted at the discretion of the Investigator on Days 3 to 5 after the first 4- or 8-mg injection of CAM2038 for subjects experiencing significant pain. Titration was performed weekly up to 10 weeks. The Follow-up Period was 4 weeks after the Open-Label Safety Extension Phase.

Figure 8*:* **Overview of Open-Label Safety Extension Phase for De Novo Subjects**



[1] One supplemental dose was allowed at the discretion of the Investigator on Day 3-5 after the first 4 or 8 mg injection CAM2038 for subjects experiencing significant pain. Titration was weekly up to 10 weeks. Follow up was within 4 weeks after the Open-Label Safety Extension Phase.

Study participants

Inclusion criteria double blind phase

1. Written informed consent provided prior to the conduct of any study-related procedures.
2. Male or non-pregnant, non-lactating female subject, greater than or equal to 18 years old.
3. Body mass index (BMI) between 18 and 38 kg/m2, inclusive.
4. Treated with daily opioids for moderate to severe CLBP for a minimum of 3 months prior to screening.
5. On a stable dose of ≥40 mg/day of oral morphine or MED during the 14 days prior to screening. Prior to implementation of Amendment #7 dated 1 May 2017 only patients on a stable dose of ≥80 mg/day of oral morphine or MED were eligible)
6. Systolic blood pressure ≥100 mmHg and diastolic blood pressure ≥60 mmHg.
7. Female subject of childbearing potential who was willing to use a reliable method of contraception during the entire study (screening to final follow-up). To be considered not of childbearing potential, female subjects must have been surgically sterile (hysterectomy or bilateral oophorectomy, or bilateral tubal ligation with surgery at least 6 weeks before screening).
8. Male subject who was willing to use reliable contraception.
9. Willing and able to comply with all study procedures and requirements.

Exclusion criteria double blind phase

1. Positive for hepatitis B surface antigen, hepatitis C RNA, or antibodies to human immunodeficiency virus (HIV).
2. Clinically significant symptoms, medical conditions, or other circumstances which, in the opinion of the Investigator, would have precluded compliance with the protocol, adequate cooperation in the study, or obtaining informed consent, or may have prevented the subject from safely participating in the study, including the following:
    a. Severe respiratory insufficiency, respiratory depression, airway obstruction, gastrointestinal motility disorders, biliary tract disease, severe hepatic insufficiency, or planned surgery; or

b. Bipolar disorder.

3. Current diagnosis of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defined moderate to severe substance use disorder (including alcohol), other than caffeine or nicotine.
4. Female subject who was planning to become pregnant during the study.
5. Surgical procedure(s) for CLBP within 6 months prior to screening.
6. Concomitant disease(s) that could have prolonged the QTcF interval, such as autonomic neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, Long QT Syndrome, or family history of Long QT Syndrome.
7. QTcF >450 ms for males and >470 ms for females, or clinically significant electrocardiogram (ECG) abnormality at screening, at the Investigator's discretion.
8. Currently taking medications that had the potential to prolong the QTcF interval or may have required such medications during the course of the study and had clinically significant abnormalities on screening ECG readings, as determined by the Investigator.
9. A nerve or plexus block, including epidural steroid injections or facet blocks, within 1 month prior to screening or botulinum toxin injection in the lower back region within 3 months of screening.
10. History of chemotherapy or confirmed malignancy (except basal cell carcinoma) within the past 2 years.
11. Any other acute or chronic pain condition that could have interfered with the subject's ability to report his or her CLBP accurately and consistently and/or interfered with the study staff's ability to assess the subject's CLBP.
12. An active or pending workman's compensation, insurance claim, or litigation related to back pain (i.e., primary claim was back pain).
13. Clinically significant history, in the opinion of the Investigator, of suicidal ideation or evidence that the subject was actively suicidal.
14. Clinically significant history of major depressive disorder that was poorly controlled with medication, per Investigator judgment.
15. Hypersensitivity or allergy to BPN, other opioids, or excipients of CAM2038.
16. Hypersensitivity or allergy to acetaminophen.
17. Use of strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4), such as some azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., clarithromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir) within the 30 days prior to screening.
18. Used or planned to use natural supplements that could have affected CYP3A4, such as St. John's Wort, throughout the study.
19. Had a major bleeding disorder, such as hemophilia, or was treated with high levels of anticoagulants per the Investigator's discretion.
20. Current or confirmed past diagnosis of Sphincter of Oddi dysfunction.
21. Had a significant hepatic disease, as indicated by screening clinical laboratory assessment results (aspartate aminotransferase, alanine aminotransferase, or lactate dehydrogenase values ≥3 × the upper limit of normal [ULN]) or had a creatinine value >1.5 × ULN).
22. An employee of the Investigator or the study site with direct involvement in the study or other studies under the direction of the Investigator or study site or a family member of the Investigator.
23. Any pending legal action that could have prohibited participation in or compliance with the study.

<u>Criteria for entry to open label titration period</u>

1. After at least a 12-hour washout from the last IR morphine dose, subject must have had a COWS score ≥5 and an API pain score over the past 24 hours ≥5 in order to receive a test dose of Buprenex.
2. Subject passed all baseline criteria, including a normal QTcF, had no change in QTcF >30 ms at 1 hour after the test dose with Buprenex (Amendment 5 Dated 09 NOV 2016 updated the ECG criterion following administration of the Buprenex test-dose from a QTcF threshold from "changes >10 ms" to "changes >30 ms") and had a COWS score <5 after the test dose with Buprenex.

Note:

- Subjects who were taking BPN at screening did not transition to IR morphine, but were required to participate in the down titration and refrain from taking BPN for 12 to 24 hours to achieve the desired washout prior to receiving the Buprenex test dose.
- Subjects who were taking BPN at screening were required to follow the same Day 1 procedures (e.g., confirmation of pain scores, COWS assessment, and Buprenex test dose) as subjects not taking BPN at screening.

Criteria for randomization into the double-blind treatment period

1. Subjects had been on a stable dose of CAM2038 q1w for at least 2 consecutive weeks.
2. CAM2038 was titrated to a dose that provided analgesia (i.e., 7-day API score of ≤4 and at least 2 points below the value at the start of the Open-Label Titration Period) and was well tolerated for 7 days before randomization.
3. Required no more than an average of 1 dose of hydrocodone/acetaminophen 5 mg/325 mg/day during the previous 7 days prior to randomization. (Note prior to implementation of Amendment 5 dated 9 Nov 2016, the upper limit for rescue therapy was 30 mg/1950 mg hydrocodone/acetaminophen during 4 of the 5 days prior to randomization.)
4. Demonstrated study medication (CAM2038) compliance ≥80% during the previous 14 days.
5. Demonstrated daily compliance with pain intensity scoring for ≥11 of the previous 14 days, including the previous 3 days prior to randomization.

Criteria for entering the extension phase

Rollover subjects:

1. Signed the informed consent for the Open-Label Safety Extension Phase.
2. Completed the Double-Blind Phase of the study.

Inclusion criteria de-novo subjects (note exclusion criteria were the same as for the double blind phase):

1. Written informed consent provided prior to the conduct of any study-related procedures.
2. Male or non-pregnant, non-lactating female subject, greater than or equal to 18 years old.
3. BMI between 18 and 38 kg/m2, inclusive.
4. Treated with daily opioids for moderate to severe chronic pain disorder such as CLBP or osteoarthritis for a minimum of 3 months prior to screening.
5. On a stable dose of ≥40 mg/day of oral morphine or MED during the 14 days prior to screening.
6. Systolic blood pressure ≥100 mmHg and diastolic blood pressure ≥60 mmHg.
7. Female subject of childbearing potential who was willing to use a reliable method of contraception during the entire study (screening to final follow-up). To be considered not of childbearing potential, female subjects had to be surgically sterile (hysterectomy or bilateral oophorectomy, or bilateral tubal ligation with surgery at least 6 weeks before screening).
8. Male subject who was willing to use reliable contraception.
9. Willing and able to comply with all study procedures and requirements.

Inclusion criteria for the open label titration period and the open label enrolment period were similar to those for open label titration and randomisation periods of the double blind controlled phase.

Treatments

Transition Period (Post-Screening to Test Dose/Day 1)

During the Transition Period, subject's current opioid dose was down-titrated by approximately 25% per day to ≤80 mg/day MED for subject whose screening MED was ≥80 mg/day; or to ≤40 mg/day MED for subject whose screening MED was between 40 mg and 79 mg/day

With the exception of subjects down-titrating their BPN doses*, subjects were transitioned to an IR morphine for at least 2 days before they entered the Open-Label Titration Period as follows:

- 15 mg QID - subjects whose screening opioid dose was ≥80 mg/day MED
- 15 mg TID - subjects whose screening opioid dose was between 40 and 79 mg/day MED

*Subjects who were taking BPN at screening did not transition to IR morphine, but were required to refrain from taking BPN for 12 to 24 hours as a washout.

Test Dose (Day 1 of Open-Label Titration Period)

Subjects were required to refrain from IR morphine for at least 12 hours or from their previous BPN dose for 12 to 24 hours in order to receive the test dose of BPN (IM Buprenex 30 mg).

Open-Label Titration Period

Subjects who tolerated the Buprenex test dose received the following treatments:

- 4 mg CAM2038 q1w - subjects whose screening opioid dose was between 40 and 79 mg/day MED
- 8 mg CAM2038 q1w - subjects whose screening opioid dose was ≥80 mg/day MED

During the first week of the Open-Label Titration Period, subjects who experienced significant pain could, at the discretion of the Investigator, receive a second dose of CAM2038 q1w (i.e. a supplemental dose) at their respective doses on Day 3, 4, or 5. After the first week, subjects attended weekly clinic visits where additional dose adjustments could be made by increasing or decreasing the dose level of CAM2038 q1w.

At the end of the Open-Label Titration Period, subjects who were receiving:

- 4, 8, or 12 mg CAM2038 q1w were randomized to continue their respective 4, 8, or 12 mg CAM2038 q1w dosing, or to receive corresponding placebo q1w, for a total treatment duration of 12 weeks (12 injections in the Double-Blind Treatment Period).
- 16, 24, or 32 mg CAM2038 q1w were randomized to receive CAM2038 q4w (64, 96, or 128 mg according to dose conversions) or to receive corresponding placebo q4w, for a total treatment duration of 12 weeks (3 injections in the Double-Blind Treatment Period).

Table 7*:* **Dose Conversions between Weekly (q1w) and Monthly (q4w) CAM2038**

CAM2038 q1w Dose	CAM2038 q4w Dose
16 mg	64 mg
24 mg	96 mg
32 mg	128 mg

Open-Label Safety Extension Phase

The dose titration schedule below provides guidance that was used regarding titration of doses for rollover subjects upon enrollment into the Open-Label Safety Extension Phase of the study following participation in the Double-Blind Treatment Period.

- All subjects were started on CAM2038 weekly during the open-label safety extension.
- Subjects completing the Double-Blind Phase on 4, 8, or 12 mg CAM2038/placebo q1w continued on the same dose of active treatment (open-label CAM2038) without need for titration.
- Subjects completing the Double-Blind Phase on 64, 96, or 128 mg CAM2038/placebo q4w begun open-label treatment at the corresponding equivalent weekly dose they last received prior to transition to the monthly dosing regimen. The subject could transition to monthly dosing upon return to the clinic 1 week following the initial dose. The Investigator used his or her discretion to extend the transition period or to down-titrate the subject, in case of poor tolerability.

Table 8*:* **Open-Label Safety Extension Phase Dose Schedule for Rollover Subjects**

Dose in the Double-Blind Treatment Period	Titration Schedule
4 mg CAM2038/placebo q1w	Remained at 4 mg CAM2038 q1w
8 mg CAM2038/placebo q1w	Remained at 8 mg CAM2038 q1w
12 mg CAM2038/placebo q1w	Remain at 12 mg CAM2038 q1w
64 mg CAM2038/placebo q4w*	Started at 16 mg CAM2038 q1w
96 mg CAM2038/placebo q4w*	Started at 24 mg CAM2038 q1w
128 mg CAM2038/placebo q4w*	Started at 32 mg CAM2038 q1w

See methods (open label titration and double blind treatment periods)

Objectives

The primary objective of this study was to evaluate the efficacy of long-acting SC injectable depots of BPN (CAM2038 q1w and CAM2038 q4w) compared to placebo on average pain intensity (API) scores, as measured on an 11-point, numerical rating scale (NRS-11) in subjects who were currently taking daily opioids for moderate to severe CLBP.

The secondary objectives of the study were:

- To evaluate change from baseline in the weekly average of (daily) worst pain intensity (WAWPI) scores at Week 12 of the Double-Blind Treatment Period based on the NRS-11.
- To evaluate the safety and tolerability of treatment with CAM2038 q1w and CAM2038 q4w in subjects currently taking daily opioids for moderate to severe CLBP.

Open label extension phase objectives

The primary objective of the Open-Label Safety Extension Phase was to evaluate the safety and tolerability of treatment with CAM2038 q1w and CAM2038 q4w for at least 52 weeks in subjects with moderate to severe chronic pain requiring daily treatment with opioids. (Note: In the protocol and statistical analysis plan (SAP) it stated "up to 52 weeks", but to collect a full year of safety data, the data was collected for "at least 52 weeks").

The secondary objectives of the Open-Label Safety Extension Phase were:

- To evaluate the steady-state PK of BPN for CAM2038 q1w and CAM2038 q4w in subjects with moderate to severe chronic pain requiring daily treatment with opioids.

- To evaluate the efficacy and safety of CAM2038 q1w and CAM2038 q4w administration for at least 52 weeks in the treatment of subjects with moderate to severe chronic pain requiring daily treatment with opioids. (Note: In the protocol and SAP it stated "up to 52 weeks", but to collect a full year of safety data, the data was collected for "at least 52 weeks").

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline in weekly average of (daily) average pain intensity (WAAPI) and the primary time point was Week 12 of the Double-Blind Phase.

Secondary endpoints (per final protocol):

- Change from baseline in the weekly average of (daily) worst pain intensity (WAWPI) scores at Week 12 of the Double- Blind Phase, based on an NRS-11 (11 point rating scale from 0 to 10).
- Percentage of subjects with a 30% or greater decrease in average pain intensity (API) from baseline to Week 12 of the Double-Blind Phase.
- Rescue medication usage (number of days used and total dose) during the Double-Blind Phase.
- Change from baseline to Week 12 of the Double-Blind Phase in EQ-5D-5L score.
- Change from baseline to Week 12 of the Double-Blind Phase in Work Productivity and work productivity and activity impairment (WPAI) score.
- Time to loss of efficacy, defined as discontinuation of study drug for lack of efficacy.

Exploratory endpoints (per final protocol):

- Change from baseline to Week 12 of the Double-Blind Phase in Clinical Global Impression of Improvement (CGI-I) scale (as assessed by the Investigator).
- Change from baseline to Week 12 of the Double-Blind Phase in Patient Global Impression of Improvement (PGI-I) scale (as assessed by the subject).

Sample size

Considering a titration success rate of 60%, it was planned that this study would enrol approximately 875 subjects in order to randomize 340 subjects to study drug treatment in the double-blind treatment phase.

It was estimated that 170 subjects per treatment group would provide 90% power with a 2-sided test at a 5% significance level and standard deviation of API at Week 12 of 2.0 to detect a treatment difference of 0.7 units (or a standardized effect of 0.35) in change from baseline in the WAAPI scores at Week 12. The statistical test on which the sample size calculation was based was not stated in the study protocol or SAP.

Enrolment in the Open-Label Safety Extension Phase continued until a sufficient number of subjects were recruited to obtain at least 52 weeks of exposure safety information in 100 subjects; however, because Site 077 was terminated, this target was not met (58 patients were exposed to CAM2038 continuously for ≥52 weeks in trial HS-16-555) and additional subjects were not enrolled to meet this target.

Randomisation

Subjects who met the eligibility criteria were randomized in a 1:1 ratio (Group 1: active CAM2038 SC injections or Group 2: placebo SC injections). Initially randomisation was performed without stratification. The original randomisation schedule was retired and all subsequent randomisations were stratified based on double blind dosing regimen: patients who were titrated to the lower dose levels of CAM2038 at the end of the titration period (4, 8 or 12 mg CAM2038 q1w) were randomised to either CAM2038 weekly or placebo weekly, while patients who were titrated to the higher dose levels of CAM2038 at the end of the titration period (16, 24 or 32 mg CAM2038 q1w) were randomised to either CAM2038 monthly or placebo monthly. This change was documented in protocol amendment 7, dated 01 MAY 2017.

The trial used central randomisation using a web-based Interactive Response Technology (IRT) system. The original and updated randomization schedules were generated by an independent statistician and loaded into the system. In each case, the block size for treatment randomisation was 4 and the number of blocks for treatment randomisation was 150 (for a total of 600=4 x 150 patients).

Blinding (masking)

The study was double blinded during the double blind period. 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.

There was a slight difference in colour and fill volume between the placebo and active CAM2038 q4w; however, the viscosity was the same. To maintain the blind given the differences in colour and fill volume, the following processes were implemented during the Double-Blind Treatment Period:

- The injecting clinician and any other staff involved in the injection process did not participate in subject evaluations, nor did they discuss any information regarding the injections with the subjects or other study staff.
- To keep the subjects blinded, appropriate steps were taken to ensure that the subject was unable to view the syringe at all times.
- The study staff did not ask the injecting clinician or any other staff member involved in the injection process for information regarding subject group assignment that might have inadvertently unblinded the study staff.

Under normal circumstances, the blind was not to be broken until all subjects had completed treatment. In case of emergency, and only if the information was required by the Investigator to ensure the subject's safety in managing a medical condition, the treatment could have been unblinded at the site by using a code break module.

Statistical methods

Statistical Analysis Plan

Separate statistical analysis plans were prepared for the double-blind treatment and open-label safety extension phases of study HS-16-555.

The final version (v1.0) of the SAP for the double-blind treatment phase is dated 31 AUG 2018. The last subject completed the double-blind treatment phase on 09 MAY 2018 and the date of database lock was 10 SEP 2018.

The final version (v2.0) of the SAP for the open-label extension phase is dated 29 APR 2019; version 1.0 of the SAP is dated 03 APRIL 2019. This SAP was completed after the double-blind treatment phase data were unblinded but prior to the open-label safety extension phase database lock on 03 MAY 2019.

The final versions of both SAPs are based on version 10.0 (amendment 9) of the study protocol, dated 12 APR 2018.

Changes to the planned analyses

Several changes to the analysis populations, analyses, endpoints and confirmatory testing strategy for the double-blind treatment phase were made prior to study unblinding. These changes were reflected in the final SAP (for the double-blind treatment phase) but not in the final protocol (v10.0): the applicant stated that a protocol amendment was not prepared with these revisions because the last subject's last visit in the double-blind treatment phase had already occurred. Differences between the final SAPs for the double-blind treatment and open-label safety extension phases and the final study protocol were summarised in the CSR. The most important changes to the planned analyses are summarised below:

Changes to the Population Definitions

- The primary analysis population was changed from an ITT population to a modified-ITT population in the SAP due to concerns related to the two clinical sites whose participation in the study was terminated as a result of major GCP violations (sites 068 and 077).
- For the primary safety summaries, data from Sites 068 and 077 were excluded due to an inability to verify compliance with AE reporting requirements, leading to a possible underreporting of AEs. Supportive safety summaries including data from these sites were provided for completeness.
- The definition of the Per-Protocol (PP) population was changed to be based on the mITT rather than ITT population.

Changes to the Endpoint Analyses

Primary Efficacy Endpoint in the double-blind treatment period:

- Per protocol, electronic diaries were to be used for capturing the subjects' pain scores throughout the study. However, there were certain geographical areas where connectivity issues were reported with the electronic diaries. As a result, sites were permitted to utilize a paper diary in situations where consistent connection issues were observed; however, this was not updated in the study protocol. In the Double-Blind Treatment Phase 86 subjects (173 subjects including Site 077) used paper diaries, in the Open-Label Safety Extension Phase 44 subjects (85 including Site 077) used paper diaries. For this reason, the primary endpoint data were based only on the electronic diary data, and additional sensitivity analyses were performed using paper diary data.

Secondary Efficacy Endpoints in the double-blind treatment period:

- Per protocol, the percentage of subjects with a 30% or greater decrease in API from baseline to Week 12 of the Double-Blind Treatment Period was proposed. This endpoint was revised in the SAP to consist of the percentage of subjects with a 30% and 50% or greater decrease in API from the Open-Label Titration Period baseline to Week 12 of the Double-Blind Treatment Period. A 50% or greater reduction was tested first in the hierarchy. The baseline used to calculate the percent improvement was clarified to be the last observation obtained prior to first injection of CAM2038 (titration baseline) rather than the time subjects were randomized, since by the time of randomisation, subjects' pain was effectively managed and no further improvements, especially for placebo, was expected.
- Change from baseline to Week 12 of the double-blind treatment period in the PGI-I scale (as assessed by each subject) was added to the testing hierarchy in the SAP; the endpoint was previously an exploratory endpoint. The applicant stated that this endpoint was added because it is a standard quality of life assessment used in clinical studies for chronic pain.
- Per protocol, rescue medication usage (number of days used and total dose used) during the double-blind phase was to be assessed; however, as is described in the SAP, there were technical issues with the collection of rescue medication data. In some cases, subjects entered data multiple times (i.e. more than 30 times per day), possibly due to poor connectivity. The applicant stated that drug reconciliation data supports that many of these entries were replicate entries, in error. As a result of these issues, the data for total rescue medication dosage was not reliable. Therefore, the electronic diary was utilised to derive only the number of days that rescue medication was utilised. The definition of the endpoint was revised accordingly and this endpoint was moved from fourth to last place in the testing hierarchy. In some cases, a paper diary may have been used as an exception; however, endpoint analyses were based only on e-diary data.

Changes to the confirmatory testing strategy

- The testing hierarchy was revised in the SAP to promote time to loss of efficacy from the last endpoint tested to the 5th endpoint tested and move rescue medication days to the last endpoint tested. This CSR states that this change was primarily a result of the issues in data collection for rescue medication usage.

- Additionally, as mentioned above, the 50% responder rate was added and placed in the hierarchy before 30%, and the PGI-I scale was added and placed in the hierarchy before the WPAI and the EQ-5D-5L endpoints. The CSR states that these changes were made based on clinical relevance.

Post-hoc analyses

A number of post-hoc analyses, not specified in the final SAP, were performed and presented in the CSR. The applicant stated that the rationale for generating most of the additional tables was because these tables were inadvertently missed from the original analysis, or in order to align the Double-Blind Treatment Phase tables with those generated for the Open-Label Safety Extension Phase. In addition, a series of subgroup analyses were carried out for the primary efficacy endpoint (change from baseline in WAAPI to Week 12) that were also missing from the original SAP-derived output (i.e., by sex, age, race, and for the post hoc per-protocol population).

Importantly, the PP Population defined in the SAP for the double blind treatment phase was not used for any analyses as the study sponsor failed to define any major protocol deviation criteria prior to database lock. The study sponsor instead conducted a review of all protocol deviations after database lock, excluding subjects with major protocol deviations from the post hoc PP population; this post hoc PP Population was then used for all per-protocol analyses reported in the CSR.

Analysis Populations

Four analysis populations were used for the randomized double-blind treatment phase of the study; these populations were modified from the original protocol, as summarized above.

Double-blind treatment period

The **Randomized Population** consisted of all subjects who had been assigned random treatment.

The **modified Intent-to-Treat (mITT) Population** consisted of all randomised subjects with the exclusion of subjects from Sites 068 and 077 due to persistent site non-compliance. The mITT population was the primary analysis population.

The **Primary Safety Population** included all subjects from sites other than 068 and 077 who had received any dose of CAM2038 on Day 1 of the Open-Label Titration Period. Analyses based on this population grouped subjects according to the treatment they received rather than the treatment they were randomised to receive.

The **Safety Population** consisted of all subjects who had received any dose of CAM2038 on Day 1 of the Open-Label Titration Period. Analyses based on this population grouped subjects according to the treatment they received rather than the treatment they were randomized to receive.

No analyses were conducted using the per-protocol population described in the SAP. The **post-hoc Per Protocol (PP) population** was used for post-hoc per protocol efficacy analyses; it was based on the mITT population and excluded subjects with major protocol deviations as determined after the database lock. In general, subjects with deviations that could have impacted on the efficacy results were excluded from the post hoc PP Population.

Open-label safety extension phase

Note that no subjects from Site 068 were enrolled in the open-label safety extension phase.

The **Overall Safety Population** consisted of all subjects who received at least 1 dose of CAM2038 in the Open-Label Safety Extension Phase (including Open-Label Titration Period for de novo subjects). Results were presented both including and excluding data for Site 077.

The **Treatment Completion Population** consisted of all subjects who were enrolled into the Open-Label Safety Extension Phase and completed treatment. Results were presented both including and excluding data for Site 077.

The **Integrated Full Exposure Safety Populations** consisted of all subjects who had been exposed to study drug for at least 52 weeks, where exposure included the drug exposure to CAM2038 or placebo in the Double-Blind Phase (including Open-Label Titration Period for these subjects). Results were presented both including and excluding data for Site 077.

The 2 sub-populations included the following:

- subjects who completed the study with 52 weeks or more of exposure to CAM2038 in the double-blind and open-label safety extension phases.
- subjects who completed the study with 52 weeks or more of exposure to study drug, i.e. rollover subjects who completed the double-blind and open-label safety extension phases and were randomized to either CAM2038 or placebo in the double-blind treatment period, and de novo subjects who completed 52 weeks of treatment in the open-label safety extension phase.

The **modified Intent-to-Treat (mITT) Population** consisted of all subjects with efficacy data, excluding subjects from Site 077. Efficacy analyses were based on the mITT Population.

- For rollover subjects who were randomised to CAM2038 in the Double-Blind Treatment Period, data from the Open-Label Titration Period, the Double-Blind Treatment Period and the Open-Label Enrolment Period were included.
- For rollover subjects who were randomised to placebo, data were to be presented only for the Open-Label Titration Period of the Double-Blind Phase and the Open-Label Enrolment Period of the Open-Label Safety Extension Phase; however, in the analysis, data were presented also for the Double Blind Treatment Period.

The **PK population** consisted of all subjects who received CAM2038 in the Open-Label Safety Extension Phase from whom at least 1 measurable plasma concentration of BPN was obtained.

Type I error control

There was only one primary comparison for the double-blind treatment phase of the study. The null hypothesis of no treatment difference was tested at a two-sided significance level of 0.05 for the primary and each secondary efficacy endpoint in the following order:

1. Change from baseline in the weekly average of (daily) average pain intensity score (WAAPI) at week 12
2. Change from baseline in the weekly average of (daily) worst pain intensity (WAWPI) scores at week 12 of the Double-Blind Treatment Phase
3. Percentage of subjects with a 50% or greater decrease in API from the Open-Label Titration Phase baseline to week 12 of the Double-Blind Treatment Phase
4. Percentage of subjects with a 30% or greater decrease in API from the Open-Label Titration Phase baseline to week 12 of the Double-Blind Treatment Phase
5. Time to loss of efficacy, defined as discontinuation from the study or study drug for lack of efficacy
6. Change from baseline to week 12 of the Double-Blind Treatment Phase in PGI-I scale (as assessed by the subject)
7. Change from baseline to week 12 of the Double-Blind Treatment Phase in WPAI score
8. Change from baseline to week 12 of the Double-Blind Treatment Phase in EuroQoL Group EQ-5D-5L score
9. Rescue medication usage (number of days) during the Double-Blind Treatment Phase

In order to protect the family-wise type I error rate at the 0.05 level, the null hypothesis for each endpoint in the hierarchy could not be rejected unless the null hypotheses for all preceding endpoints had also been rejected.

As previously stated, the hierarchy of the secondary endpoints was revised during the finalisation of the SAP and prior to database lock.

Analysis of primary endpoint – Change from baseline in the weekly average of daily average pain intensity score (WAAPI) at week 12

WAAPI scores were calculated for each weekly interval (i.e., 7-day intervals) relative to randomisation date for all subjects. The baseline WAAPI score was the WAAPI at Week 0. WAAPI at Week 0 was the average of available (non-missing) APIs captured during the 7 days prior to randomisation date. WAAPI at Week 12 was the average for the APIs captured from Day 78 to Day 84. The changes from baseline at any post-baseline time point were calculated as baseline minus post-baseline, so that a positive change was indicative of improvement.

The primary analysis for the double-blind treatment period was performed based on the mITT Population.

WAAPI over time was performed by longitudinal data analysis using mixed-model repeated measures (MMRM) methods. All post-randomisation baseline observations were utilised; missing values were not imputed (only observed values were used in the data analysis). The model included treatment, post-baseline weeks, treatment by week interaction as fixed effects, and baseline WAAPI as the covariate. The covariance was assumed to be unstructured. If the estimates did not converge, SAS default covariance structure (variance components) was assumed. The estimated treatment effects, treatment differences, and the 2-sided 95% CIs of the treatment differences at all post-baseline time points were presented.

Handling of missing data in primary endpoint

The MMRM method is valid if the "missing at random" assumption holds. The applicant highlighted that the study was designed to minimise missing values:

(a) Subjects who discontinued taking study medication were permitted to remain in the study, and safety and efficacy data could continue to be collected from these subjects;
(b) Liberal use of rescue medication was allowed during the study, and data collection continued even after subjects took rescue medications, and
(c) Robust efficacy data collection procedures were used in the study.

As the MMRM analysis does not impute missing values, sensitivity analyses with various missing value imputation methods were performed. Sensitivity analyses based on the a) Random Replacement Method and b) Tipping Point Method were performed to assess the robustness of the primary efficacy data.

Random replacement method

Missing change from baseline in WAAPI at Week J were imputed with randomly generated values from a normal distribution using a seed of 153928221. The normal distribution was assumed to have a mean x and a standard deviation of y, where x and y are the mean and standard deviation of the changes at Week J based on all subjects (i.e., subjects from both treatment groups) with non-missing values. The applicant noted that, if treatment is effective, the results of this missing value imputation method will be more conservative (i.e., biased in favour of the control).

Tipping point method

Missing change values at Week J from placebo subjects were imputed with the value that is equal to the mean changes among placebo subjects at that week. Missing change values from active treatment subjects were imputed with the value that was k% worse than the mean WAAPI from the placebo group at that week, where k=0, 5, 10, 20, 30, 40…100, until tipping (i.e., the treatment difference at Week 12 is no longer significant at a two-sided significance level of 0.05).

Additional sensitivity analyses included:

- Inclusion of paper diary data for the primary analysis - the primary efficacy variable was analysed including available paper diary data collected.
- Exclusion of weekly average diary entries that did not have at least 5 daily entries during randomisation baseline week (Week -1) and at the end of treatment (Week 12) – the primary efficacy variable was analysed after treating WAAPI for any given week as missing if average pain scores were available for less than 5 days in that week.
- Exclusion of subjects who did not complete at least 4 weeks of treatment - the primary efficacy variable was analysed in subjects who participated in the study for at least 4 weeks of the Double-Blind Treatment Phase.
- Exclusion of subjects who did not complete at least 8 weeks of treatment - the primary efficacy variable was analysed in subjects who participated in the study for at least 8 weeks of the Double-Blind Treatment Period.

Analysis of ranked secondary endpoints

Change from Baseline in the Weekly Average of Daily WPI Scores at Week 12 of the Double-Blind Treatment Phase

This variable, based on an NRS-11, over time was analysed using MMRM methods (consistent with analyses used for the primary efficacy variable). Briefly, the model included treatment, post-baseline weeks, treatment by week interaction as fixed effects, and baseline WPI as the covariate. The primary comparison was the treatment difference at Week 12.

Proportion of Responders with a ≥30% and ≥50% Reduction from the Open-Label Titration Period Baseline in API Score to week 12 of the Double-Blind Treatment Phase

Percent reduction from the Open-Label Titration Period baseline in NRS-11 score was derived as 100*(Titration Baseline pain score – Week 12 API) /(Titration Baseline pain score). A subject was a responder if the percent reduction was at least 30% and 50%. A subject with missing week 12 API was considered a non-responder.

This variable was analysed using the chi-square test. The percentages, the difference of the percentages, and the 2-sided 95% CI of the treatment difference are presented. The 95% CI of the treatment difference were calculated using normal approximation.

A post hoc analysis was completed which summarized percentage of subjects with a 30% or greater decrease in API score from the Open-Label Titration Period baseline and Screening baseline to Week 12. A post hoc responder analysis was also completed for the percentage of subjects with a 30% or greater and 50% or greater decrease in API from Screening baseline to Week 12 of the Double-Blind Treatment Period.

Time to Loss of Efficacy

Lack of efficacy was defined as discontinuation from the study or study drug for lack of efficacy. Time to loss of efficacy in days was compared between treatment groups using the log-rank test. The time-to-event "survival" curve was presented using the Kaplan-Meier method. Median time-to-event and the 95% CI of the median times were not presented as they could not be estimated. In these time-to-event analyses, subjects who did not have the event during the entire study were censored at Day 84 (end of Week 12 day).

As a post hoc analysis, the log rank test was repeated using weeks rather than days as the duration unit.

Change from Baseline to week 12 in PGI-I Scale

Change from baseline in PGI-I was evaluated by longitudinal data analysis using MMRM methods (consistent with analyses used for the primary efficacy variable). Briefly, the model included treatment, post-baseline weeks, treatment by week interaction as fixed effects, and baseline PGI-I as the covariate. The primary comparison was the treatment difference at Week 12.

Change from the Open-Label Titration Period Baseline to week 12 of the Double-Blind Treatment Phase in WPAI Score

This variable was analysed using MMRM methods (consistent with analyses used for the primary efficacy variable). Briefly, the model included treatment, post-baseline weeks, treatment by week interaction as fixed effects, and baseline Open-Label Titration Period WPAI as the covariate. The primary comparison was the treatment difference at Week 12.

Change from the Open-Label Titration Period Baseline to week 12 of the Double-Blind Treatment Phase in EuroQoL Group EQ-5D-5L Score

This variable was analysed using MMRM methods (consistent with analyses used for the primary efficacy variable). Briefly, the model included treatment, post-baseline weeks, treatment by week interaction as fixed effects, and baseline Open-Label Titration Period EQ-5D-5L score as the covariate. The primary comparison was the treatment difference at Week 12.

Rescue Medication Usage (Number of Days) During the Double-Blind Treatment Phase

Rescue medication usage was collected from the electronic diaries and in some cases from paper diaries.

There were technical issues with the electronic diaries for rescue medication usage (i.e. duplicate data entries due to poor internet connectivity). As a result, the total rescue dosage was not reliable. Therefore, only the electronic diary source of rescue medication usage was utilised to derive the number of days of rescue medication use.

The number of days that rescue medication was used was normalized on a weekly basis in the analysis (i.e., number of days that rescue medication was used per week) based on the electronic diaries. Specifically, number of days that rescue medication was used per week was derived as 7*(X/Y), where X=total number of days that rescue medication was taken during the week and Y=total number of days that diaries were available in that week. This variable was analysed using MMRM methods for longitudinal data analysis (consistent with analyses used for the primary efficacy variable). It is noted that the primary comparison for this endpoint was not explicitly stated in the SAP.

Analysis of efficacy endpoints – Open-Label Safety Extension Phase

Twenty-four hour API, WPI and rescue medication use was collected daily by electronic diary. Paper diary entries were collected in situations where electronic diary transmission issues occurred and where electronic diaries were unavailable. For cases where both electronic and paper diaries were available, only the data from the electronic source was used. Pain-related efficacy evaluation was based on electronic diary data only.

Efficacy evaluation in the Open-Label Safety Extension Phase was not the primary objective. All efficacy variables were summarized using the efficacy population in a manner similar to the methods discussed for the Double Blind Treatment Phase with baseline assessments completed prior to dosing on Visit 14 for both de novo subjects and rollover subjects (i.e. the enrollment visit for de novo subjects and the randomisation visit for rollover subjects). The efficacy variables included the following:

- Change from baseline in the WAAPI scores over time based on an NRS-11;
- Change from baseline in the WAWPI scores over time based on an NRS-11;
- Time to loss of efficacy, defined as discontinuations from the study or study treatment for lack of efficacy;
- Change from baseline in the CGI-I and PGI-I scale over time
- Change from the baseline in WPAI Score (Analysis for WPAI was completed in accordance with the protocol but was not pre-defined in the SAP)
- Change from baseline in EuroQoL Group EQ-5D-5L scores over time; and
- Rescue medication use

These efficacy summaries were presented for the entire mITT Population and for the de novo and rollover subject populations. For rollover subjects who were randomized to placebo, data were to be presented only for the Open-Label Titration Period of the Double-Blind Phase and the Open-Label Enrollment Period

of the Open-Label Safety Extension Phase; however, in the analysis, data were presented also for the Double Blind Treatment Period in the Double-Blind Phase.

In addition to the planned analyses, post hoc analyses were completed for the percentage of subjects with a 30% or greater decrease in API score over time from Titration Baseline and Screening Baseline to end of treatment (i.e., the end of the Open-Label Enrollment Period).

Subgroup analyses

No subgroup analyses were specified in the final SAP or protocol for the double-blind treatment period. Post-hoc subgroup analyses of the primary efficacy variable were performed by sex (male/female), age group (<65 years/ ≥65 years), and race (white/non-white) in the mITT population.

Multicentre study

No analyses of individual centers or treatment-by-center interactions were performed; however, due to persistent non-compliance observed at Site 068 and Site 077, the ITT population was modified to exclude these 2 sites.

Interim analyses

No interim analyses were planned or conducted

.*Results*

Participant flow

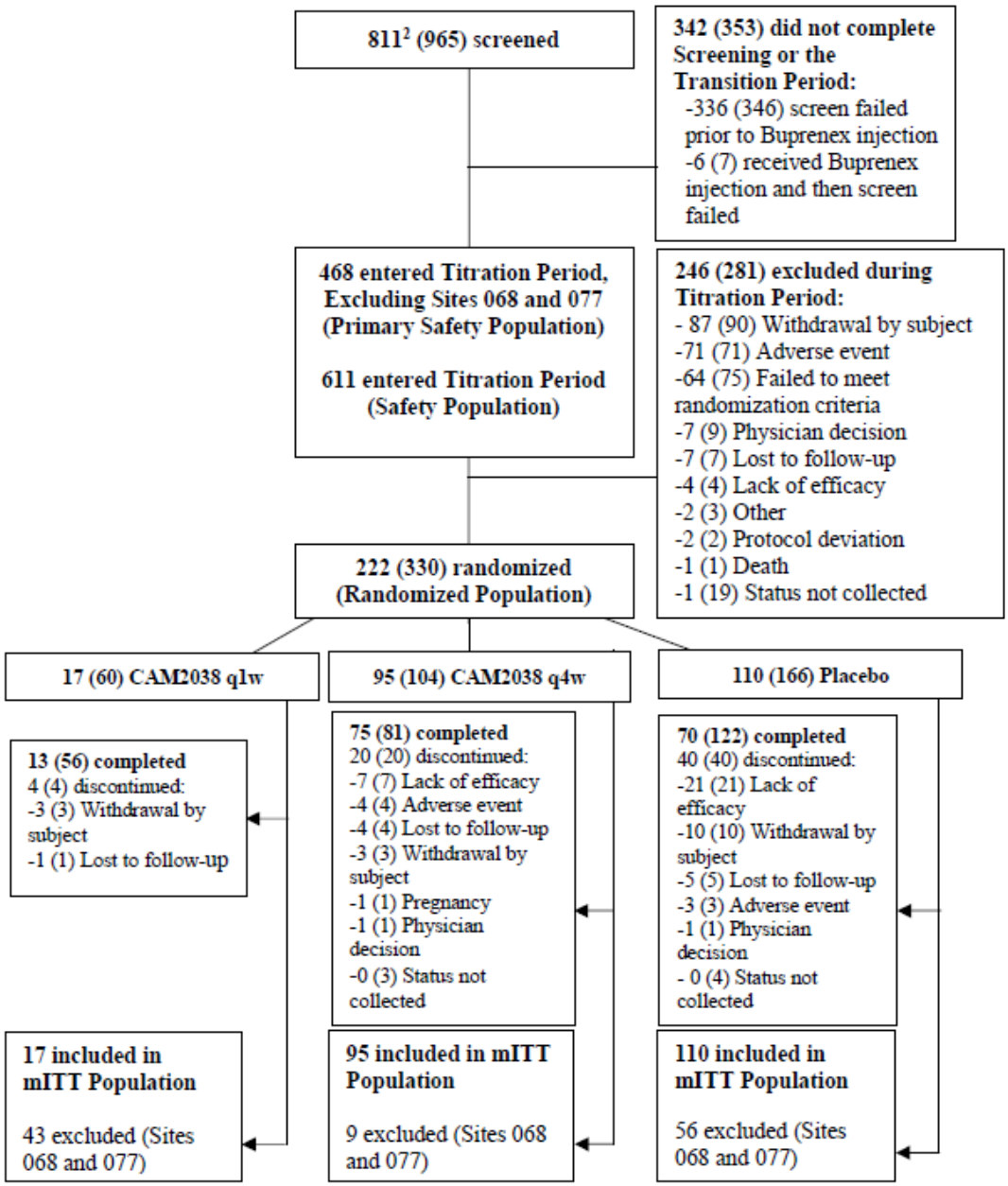
A total of 811 subjects were screened for enrolment into the double blind phase of the study (subjects in sites 068 and 077 were excluded due to potential GCP issues and concerns regarding compliance with reporting of AEs). Of the 881, 468 entered the open label titration period and all received at least 1 dose of CAM2038.

A total of 245/468 subjects (52.4%) discontinued from the Open-Label Titration Period, and 1 (0.2%) subject did not have information collected regarding completion status. The primary reasons for discontinuation were withdrawal by subject (n = 87 [18.6%]), discontinuation due to AE(s) (n = 71 [15.2%]), and failure to meet randomization criteria (n = 64 [13.7%]).

Two hundred and twenty two completed the open label titration period and were randomised to the double blind treatment period (n = 112 CAM2038 and n = 110 placebo).

Overall, 158 subjects (71.2%) completed the Double-Blind Phase; 13/17 subjects (76.5%) in the CAM2038 q1w group, 75/95 subjects (78.9%) in the CAM2038 q4w group and 70/110 subjects (63.6%) in the Placebo group. A higher proportion of subjects in the placebo arm (19.1%) discontinued due to lack of efficacy than in the CAM2038 (6.3%).

Figure 9: **Subject Disposition (Double-Blind Phase [including Sites 068 and 077[1]])**



Source: Listing 16.2.5.5, Table 14.1.1.1, Table 14.1.1.2, Table 14.1.1.3, Table 14.1.1.4 and Table 14.1.1.5.
[1] Subject disposition is presented excluding Sites 068 and 077. Numbers in parentheses represent total counts including Sites 068 and 077.
[2]One additional subject entered the study, but all source data were lost for this subject; therefore, this subject is not counted in the total numbers presented, with the exception of total number enrolled.

Open label extension phase

Excluding Site 077, a total of 57 subjects (CAM2038 n = 24; Placebo n =33) from the Double-Blind Phase (rollover subjects) and 75 de novo subjects, for a total of 132 subjects, received at least one dose of CAM2038 and were included in the Overall Safety Population of the Open-Label Safety Extension Phase. Of the de-novo subjects 20 had actually completed the double-blind phase but had not rolled over to the open label extension within 28 days and were enrolled into the extension phase with new study numbers.

Thirty-nine de-novo and 38 roll over patients completed the extension phase.

Recruitment

The study was conducted in the USA at 83 study sites. The first subject in the double blind phase was enrolled on 13 September 2016 and the last subject completed on 9 May 2018. The first subject was enrolled in the open label extension study on 19 September 2017 and the last subject completed on 8 February 2019. Due to GCP infringements patients at two study sites (068 and 077) were removed from the study.

Conduct of the study

The protocol was amended nine times. The first subject was enrolled under Version 5 of the protocol (dated 1 September 2016).

Patients from two site 068 and 077 were excluded from the efficacy study population due to potential GCP issues, including concerns about data integrity and an inability to verify compliance with AE reporting requirements.

Fifteen subjects received expired drug products during the course of the study.

- 5 subjects received expired IR morphine
- 7 subjects received expired rescue medication (hydrocodone/acetaminophen 5 mg/325 mg)
- 3 subjects received expired CAM2038

None of the subjects were discontinued due to administration of expired study drug, and 8 of the 9 sites underwent additional training to ensure appropriate drug dispensing for the remainder of the study. In the case of 1 study site (Site 033), the protocol deviation was identified at study closeout; therefore, no additional preventative actions were implemented. Two of the 3 subjects who received expired CAM2038 received expired drug during the Open-Label Safety Extension Phase, while the third subject received expired study drug during the final week of the Open-Label Titration Period, prior to being randomized to receive placebo during the Double-Blind Treatment Period. It is therefore unlikely that these protocol deviations related to administration of expired study drug would have impacted the efficacy or safety endpoints.

Just over a third in each treatment arm in the mITT population had at least one CSR-reportable protocol deviation/protocol violation, 41/112 (36.6%) in the CAM2038 arm and 41/110 (37.3%) in the placebo arm. The Applicant has categorised most of the deviations as minor. However a definition for what is considered a major or minor protocol deviation has not been supplied by the Applicant. In fact the Applicant performed a post-hoc review to determine which deviations might have had an impact on efficacy results.

Twenty five (22.3%) in the CAM2038 arm and 27 (24.5%) in the placebo arm took prohibited concomitant medications. This was the most common deviation. Although there were a number of subjects who reported using prohibited concomitant medications, these subjects were not excluded from the post hoc PP Population because it was not possible to determine whether the subjects had been using the prohibited medication prior to study start, without a change in dose during the study.

The next commonest deviation was that related to randomization criterion #2 which required subjects to be titrated to a CAM2038 dose that provided analgesia (i.e., a 7-day API score of ≤4 and at least 2 points below the value at the start of the Open-Label Titration Period), as well as being well-tolerated for 7 days prior to randomization, 6/112 (5.4%) subjects in the CAM2038 group and 3/110 (2.7%) in the placebo group failed to meet this criterion. The remaining deviations are listed in Table 9:

Table 9*:* **Summary of CSR-Reportable Protocol Deviations**

Protocol deviation	**Modified intent to treat population (n [%])**	
	CAM2038 n=112	**Placebo n=110**
Number of subjects with at least 1 deviation	41 (36.6)	41 (37.3)
Entry Criteria		
No. 1 – API	4 (3.6)	2 (1.8)
No. 1 – COWS	4 (3.6)	1 (0.9)
No. 2 QTcF	0	1 (0.9)
Exclusion Criteria		
No. 10 – Chemotherapy or confined Malignancy	1 (0.9)	0
No. 15 – Hypersensitivity	1 (0.9)	1 (0.9)
No. 17 – CYP inhibitors or inducers	1 (0.9)	0
No. 18 – Supplements impacting CYP	1 (0.9)	0
No. 2b – Bipolar disorder	1 (0.9)	2 (1.8)
No. 3 – Substance use disorder	0	1 (0.9)
Inclusion Criteria		
No. 3 – BMI	0	2 (1.8)
No. 5 – Dose at Screening	0	1 (0.9)
No. 6 – Blood pressure	1 (0.9)	1 (0.9)
No. 8 – Male contraception	1 (0.9)	0
Randomization Criteria		
No. 2 – API	6 (5.4)	3 (2.7)
No. 5 – Compliance	3 (2.7)	3 (2.7)
No. 3 – Rescue utilization	3 (2.7)	0
Other		
Informed consent	2 (1.8)	3 (2.7)
Investigational product	0	3 (2.7)
Prohibited concomitant medications	25 (22.3)	27 (24.5)

Source: Table 14.4.17. API=average pain intensity; BMI=body mass index; COWS=Clinical Opiate Withdrawal Scale; CYP=cytochrome; QTcF=QT interval corrected using Frederica's formula.

Baseline data

The mean age in the mITT population for the randomised period was similar in both treatment population (53.7 years in the CAM2038 group and 54.7 years in the placebo group. Fifty-eight-point-nine percent of the CAM 2038 group were female compared to 50.9% in the placebo group. Almost 90% of the study population was White in each treatment arm. Pain scores at the start of the transition open label period were similar in each arm with a mean score of 7 in each arm (Table 10). All study patients in the randomised period had a history of chronic low back pain with 74.1% in the CAM2038 and 78.2% in the placebo arm having a history of bone or joint related pain. Sixteen-point-one percent of those in the CAM2038 arm and 12.7% in the placebo arm reported nerve related pain.

Seventy-eight-point-six percent in the CAM2038 group and 79.1% in the placebo group were treated with natural opium alkaloids prior to the titration phase and 15.2% were treated with oripaine derivatives in the CAM2038 arm and 19.1% in the placebo arm.

The most commonly used individual drugs were oxycodone/acetaminophen (24.1% in the CAM2038 arm 22.7% in the placebo arm%]), oxycodone (18.8% in the CAM2038 arm and 13.6% in the placebo arm), hydrocodone/acetaminophen (12.5% in the CAM2038 arm and 17.3% in the placebo arm, morphine sulfate (16.1% CAM2038 and 12.7% placebo); morphine (10.7% CAM 2038 and 10% placebo), acetylsalicylic acid (32 subjects [14.4%]), buprenorphine 15.2% CAM2038 19.1% placebo.

Table 10: **Demographic Data (Primary Safety and Modified Intent-to-Treat Populations)**

Demographic Variable	Primary Safety Population Total	Modified Intent-to-Treat Population		
	Total N=468	CAM2038 n=112	Placebo n=110	Total N=222
Age (years), mean (SD)	54.1 (11.03)	53.7 (12.19)	54.7 (11.36)	54.2 (11.77)
Sex, n (%)				
Male	214 (45.7)	46 (41.1)	54 (49.1)	100 (45.0)
Female	254 (54.3)	66 (58.9)	56 (50.9)	122 (55.0)
Race, n (%)				
White	401 (85.7)	100 (89.3)	97 (88.2)	197 (88.7)
Black or African American	61 (13.0)	10 (8.9)	12 (10.9)	22 (9.9)
Asian	2 (0.4)	0	1 (0.9)	1 (0.5)
American Indian or Alaskan Native	1 (0.2)	1 (0.9)	0	1 (0.5)
Native Hawaiian or other Pacific Islander	1 (0.2)	1 (0.9)	0	1 (0.5)
Other	2 (0.4)	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	50 (10.7)	11 (9.8)	11 (10.0)	22 (9.9)
Not Hispanic or Latino	414 (88.5)	101 (90.2)	97 (88.2)	198 (89.2)
Unknown/ Not reported	4 (0.9)	0	2 (1.8)	2 (0.9)
Pain Score at Start of Open-Label Titration Period, mean (SD)	7.2 (1.36)	7.0 (1.42)	7.0 (1.39)	7.0 (1.40)
BMI (kg/m^2), mean (SD)	29.2 (5.12)	29.1 (4.78)	29.3 (5.27)	29.2 (5.02)

Source: Table 14.1.2.2 and Post Hoc Table 1
BMI=body mass index; SD=standard deviation

Daily dose of morphine equivalent at screening is shown in Table 11 along with last stable dose of CAM2038 received before randomisation. Almost all participants were receiving a MED of < 200mg daily in both treatment arms. In the CAM2038 arm 38.4% were receiving a MED/day of 40 to 79mg, 21.4% a MED/day of 80 to 99mg and 29.5% a MED/day of 100 to 199mg. In the placebo arm 32.7% were receiving a MED/day of 40 to 79mg, 26.4% of 80 to 99mg and 30% of 100 to 199mg. The majority of patients in both treatment arms transitioned to a depot dose of CAM2038 32mg weekly (56.3% in the CAM2038 arm and 60.9% in the placebo arm). Forty-eight percent of those on a screening MED/day of 40 to 79mg transitioned to the highest depot dose prior to randomisation.

Table 11:

POSTHOC Summary of Screening Morphine Equivalent Dose and CAM2038 Dose at End of Titration Period (mITT Population)								
		Last Stability Dose Received Prior to Randomization						
	MED at	4mg	8mg	12mg	16mg	24 mg	32 mg	Total
Treatment	screening	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
CAM2038 N = 112	40-79mg	4 (3.6%)	4 (3.6%)	4 (3.6%)	8 (7.1%)	4 (3.6%)	19 (17%)	43 (38.4%)
	80-99mg	1 (0.9%)	1 (0.9%)	2 (1.8%)	5 (5.4%)	7 (6.3%)	7 (6.3%)	24 (21.4%)
	100-199mg		1 (0.9%)		3 (2.7%)	3 (2.7%)	26 (23.2%)	33 (29.5%)
	200-299mg					1 (0.9%)	2 (1.8%)	3 (2.7%)
	300-399mg						3 (2.7%)	3 (2.7%)
	≥ 400mg						6 (5.4%)	6 (5.4%)
	Total	5 (4.5%)	6 (5.4%)	6 (5.4%)	17 (15.2%)	15 (13.4%)	63 (56.3%)	112 (100%)
Placebo n = 110	40-79mg	2 (1.8%)	4 (3.6%)	3 (2.7%)	1 (0.9%)	7 (6.4%)	19 (17.3%)	36 (32.7%)
	80-99mg	1 (0.9%)	2 (1.8%)	4 (3.6%)	2 (1.8%)	4 (3.6%)	16 (14.5%)	29 (26.4%)
	100-199mg		1 (0.9%)	1 (0.9%)	3 (2.7%)	4 (3.6%)	24 (21.8%)	33 (30%)
	200-299mg				1 (0.9%)	2 (1.8%)	2 (1.8%)	5 (4.5%)
	300-399mg				1 (0.9%)		3 (2.7%)	4 (3.6%)
	≥ 400mg						3 (2.7%)	3 (2.7%)
	Total	3 (2.7%)	7 (6.4%)	8 (7.3%)	8 (7.3%)	17 (15.5%)	67 (60.9%)	110 (100%)

Concomitant medications

Although concomitant opium alkaloid use during the study was prohibited by protocol unless approved by the Medical Monitor, a number of subjects reported use during the Double-Blind Treatment Period (Listing 16.2.4.5). The majority of subjects (94%; 51 of 54 subjects) in the CAM2038 group, who received opium alkaloids, initiated use after their last dose of CAM2038 (these subjects did not roll over into the Open-Label Safety Extension Phase). In the 3 subjects who did continue to receive CAM2038 in the Open-Label Safety Extension Phase, the opium alkaloid was taken for 1 day only, for the treatment of breakthrough pain and prior to receiving the first dose of CAM2038. For the placebo group, 43 of the 45 subjects (96%) who received opium alkaloids did not continue into the Open-Label Safety Extension Phase. Forty-two (93%) of these subjects started the opium alkaloid after receiving their last injection of placebo, and the one subject who received a subsequent injection was prescribed the opium alkaloid to treat an SAE of appendicitis. In 1 of the 2 subjects who received placebo during the Double-Blind Treatment Period and continued into the Open-Label Safety Extension Phase, the opium alkaloid was taken for the treatment of breakthrough pain, prior to receiving treatment with placebo in the Double-Blind Treatment Period, and subsequently, the Open-Label Safety Extension Phase. In the second subject, opium alkaloids were administered for the treatment of breakthrough pain after receiving the final dose of placebo in the Double-Blind Treatment Period. The subject discontinued the use of the opium alkaloid prior to receiving the first dose of CAM2038 in the Open-Label Safety Extension Phase. Therefore, in both the CAM2038 and Placebo groups, it was not anticipated that use of the opium alkaloids would have impacted the efficacy or safety results.

A greater proportion in the CAM2038 group took gapapentin, pregabalin or topiramate than did those in the placebo arm (33% v 22.7%). Likewise a higher proportion in the CAM2038 arm reported using 'other antidepressants' (30.4% v 20.9%).

Numbers analysed

Data from the electronic diaries of 75/112 (67%) participants in the CAM2038 arm and from 69/110 (62.7%) in the placebo arm (mITT population) was available for analysis at Week 12 of the randomised controlled period

Outcomes and estimation

Weekly average of daily API scores (WAAPI) were based on an NRS-11, an 11-point scale with anchors at 0 (no pain) and 10 (worst pain imaginable). For the purposes of the primary analysis, the average available API scores captured during the 7 days prior to Treatment Day 1 (first randomized treatment day in the Double-Blind Treatment Period) were considered baseline (Week 0). Change from baseline was calculated as baseline score (Week 0) minus post-baseline score (Week 1 to Week 12, where Week 12 is the primary time point); therefore, negative change from baseline values were indicative of an increase in API i.e., a worsening of pain intensity.

Primary endpoint

A summary of the primary analysis results is presented in Table 12. For the primary efficacy endpoint, WAAPI change from baseline (Week 0) to Week 12 was statistically significantly lower for the CAM2038 treatment group compared with the Placebo treatment group (LS Mean Difference [95% CI] = 1.030 [0.493, 1.568], p<0.001), demonstrating a smaller increase in pain in the CAM2038 treatment group compared to the Placebo treatment group. These statistically significantly lower WAAPI change from baseline values were observed for the CAM2038 treatment group beginning at Week 3 and continuing to Week 12 (p<0.05 for each time point).

Table 12:

Table 14.2.1.1.2 Summary Results for Change from Baseline in Weekly Average of Average Pain Intensity (WAAPI) to the Primary Time Point at Week 12 mITT Population, Based on e-Diary Data

Visit		CAM2038 (n = 112)	Placebo (n = 110)	Change from baseline CAM2038	Change from baseline placebo
Baseline	N	109	110		
	Mean (SD)	2.7 (1.26)	2.4 (1.25)		
	Median (min, max)	3.0 (0.0, 8.0)	2.6 (0.0, - 6.3)		
WEEK 1	N	104	107	104	107
	Mean (SD)	3.0 (1.44)	2.9 (1.36)	-0.4 (0.86)	-0.5 (0.81)
	Median (min, max	3.1 (0.0, 7.1	2.9 (0.0, 6.7)	-0.2 (-3.3, 1.7	-0.4 (-4.1, 0.9)
WEEK 2	N	100	105	100	105
	Mean (SD)	3.3 (1.57)	3.2 (1.61)	-0.7 (1.12)	-0.8 (1.30)
	Median (min, max	3.2 (0.0, 7.3)	3.0 (0.0, 9.7)	-0.4 (-4.5, 2.4)	-0.6 (-7.1, 1.5)
WEEK 3	N	94	101	94	101
	Mean (SD)	3.3 (1.67)	3.5 (1.6)	-0.7 (1.23)	-1.2 (1.39)
	Median (min, max	3.0 (0.0 , 8.0)	3.3 (0.0, 7.6)	-0.3 (-5.2, 1.6)	-0.9 -6.2 – 1.4
WEEK 4	N	89	98	89	98
	Mean (SD)	3.2 (1.65)	3.7 (1.78)	-0.6 (1.21)	-1.5 (1.51
	Median (min, max	3.0 (0.0 , 7.9)	4.0 (0.0, 8.3)	-0.1 (-4.0, 2.4)	-1.1 (-7.0, 1.4)
WEEK 5	N	87	89	87	89
	Mean (SD)	3.1 (1.48)	3.7 (1.84)	-0.5 (1.17)	-1.5 (1.54)

	Median (min, max	3.0 (0.0, 8.1)	3.8 (0.0, 10.0)	-0.1 (-4.3, 3.0)	-1.2 (-6, 1.1)
WEEK 6	N	86	88	86	88
	Mean (SD)	3.2 (1.66)	4.0 (1.93)	-0.6 (1.32)	-1.7 (1.80)
	Median (min, max	3.1 (0.0, 8.5)	4.0 (0.0, 10.0)	-0.3 (-4.5, 2.8)	-1.1 (-7.3, 1.7)
WEEK 7	N	85	81	85	81
	Mean (SD)	3.2 (1.67)	4.0 (2.03)	-0.6 (1.33)	-1.7 (1.87)
	Median (min, max	3.0 (0.0, 8.3)	4.0 (0.0, 8.7)	-0.3 (-5.4, 2.1)	-1.2 (-7.3, 1.6)
WEEK 8	N	83	80	83	80
	Mean (SD)	3.3 (1.63)	4.2 (2.07)	-0.7 (1.25)	-1.9 (1.95)
	Median (min, max	3.0 (0.0, 9.3)	4.2 (0.0, 9.0)	-0.4 (-5.3, 3.0)	-1.3 (-7.0, 1.5)
WEEK 9	N	81	76	81	76
	Mean (SD)	3.1 (1.73)	3.9 (1.95)	-0.6 (1.31)	-1.6 (1.80)
	Median (min, max	3.0 (0.0, 8.7)	4.0 (0.0, 9.0)	-0.3 (-5.7, 3.0)	-1.2 (-6.7, 1.1)
WEEK 10	N	81	77	81	77
	Mean (SD)	3.2 (1.81)	3.9 (1.99)	-0.7 (1.47)	-1.6 (1.85)
	Median (min, max	3.0 (0.0, 9.0)	3.8 (0.0, 9.0)	-0.3 (-5.7, 2.3)	-1.2 (-7.1, 1.1)
WEEK 11	N	82	72	82	72
	Mean (SD)	3.3 (1.80)	4.0 (2.04)	-0.7 (1.50)	-1.8 (1.95)
	Median (min, max	3.2 (0.0, 9.0)	3.9 (0.0, 9.0)	-0.5 (-6.0, 2.4)	-1.2 (-7.3, 1.1)
WEEK 12	N	75	69	75	69
	Mean (SD)	3.5 (1.93)	4.1 (2.09)	-0.9 (1.62)	-1.9 (1.97)
	Median (min, max	3.2 (0.0, 9.5)	4.0 (0.0, 9.0)	-0.5 (-6.7, 2.7)	-1.6 (-7.3, 1.1)

Table 13:

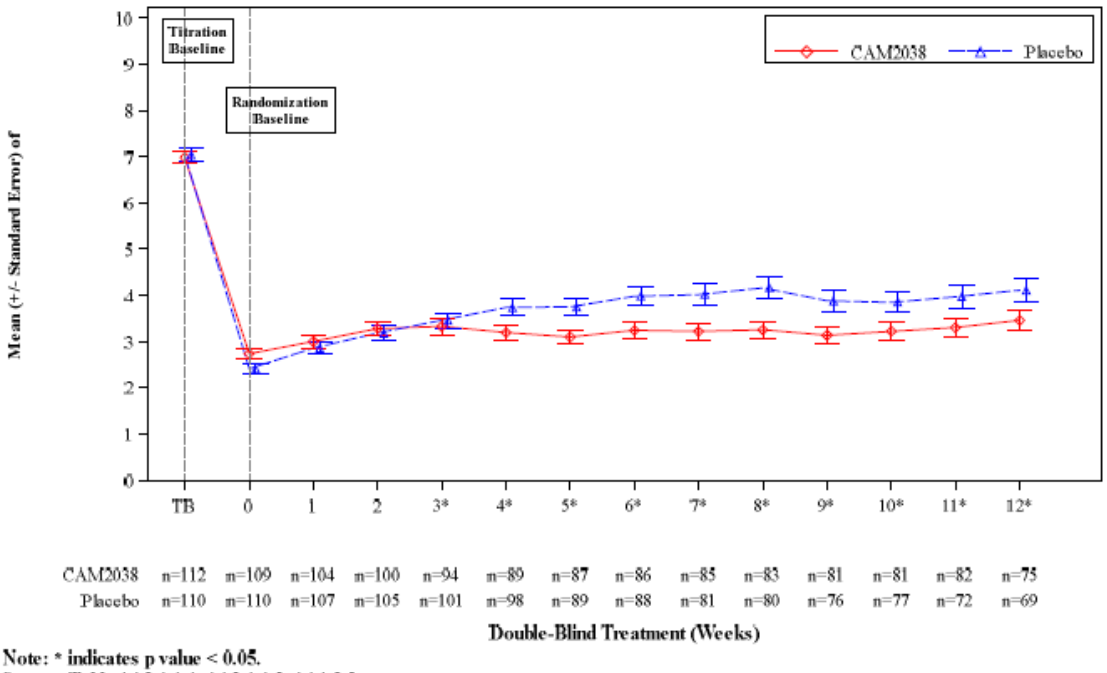
WAAPI Change from Baseline[1] to Week 12 of the Double-Blind Treatment Period (mITT Population; MMRM)

		CAM2038 N=112	Placebo N=110
Baseline Score	N	109	110
	Mean (SD)	2.7 (1.26)	2.4 (1.25)
	Median	3.0	2.6
	Range	0.0 – 8.0	0.0 – 6.3
Change from Baseline to Week 12[2]	N	75	69
	Mean (SD)	-0.9 (1.62)	-1.9 (1.97)
	Median	-0.5	-1.6
	Range	-6.7 – 2.7	-7.3 – 1.1
LS Mean difference from Placebo	LSM (SE)	1.030 (0.273)	
	95% CI	0.493, 1.568	
	p-value	**<0.001**	

Source: Table 14.2.1.1.1 and Table 14.2.1.1.2
CI=confidence interval; LSM=least square mean; mITT=Modified Intent-to-Treat; MMRM=Mixed-model repeated measures; SD=standard deviation; SE=standard error; WAAPI=weekly average of (daily) average pain intensity.
Note: p-values in bold indicate statistical significance.
[1] Score is based on NRS-11, an 11-point scale with anchors at 0 (no pain) and 10 (worst pain imaginable).
[2] A larger negative change from baseline value was indicative of a greater increase in pain at Week 12.

Figure 10:

Mean (± Standard Error) of Pain Scores at the Beginning of the Open-Label Titration Period and of WAAPI Scores over Time during the Double-Blind Treatment Period (mITT Population)



Note: * indicates p value < 0.05.
Source: Table 14.2.1.1.1, 14.2.1.1.2, 14.1.2.2.

Sensitivity analyses

A number of sensitivity analyses were performed including an: MMRM analysis in the MITT population using data from both electronic and paper diaries; a Random Replacement Method analysis results for change from baseline in WAAPI to each weekly interval including the primary time point (e-diary only); a tipping point sensitivity analysis; a sensitivity analysis to evaluate compliance with electronic diary reporting of pain score (which excluded diaries that did not have at least 5 daily entries; as well as an analysis of which excluded subjects who did not complete at least 8 weeks of diary entries

Results from the MMRM sensitivity analysis in the mITT population using both electronic and paper diary sourced data were similar to the primary analysis using e-diary data only (Table 14).

Table 14 (14.2.1.2.1):

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14.2.1.2.1
Sensitivity MMRM Analysis Results for Change from Baseline in Weekly Average of Average Pain Intensity (WAAPI) to the Primary Time Point at Week 12
mITT Population, Based on e-Diary and Paper Data

	VISIT		CAM2038 (N=112)	PLACEBO (N=110)	DIFFERENCE (CAM2038 – PLACEBO)	P-VALUE TREATMENT
ESTIMATES	WEEK 1	LSMEAN (SE)	-0.407 (0.081)	-0.504 (0.082)	0.096 (0.116)	0.405
		95% CI	(-0.567 , -0.247)	(-0.665 , -0.342)	(-0.131 , 0.324)	
	WEEK 2	LSMEAN (SE)	-0.732 (0.113)	-0.875 (0.114)	0.143 (0.161)	0.376
		95% CI	(-0.956 , -0.509)	(-1.100 , -0.650)	(-0.175 , 0.461)	
	WEEK 3	LSMEAN (SE)	-0.786 (0.125)	-1.192 (0.125)	0.406 (0.177)	0.023
		95% CI	(-1.032 , -0.540)	(-1.439 , -0.945)	(0.056 , 0.755)	
	WEEK 4	LSMEAN (SE)	-0.775 (0.138)	-1.481 (0.139)	0.706 (0.196)	<.001
		95% CI	(-1.048 , -0.503)	(-1.754 , -1.208)	(0.320 , 1.092)	
	WEEK 5	LSMEAN (SE)	-0.672 (0.139)	-1.593 (0.141)	0.920 (0.198)	<.001
		95% CI	(-0.947 , -0.398)	(-1.871 , -1.315)	(0.529 , 1.311)	
	WEEK 6	LSMEAN (SE)	-0.815 (0.158)	-1.849 (0.161)	1.035 (0.226)	<.001
		95% CI	(-1.126 , -0.503)	(-2.166 , -1.532)	(0.589 , 1.480)	
	WEEK 7	LSMEAN (SE)	-0.807 (0.173)	-2.030 (0.176)	1.222 (0.247)	<.001
		95% CI	(-1.148 , -0.467)	(-2.377 , -1.682)	(0.736 , 1.709)	
	WEEK 8	LSMEAN (SE)	-0.914 (0.175)	-2.141 (0.178)	1.227 (0.250)	<.001
		95% CI	(-1.258 , -0.570)	(-2.492 , -1.790)	(0.735 , 1.719)	
	WEEK 9	LSMEAN (SE)	-0.775 (0.162)	-1.871 (0.166)	1.096 (0.232)	<.001
		95% CI	(-1.094 , -0.456)	(-2.198 , -1.544)	(0.639 , 1.553)	

P-VALUE, LSMEAN(SE), AND 95% CI WERE BASED ON THE MIXED MODEL REPEATED MEASURES METHOD WITH TREATMENT, POST-BASELINE WEEK, TREATMENT BY WEEK INTERACTION AS FIXED EFFECTS, AND BASELINE VALUE AS THE COVARIATE. THE COVARIANCE WAS ASSUMED TO BE UNSTRUCTURE.

SOURCE: 16.2.6.1.2; TABLE: T020100BA.LIS; RUN: 27JUL2020 22:08
PROGRAM: C:\TCM\BRAEBURN\CAM2038_PAIN\HS-16-555\PGM\TABLES\T020100.SAS
BRAEBURN, CAM2038 14.2.1.2.1 FINAL

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14.2.1.2.1

Sensitivity MMRM Analysis Results for Change from Baseline in Weekly Average of Average Pain Intensity (WAAPI) to the Primary Time Point at Week 12
mITT Population, Based on e-Diary and Paper Data

	VISIT		CAM2038 (N=112)	PLACEBO (N=110)	DIFFERENCE (CAM2038 – PLACEBO)	P-VALUE TREATMENT
ESTIMATES	WEEK 10	LSMEAN (SE)	-0.795 (0.173)	-1.905 (0.178)	1.110 (0.249)	<.001
		95% CI	(-1.136 , -0.455)	(-2.256 , -1.554)	(0.620 , 1.600)	
	WEEK 11	LSMEAN (SE)	-0.901 (0.178)	-2.052 (0.183)	1.151 (0.255)	<.001
		95% CI	(-1.252 , -0.551)	(-2.413 , -1.691)	(0.647 , 1.654)	
	WEEK 12	LSMEAN (SE)	-1.063 (0.185)	-2.065 (0.191)	1.003 (0.266)	<.001
		95% CI	(-1.427 , -0.698)	(-2.443 , -1.688)	(0.478 , 1.528)	

P-VALUE, LSMEAN(SE), AND 95% CI WERE BASED ON THE MIXED MODEL REPEATED MEASURES METHOD WITH TREATMENT, POST-BASELINE WEEK, TREATMENT BY WEEK INTERACTION AS FIXED EFFECTS, AND BASELINE VALUE AS THE COVARIATE. THE COVARIANCE WAS ASSUMED TO BE UNSTRUCTURE.

SOURCE: 16.2.6.1.2, TABLE: T020100BA.LIS, RUN: 27JUL2020 22:08
PROGRAM: C:\TGM\BRAEBURN\CAM2038_PAIN\HS-16-555\PGM\TABLES\T020100.SAS
BRAEBURN, CAM2038 14.2.1.2.1 FINAL

Results for the Random Replacement Method analyses, wherein missing data at any given week were imputed with randomly generated values from a normal distribution, showed statistically significantly lower WAAPI scores observed for the CAM2038 treatment group compared with the Placebo treatment group beginning at Week 3 and continuing to the primary time point of Week 12 ($p<0.05$ for all time points). However the difference the LS mean difference in change from baseline versus placebo was lower 0.729 (95% CI: 0.229, 1.228)

Results were also similar to the primary analysis with an MMRM analysis of e-diary data where those whose weekly average diary entries were less than 5 were excluded. The LS mean difference from baseline between CAM2038 (n=62) and placebo (n=55) at week 12 was 1.078 (95% CI: 0.514 to 1.641).

Post-hoc per protocol analysis of primary efficacy variable

A post hoc analysis to evaluate differences in weekly average pain intensity between treatments in the post hoc PP population was completed.

Mean (SD) baseline WAAPI values did not differ from those in the overall mITT Population. Consistent with the mITT Population results, WAAPI change from baseline (Week 0) to Week 12 was statistically significantly lower for the CAM2038 treatment group compared with the Placebo treatment group (LS Mean Difference [95% CI] = 0.995 [0.417, 1.572], $p<0.001$); statistically significantly lower WAAPI change from baseline values were also observed for the CAM2038 treatment group beginning at Week 3 and continuing to Week 12 ($p<0.05$ for each time point). N =65 at week 12 in CAM2038 arm and N=61 in the placebo arm.

Secondary endpoints

Weekly average of daily worst pain intensity (WAWPI)

Weekly average WPI scores (WAWPI) were based on an NRS-11, an 11-point scale with anchors at 0 (no pain) and 10 (worst pain imaginable). For the purposes of the secondary analysis, the average available WPI scores captured during the 7 days prior to Treatment Day 1 (first randomized treatment day in the Double-Blind Treatment Period) were considered baseline (Week 0). Change from baseline was calculated as baseline minus post-baseline; therefore, negative change from baseline values were indicative of increased WPI.

Mean (SD) randomization baseline WAWPI values were similar for the CAM2038 (3.8 [1.59]) and the Placebo treatment groups (3.7 [1.65]). Both treatment groups showed minimal increases in score (<1 point for CAM2038 and approximately 2 points for Placebo) over the 12-week Double-Blind Treatment Period. Results for the WAWPI change from baseline values to Week 12 (e-diary) were consistent with the primary endpoint results for WAAPI, with statistically significantly lower change from baseline values for CAM2038 as compared with Placebo at Week 12 (LS Mean Difference = 1.108 [95% CI: 0.525, 1.691], p<0.001), indicating lower WAWPI for CAM2038 (Table 15). Statistically significantly lower WAWPI values were observed for CAM2038 beginning at Week 3 and continuing to Week 12 (p<0.05 for all time points). In general, the results for the combined e-diary and paper data were consistent, with the exception of the Week 3 results, which did not statistically significantly differ between the 2 treatment groups. At Week 12 the LS mean difference from baseline for CAM2038 compared to placebo was 1.010 (95%CI: 0.442, 1.577).

Table 15*:*

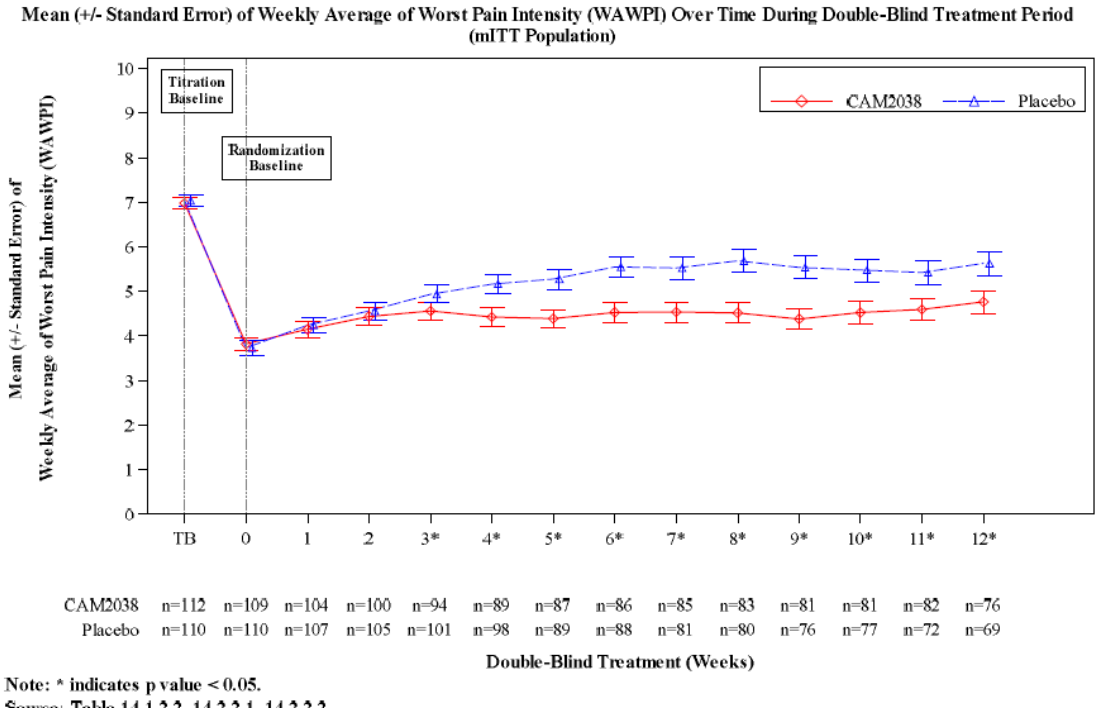
WAWPI Change from Baseline to Week 12 of the Double-Blind Treatment Period (mITT Population; MMRM)

Weekly Average of (Daily) Worst Pain Intensity (WAWPI)[1]		CAM2038 N=112	Placebo N=110
Baseline Score	N	109	110
	Mean (SD)	3.8 (1.59)	3.7 (1.65)
	Median	4.0	3.7
	Range	0.4 – 8.2	0.0 – 9.0
Change from Baseline to Week 12	N	76	69
	Mean (SD)	-1.1 (1.81)	-2.2 (2.18)
	Median	-1.0	-1.5
	Range	-6.4 – 2.7	-8.0 – 1.1
LS Mean difference from Placebo	LSM (SE)	1.108 (0.296)	
	95% CI	0.525, 1.691	
	p-value	**<0.001**	

Source: Table 14.2.2.1 and Table 14.2.2.2.
CI=confidence interval; LSM=least squa0re mean; mITT=Modified Intent-to-Treat; MMRM=mixed-model repeated measures; SD=standard deviation; SE=standard error; WAWPI=weekly average of (daily) worst pain intensity.
Note: p-values in bold indicate statistical significance.
A larger negative change from baseline value was indicative of a greater increase in pain at Week 12.
[1] Score is based on NRS-11, an 11-point scale with anchors at 0 (no pain) and 10 (worst pain imaginable).

Figure 11*:*

Mean (± Standard Error) of Pain Scores at the Beginning of the Open-Label Titration Period and of WAWPI Scores over Time during the Double-Blind Treatment Period (mITT Population)



Note: The titration baseline pain score in this figure was the average pain score over the last 24 hours at the start of the titration period (recorded on paper). This pain score was used as the titration baseline pain score for both the WAAPI figure and the WAWPI figure.

Proportion of Responders from the Open-Label Titration Period to Week 12: Weekly Average of Daily Average Pain Intensity (WAAPI)

The testing hierarchy started with the proportion of subjects experiencing a ≥50% reduction in pain score from the Open-Label Titration Period baseline to Week 12 of the Double-Blind Treatment Period. By this definition, 44 (39.3%) subjects in the CAM2038 group achieved a ≥50% reduction in WAAPI versus 32 (29.1%) subjects in the Placebo group. A higher proportion of subjects in the CAM2038 group achieved a ≥30% reduction in WAAPI (60 subjects [53.6%]) compared with the Placebo group (47 [42.7%]).

A chi-square test was used to compare the proportion of responders to CAM2038 and Placebo (Table 16). There were no statistically significant differences observed in the proportion of responders between the 2 treatment groups at the ≥30% cut-off (proportion difference CAM2038 - Placebo [95%CI] = 10.8% [-2.2, 23.9], p=0.106) and the testing hierarchy was broken at this step.

A similar difference in proportion of responders between treatment groups was observed for the ≥50% cut off (10.2% [-2.2., 22.6], nominal p=0.109).

Table 16:

Proportion of Responders With a 30% and 50% Reduction in WAAPI from the Open-Label Titration Period Baseline to Week 12 of the Double-Blind Treatment Period (mITT Population)

WAAPI: Proportion of Responders		CAM2038 (N=112)	Placebo (N=110)
≥30% improvement	Responders (n [%])	60 (53.6)	47 (42.7)
	Proportion Difference (% [95% CI])	10.8 (-2.2, 23.9)	
	p-value[1]	0.106	
≥50% improvement	Responders (n [%])	44 (39.3)	32 (29.1)
	Proportion Difference (% [95% CI])	10.2 (-2.2, 22.6)	
	p-value[1]	0.109	

Source: Table 14.2.3.1 and Table 14.2.3.2
CI=confidence interval; mITT=Modified Intent-to-Treat; WAAPI=weekly average of (daily) average pain intensity.
[1] p-value was based on the Chi-Square test

Time to loss of efficacy

Time to loss of efficacy was defined as the time to the discontinuation of study participation or study drug due to lack of efficacy. However, the reason for discontinuation from study drug was not captured in the eCRF, only the reason for discontinuation from trial. Baseline for this measure was considered randomization baseline.

The time-to-event "survival" curve is presented using the Kaplan-Meier method in Figure 13. The median, 25th percentile, and 75th percentile for time to lack of efficacy could not be estimated due to insufficient data points (i.e., all data points were below 50%); however, the number and proportion of subjects who were and were not discontinued due to lack of efficacy were summarized. The number of subjects who were discontinued due to lack of efficacy was numerically lower for the CAM2038 treatment group (7 subjects [6.3%]) compared with the Placebo treatment group (21 subjects [19.1%]; nominal p=0.003, based on the log-rank test). However, it is unclear how data from subjects who discontinued study drug or withdrew from the study were handled in this analysis.

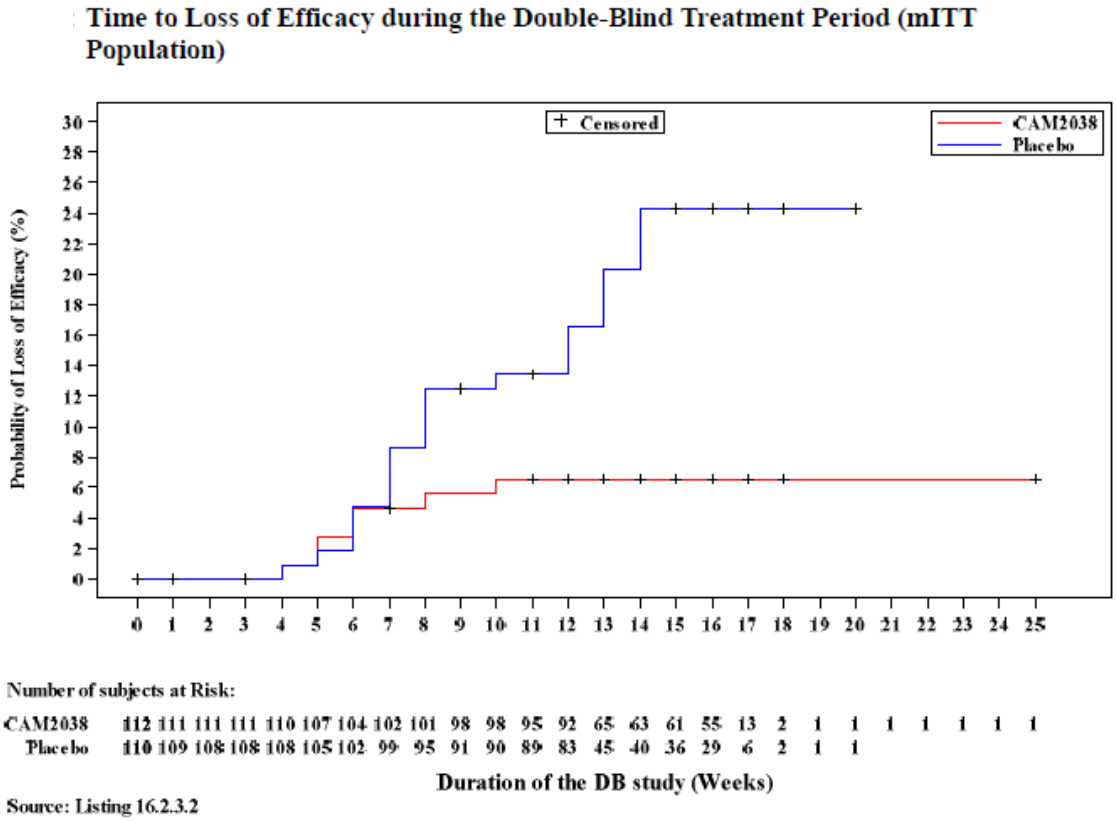
Table 17:

Reason for discontinuation from trial by week in the double-blind treatment period, HS-16-555 (mITT population)

Treatment group	Reason for discontinuation	W1 n	W2 n	W4 n	W5 n	W6 n	W7 n	W8 n	W9 n	W10 n	W11 n	W12 n	W13 n	W14 n	W15 n	W16 n	W18 n	W25 n	Total n
CAM2038	Adverse event	0	0	0	1	0	0	0	1	0	1	0	1	0	0	0	0	0	4
CAM2038	Lack of efficacy	0	0	0	2	3	0	0	1	0	1	0	0	0	0	0	0	0	7
CAM2038	Lost to follow-up	1	0	0	1	0	0	0	0	0	0	1	1	0	0	0	0	1	5
CAM2038	Physician decision	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
CAM2038	Pregnancy	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
CAM2038	Withdrawal by patient	0	0	1	0	1	0	1	0	1	1	0	1	0	0	0	0	0	6
Placebo	Adverse event	0	0	0	0	0	0	0	0	0	0	0	2	1	0	0	0	0	3
Placebo	Lack of efficacy	0	0	0	1	1	4	3	4	0	1	1	2	2	2	0	0	0	21
Placebo	Lost to follow-up	0	0	0	0	0	0	0	0	0	0	1	2	1	0	0	1	0	5
Placebo	Physician decision	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Placebo	Withdrawal by patient	1	1	0	2	2	0	0	1	0	0	0	2	0	1	0	0	0	10

mITT: modified intention-to-treat; n: number of patients; W: week
Weeks without discontinuations are not included in the table.

Figure 12:



Patient Global Impression of Improvement Scale (PGI-I)

The Applicant evaluated change from baseline (average PGI-I score captured during 7 days prior to the first randomised treatment day in the randomisation period to Week 12 of the double blind period. Change form baseline was moderate in both groups with a nominally statistically significant difference in favour of CAM 2038 (Table 18):

Table 18: Change from Baseline in PGI-I[1] to Week 12 of the Double-Blind Treatment Period (MMRM; mITT Population)

		CAM2038 N=112	Placebo N=110
Baseline Score	N	111	110
	Mean (SD)	6.0 (0.96)	6.2 (0.74)
	Median	6.0	6.0
	Range	3.0 – 7.0	4.0 – 7.0
Change from Baseline to Week 12/Week 23 [Baseline – Week 12][2]	N	107	106
	Mean (SD)	0.4 (1.48)	1.5 (1.63)
	Median	0	1.0
	Range	-4.0 – 6.0	-2.0 – 6.0
LS Mean difference from Placebo	LSM (SE)	-0.957 (0.197)	
	95% CI	-1.346, -0.569	
	p-value	**<0.001**	

Source: Table 14.2.4.1 and Table 14.2.4.2
CI=confidence interval; CLBP=chronic low back pain; LSM=least square mean; mITT=Modified Intent-to-Treat; MMRM= mixed-model repeated measures; PGI-I=Patient Global Impression of Improvement; SD=standard deviation; SE=standard error.
Note: p-values in bold indicate statistical significance
[1] PGI-I scale is a 7-point scale where a score of 1 is "much worse" and a score of 7 is "much better"
[2]A positive change from baseline value was indicative of an increase in perceived worsening of CLBP at Week 12/Week 23, while a negative change from baseline value was indicative of an improvement in CLBP at Week 12/Week 23; higher positive change from baseline scores implied a greater worsening of subject perceived CLBP.

Work Productivity and Activity Impairment (WPAI)

For both the placebo and CAM2038 treatment groups, WPAI scores across domains were highest at baseline, with slightly higher mean Open-Label Titration Period Baseline scores for all domains of the WPAI in the Placebo treatment group as compared with the CAM2038 treatment group, During the Double-Blind Treatment Period (i.e., Weeks 15 to 23), most of the WPAI domain scores were relatively stable. Only the WPAI-Activity Impairment domain showed statistically significant differences in change from baseline values between the CAM2038 and Placebo treatment groups at Week 12/Week 23 (LS Mean difference [95%CI] = 8.087 [2.487, 13.687], nominal p=0.005), with a higher change from Open-Label Titration Period Baseline value for the CAM2038 treatment group, indicating a greater improvement in activity from baseline to Week 12/Week 23 with CAM2038 treatment.

EuroQol Group 5-Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L)

There were, in general, no differences between the treatment groups for any of the EQ-5D-5L subscales at any time point. For both placebo and CAM2038 treatment groups, the values of the weighted health-state index score "Health Today" were lowest at baseline but increased over the duration of the Open-Label Titration Period (i.e., Weeks 1 to 11). There were no statistically significant differences in Health Today change from baseline values between the CAM2038 and Placebo treatment groups at Week 12/ Week 23. A statistically significant lower Health Today change from baseline score was, however, observed for the CAM2038 treatment group (mean [SD] change from baseline of -11.3 [19.32]) compared with Placebo (mean [SD] change from baseline of -8.3 [19.95]) at Week 8/Week 19 (LS Mean difference [95%CI] = -5.432 [-10.03 to -0.838], nominal p=0.021), indicating improved overall health at this time point.

Rescue medication use

Given the potential for rescue medication to confound the outcomes of the primary endpoint a secondary endpoint of rescue medication usage (number of days and total dose during the double blind phase) had been included. Use of rescue medication was to have been recorded on the electronic diary. However due to problems with the electronic diaries for rescue medication usage (i.e. duplicate data entries due to poor internet connectivity), the total rescue dosage was not reliable. Therefore, the electronic diary source of rescue medication usage was utilized only to derive the number of days of rescue medication use. The number of days that rescue medication was used was normalized on a weekly basis in the analysis (i.e., number of days that rescue medication was used per week) based on the electronic diaries. Specifically, number of days that rescue medication was used per week was derived as 7*(X/Y), where X=total number of days that rescue medication was taken during the week and Y=total number of days that diaries were available in that week. This variable was analysed using MMRM methods for longitudinal data analysis using (consistent with analyses used for the primary efficacy variable).

The actual number of days by week on which rescue medication was used was slightly lower for the CAM2038 arm than placebo e.g. at Week 12 mean number of days was 4.7 in the CAM2038 arm and 5.7 in the placebo arm. At Week 12 MMRM analysis of change from baseline in weekly number of days rescue medication was used in the mITT population (based on e-diary data) in the CAM2038 population showed an LS mean difference of 0.704 days (95% CI: -0.002 to 1.410).

Ancillary analyses

Efficacy in the open label extension population

A total of 132 subjects entered the Open-Label Safety Extension Phase and were included in the Overall Safety Population (57 rollover subjects who completed the double-blind phase after the OLE phase was added and 75 de novo subjects, including 20 subjects who had completed the double-blind phase before the OLE phase was added; excluding Site 077).

Table 19:

Roll over from the double-blind phase to the open-label extension phase, HS-16-555

	CAM2038 n	Placebo n
Randomized in the DB treatment period	112	110
Completed the DB phase - total	88	70
Completed the DB phase before the OLE phase was added	24	13
Completed the DB phase before the OLE phase was added but were later enrolled in the OLE phase as de novo patients	13	7
Completed the DB phase before the OLE phase was added but did not continue to the OLE phase	**11**	**6**
Completed the DB phase after the OLE phase was added	64	57
Completed the DB phase after the OLE phase was added and continued to the OLE phase as rollover patients	24	33
Completed the DB phase after the OLE phase was added but did not continue to the OLE phase	**40**	**24**

DB: double-blind; OLE: open-label extension

Of these 132 subjects, 109 subjects were enrolled into the Open-Label Enrollment Period and were included in the Overall Safety Population, Enrollment Subjects Only, i.e., the mITT Population. A total of 88 subjects completed treatment and were included in the Treatment Completion Population, 86 subjects who were exposed to the study drug for at least 52 weeks were included in the Integrated Full Exposure Safety Population, and 58 subjects who were exposed to CAM2038 for at least 52 weeks were included in the Continuous Integrated Full Exposure Safety Population. Among the 77 subjects who had completed the double-blind phase, 60 completed the OLE phase:

Table 20:

Number of patients who completed the double-blind phase and the open-label extension phase, HS-16-555

	CAM2038	Placebo
Completed the DB phase	**88**	**70**
Continued to the OLE phase	**37**	**40**
Continued to the OLE phase as rollover patients	24	33
Continued to the OLE phase as de novo patients	13	7
Completed the OLE phase after continuing from the DB phase	**32**	**28**
Completed rollover patients	21	25
Completed de novo patients	11	3

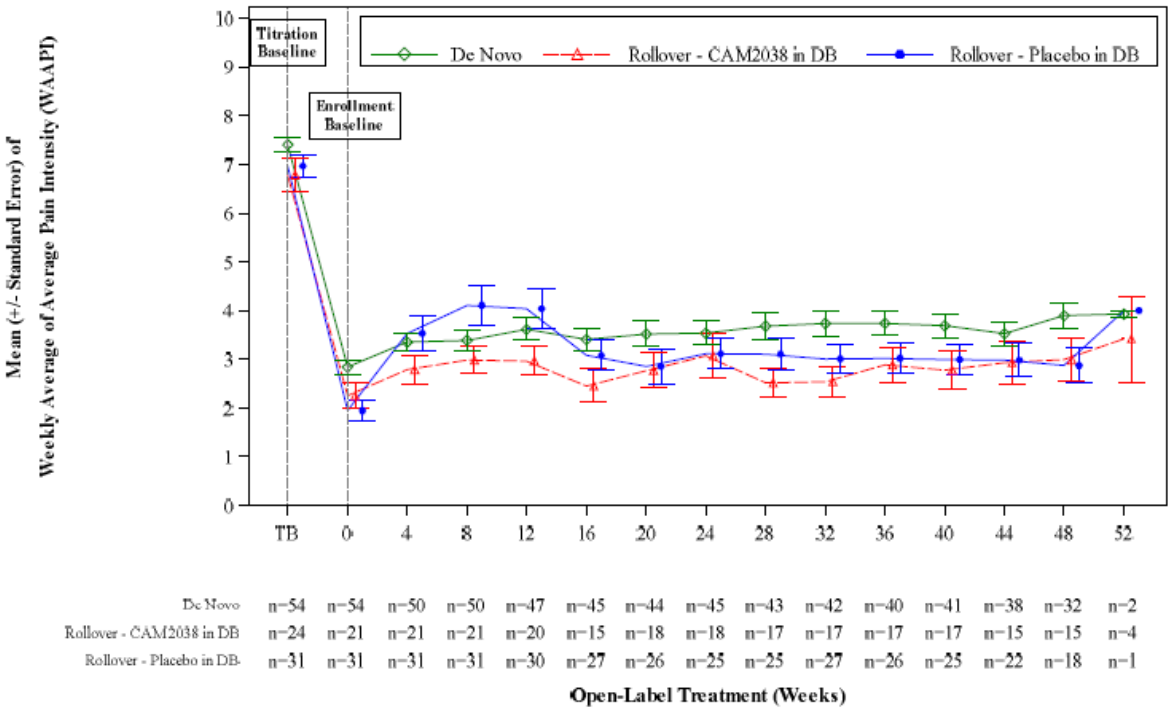
DB: double-blind; OLE: open-label extension

For the purposes of the Open-Label Safety Extension Phase, the average available API scores captured during the 7 days prior to the first Open-Label Safety Extension Phase dose at Visit 14 for de novo subjects (Enrollment Visit) and the 7 days prior to Treatment Day 1 (first randomized treatment day in the Double-Blind Treatment Period, i.e. Visit 14) for rollover subjects were considered baseline (Week 0). Change from baseline was calculated as baseline score (Week 0) minus post-baseline score (Week 1 to Week 52); therefore, negative change from baseline values were indicative of an increase in WAAPI, i.e., a worsening of pain intensity. Descriptive statistics for WAAPI scores by week and change from baseline values are summarized by subject group in Table 14. Mean pain scores at the Open-Label Titration Period baseline and mean WAAPI scores over time in the Open-Label Enrollment Period of the Open-Label Safety Extension Phase are presented in Figure 14. For the de novo group, the mean (SD) Enrollment Baseline pain scores (i.e. Visit 14 scores) were relatively low at 2.84 (1.08) but were slightly higher than the Randomization Baseline pain scores for the 2 rollover groups. Within the rollover group, Placebo rollover subjects had lower mean (SD) baseline WAAPI scores (1.94 [1.13]) compared with CAM2038 rollover subjects (2.26 [1.16]).

For de novo subjects, beginning at Week 2, WAAPI scores increased, indicative of increased pain intensity (negative change from baseline value). These increases in pain scores continued until approximately Week 12 (mean change from baseline range from Week 1 to Week 52: 0.039 to -1.216), where they decreased slightly. The pain scores then plateaued until Week 43, where there was a slight increase in pain score (-1.026). A similar pattern was observed for the CAM2038 rollover subjects; however, fluctuations were minimal over the 52 weeks of treatment (mean change from baseline ranging from -0.211 to -0.872). Placebo rollover subjects showed a greater increase in WAAPI scores between Weeks 1 and 12 (i.e., during the Double-Blind Treatment Period when they received placebo), followed by a gradual decrease and stabilization by Week 24 (mean change from baseline ranging from -0.70 to -2.165), although the Placebo rollover subjects had larger increase from baseline in WAAPI scores than the de novo and CAM2038 rollover subjects (Table 14.

Figure 13*:*

Mean (± Standard Error) of Pain Scores at the Open-Label Titration Period Baseline and of WAAPI Scores over Time during the Open-Label Enrollment Period (mITT Population)



Source: Table 14.2.1OLE, 14.1.2.3OLE.

Sub-group analyses

Post hoc sub-group analyses by sex, age (< 65 years and ≥ 65 years) and race using data from electronic diaries only were carried out for the primary endpoint.

In general, mean (SD) baseline WAAPI values were consistent with the overall mITT Population results for all subgroups (i.e., sex, age, race), with slightly higher baseline scores for the CAM2038 group compared with the Placebo treatment group. When the WAAPI data were dichotomized by sex, no significant treatment differences were observed in the primary efficacy endpoint (WAAPI change from baseline to Week 12) in the males only subgroup; however, statistically significantly lower WAAPI scores for CAM2038 (suggesting a smaller increase in pain) were observed at Week 5 (p=0.036) and Week 9 (p=0.032). In contrast, findings in female subjects were consistent with the overall mITT population with statistically significantly lower scores for CAM2038 treatment group compared with the Placebo treatment group across all 12 weeks of treatment (p<0.05 for all time points).

When data were subdivided by age and race, results were consistent with the overall mITT population with statistically significantly lower scores for CAM2038 treatment group compared with the Placebo treatment group for the primary efficacy endpoint, WAAPI change from baseline (Week 0) to Week 12 (p<0.05 for all subgroups), demonstrating a reduction in pain compared to placebo regardless of age or race.

Summary of main study

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 21*:* **Summary of Efficacy for trial HS-16-555**

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Enriched-Enrollment Withdrawal, Multicenter Study to Evaluate the Efficacy and Safety of a Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Subjects with Moderate to Severe Chronic Low Back Pain Currently Treated with Daily Opioids			
Study identifier	HS-16-555, NCT02946073		
Design	Phase 3, randomised, double-blind, placebo-controlled, enriched-enrolment withdrawal, repeated-dose, multi-centre trial with an open-label safety extension phase		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 2+10 weeks At least 52 weeks
Hypothesis	Superiority		
Treatments groups	CAM2038		Titration period of the double-blind phase and open-label safety extension phase: 4, 8, 12, 16, 24 or 32 mg CAM2038 q1w Up to 10 weeks until a stable dose was reached. 468 patients in the double-blind phase, 75 de novo patients in the open-label safety extension phase Double-blind treatment period: 4, 8 or 12 mg CAM2038 q1w 64, 96 or 128 mg CAM2038 q4w 12 weeks 112 patients Open-label extension treatment period: 4, 8 or 12 mg CAM2038 q1w 64, 96 or 128 mg CAM2038 q4w At least 52 weeks 109 patients (55 rollover patients from the DB phase and 54 de novo patients)
	Placebo		Double-blind treatment period: 0.16 mL, 0.18 mL, 0.24 mL, 0.27 mL, 0.36 mL or 0.64 mL for q1w or q4w. 12 weeks 110 patients
Endpoints and definitions	Primary endpoint	WAAPI	The primary efficacy endpoint was the change from baseline in Weekly Average of (Daily) API (WAAPI), and the primary time point was Week 12 of the Double-blind treatment period

	Secondary endpoints	WAWPI	The key secondary efficacy endpoint was the change from baseline in the weekly average of (daily) worst pain intensity (WAWPI) scores at Week 12 of the Double-blind treatment period
		Proportion of responders with 50% improvement in WAAPI from the open-label titration baseline	Percentage of patients with a 50% or greater decrease in API from the open-label titration period baseline to Week 12 of the double-blind treatment period.
		Proportion of responders with 30% improvement in WAAPI from the open-label titration baseline	Percentage of patients with a 30% or greater decrease in API from the open-label titration period baseline to Week 12 of the double-blind treatment period.
Database lock	Double-blind phase: 10-Sep-2018 Open-label safety extension phase: 03-May-2019		
Results and Analysis			

Analysis description	**Change from Baseline to Week 12 in WAAPI score - Primary Analysis (pre-specified)**		
Analysis population and time point description	Modified intent to treat (mITT) The mITT Population consisted of all randomised patients, except for patients from Sites 068 and 077 due to persistent site non-compliance Time point: Week 12 of the double-blind treatment period		
Descriptive statistics and estimate variability	Treatment group	CAM2038	Placebo
	Number of subjects	109	110
	WAAPI (baseline score) (mean) Standard deviation	2.7 1.26	2.4 1.25
	WAAPI (change from baseline to Week 12) (mean) Standard deviation Calculated as baseline minus post-baseline	-0.9 1.62	-1.9 1.97
	Primary endpoint	Comparison groups	CAM2038 vs Placebo

Effect estimate per comparison			
		Least square mean difference between treatment groups at Week 12	1.030
		95% confidence interval (standard error)	0.493, 1.568 (0.273)
		P-value (Mixed-model repeated measures)	<0.001
Analysis description	**Change from Baseline to Week 12 in WAWPI score - Secondary analysis (pre-specified)**		
Analysis population and time point description	Modified intent to treat (mITT) The mITT Population consisted of all randomised patients, except for patients from Sites 068 and 077 due to persistent site non-compliance Time point: Week 12 of the double-blind treatment period		
Descriptive statistics and estimate variability	Treatment group	CAM2038	Placebo
	Number of subjects	109	110
	WAWPI (baseline score) (mean) Standard deviation	3.8 1.59	3.7 1.65
	WAWPI (change from baseline to Week 12) (mean) Standard deviation Calculated as baseline minus post-baseline	-1.1 1.81	-2.2 2.18
Effect estimate per comparison	Key secondary endpoint	Comparison groups	CAM2038 vs Placebo
		Least square mean difference between treatment groups at Week 12	1.108
		95% confidence interval (standard error)	0.525, 1.691 (0.296)
		P-value (Mixed-model repeated measures)	<0.001
Analysis description	**Proportion of responders with 50% improvement in WAAPI from the open-label titration baseline - Secondary analysis (pre-specified)**		

Analysis population and time point description	Modified intent to treat (mITT) The mITT Population consisted of all randomised patients, except for patients from Sites 068 and 077 due to persistent site non-compliance Time point: Week 12 of the double-blind treatment period		
Descriptive statistics and estimate variability	Treatment group	CAM2038	Placebo
	Number of subjects	112	110
	Responders (n [%]) at Week 12	44 (39.3)	32 (29.1)
Effect estimate per comparison	Secondary endpoint	Comparison groups	CAM2038 vs Placebo
		Proportion difference (95% confidence interval)	10.2 (-2.2, 22.6)
		p-value based Chi-Square test	0.109
Analysis description	**Proportion of responders with 30% improvement in WAAPI from the open-label titration baseline - Secondary analysis (pre-specified)**		
Analysis population and time point description	Modified intent to treat (mITT) The mITT Population consisted of all randomised patients, except for patients from Sites 068 and 077 due to persistent site non-compliance Time point: Week 12 of the double-blind treatment period		
Descriptive statistics and estimate variability	Treatment group	CAM2038	Placebo
	Number of subjects	112	110
	Responders (n [%]) at Week 12	60 (53.6)	47 (42.7)
Effect estimate per comparison	Secondary endpoint	Comparison groups	CAM2038 vs Placebo
		Proportion difference (95% confidence interval)	10.8 (-2.2, 23.9)
		p-value based Chi-Square test	0.106

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

N/a

Clinical studies in special populations

N/a

Supportive study(ies)

Reference was made in the Clinical Overview Addendum to a phase 2 study HS-15-549 submitted in support of the original marketing authorisation which is used to support that the indication should also include those with moderate to severe opioid dependence.

The primary objective of the study was to evaluate steady state pharmacokinetics with efficacy as an exploratory measure. Even if the true effect size was agreed to be as presented and deemed to be clinically relevant the currently submitted data is insufficient to support the widening of the indication to all patients with chronic pain and opioid dependence.

There were three study groups. Patients in Group 1 (N=28) received treatment with 32 mg CAM2038 q1w for 13 weeks (7+6 weeks), patients in Group 2 (N=20) received treatment with 128 mg CAM2038 q4w for 16 weeks and 32 mg CAM2038 q1w for 6 weeks, and patients in Group 3 (N=17) received treatment with 24 mg SL BPN/NX for 1 week and 160 mg CAM2038 q4w for 16 weeks. The average of the average daily pain (AADP) at a visit was defined as the average of the non-missing average daily pain score since the previous visit, and the average of the worst daily pain (AWDP) at a visit was defined as the average of the non-missing worst daily pain score since the previous visit. Baseline was defined as the 7 days before the first CAM2038 dose, i.e. the baseline pain scores corresponded to the pain scores recorded during treatment with SL BPN/NX in all treatment groups. Missing values were not imputed.

The results showed that both the AADP and the AWDP scores were well-maintained from baseline and over time during treatment with CAM2038, with a trend of decreasing pain scores after baseline in all treatment groups.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of the claimed indication "Treatment of moderate to severe chronic pain in patients with opioid dependence" the Applicant submitted one phase 3 randomised, double-blind placebo-controlled, enriched-enrolment withdrawal multicentre study in a USA study population already receiving opiate treatment for chronic low back pain. The study also had an open label extension phase which allowed for the recruitment of new patients with a history of chronic pain of any type. The Applicant did not seek scientific advice in the EU but it appears advice was sought from the FDA. The use of a randomised withdrawal trial as a pivotal study is questioned given that efficacy has not been demonstrated in a conventional randomised placebo-controlled parallel group trial.

The double blind phase of the study included a screening period (up to 2 weeks), a transition period (up to 2 weeks), an open-label titration period (up to 10 weeks), a double-blind treatment period including a final study visit (12 weeks), and a follow-up period (4 weeks). The overall duration of participation for the double-blind phase was up to 30 weeks. Those who transitioned to the open label extension phase from the double blind phase or were recruited de-novo to and completed the open label extension phase would be expected to have an exposure to CAM2038 of 52 weeks. The use of a placebo control in the controlled phase is considered acceptable and is in line with the relevant EMA guideline (EMA/CHMP/970057/2011 Guideline on the clinical development of medicinal products intended for the treatment of pain).

The sought indication is for the treatment of moderate to severe chronic pain in patients who are opioid dependent. The controlled phase of the study recruited patients with a history of daily opioid use in the treatment of low back pain for a minimum of 3 months prior to screening and with a stable dose of ≥ 40mg/day or oral morphine or MED in the 14 days prior to screening. To proceed to the open label titration phase subjects were required to have a COWS score ≥ 5 following a 12 hour wash out period. Scores of 5 to 12 on the COWS scale indicate mild withdrawal symptoms. Those with a diagnosis of DSM-5 defined moderate to severe substance misuse disorder other than caffeine or nicotine were excluded from the study. Therefore the study population across all phases could be judged to reflect only those

with mild/moderate opioid dependence and in the randomised controlled period those with chronic pain due to low back pain only. This is not in line with the proposed indication.

The primary endpoint for the study was the change from baseline in weekly average of daily average pain intensity (WAAPI), at week 12 of the Double-Blind Treatment Period. The primary endpoint is considered appropriate. Pain was measured using an 11 point numeric rating scale each evening. EMA guidelines recommend that pain is measured twice daily, i.e. morning and evening, in order to capture the variation in pain levels throughout the day (EMA/CHMP/970057/2011 Guideline on the clinical development of medicinal products intended for the treatment of pain).

Data on pain scores and use of rescue medication was to have been obtained from electronic patient diaries. Unfortunately due to connectivity problems some participants had to use paper diaries. This had major implications for the collection of data on rescue medication usage as it was impossible to quantify the dosage of rescue medication received by study participants. This raises concerns about the validity of the generated database for key efficacy endpoints and consequently whether the efficacy results can be used to support the application.

It appears that there were no GCP inspections during the course of the study. However the participation of two study sites was terminated by the sponsor due to major GCP violations. It should also be borne in mind that approximately one-third of randomised patients were excluded from the study due to GCP infringements which hampers the validity of the clinical data from the pivotal study as a whole. Therefore as it is important that the remaining data can be verified to be GCP compliant a GCP inspection is therefore requested.

Efficacy data and additional analyses

In the primary analysis using data from electronic diaries only the change in weekly average of daily average pain intensity from baseline at randomisation at Week 12 was -0.9 in the CAM2038 arm and -1.9 in the placebo arm. The LS mean difference from placebo was 1.030 (95% CI: 0.493 to 1.568) with $p < 0.001$.

An additional MMRM sensitivity analysis using a combination of electronic and paper diaries produced similar results to the primary analysis, as did an analysis using data only from electronic diaries with at least 5 pain records per week. Similar results were also seen in a post hoc per protocol analysis. A sensitivity analysis using the Random Replacement Method in the mITT population with e-diary data only, showed an attenuation in effect size though the results remained statistically significant.

Although the study appears to have met its primary endpoint and the sensitivity analyses supported the primary analysis there are a number of problems with the study which may undermine the study results. These include the GCP infringements that led to the exclusion of two sites, problems with use of electronic diaries with regard to recording pain scores and use of rescue medication. There was also greater use of other opioids and agents such as gabapentin and pregabalin in the CAM2038 compared to the placebo arm. All of these factors could have confounded the results of the primary endpoint. Thus the magnitude of the true effect size could be even smaller than 1 point on the 11-point NRS scale.

In addition the clinical relevance of the difference from baseline at Week 12 between CAM2038 and placebo of approximately 1 point on an 11-point scale is questioned. Throughout the 12 week randomised controlled treatment period pain scores in both treatment arms, though higher in the placebo arm, remained well below the screening phase/titration baseline values of 7 (see table 12) with the highest WAAPI in the placebo arm at 4.2 in Week 8 and the highest WAAPI in the CAM2038 arm at 3.5 at Week 12 in the CAM2038 arm, demonstrating a strong placebo effect.

Aside from the small effect size, the utility of this product in the target indication could be questioned given the low level of progression from the titration period to the double blind treatment period, the high level of drug/study discontinuation during the 12-week double blind treatment period, and the apparently low level of progression of those in the CAM2038 arm who completed the double blind treatment period to the open label extension phase.

A total of 37 patients from the CAM2038 group (24 rollover patients and 13 de novo patients) entered into the OLE form a total of 88 in the DB phase. Where as 40 patients from the placebo group (33 rollover patients and 7 de novo patients) continued from the double-blind phase to the OLE Phase for a total of 70 in the DB phase. Thus it would appear the proportion of patients who might potentially benefit from Buvidal could be quite small, this also questions the utility.

Those with moderate to severe opioid dependence were not included in Study HS-16-555. The Applicant would appear to be substantiating the inclusion of this wider group based on the summary results included in the Clinical Overview addendum of the partially randomised open label HS-15-549 study that compared 3 weekly injections of 32mg CAM2038 or four 128mg monthly CAM2038 to daily doses of 24 mg SL BPN/NX given for 7 days. This study was submitted in support of the original MA for Buvidal and has not been re-submitted. The primary objective of the study was to evaluate steady state pharmacokinetics with efficacy as an exploratory measure. Even if the true effect size was agreed to be as presented and deemed to be clinically relevant the currently submitted data is insufficient to support the proposed indication.

There are remaining major objections/issues on the robustness of the Data from a GCP perspective, the intended population/indication and the treatment effect. Following review of the responses and if acceptable the proposed indication could potentially be resolved.

Additional expert consultation

N/a

Assessment of paediatric data on clinical efficacy

N/a

2.4.4. Conclusions on the clinical efficacy

There are a number of issues that still need to be resolved including 2 Major Objections raised due to efficacy are raised by the Rapporteur

1) Need for a GCP inspection
2) Effect size

2.5. Clinical safety

Introduction

The current clinical development programme with CAM2038 in patients with chronic pain consists of 2 clinical trials ; one Phase 2 trial (HS-15-549) in patients with OUD and moderate to severe chronic non-cancer pain and one Phase 3 trial (HS-16-555) in **opioid experienced patients with chronic pain**. Trial HS-15-549 was part of the initial MAA and has, hence, already been assessed during the initial review.

Safety assessments in HS-16-555 included recording of AEs and evaluation of clinical laboratory data, vital signs, physical examination findings, injection site examinations, Columbia-Suicide Severity Rating Scale (C-SSRS) scores, Clinical Opiate Withdrawal Scale (COWS) scores, Subjective Opiate Withdrawal Scale (SOWS) scores and urine drug screen results.

Extent of Exposure

Trials Included in the Initial MAA

In the initial MAA, 729 subjects were exposed to at least one injection of CAM2038 including 135 healthy volunteers and 594 patients with OUD, of whom **65 patients in HS-15-549** had moderate to severe chronic non-cancer pain (Study HS-15-549)

Study HS-15-549 (phase II)

HS-15-549 was a Phase 2, open-label, randomized study assessing steady-state PK, efficacy and safety of CAM2038 q1w and CAM2038 q4w in patients in with 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.

In the phase II study HS-15-549 study (included in the original MAA) in patients in with a current diagnosis of moderate to severe opioid dependence and with a history of moderate to severe chronic non-cancer pain, the mean duration of exposure to CAM2038 was 65.5 days (range: 8 – 93) in Group 1 (CAM2038 q1w 32 mg), 123.2 days (range: 29 – 158) in Group 2 (CAM2038 q4w 128 mg), and 103.4 days (range: 57 – 113) in Group 3 (CAM2038 q4w 160 mg)

The majority of subjects received CAM2038 for at least 9 weeks (53.6%) in Group 1, for at least 22 weeks (60.0%) in Group 2, and for at least 16 weeks (70.6%) in Group 3.

Trial HS-16-555

Trial HS-16-555 (conducted in patients with chronic pain and not included in the initial MAA) was a Phase 3, placebo-controlled, multi-centre, double-blind, EEW, randomised trial evaluating the efficacy and safety of CAM2038 in opioid-experienced patients with moderate to severe CLBP or other chronic pain conditions such as osteoarthritis, that required continuous, around the- clock treatment with opioids at a MED ≥40 mg/day. **The primary safety population of the titration period includes 468 patients who received at least 1 dose of CAM2038.** The primary safety population of the double-blind treatment period is identical to the mITT population used for the efficacy analyses and includes 222 patients with even distribution between the **CAM2038 (112 patients**) and placebo (110 patients) groups.

The mean duration of exposure in the double-blind treatment period was **76.2 days** in the CAM2038 group and 72.1 days in the placebo group. Most patients in both groups were exposed for ≥12 weeks (72.3% for CAM2038 and 61.8% for placebo).

In the overall safety population in the OLE phase (N=132), the mean duration of exposure (counted from the first CAM2038 dose in the titration period for de novo patients and from the first CAM2038 dose in the OLE treatment period for rollover patients) was 36.5 weeks for de novo patients, 35.9 weeks for CAM2038 rollover patients and 32.5 weeks for placebo rollover patients. Most of the de novo patients were exposed to CAM2038 for ≥8 weeks (82.7%) and 50.7% were exposed for ≥52 weeks.

58 patients were exposed to CAM2038 continuously for ≥52 weeks in trial HS-16-555

The safety evaluation for the Double-Blind Phase focuses on the Primary Safety Population for both the Open-Label Titration Period and the Double-Blind Treatment Period. While the Safety Population includes 2 additional clinical sites (Sites 068 and 077), these sites were determined to have critical quality issues. These quality issues may have resulted in unreliable documentation of safety data, including under-reporting of AEs. Source tables for the Safety Population have been provided for completeness, but are only briefly discussed.

Likewise, the safety evaluation for the Open-Label Safety Extension Phase focuses on the Overall Safety Population, excluding Site 077, for both the Open-Label Titration Period and the Open-Label Enrollment Period.

Trial HS-16-555 trial

Adverse Events

Brief Summary of Adverse Events

Double-Blind Phase

Open-Label Titration Period

Primary Safety Population:

A total of 300 of 468 subjects (64.1%) had at least 1 TEAE during this period of the study, with a total of 1157 TEAEs; 37.0% of subjects had TEAEs suspected to be related to CAM2038. Ten subjects (2.1%) had SAEs, including 1 SAE with a fatal outcome (0.2%). The death (unknown cause) was not considered to be related to the study drug.

Seventy-two (15.4%) subjects experienced TEAEs leading to withdrawal of study drug and study discontinuation. The majority of subjects had mild or moderate TEAEs, however, 24 subjects (5.1%) had severe TEAEs. A total of 69 subjects (14.7%) had injection site TEAEs.

Safety Population (included an additional 143 subjects)
A total of 321 of the 611 subjects (52.5%) had at least 1 TEAE (1209 TEAEs overall), and 175 subjects (28.6%) had TEAEs that were suspected to be related to study drug.

Double-Blind Treatment Period

A total of 79 of the 222 subjects (35.6%) in the Primary Safety Population reported at least 1 TEAE and the incidence of subjects with TEAEs was higher in the CAM2038 treatment group (44 subjects [39.3%]) compared to the Placebo treatment group (35 subjects [31.8%]). A total of 199 TEAEs were reported overall, with 111 TEAEs reported in the CAM2038 treatment group and 88 TEAEs reported in the Placebo treatment group.

The incidence of subjects with TEAEs suspected to be drug-related was relatively low overall (19 subjects [8.6%]) but higher in the CAM2038 treatment group (13 subjects [11.6%]) than in the Placebo treatment group (6 subjects [5.5%]).

Six subjects (2.7%) experienced SAEs during the Double-Blind Treatment Period of the study; 3 subjects (2.7%) in each treatment group, including 1 subject (0.9%) in the Placebo group who died. The death (cancer progression) was not considered to be related to the study drug. In addition, 4 subjects (3.6%) in the CAM2038 treatment group experienced TEAEs resulting in withdrawal of study drug as well as study discontinuation, while in the Placebo treatment group, 2 subjects (1.8%) experienced TEAEs leading to withdrawal of study drug and study discontinuation.

The majority of TEAEs were mild or moderate in intensity; however, 3 subjects (2.7%) had severe TEAEs in the CAM2038 treatment group and 5 subjects (4.5%) had severe TEAEs in the Placebo treatment group In addition, injection site TEAEs were experienced by 3 subjects (2.7%) in the CAM2038 treatment group and 4 subjects (3.6%) in the Placebo treatment group.

Table 22***: Summary of Treatment-Emergent Adverse Events — Double-Blind Treatment Period of the Double-Blind Phase (Primary Safety Population)***

	CAM2038 N=112	Placebo N=110	Total N=222
Number of subjects (%) with any TEAE [number of TEAEs]	44 (39.3%) [111]	35 (31.8%) [88]	79 (35.6%) [199]
Number of subjects (%) with TEAEs suspected to be drug-related	13 (11.6%)	6 (5.5%)	19 (8.6%)
Number of subjects (%) with SAEs	3 (2.7%)	3 (2.7%)	6 (2.7%)
Number of subjects (%) with TEAEs that resulted in death	0	1 (0.9%)	1 (0.5%)
Number of subjects (%) with TEAEs that led to withdrawal of study drug	4 (3.6%)	2 (1.8%)	6 (2.7%)
Number of subjects (%) with TEAEs that led to study discontinuation	4 (3.6%)	2 (1.8%)	6 (2.7%)
Number of subjects (%) with severe TEAEs	3 (2.7%)	5 (4.5%)	8 (3.6%)
Number of subjects (%) with injection site TEAEs	3 (2.7%)	4 (3.6%)	7 (3.2%)

During the Double-Blind Treatment Period, the incidence of subjects with at least 1 TEAE was slightly lower in the Safety Population compared with the Primary Safety Population.

A total of 99 of the 330 subjects (30.0%) reported at least 1 TEAE (226 TEAEs overall), including 55 subjects (33.5%) in the CAM2038 treatment group and 44 subjects (26.5%) in the Placebo treatment group. Thus, the Safety Population included an additional 108 subjects compared to the Primary Safety Population, and 20 of these subjects reported 27 additional TEAEs.

There were no additional deaths, subjects with SAEs, TEAEs leading to withdrawal of study drug or study discontinuation, or TEAEs that were suspected to be drug related, as compared to the Primary Safety Population. The incidence of subjects with these events was lower in the Safety Population due to the larger study population with relatively few additional TEAEs. There were no additional subjects in the Safety Population who had injection site TEAEs compared to the Primary Safety Population; however, 2 additional subjects in the CAM2038 group had severe TEAEs.

Open-Label Safety Extension Phase

Open-Label Titration Period

A total of 56 of the 121 subjects (46.3%) experienced at least 1 TEAE during the Open-Label Titration Period of the Open-Label Safety Extension Phase, which included up to 10 doses of CAM2038 q1w for de novo subjects and 1 or more doses of CAM2038 q1w for the rollover subjects who had been on a monthly dosing schedule during the Double-Blind Treatment Period. Consequently, the incidence of subjects reporting at least 1 TEAE was higher in de novo subjects (41 subjects [54.7%] with a total of 142 TEAEs) compared to rollover subjects (6 subjects [28.6%] in the CAM2038 group who reported 11 TEAEs and 9 subjects [36.0%] in the Placebo group who reported 31 TEAEs). Nearly half of de novo subjects (20 of 41 subjects [26.7% overall]) had drug-related TEAEs. The majority of Placebo rollover subjects had drug-related TEAEs (8 of 9 subjects [32.0% overall]), while only 1 CAM2038 rollover subject (4.8%) had a drug-related TEAE. There were no deaths in the Open-Label Titration Period, but 2 subjects (1.7%) experienced SAEs (1 de novo subject and 1 Placebo rollover subject).

Five subjects (4.1% overall) had TEAEs that led to withdrawal of study drug and study discontinuation: 4 de novo subjects (5.3%) and 1 Placebo rollover subject (4.0%). Six subjects (5.0%) had severe TEAEs: 2 de novo subjects (2.7%), 1 CAM2038 rollover subject (4.8%) and 3 Placebo rollover subjects (12.0%). Thirteen subjects (10.7% overall) had injection site TEAEs, the majority of which were de novo subjects (14.7%), with 2 Placebo rollover subjects (8.0%) also experiencing injection site TEAEs.

When examining data for the Overall Safety Population, Enrollment Subjects Only (excluding Site 077), the incidence of subjects with TEAEs overall was the same for CAM2038 rollover subjects (28.6%), while slightly lower for de novo subjects (48.1%) and Placebo rollover subjects (30.4%) compared to the Overall Safety Population.
In the Overall Safety Population, including Site 077, a total of 62 of the 139 subjects (44.6%) experienced at least 1 TEAE during the Open-Label Titration Period of the Safety Extension Phase.

This population included an additional 10 subjects from Site 077, with 6 of these subjects reporting 10 additional TEAEs. Due to the small number of TEAEs reported by subjects at Site 077 during this period, the patterns of data were similar to those observed in the Overall Safety Population, excluding Site 077. There were no additional deaths, SAEs, or TEAEs leading to withdrawal of study drug or study discontinuation in the populations including Site 077 compared to those excluding Site 077.

Open-Label Enrollment Period

A summary of TEAEs that occurred during the Open-Label Enrollment Period in the Overall Safety Population, Enrollment Subjects Only, excluding Site 077, is provided in Table 23. Overall, 87 of the 109 subjects (79.8%) experienced a total of 397 TEAEs during the Open-Label Enrollment Period.

The incidence of subjects with TEAEs was higher during this period compared to any of the preceding periods, likely because it was the longest duration of study participation compared to any other single period. While the incidence of subjects with TEAEs was higher in rollover subjects (83.6%) compared to de novo subjects (75.9%), the total number of TEAEs was higher in de novo subjects compared to rollover subjects overall (249 vs. 148 events) despite similar sample sizes of 54 and 55 subjects, respectively. Most subjects had TEAEs that were not considered to be drug-related; overall, 20 subjects (18.3%) had drug-related TEAEs, with a lower incidence for rollover subjects (14.5%) compared to de novo subjects (22.2%).

There were no deaths, but 14 subjects (12.8%) overall experienced SAEs, with a similar incidence for de novo and rollover subjects (13.0% and 12.7%, respectively). Four subjects (3.7%) had TEAEs leading to withdrawal of study drug and discontinuation from the study: 3 de novo subjects (5.6%) and 1 rollover subject (1.8%). Thirteen subjects (11.9%) had severe TEAEs: 5 de novo subjects (9.3%) and 8 rollover subjects (14.5%).

Eleven subjects (10.1%) had injection site TEAEs, with a slightly higher incidence in de novo subjects (11.1%) vs. rollover subjects (9.1%).

*Table 23**: Summary of Treatment-Emergent Adverse Events — Open-Label Enrollment Period of the Open-Label Safety Extension Phase (Overall Safety Population, Excluding Site 077)***

	De Novo Subjects (N=54)	Rollover Subjects			Total (N=109)
		CAM2038 (N=24)	Placebo (N=31)	Total (N=55)	
Number of subjects (%) with any TEAE [number of TEAEs]	41 (75.9%) [249]	21 (87.5%) [65]	25 (80.6%) [83]	46 (83.6%) [148]	87 (79.8%) [397]
Number of subjects (%) with TEAEs suspected to be drug-related	12 (22.2%)	2 (8.3%)	6 (19.4%)	8 (14.5%)	20 (18.3%)
Number of subjects (%) with SAEs	7 (13.0%)	3 (12.5%)	4 (12.9%)	7 (12.7%)	14 (12.8%)
Number of subjects (%) with TEAEs that resulted in death	0	0	0	0	0
Number of subjects (%) with TEAEs that led to withdrawal of study drug	3 (5.6%)	0	1 (3.2%)	1 (1.8%)	4 (3.7%)
Number of subjects (%) with TEAEs that led to study discontinuation	3 (5.6%)	0	1 (3.2%)	1 (1.8%)	4 (3.7%)
Number of subjects (%) with severe TEAEs	5 (9.3%)	2 (8.3%)	6 (19.4%)	8 (14.5%)	13 (11.9%)
Number of subjects (%) with injection site TEAEs	6 (11.1%)	2 (8.3%)	3 (9.7%)	5 (9.1%)	11 (10.1%)

Source: Table 14.3.2.1.5OLE
SAE=serious adverse event; TEAE=treatment-emergent adverse event.

In the Overall Safety Population, Enrollment Subjects Only, including Site 077, the incidence of subjects reporting at least 1 TEAE was lower compared to the population excluding Site 077. A total of 121 of the 176 subjects (68.8%) experienced a TEAE, with 451 TEAEs reported overall. Thus, Site 077 represented an additional 67 subjects during the Enrollment Period, 34 of whom reported an additional 54 TEAEs. There were no additional deaths, SAEs orTEAEs leading to discontinuation from the study drug or study.

The incidence of subjects with TEAEs in the Treatment Completion Population was similar to the Overall Safety Population, Enrollment Subjects Only, for most groups, although the incidence of subjects with TEAEs was slightly higher in de novo subjects compared to de novo subjects in the Overall Safety Population (82.1% vs. 75.9%).
The results for the Treatment Completion Population, including Site 077, were similar those of the Treatment Completion Population, excluding Site 077.

Integrated Full Exposure (Double-Blind Phase and Open-Label Safety Extension Phase)

Table 24: ***Summary of Treatment-Emergent Adverse Events — Double-Blind and Open-Label Safety Extension Phases (Integrated Full Exposure Safety Populations, Excluding Site 077)***

	Integrated Full Exposure Safety Population				Continuous Integrated Full Exposure Safety Population (N=58)
	De Novo Subjects (N=38)	CAM2038 (N=20)	Placebo (N=28)	Total (N=86)	
Number of subjects (%) with any TEAE [number of TEAEs]	34 (89.5%) [293]	19 (95.0%) [153]	26 (92.9%) [169]	79 (91.9%) [615]	53 (91.4%) [446]
Number of subjects (%) with TEAEs suspected to be drug related	11 (28.9%)	9 (45.0%)	14 (50.0%)	34 (39.5%)	20 (34.5%)
Number of subjects (%) with SAEs	4 (10.5%)	2 (10.0%)	2 (7.1%)	8 (9.3%)	6 (10.3%)
Number of subjects (%) with TEAEs that resulted in death	0	0	0	0	0
Number of subjects (%) with TEAEs that led to withdrawal of study drug	0	0	0	0	0
Number of subjects (%) with TEAEs that led to study discontinuation	0	0	0	0	0
Number of subjects (%) with severe TEAEs	3 (7.9%)	2 (10.0%)	8 (28.6%)	13 (15.1%)	5 (8.6%)
Number of subjects (%) with injection site TEAEs	7 (18.4%)	3 (15.0%)	9 (32.1%)	19 (22.1%)	10 (17.2%)

Analysis of Adverse Events
Double-Blind Phase

Open-Label Titration Period

Most Common Adverse Events

The most common TEAEs in the Primary Safety Population during the Open-Label Titration Period were those classified by SOC as Gastrointestinal disorders, General disorders and administration site conditions, and Nervous system disorders.

The most common individual TEAEs observed during the Open-Label Titration Period were nausea (87 subjects [18.6%]) and vomiting (64 subjects [13.7%]). Other commonly reported TEAEs were constipation (25 subjects [5.3%]), dizziness (38 subjects [8.1%]), headache (28 subjects [6.0%]) and injection site reactions, including injection site pruritus (40 subjects [8.5%]), injection site erythema (32 subjects [6.8%]), injection site pain (29 subjects [6.2%]), and injection site swelling (25 subjects [5.3%]). More than 5% of subjects reported TEAEs in other SOCs, including Infections and infestations, Musculoskeletal and connective tissue disorders, Injury, poisoning and procedural complications, Psychiatric disorders, and Skin and subcutaneous tissue disorders. However, any individual TEAEs within these SOCs occurred in fewer than 5% of subjects.

Table 25***: Number of Subjects (%) with Treatment-Emergent Adverse Events Occurring in At Least 5% of Subjects by System Organ Class and Preferred Term — Open-Label Titration Period of the Double-Blind Phase (Primary Safety Population)***

System Organ Class	Total CAM2038 N=468
Gastrointestinal disorders	**138 (29.5%)**
Nausea	87 (18.6%)
Vomiting	64 (13.7%)
Constipation	25 (5.3%)
General disorders and administration site conditions	**99 (21.2%)**

System Organ Class	Total CAM2038 N=468
Injection site pruritus	40 (8.5%)
Injection site erythema	32 (6.8%)
Injection site pain	29 (6.2%)
Injection site swelling	25 (5.3%)
Nervous system disorders	**93 (19.9%)**
Dizziness	38 (8.1%)
Headache	28 (6.0%)

Injection Site Adverse Events

A total of 69 subjects (14.7%) in the Primary Safety Population had at least 1 injection site TEAE. There were no individual injection site TEAEs that occurred in more than 10% of subjects. However, injection site TEAEs occurring in ≥5% of subjects included injection site pruritus, injection site erythema, injection site pain, and injection site swelling. The remaining injection site TEAEs were observed in fewer than 5% of subjects.
Fourteen subjects reported injection site induration; however, 10 of these subjects were participating at a single site (Site 74), suggesting that the event may have been related to injection technique.

Double-Blind Treatment Period

Most Common Adverse Events

In the Primary Safety Population, ≥5% of subjects in both treatment groups reported TEAEs that were classified by SOC as Infections and infestations, Investigations, General disorders and administration site conditions, or Nervous system disorders. In addition, ≥5% of subjects in the CAM2038 treatment group reported TEAEs that were classified by SOC as Musculoskeletal and connective tissue disorders, Gastrointestinal disorders, Injury, poisoning and procedural complications, Psychiatric disorders, or Skin and subcutaneous disorders. However, only 1 individual TEAE occurred in more than 5% of subjects. Therefore, TEAEs that occurred in at least 2% of subjects in either treatment group of the Primary Safety Population are summarized by SOC and preferred term in Table below. The most common individual TEAEs in the CAM2038 treatment group were back pain (7 subjects [6.3%]), fall (5 subjects [4.5%]) and oedema peripheral (3 subjects [2.7%]). The remaining TEAEs in this treatment group occurred in fewer than 2% of subjects (i.e., only 1 or 2 subjects). The most common TEAEs in the Placebo treatment group were injection site TEAEs (injection site erythema, injection site pain, and injection site swelling), which occurred in 3 subjects (2.7%) each. All other individual TEAEs in this treatment group occurred in fewer than 2% of subjects.

Although there were a greater number of subjects who reported the TEAE of "back pain" in the CAM2038 treatment group (6.3%) vs. the Placebo treatment group (1.8%), these were all assessed as mild to moderate intensity and not related to study drug. Only 1 subject had a TEAE assessed as related to study drug within the SOC Musculoskeletal and connective tissue disorders (joint swelling in the CAM2038 treatment group). Within the SOC Injury, poisoning and procedural complications, the TEAE of "fall" occurred more frequently in the CAM2038-treated compared to the Placebo-treated subjects (4.5% vs. 0.9%); however, all were assessed as mild or moderate intensity and none were considered related to study drug. Within the SOC General disorders and administration site conditions, the incidence of subjects with peripheral oedema was higher in the CAM2038 group; 2 were assessed of mild intensity and 1 was assessed of severe intensity, however, none were considered related to study drug. Injection site TEAEs occurred more frequently in subjects in the Placebo treatment group.

*Table 26**: Number of Subjects (%) with Treatment-Emergent Adverse Events Occurring in At Least 2% of Subjects in Either Treatment Group by System Organ Class and Preferred Term — Double-Blind Treatment Period of the Double-Blind Phase (Primary Safety Population)***

System Organ Class Preferred Term	CAM2038 N=112	Placebo N=110	Total N=222
Musculoskeletal and connective tissue disorders	**15 (13.4%)**	**5 (4.5%)**	**20 (9.0%)**
Back pain	7 (6.3%)	2 (1.8%)	9 (4.1%)
General disorders and administration site conditions	**8 (7.1%)**	**6 (5.5%)**	**14 (6.3%)**
Injection site erythema	2 (1.8%)	3 (2.7%)	5 (2.3%)
Injection site pain	1 (0.9%)	3 (2.7%)	4 (1.8%)
Injection site swelling	1 (0.9%)	3 (2.7%)	4 (1.8%)
Oedema peripheral	3 (2.7%)	0	3 (1.4%)
Injury, poisoning and procedural complications	**8 (7.1%)**	**3 (2.7%)**	**11 (5.0%)**
Fall	5 (4.5%)	1 (0.9%)	6 (2.7%)

Injection Site Adverse Events

Fewer than 5% of subjects experienced injection site TEAEs overall, with a slightly higher incidence of subjects in the Placebo treatment group compared to the CAM2038 treatment group. In the CAM2038 treatment group, 2 subjects (1.8%) experienced injection site erythema, and 1 subject (0.9%) each had TEAEs of injection site pain and injection site swelling. In the Placebo treatment group, 3 subjects (2.7%) each had TEAEs of injection site erythema, injection site pain and injection site swelling, while 1 subject each (0.9%) had TEAEs of injection site abscess and injection site cellulitis. All injection site TEAEs were considered to be drug-related in the CAM2038 and Placebo treatment groups. With the exception of a severe TEAE of injection site abscess observed in the Placebo treatment group, most injection site TEAEs were considered mild or moderate in severity.

Drug-Related Adverse Events

In the CAM2038 treatment group of the Primary Safety Population, most TEAEs were assessed as not related to study drug Drug-related TEAEs reported by more than 1 subject in the CAM2038 treatment group were constipation (2 subjects [1.8%]) and injection site erythema (2 subjects [1.8%]). Similarly, most TEAEs observed after administration of Placebo were not considered to be drug-related.
TEAEs reported by more than 1 subject in the Placebo treatment group were injection site erythema (3 subjects [2.7%]), injection site pain (3 subjects [2.7%]) and injection site swelling (3 subjects [2.7%]).

Adverse Events by Intensity

The majority of TEAEs were mild or moderate in intensity in both the CAM2038 and Placebo treatment groups of the Primary Safety Population. Three subjects (2.7%) in the CAM2038 treatment group experienced severe TEAEs during the Double- Blind Treatment Period, including 1 subject with oedema peripheral, 1 subject with cholecystitis and cholelithiasis, and 1 subject with lumbar spinal stenosis and cauda equina syndrome. Five subjects (4.5%) in the Placebo treatment group had severe TEAEs, including 1 subject each (0.9%) with severe pancreatic carcinoma, metastases to liver and constipation; pain in extremity; injection site abscess; appendicitis; and migraine.
None of the severe TEAEs in the CAM2038 treatment group were considered drug-related, while the severe TEAEs of constipation and injection site abscess observed in the Placebo treatment group were considered to be related to study drug

Adverse Events in the Safety Population

Patterns of TEAEs in this population were similar to the Primary Safety Population, although with a lower incidence of subjects with TEAEs

Adverse Events by Dose in the Open-Label Titration and Double-Blind Treatment Periods

Weekly doses

As summarized in the table below there was no clear dose-relationship of CAM2038 q1w to the incidence of subjects with TEAEs overall, with the highest incidence of subjects with TEAEs observed with 4 mg CAM2038 q1w (37.3%; 22.9% suspected to be drug-related) and the lowest incidence with 12 mg CAM2038 q1w (13.8%; 7.9% suspected to be drug-related).

Table 27***: Summary of Adverse Events by Dose (Primary Safety Population, Double Blind Phase)***

	Weekly						
Category	4 mg (N=83)	8 mg (N=217)	12 mg (N=203)	16 mg (N=188)	24 mg (N=162)	32 mg (N=134)	Total (N=222)
Subjects with any treatment-emergent AEs,n (%)	31 (37.3%)	55 (25.3%)	28 (13.8%)	37 (19.7%)	32 (19.8%)	44 (27.2%)	133 (59.9%)
Number of treatment-emergent AEs	60	102	43	56	67	88	416
Subjects with serious AEs,n (%)	0	1 (0.5%)	0	1 (0.5%)	0	0	2 (0.9%)
Subjects with suspected to be drug related AEs,n (%)	19 (22.9%)	30 (13.8%)	16 (7.9%)	21 (11.2%)	18 (11.1%)	18 (11.1%)	70 (31.5%)
Subjects with AEs that led to drug withdrawn,n (%)	0	0	0	0	0	0	0
Subjects with AEs that led to study discontinuation,n (%)	0	0	0	0	0	0	0
Subjects with AEs that resulted in death,n (%)	0	0	0	0	0	0	0

Monthly doses

There was also no clear dose-relationship between CAM2038 q4w and the incidence of subjects with TEAEs overall (35.3% with 64 mg, 40.0% with 96 mg, and 38.1% with 128 mg CAM2038 q4w).

*Table 28****: Summary of Adverse Events by Dose (Primary Safety Population, Double Blind Phase)***

	Monthly			
Category	64 mg (N=17)	96 mg (N=15)	128 mg (N=63)	Total (N=95)
Subjects with any treatment-emergent AEs,n (%)	6 (35.3%)	6 (40.0%)	24 (38.1%)	36 (37.9%)
Number of treatment-emergent AEs	17	14	61	92
Subjects with serious AEs,n (%)	0	0	2 (3.2%)	2 (2.1%)
Subjects with suspected to be drug related AEs,n (%)	1 (5.9%)	2 (13.3%)	8 (12.7%)	11 (11.6%)
Subjects with AEs that led to drug withdrawn,n (%)	0	0	4 (6.3%)	4 (4.2%)
Subjects with AEs that led to study discontinuation,n (%)	0	0	4 (6.3%)	4 (4.2%)
Subjects with AEs that resulted in death,n (%)	0	0	0	0

Open-Label Safety Extension Phase

Open-Label Titration Period

Most Common Adverse Events

Note that for rollover subjects, TEAEs during the Open-Label Titration Period reflect only the CAM2038 q1w adjustment dose for the subjects who were on CAM2038 q1w in the Double-Blind Phase. Thus, the reporting periods for de novo and placebo rollover subjects differ (10 weeks v. 1-2 weeks), which should be taken into consideration when interpreting TEAE results.

In de novo subjects, the most common TEAEs during the Open-Label Titration Period were those classified as infections and infestations, followed by gastrointestinal disorders and general disorders and administration site conditions, and then injury, poisoning and procedural complications, musculoskeletal and connective tissue disorders, investigations, nervous system disorders, and psychiatric disorders. In Placebo rollover subjects, the most common TEAEs were those classified as gastrointestinal disorders, nervous system disorders, and general disorders and administration site conditions.

In CAM2038 rollover subjects, the most common TEAEs were those classified as metabolism and nutrition disorders, and infections and infestations. The most commonly reported TEAEs overall were nausea (16 subjects [13.2%]), vomiting (11 subjects [9.1%]) and upper respiratory tract infection (7 subjects [5.8%]). These events were more commonly reported by de novo and Placebo rollover subjects than by CAM2038 rollover subjects. De novo subjects also reported more injection site TEAEs than rollover subjects (13 subjects [10.7%] in total, of which 11 subjects [14.7%] were de novo subjects).

The most commonly reported injection site TEAEs in de novo subjects were injection site pruritus (6 subjects [8.0%]) injection site erythema (6 subjects [8.0%]), injection site pain (5.3%) and injection site swelling (5.3%).

TEAEs classified as infections and infestations, and general disorders and administration site conditions were reported by a higher proportion of de novo subjects; slight imbalances between groups were also seen in the SOCs injury, poisoning and procedural complications, investigations, musculoskeletal and connective tissue disorders, and psychiatric disorders. These imbalances were mediated primarily by higher incidences of subjects with individual TEAEs of nausea, vomiting and constipation in de novo subjects compared to CAM2038 rollover subjects, the majority of which were considered related to study drug, as well as drug-related injection site TEAEs and upper respiratory tract infections (all unrelated to study drug).

In contrast, gastrointestinal disorders and nervous system disorders were observed in a higher incidence of Placebo rollover subjects compared to CAM2038 rollover subjects.
This was primarily related to a higher incidence of subjects with nausea and vomiting, as well as headache and dizziness in this group, the majority of which were considered related to study drug.

Table 29***: Number of Subjects (%) with Treatment-Emergent Adverse Events in At Least 5% of Subjects in Any Group by System Organ Class — Open-Label Titration Period of the Open-Label Safety Extension Phase (Overall Safety Population, Excluding Site 077)***

System Organ Class Preferred Term	De Novo N=75	Rollover Subjects			Total N=121
		CAM2038 N=21	Placebo N=25	Total N=46	
At least one TEAE	**41 (54.7%)**	**6 (28.6%)**	**9 (36.0%)**	**15 (32.6%)**	**56 (46.3%)**
Gastrointestinal disorders	**14 (18.7%)**	**1 (4.8%)**	**7 (28.0%)**	**8 (17.4%)**	**22 (18.2%)**
Nausea	9 (12.0%)	1 (4.8%)	6 (24.0%)	7 (15.2%)	16 (13.2%)
Vomiting	7 (9.3%)	0	4 (16.0%)	4 (8.7%)	11 (9.1%)
Constipation	4 (5.3%)	0	0	0	4 (3.3%)
General disorders and administration site conditions	**14 (18.7%)**	**0**	**3 (12.0%)**	**3 (6.5%)**	**17 (14.0%)**
Injection site pruritus	6 (8.0%)	0	2 (8.0%)	2 (4.3%)	8 (6.6%)
Injection site erythema	6 (8.0%)	0	0	0	6 (5.0%)
Injection site pain	4 (5.3%)	0	0	0	4 (3.3%)
Injection site swelling	4 (5.3%)	0	0	0	4 (3.3%)
Infections and infestations	**19 (25.3%)**	**2 (9.5%)**	**1 (4.0%)**	**3 (6.5%)**	**22 (18.2%)**
Upper respiratory tract infection	6 (8.0%)	0	1 (4.0%)	1 (2.2%)	7 (5.8%)
Nervous system disorders	**6 (8.0%)**	**1 (4.8%)**	**5 (20.0%)**	**6 (13.0%)**	**12 (9.9%)**
Dizziness	2 (2.7%)	0	2 (8.0%)	2 (4.3%)	4 (3.3%)
Headache	0	0	2 (8.0%)	2 (4.3%)	2 (1.7%)

Drug-Related Adverse Events

Drug-related TEAEs during the Open-Label Titration Period occurred with the highest incidence of subjects in Placebo rollover subjects (8 subjects [32.0%]) followed by de novo subjects (20 subjects [26.7%]). Excluding injection site reactions, the most common drug-related TEAEs were nausea, vomiting, dizziness and headache in Placebo rollover subjects, and nausea, vomiting and constipation in de novo subjects. Only 1 CAM2038 rollover subject had a drug-related TEAE (somnolence) that occurred the day after receiving CAM2038 q1w 32 mg (after switching from 128 mg CAM2038 q4w in the Double-Blind Phase;

Adverse Events by Intensity

The majority of subjects in the Overall Safety Population, excluding Site 077 had TEAEs that were considered mild or moderate in intensity during the Open-Label Titration Period. Overall, 6 subjects (5.0%) experienced severe TEAEs; 3 Placebo rollover subjects (12.0%), 2 de novo subjects (2.7%) and 1 CAM2038 rollover subject (4.8%) none of which were injection site TEAEs Of the de novo subjects, 1 experienced severe syncope (not related to study drug) and 1 subject experienced severe constipation and gastrooesophageal reflux disease (related to study drug), while the CAM2038 rollover subject had severe bronchitis (not related)
In the Placebo rollover group, 1 subject had severe nausea, vomiting and dizziness and another subject had severe nausea, vomiting, dizziness, myalgia and headache, all of which were considered related to study drug. One additional subject in this group had severe sleep apnoea syndrome (also an SAE), but this was not considered related to study drug.

Open-Label Enrolment Period

Most Common Adverse Events

At least 5% of subjects overall experienced TEAEs classified by SOC as Infections and infestations, Investigations, General disorders and administration site conditions, Injury, poisoning and procedural complications, or Musculoskeletal and connective tissue disorders. More than 10% of subjects overall experienced TEAEs classified by SOC as Gastrointestinal disorders or Metabolism and nutrition disorders.

The incidence of subjects reporting a TEAE classified as a musculoskeletal disorder was higher in rollover subjects overall (23.6%) compared to de novo subjects (7.4%). This was mediated primarily by a higher incidence of subjects who experienced arthralgia, back pain and musculoskeletal pain in the rollover group (10.9%, 5.5% and 7.3%, respectively) compared to 0 to 1.9% of subjects in the de novo group. Injury, poisoning and procedural complications were also observed with a higher incidence in rollover subjects (20.0%) compared to de novo subjects (11.1%); the most common event in this category (fall) was higher in Placebo rollover subjects (9.7%) compared to de novo subjects (3.7%). In contrast, investigations and renal and urinary disorders were observed with a higher incidence in de novo subjects (29.6% and 14.8%, respectively) compared to rollover subjects (9.1% and 3.6%, respectively); the most common events in these SOCs (blood glucose increased, aspartate aminotransferase increased and proteinuria) were also higher in de novo subjects (5.6% to 11.1%) than in rollover subjects (0% to 3.6%).

Musculoskeletal and connective tissue disorders were observed in a higher incidence of CAM2038 rollover subjects compared to Placebo rollover subjects (33.3% vs. 16.1%), as were psychiatric disorders (12.5% vs. 0%). This was mediated primarily by a higher incidence of subjects with the most common events in these SOCs, i.e., arthralgia (16.7% vs. 6.5%), back pain (12.5% vs. 0%) and insomnia (8.3% vs. 0%). However, the incidence of subjects with TEAEs classified into other SOCs was higher in Placebo rollover subjects compared to CAM2038 rollover subjects, including general disorders and administration site conditions (19.4% vs. 12.5%), infections and infestations (32.3% vs. 20.8%), injury, poisoning and procedural complications (25.8% vs. 12.5%), and investigations (16.1% vs. 0%). In the general disorders and administration site conditions SOC, oedema peripheral was observed in a higher incidence of Placebo rollover subjects compared to CAM2038 rollover subjects (9.7% vs. 0%), while injection site pruritus and injection site erythema were observed in a slightly higher incidence of subjects (both 6.5% vs. 4.2%).

Among infections and infestations, influenza occurred in a higher incidence of CAM2038 rollover subjects (12.5% vs. 3.2% of Placebo rollover subjects); however, the other common TEAEs in this SOC were observed in a slightly higher incidence of Placebo rollover subjects (urinary tract infection 9.7% vs. 8.3%; nasopharyngitis 6.5% vs. 4.2%, and sinusitis 6.5% vs. 0%). The differences in incidence of subjects with injury, poisoning and procedural complications SOC were mediated primarily by a higher incidence of subjects with TEAEs of fall in Placebo vs. CAM2038 rollover subjects (9.7% vs. 0%). While no CAM2038 rollover subjects had TEAEs classified as investigations, the most common TEAE in this SOC (GGT increased) was observed in 6.5% of Placebo rollover subjects.

Table 30***: Number of Subjects (%) with Treatment-Emergent Adverse Events in At Least 5% of Subjects in Any Group by System Organ Class — Open-Label Enrollment Period of the Open-Label Safety Extension Phase (Overall Safety Population, Enrollment Subjects Only, Excluding Site 077)***

System Organ Class Preferred Term	De Novo Subjects N=54	Rollover Subjects			Total N=109
		CAM2038 N=24	Placebo N=31	Total N=55	
At least one TEAE	**41 (75.9%)**	**21 (87.5%)**	**25 (80.6%)**	**46 (83.6%)**	**87 (79.8%)**
Gastrointestinal disorders	**8 (14.8%)**	**4 (16.7%)**	**4 (12.9%)**	**8 (14.5%)**	**16 (14.7%)**
Nausea	4 (7.4%)	1 (4.2%)	1 (3.2%)	2 (3.6%)	6 (5.5%)
Vomiting	3 (5.6%)	1 (4.2%)	2 (6.5%)	3 (5.5%)	6 (5.5%)
General disorders and administration site conditions	**8 (14.8%)**	**3 (12.5%)**	**6 (19.4%)**	**9 (16.4%)**	**17 (15.6%)**
Injection site pruritus	2 (3.7%)	1 (4.2%)	2 (6.5%)	3 (5.5%)	5 (4.6%)
Injection site erythema	1 (1.9%)	1 (4.2%)	2 (6.5%)	3 (5.5%)	4 (3.7%)
Oedema peripheral	1 (1.9%)	0	3 (9.7%)	3 (5.5%)	4 (3.7%)
Injection site swelling	3 (5.6%)	0	0	0	3 (2.8%)
Infections and infestations	**15 (27.8%)**	**5 (20.8%)**	**10 (32.3%)**	**15 (27.3%)**	**30 (27.5%)**
Urinary tract infection	4 (7.4%)	2 (8.3%)	3 (9.7%)	5 (9.1%)	9 (8.3%)
Influenza	1 (1.9%)	3 (12.5%)	1 (3.2%)	4 (7.3%)	5 (4.6%)
Nasopharyngitis	1 (1.9%)	1 (4.2%)	2 (6.5%)	3 (5.5%)	4 (3.7%)
Sinusitis	2 (3.7%)	0	2 (6.5%)	2 (3.6%)	4 (3.7%)

System Organ Class Preferred Term	De Novo Subjects N=54	Rollover Subjects			Total N=109
		CAM2038 N=24	Placebo N=31	Total N=55	
Injury, poisoning and procedural complications	**6 (11.1%)**	**3 (12.5%)**	**8 (25.8%)**	**11 (20.0%)**	**17 (15.6%)**
Fall	2 (3.7%)	0	3 (9.7%)	3 (5.5%)	5 (4.6%)
Investigations	**16 (29.6%)**	**0**	**5 (16.1%)**	**5 (9.1%)**	**21 (19.3%)**
Blood glucose increased	6 (11.1%)	0	0	0	6 (5.5%)
Gamma-glutamyltransferase increased	3 (5.6%)	0	2 (6.5%)	2 (3.6%)	5 (4.6%)
Aspartate aminotransferase increased	3 (5.6%)	0	0	0	3 (2.8%)
Metabolism and nutrition disorders	**7 (13.0%)**	**3 (12.5%)**	**3 (9.7%)**	**6 (10.9%)**	**13 (11.9%)**
Hyperglycaemia	0	0	2 (6.5%)	2 (3.6%)	2 (1.8%)
Musculoskeletal and connective tissue disorders	**4 (7.4%)**	**8 (33.3%)**	**5 (16.1%)**	**13 (23.6%)**	**17 (15.6%)**
Arthralgia	1 (1.9%)	4 (16.7%)	2 (6.5%)	6 (10.9%)	7 (6.4%)
Back pain	1 (1.9%)	3 (12.5%)	0	3 (5.5%)	4 (3.7%)
Musculoskeletal pain	0	2 (8.3%)	2 (6.5%)	4 (7.3%)	4 (3.7%)
Pain in extremity	0	2 (8.3%)	0	2 (3.6%)	2 (1.8%)
Nervous system disorders	**4 (7.4%)**	**3 (12.5%)**	**3 (9.7%)**	**6 (10.9%)**	**10 (9.2%)**
Headache	2 (3.7%)	2 (8.3%)	0	2 (3.6%)	4 (3.7%)
Psychiatric disorders	**5 (9.3%)**	**3 (12.5%)**	**0**	**3 (5.5%)**	**8 (7.3%)**
Insomnia	1 (1.9%)	2 (8.3%)	0	2 (3.6%)	3 (2.8%)
Renal and urinary disorders	**8 (14.8%)**	**1 (4.2%)**	**1 (3.2%)**	**2 (3.6%)**	**10 (9.2%)**
Proteinuria	3 (5.6%)	0	0	0	3 (2.8%)

Drug-Related Adverse Events

The incidence of subjects with drug related TEAEs was markedly lower than the incidence of subjects with TEAEs overall (18.3% vs. 79.8%). The most commonly reported drug-related TEAEs were injection site pruritus (5 subjects [4.6%]), injection site erythema (4 subjects [3.7%]), injection site pain and injection site swelling (3 subjects [2.8%] each) and nausea, vomiting, injection site bruising and injection site nodule (2 subjects [1.8%] each).The incidence of subjects with at least 1 drug-related TEAE was slightly higher in de novo subjects (22.2%) than in rollover subjects (14.5%), although this was primarily due to a lower incidence of CAM2038 rollover subjects with drug-related TEAEs (8.3%), whereas the incidence of Placebo rollover subjects with drug-related TEAEs (19.4%) was more similar to the de novo subjects. As with drug-related TEAEs overall, the incidence of subjects with non-injection site TEAEs was similar between de novo subjects (13.0%) and Placebo rollover subjects (12.9%), while no subjects in the CAM2038 rollover group experienced drug-related TEAEs. With the exception of vomiting in 2 Placebo rollover subjects (6.5%), all other drug-related non-injection site-related TEAEs occurred in only single de novo (1.9%) or Placebo rollover subjects (3.2%).

Adverse Events by Intensity

The majority of TEAEs during the Open-Label Enrolment Period in the Overall Safety Population, Enrollment Subjects Only, excluding Site 077, were mild (reported by 30.3% of subjects) or moderate (reported by 37.6% of subjects) in intensity: 13 subjects (11.9%) overall had at least 1 severe TEAE. The incidence of subjects with at least 1 severe TEAE was higher in rollover (14.5%) compared to de novo (9.3%) subjects. However, this was primarily due to the higher incidence observed in Placebo

rollover subjects (19.4%), while the incidence in CAM2038 rollover subjects (8.3%) was more similar to de novo subjects. While a higher proportion of rollover subjects (7.3%) than de novo subjects (1.9%) reported severe TEAEs, the severe injection site TEAE occurred in a de novo subject (1.9%). Mild and moderate non-injection site TEAEs occurred in 29.4% and 35.8% of subjects overall, respectively, while 12 subjects (11.0%) had severe noninjection site TEAEs . Only 3 subjects had severe TEAEs that were considered drug-related, including the de novo subject with severe injection site pruritus (as discussed above), and 2 Placebo rollover subjects (one each with severe vomiting and oedema peripheral).

Adverse Events by Dose in the Open-Label Titration and Enrollment Periods

Table 31***: Overall Summary of Adverse Events by Treatment Dosing Frequency and Dose Overall Safety Population Excluding Site 077, Enrollment Subjects Only***

	Weekly						
Category	4 mg (N=40)	8 mg (N=107)	12 mg (N=102)	16 mg (N=96)	24 mg (N=88)	32 mg (N=68)	Total (N=109)
Subjects with any treatment-emergent AEs	16 (40.0%)	27 (25.2%)	21 (20.6%)	20 (20.8%)	20 (22.7%)	25 (28.4%)	71 (65.1%)
Number of treatment-emergent AEs	35	170	46	40	45	71	407
Subjects with serious AEs	0	0	0	0	0	2 (2.3%)	2 (1.8%)
Subjects with suspected to be drug related AEs	6 (15.0%)	15 (14.0%)	10 (9.8%)	13 (13.5%)	15 (17.0%)	11 (12.5%)	39 (35.8%)
Subjects with AEs that led to drug withdrawn	0	0	0	0	0	0	0
Subjects with AEs that led to study discontinuation	0	0	0	0	0	0	0
Subjects with AEs that resulted in death	0	0	0	0	0	0	0

	Monthly			
Category	64 mg (N=10)	96 mg (N=22)	128 mg (N=67)	Total (N=95)
Subjects with any treatment-emergent AEs	9 (90.0%)	13 (59.1%)	53 (79.1%)	74 (77.9%)
Number of treatment-emergent AEs	26	60	193	279
Subjects with serious AEs	0	3 (13.6%)	11 (16.4%)	14 (14.7%)
Subjects with suspected to be drug related AEs	2 (20.0%)	6 (27.3%)	11 (16.4%)	18 (18.9%)
Subjects with AEs that led to drug withdrawn	0	2 (9.1%)	2 (3.0%)	4 (4.2%)
Subjects with AEs that led to study discontinuation	0	2 (9.1%)	2 (3.0%)	4 (4.2%)
Subjects with AEs that resulted in death	0	0	0	0

The incidence of subjects with TEAEs overall was higher with CAM2038 q4w (74 subjects [77.9%]) compared to CAM2038 q1w (71 subjects [65.1%]) although the number of TEAEs was higher for the CAM2038 q1w subjects compared to CAM2038 q4w subjects (407 and 279, respectively). The incidence of subjects with TEAEs was highest at the low doses of CAM2038 q1w (40.0% at 4 mg) and CAM2038 q4w (90.0% at 64 mg CAM2038 q4w); however, the sample sizes were small at these dose levels

compared to the other dose levels (N=40 and 10, respectively). For the other CAM2038 q1w doses (8 to 32 mg), the incidences of subjects with TEAEs were relatively similar (20.6% to 28.4%). The incidence of subjects with SAEs was higher with CAM2038 q4w (14 subjects [14.7%]) compared to CAM2038 q1w (2 subjects [1.8%]).

Serious adverse event/deaths/other significant events

Deaths

Double-Blind Phase

*Table 32**: Summary of All Adverse Events Causing Death by System Organ Class and Preferred Term Primary Safety Population, Double Blind Phase***

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Summary of All Adverse Events Causing Death by System Organ Class and Preferred Term
Primary Safety Population, Double Blind Phase

SYSTEM ORGAN CLASS	PREFERRED TERM	CAM2038 (N=112) n (%)	PLACEBO (N=110) n (%)	TOTAL (N=222) n (%)
At Least One AEs		0 (0.0%)	1 (0.9%)	1 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		0 (0.0%)	1 (0.9%)	1 (0.5%)
	Pancreatic carcinoma	0 (0.0%)	1 (0.9%)	1 (0.5%)

One subject in the Placebo treatment group had an SAE of pancreatic carcinoma leading to death in the Double-Blind Treatment Period of this study (Primary Safety Population). One additional subject died during the Open-Label Titration Period prior to randomization to a treatment group and the cause of death could not be confirmed by the Investigator (initially suspected suicide that could not be confirmed by documentation). In addition, 1 subject died due to sepsis before the first dose of CAM2038 q1w. None of the deaths was considered to be related to study drug.

Open-Label Safety Extension Phase

There were no deaths during the Open-Label Safety Extension Phase.

Other Serious Adverse Events

Double-Blind Phase

Open-Label Titration Period

Ten subjects (2.1%) experienced SAEs during the Open-Label Titration Period. This included subjects with non-cardiac chest pain and musculoskeletal pain; intervertebral disc protrusion; cellulitis; hemiparesis; pleuritic pain; nausea, vomiting and asthenia; dysphagia; schizoaffective disorder; multiorgan failure and hepatic failure; and non-cardiac chest pain.

Table 33***: Number of Subjects (%) with Serious Adverse Events by System Organ Class — Open-Label Titration Period of the Double-Blind Phase (Primary Safety Population)***
System Organ Class Total CAM2038

System Organ Class	Total CAM2038 N=468
At least 1 SAE	**10 (2.1%)**
Gastrointestinal disorders	**2 (0.4%)**
Dysphagia	1 (0.2%)
Nausea	1 (0.2%)
Vomiting	1 (0.2%)
General disorders and administration site conditions	**5 (1.1%)**
Asthenia	1 (0.2%)
Death	1 (0.2%)
Multi-organ failure	1 (0.2%)
Non-cardiac chest pain	2 (0.4%)
Hepatobiliary disorders	**1 (0.2%)**
Acute hepatic failure	1 (0.2%)
Infections and infestations	**1 (0.2%)**
Cellulitis	1 (0.2%)
Musculoskeletal and connective tissue disorders	**1 (0.2%)**
Musculoskeletal pain	1 (0.2%)
Nervous system disorders	**1 (0.2%)**
Hemiparesis	1 (0.2%)
Psychiatric disorders	**1 (0.2%)**
Schizoaffective disorder	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	**1 (0.2%)**

System Organ Class	Total CAM2038 N=468
Pleuritic pain	1 (0.2%)

Three subjects had SAEs that were considered by the Investigator to be related to study drug.

One subject experienced nausea, intractable vomiting and asthenia (all of severe intensity) 5 hours after receiving the first dose of 4 mg CAM2038 q1w in the Open-Label Titration Period. The subject was hospitalized, and the SAE resolved within 3 days. Treatment included intravenous fluids, metoclopramide and ondansetron. The study drug was discontinued due to the SAEs and the subject discontinued the study. The Sponsor concurred with the Investigator's causality assessment.

One subject experienced **acute hepatic failure (severe) and multiple organ dysfunction syndrome** (severe) and was admitted to the hospital the day after the first dose of 8 mg CAM2038 q1w in the Open-Label Titration Period. The subject also had altered mental status, which the Investigator attributed to the CAM2038 dose and which was treated with naloxone. The subject was treated with supportive care and was discharged from the hospital 8 days after start of the events. The study drug was discontinued due to the SAEs and the subject discontinued the study. The Investigator considered the events of acute hepatic failure and multi-organ dysfunction syndrome as related to CAM2038.

Although there was a temporal relationship between onset of the SAEs and CAM2038 administration, the subject's rapid recovery supports the Sponsor's alternative explanation of rhabdomyolysis secondary to statin use, which can lead to transient hepatic and renal failure.

One subject with a history of schizoaffective disorder, psychosis and neurological deficit secondary to previous head trauma experienced worsening of the schizoaffective disorder (severe intensity) the day after the first dose of 8 mg CAM2038 q1w in the Open-Label Titration Period. The subject was disoriented and experienced chest discomfort (when eating), shortness of breath, generalized weakness and uncontrolled hypertension (reported as non-serious AEs) and was admitted to the hospital for evaluation and treatment. The neurologist was unable to determine if the symptoms were of neurologic or psychiatric origin. Six days after admission, the event of worsening of the schizoaffective disorder was considered resolved and the subject was discharged from the hospital to a rehabilitation facility as the subject had experienced functional decline with gait dysfunction during hospitalization. The subject discontinued the study due to the event. The Investigator considered the event of schizoaffective disorder as related to study drug, but the Sponsor considers the event related to the subject's underlying medical history.

Double-Blind Treatment Period

Table 34 provides a summary of SAEs observed in the Primary Safety Population during the Double-Blind Treatment Period. Six subjects (2.7%) had SAEs during the Double-Blind Treatment Period; 3 subjects in each treatment group. Subjects in the CAM2038 treatment group had SAEs of cholecystitis, cauda equina syndrome, and mental status changes, and subjects in the Placebo treatment group had SAEs of anaemia , appendicitis, and pancreatic carcinoma and metastases to liver.

None of the SAEs during the Double-Blind Treatment Period were considered by the Investigator to be related to study drug. However, one SAE was assessed by the Sponsor as possibly related to study drug. An SAE of mental status changes (moderate intensity) occurred 1 day after the subject received the second dose of 128 mg CAM2038 q4w in the Double-Blind Treatment Period. The subject was found lying on the floor by a family member and was described as drowsy and confused. Open pill bottles had spilled on the floor, but the subject denied any suicidal ideation or overuse of narcotics. Urine drug screens tested positive for oxycodone and opiates. After treatment with naloxone and unspecified seizure medications, the subject recovered and was discharged from the hospital after 3 days. The subject subsequently discontinued from the study before the next dose due to lack of efficacy. The Investigator considered seizure and misuse of medication as possible causes of the event, but the Sponsor assessed the mental status changes as possibly related to CAM2038.

Table 34***: Number of Subjects (%) with Serious Adverse Events by System Organ Class and Preferred Term — Double-Blind Treatment Period of the Double-Blind Phase (Primary Safety Population)***

System Organ Class Preferred Term	CAM2038 N=112	Placebo N=110	Total N=222
At least 1 SAE	**3 (2.7%)**	**3 (2.7%)**	**6 (2.7%)**
Blood and lymphatic system disorders	**0**	**1 (0.9%)**	**1 (0.5%)**
Anaemia	0	1 (0.9%)	1 (0.5%)
Hepatobiliary disorders	**1 (0.9%)**	**0**	**1 (0.5%)**
Cholecystitis	1 (0.9%)	0	1 (0.5%)
Infections and infestations	**0**	**1 (0.9%)**	**1 (0.5%)**
Appendicitis	0	1 (0.9%)	1 (0.5%)

System Organ Class Preferred Term	CAM2038 N=112	Placebo N=110	Total N=222
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**1 (0.9%)**	**1 (0.5%)**
Metastases to liver	0	1 (0.9%)	1 (0.5%)
Pancreatic carcinoma	0	1 (0.9%)	1 (0.5%)
Nervous system disorders	**1 (0.9%)**	**0**	**1 (0.5%)**
Cauda equina syndrome	1 (0.9%)	0	1 (0.5%)
Psychiatric disorders	**1 (0.9%)**	**0**	**1 (0.5%)**
Mental status changes	1 (0.9%)	0	1 (0.5%)

Open-Label Safety Extension Phase

Open-Label Titration Period

Two subjects (1.7%) experienced SAEs during the Open-Label Titration Period (Overall Safety Population, excluding Site 077); a de novo subject had SAEs of acute myocardial infarction and chronic obstructive pulmonary disease (worsening) and a Placebo rollover subject had an SAE of sleep apnoea syndrome. None of these SAEs were considered by the investigator to be related to study drug and did not lead to withdrawal of study drug.

Open-Label Enrolment Period

Overall, 14 subjects (12.8%) experienced SAEs during the Open-Label Enrolment Period in the Overall Safety Population, Enrolment Subjects Only, excluding Site 077; 7 de novo subjects (13.0%) and 7 rollover subjects (12.7%). De novo subjects experienced SAEs of acute myocardial infarction and chronic obstructive pulmonary disease, intestinal obstruction, lower gastrointestinal haemorrhage (this subject also had an unrelated SAE of anaemia during Placebo treatment in the Double-Blind Treatment Period [the subject participated in the Double-Blind Phase but was enrolled as a de novo subject in the Open-Label Safety Extension Phase]), dizziness, acute kidney injury, nephrolithiasis, and accidental overdose (opioids) and wrist fracture. CAM2038 rollover subjects experienced SAEs of seizure, bradycardia and inguinal hernia and small intestinal obstruction. In the Placebo rollover group, one subject had an SAE of acute myocardial infarction (this subject also had an unrelated SAE of sleep apnoea during the Open-Label Titration Period), femur fracture, metastatic squamous cell carcinoma, and triple negative breast cancer. With the exception of the SAEs of triple negative breast cancer and wrist fracture, all of the SAEs led to hospitalization.

Except for an event of dizziness in a de novo subject, the other SAEs were assessed by the Investigator as not related to study drug and did not lead to withdrawal of study drug

The SAE of dizziness occurred 5 days after the subject had received the 4th dose of 96 mg CAM2038 q4w, the subject experienced dizziness, nausea, chills, weakness and persistent headache with photophobia. The subject reported to the emergency department, where the subject fell and hit the right side of the head (without loss of consciousness). The subject had not eaten anything during the day and had only drunk iced tea. The subject was hospitalized for observation and received treatment with paracetamol and ketorolac for pain secondary to the headache.
Computerized tomography scan, telemetry, laboratory tests and Dix-Hallpike test were negative and revealed no events. Hypovolemia was considered as a differential diagnosis and a fluid bolus was also administered. The subject recovered from the dizziness on the same day as the hospitalization.
The subject was discharged 2 days later but was discontinued from the study due to the event.

Table 35: ***Number of Subjects (%) with Serious Adverse Events by System Organ Class and*** **Preferred Term — Open-Label Enrolment Period of the Open-Label Safety Extension Phase (Overall Safety Population, Enrolment Subjects Only, Excluding Site 077)**

System Organ Class Preferred Term	De Novo (N=54)	Rollover			Total (N=109)
		CAM2038 (N=24)	Placebo (N=31)	Total (N=55)	
At least one SAE	**7 (13.0%)**	**3 (12.5%)**	**4 (12.9%)**	**7 (12.7%)**	**14 (12.8%)**
Cardiac disorders	**1 (1.9%)**	**1 (4.2%)**	**1 (3.2%)**	**2 (3.6%)**	**3 (2.8%)**
Acute myocardial infarction	1 (1.9%)	0	1 (3.2%)	1 (1.8%)	2 (1.8%)
Bradycardia	0	1 (4.2%)	0	1 (1.8%)	1 (0.9%)
Gastrointestinal disorders	**2 (3.7%)**	**2 (8.3%)**	**0**	**2 (3.6%)**	**4 (3.7%)**
Inguinal hernia	0	1 (4.2%)	0	1 (1.8%)	1 (0.9%)
Intestinal obstruction	1 (1.9%)	0	0	0	1 (0.9%)
Lower gastrointestinal haemorrhage	1 (1.9%)	0	0	0	1 (0.9%)
Small intestinal obstruction	0	1 (4.2%)	0	1 (1.8%)	1 (0.9%)
Injury, poisoning and procedural complications	**1 (1.9%)**	**0**	**1 (3.2%)**	**1 (1.8%)**	**2 (1.8%)**
Accidental overdose	1 (1.9%)	0	0	0	1 (0.9%)
Femur fracture	0	0	1 (3.2%)	1 (1.8%)	1 (0.9%)
Wrist fracture	1 (1.9%)	0	0	0	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**2 (6.5%)**	**2 (3.6%)**	**2 (1.8%)**
Metastatic squamous cell carcinoma	0	0	1 (3.2%)	1 (1.8%)	1 (0.9%)
Triple negative breast cancer	0	0	1 (3.2%)	1 (1.8%)	1 (0.9%)
Nervous system disorders	**1 (1.9%)**	**1 (4.2%)**	**0**	**1 (1.8%)**	**2 (1.8%)**
Dizziness	1 (1.9%)	0	0	0	1 (0.9%)
Seizure	0	1 (4.2%)	0	1 (1.8%)	1 (0.9%)
Renal and urinary disorders	**2 (3.7%)**	**0**	**0**	**0**	**2 (1.8%)**
Acute kidney injury	1 (1.9%)	0	0	0	1 (0.9%)
Nephrolithiasis	1 (1.9%)	0	0	0	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	**1 (1.9%)**	**0**	**0**	**0**	**1 (0.9%)**
Chronic obstructive pulmonary disease	1 (1.9%)	0	0	0	1 (0.9%)

Study HS-15-549- phase II

Overall, 33 (50.8%) subjects experienced at least 1 TEAE during the study (14 [50.0%] subjects in Group 1; 10 [50.0%] subjects in Group 2; and 9 [52.9%] subjects in Group 3). Four (6.2%) subjects had at least 1 injection site TEAE, and 32 (49.2%) subjects had at least 1 non-injection site TEAE.

Four (14.3%) subjects in Group 1, 3 (15.0%) subjects in Group 2, and 2 (11.8%) subjects in Group 3 had at least 1 CAM2038-related TEAE. Three (10.7%) subjects in Group 1, one (5.0%) subject in Group 2, and no subjects in Group 3 experienced CAM2038-related injection site AEs.

No TEAEs were reported during treatment with SL BPN/NX in Group 3. Overall, the SOC with the highest incidence of TEAEs was the Infections and Infestations SOC (23.1%) followed by Gastrointestinal Disorders (16.9%). The most common TEAEs were nausea (7.7%), toothache (6.2%), and urinary tract infection (6.2%). Most of the TEAEs were of mild or moderate intensity. One severe TEAE was reported

by a subject in Group 2 (toothache, not related). No TEAEs led to withdrawal from study drug. No subjects died or were hospitalized during the study.
No subjects experienced any protocol-defined SAEs. No pregnancies occurred during the study.
For the injection site examination, all reactions were rated as mild or moderate, with the majority of reactions rated as mild. If pain occurred at the injection site, it was to be recorded as an injection site AE, but no instances occurred.

Long-term Safety

Trials Included in the Initial MAA

Within the clinical programme included in the initial MAA, 299 patients were exposed to CAM2038 for ≥24 weeks and 132 patients were exposed to CAM2038 for ≥48 weeks. Except for injection site TEAEs, the long-term safety profile observed with CAM2038 was consistent with the known safety profile of BPN. All except 1 injection site TEAE (a severe event of transient injection site pain) associated with CAM2038 were mild or moderate and withdrawal of the IMP due to injection site TEAEs was uncommon in the initial MAA.

Trial HS-16-555

In HS-16-555, 58 patients received ≥52 weeks of uninterrupted exposure to CAM2038 and were included in the continuous integrated full exposure safety population. 53 of these 58 patients (91.4%) experienced a total of 446 TEAEs including 20 patients (34.5%) with TEAEs that were treatment-related, 6 patients (10.3%) with SAEs and 5 patients (8.6%) with severe TEAEs. Two patients (3.4%) had a total of 3 severe treatment-related TEAEs (injection site pruritus, constipation and gastrooesophageal reflux disease). In summary, the safety profile (including TEAEs, clinical laboratory findings, ECGs, vital signs, and other safety results) of this population was similar to those of the previously described safety populations supporting that long-term exposure to CAM2038 does not result in any additional safety risks to patients. The data from trial HS-16-555 support the update of the SmPC regarding long-term safety in patients treated with CAM2038 for ≥1 year.

Local Tolerability

Trials Included in the Initial MAA
Across all 7 clinical trials included in the initial MAA, 118 subjects (16.2%) receiving CAM2038 reported at least 1 injection site TEAE. The mean number of injection site TEAEs per injection was low (0.04). The most common injection site TEAEs were injection site pain (9.3% of subjects), injection site erythema (5.5%) and injection site swelling (5.5%). Most injection site TEAEs were mild (78.7%) or moderate (21.0%). One injection site TEAE (0.3%), a transient event of injection site pain, was of severe intensity.

In the double-blind, double-dummy trial HS-11-421, the percentage of patients with any injection site TEAE was similar between CAM2038 (18.8%) and SC placebo injection (22.3%).

Across all trials included in the initial MAA, the percentage of subjects with any injection site TEAE was 14.6% for CAM2038 q1w and 9.3% for CAM2038 q4w. There was a trend of increasing number of injection site TEAEs 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, injection site TEAEs increased with increasing injection volume. The increase in injection site TEAEs with increasing dose of CAM2038 q1w or CAM2038 q4w is likely to reflect the larger injection volume at higher dose levels. It should be noted that the injection volume (0.64 mL) of the highest dose (32 mg) of CAM2038 q1w is larger than the injection volume (0.18 mL) of the lowest dose (64 mg) of CAM2038 q4w. The highest rate of injection site TEAEs 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 trials) or that subjects not tolerating the treatment

are more likely to drop out. However, the number of withdrawals due to injection site TEAEs was low (5 subjects [0.7%] receiving CAM2038). No injection site TEAEs were serious.
In HS-15-549, all injection site reactions (occurring in 6.4% of patients) were mild or moderate, with most reactions being mild.

Trial HS-16-555

During the titration period of the double-blind phase of HS-16-555, the injection site TEAEs followed the same pattern as in the clinical trials included in the initial MAA with the most common being pruritus (8.5%), injection site pain (6.2%), erythema (6.8%) and swelling (5.3%).
In the double-blind treatment period of HS-16-555, less than 5% of patients had injection site TEAEs (primarily injection site erythema [2.3%], injection site swelling [1.8%], and injection site pain [1.8%]), with a slightly higher incidence in the placebo group (3.6%) than in the CAM2038 group (2.7%). During the double-blind treatment period, no injection site TEAEs in the CAM2038 group were severe, while 1 patient in the placebo group had a severe TEAE of injection site abscess. In the titration period of the OLE phase, 10.7% of patients had injection site TEAEs, most of whom were de novo subjects. During the OLE treatment period, the most Buvidal (CAM2038) for treatment of chronic pain in opioid dependence common injection site TEAEs were injection site pruritus (4.6%), injection site erythema (3.7%), injection site pain (2.8%) and injection site swelling (2.8%). Injection site TEAEs were primarily mild or moderate in intensity.

Overall Conclusion - Trials Included in the Initial MAA and Trial HS-16-555
In conclusion, although pain, erythema, swelling and itching at the injection site were common, the local tolerability of CAM2038 was good. The incidence of injection site TEAEs was similar between CAM2038 and SC placebo injections in HS-11-421 and somewhat higher in the placebo group than in the CAM2038 group in the double-blind treatment period of HS-16-555 (CAM2038: 2.7%; placebo 3.6%). Withdrawal from treatment due to any injection site TEAE was uncommon. No injection site TEAEs were serious.

Laboratory findings

Trial HS-15-549 (phase II)

In terms of clinical chemistry laboratory results, in Group 1, 1 subject had ALT values >2 × ULN or >3 × ULN during the study. In Group 2, 1 subject had an ALT value >2 × ULN at any post-Baseline visit. No subjects in Group 3 had ALT values >2 × ULN or >3 × ULN during the study.

In Group 1, 2 subjects had AST values >2 × ULN or >3 × ULN during the study. No subjects in Group 2 had AST values >2 × ULN or >3 × ULN during the study. In Group 3, one subject had AST values >2 × ULN or >3 × ULN during the study.

Trial HS-16-555

In the titration period of the double-blind phase of HS-16-555, laboratory TEAEs reported by more than 1% of patients included bacteriuria (7 patients [1.5%]; none of which was treatment related) and increased γ-glutamyltransferase (5 patients [1.1%]; none of which was treatment related).

Two TEAEs (increased hepatic enzyme and haematuria), none of which was treatment related, led to withdrawal of the IMP. None of the laboratory TEAEs reported during the double blind treatment period were considered to be treatment-related and none led to withdrawal of the IMP or trial discontinuation. In the OLE treatment period, 2 laboratory TEAEs were considered related to CAM2038; a moderate TEAE of increased amylase and a mild TEAE of abnormal liver function test.

Overall, aggregate data indicates that mean clinical laboratory values were within normal ranges and no marked group differences or changes over time were apparent.

Open-Label Titration Period

The majority of laboratory related TEAEs during the Open-Label Titration Period occurred in 1 or 2 subjects. Bacteriuria was observed in 7 subjects (1.5%) and **GGT increased was observed in 5 subjects (1.1%).** The TEAEs of hepatic enzyme increased and haematuria led to withdrawal of study drug.

Table 36*:* **Number of Subjects (%) with Laboratory-Related Adverse Events by System Organ Class and Preferred Term — Open-Label Titration Period of the Double-Blind Phase (Primary Safety Population)**

System Organ Class Preferred Term	Total CAM2038 N=468
Blood and lymphatic system disorders	
Anaemia	2 (0.4%)
Anisocytosis	1 (0.2%)
Hypochromasia	1 (0.2%)
Leukocytosis	1 (0.2%)
Infections and infestations	
Bacteriuria	7 (1.5%)
Investigations	
Gamma-glutamyltransferase increased	5 (1.1%)
Alanine aminotransferase increased	2 (0.4%)
Blood creatine phosphokinase increased	2 (0.4%)
Blood glucose increased	2 (0.4%)
Protein urine present	2 (0.4%)
Anion gap increased	1 (0.2%)
Aspartate aminotransferase increased	1 (0.2%)
Bacterial test positive	1 (0.2%)
Blood calcium decreased	1 (0.2%)
Blood chloride decreased	1 (0.2%)
Blood creatinine decreased	1 (0.2%)
Blood lactate dehydrogenase increased	1 (0.2%)
Blood lactic acid increased	1 (0.2%)
Blood potassium increased	1 (0.2%)
Blood urea increased	1 (0.2%)
Hepatic enzyme increased	1 (0.2%)
High density lipoprotein decreased	1 (0.2%)
International normalised ratio increased	1 (0.2%)
Liver function test abnormal	1 (0.2%)

System Organ Class Preferred Term	Total CAM2038 N=468
Low density lipoprotein increased	1 (0.2%)
Mean platelet volume decreased	1 (0.2%)
Neutrophil count increased	1 (0.2%)
White blood cell count increased	1 (0.2%)
Metabolism and nutrition disorders	
Hypokalaemia	2 (0.4%)
Hypercholesterolaemia	1 (0.2%)
Hyperkalaemia	1 (0.2%)
Hyperlipidaemia	1 (0.2%)
Renal and urinary disorders	
Haematuria	1 (0.2%)
Proteinuria	1 (0.2%)

Double-Blind Treatment Period

All individual laboratory-related TEAEs occurred in only 1 or 2 subjects of subjects and did not show any marked differences between treatment groups.

Table 37*:* **Number of Subjects (%) with Laboratory-Related Adverse Events by System Organ Class and Preferred Term — Double-Blind Treatment Period of the Double-Blind Phase (Primary Safety Population)**

System Organ Class Preferred Term	CAM2038 N=112	Placebo N=110	Total N=222
Blood and lymphatic system disorders			
Anaemia	0	1 (0.9%)	1 (0.5%)
Leukocytosis	0	1 (0.9%)	1 (0.5%)
Infections and infestations			
Bacteriuria	2 (1.8%)	1 (0.9%)	3 (1.4%)
Investigations			
Lipase increased	1 (0.9%)	1 (0.9%)	2 (0.9%)
Alanine aminotransferase increased	0	1 (0.9%)	1 (0.5%)
Amylase increased	1 (0.9%)	0	1 (0.5%)
Aspartate aminotransferase increased	0	1 (0.9%)	1 (0.5%)
Blood creatine phosphokinase increased	1 (0.9%)	0	1 (0.5%)
Blood creatinine increased	0	1 (0.9%)	1 (0.5%)
Blood lactate dehydrogenase increased	1 (0.9%)	0	1 (0.5%)
Blood potassium increased	0	1 (0.9%)	1 (0.5%)
Haematocrit increased	1 (0.9%)	0	1 (0.5%)
Haemoglobin increased	1 (0.9%)	0	1 (0.5%)
International normalised ratio increased	0	1 (0.9%)	1 (0.5%)
Red blood cell count increased	1 (0.9%)	0	1 (0.5%)
Metabolism and nutrition disorders			
Hypoglycaemia	1 (0.9%)	1 (0.9%)	2 (0.9%)
Hypokalaemia	0	1 (0.9%)	1 (0.5%)

None of the laboratory-related TEAEs during the Double-Blind Treatment Period were considered to be related to study drug and all of these events were considered to be mild or moderate in intensity. One event of anaemia in the Placebo treatment group was considered to be an SAE. None of the laboratory-related TEAEs led to discontinuation of study drug or study discontinuation.

Several additional laboratory-related TEAEs were observed in the Safety Population, including 3 TEAEs of blood creatine phosphokinase increased, and 1 TEAE each of alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased, urobilinogen urine increased and hypercholesterolaemia in the CAM2038 treatment group and 1 TEAE each of anaemia and blood creatinine phosphokinase increased in the Placebo treatment group.

None of the additional TEAEs were considered to be drug-related. The TEAEs of blood creatine phosphokinase increased, alanine aminotransferase increased, and aspartate aminotransferase increased in the CAM2038 treatment group were considered severe; however, none of the TEAEs led to withdrawal of study drug or discontinuation from the study.

Open-Label Titration Period

Although there were more laboratory-related TEAEs in de novo subjects in general, none of the TEAEs were observed in more than 1 subject in any of the groups, or more than 1 to 2 subjects overall (0.8% to 1.7%).

Table 38: ***Number of Subjects (%) with Laboratory-Related Adverse Events by System Organ Class and Preferred Term — Open-Label Titration Period of the Open-Label Safety Extension Phase (Overall Safety Population, Excluding Site 077)***

System Organ Class Preferred Term	De Novo Subjects N=75	Rollover Subjects			Total N=121
		CAM2038 N=21	Placebo N=25	Total N=46	
Blood and lymphatic system disorders					
Anaemia	1 (1.3%)	0	0	0	1 (0.8%)
Infections and infestations					
Bacteriuria	1 (1.3%)	0	0	0	1 (0.8%)
Investigations					
Blood creatine phosphokinase increased	1 (1.3%)	0	1 (4.0%)	1 (2.2%)	2 (1.7%)
Alanine aminotransferase increased	1 (1.3%)	0	0	0	1 (0.8%)
Aspartate aminotransferase increased	1 (1.3%)	0	0	0	1 (0.8%)
Glucose urine present	1 (1.3%)	0	0	0	1 (0.8%)
Hepatic enzyme increased	1 (1.3%)	0	0	0	1 (0.8%)
Metabolism and nutrition disorders					
Hyponatraemia	0	1 (4.8%)	0	1 (2.2%)	1 (0.8%)

Open-Label Enrollment Period

A summary of laboratory-related TEAEs that occurred during the Open-Label Enrollment Period (Overall Safety Population, Enrollment Subjects Only, excluding Site 077) is provided in Table 39.

The most common laboratory-related TEAEs overall were blood glucose increased (6 subjects [5.5%]), GGT increased (5 subjects [4.6%]) and aspartate aminotransferase increased, hyponatraemia, and proteinuria (3 subjects each [2.8%]). All other laboratory-related TEAEs occurred in 1 or 2 subjects overall (0.9% to 1.8%). Laboratory-related TEAEs classified as investigations and renal and urinary disorders occurred in a higher incidence of subjects and in more individual de novo subjects compared to rollover subjects. The majority of laboratory-related TEAEs in rollover subjects occurred in the Placebo rollover group.

Table 39***: Number of Subjects (%) with Laboratory-Related Adverse Events by System Organ* Class and Preferred Term — Open-Label Enrollment Period of the Open-Label Safety Extension Phase (Overall Safety Population, Enrollment Subjects Only, Excluding Site 077)**

System Organ Class Preferred Term	De Novo N=54	Rollover			Total N=109
		CAM2038 N=24	Placebo N=31	Total N=55	
Blood and lymphatic system disorders					
Leukocytosis	1 (1.9%)	0	1 (3.2%)	1 (1.8%)	2 (1.8%)
Anisocytosis	1 (1.9%)	0	0	0	1 (0.9%)

System Organ Class Preferred Term	De Novo N=54	Rollover			Total N=109
		CAM2038 N=24	Placebo N=31	Total N=55	
Haemorrhagic anaemia	0	0	1 (3.2%)	1 (1.8%)	1 (0.9%)
Hypochromasia	1 (1.9%)	0	0	0	1 (0.9%)
Iron deficiency anaemia	0	1 (4.2%)	0	1 (1.8%)	1 (0.9%)
Microcytic anaemia	0	0	1 (3.2%)	1 (1.8%)	1 (0.9%)
Platelet disorder	0	0	1 (3.2%)	1 (1.8%)	1 (0.9%)
Infections and infestations					
Bacteriuria	1 (1.9%)	0	0	0	1 (0.9%)
Investigations					
Blood glucose increased	6 (11.1%)	0	0	0	6 (5.5%)
Gamma-glutamyltransferase increased	3 (5.6%)	0	2 (6.5%)	2 (3.6%)	5 (4.6%)
Aspartate aminotransferase increased	3 (5.6%)	0	0	0	3 (2.8%)
Alanine aminotransferase increased	2 (3.7%)	0	0	0	2 (1.8%)
Blood alkaline phosphatase increased	2 (3.7%)	0	0	0	2 (1.8%)
Blood creatine phosphokinase increased	1 (1.9%)	0	1 (3.2%)	1 (1.8%)	2 (1.8%)
Crystal urine present	2 (3.7%)	0	0	0	2 (1.8%)
Amylase increased	0	0	1 (3.2%)	1 (1.8%)	1 (0.9%)
Blood iron decreased	1 (1.9%)	0	0	0	1 (0.9%)
Blood lactate dehydrogenase increased	1 (1.9%)	0	0	0	1 (0.9%)
Blood potassium decreased	1 (1.9%)	0	0	0	1 (0.9%)
Glucose urine present	1 (1.9%)	0	0	0	1 (0.9%)
Hormone level abnormal	0	0	1 (3.2%)	1 (1.8%)	1 (0.9%)
International normalised ratio increased	1 (1.9%)	0	0	0	1 (0.9%)
Liver function test abnormal	1 (1.9%)	0	0	0	1 (0.9%)
Total cholesterol/HDL ratio increased	1 (1.9%)	0	0	0	1 (0.9%)
Urinary casts	1 (1.9%)	0	0	0	1 (0.9%)
Urinary sediment present	1 (1.9%)	0	0	0	1 (0.9%)
Urine analysis abnormal	1 (1.9%)	0	0	0	1 (0.9%)
Urine leukocyte esterase positive	1 (1.9%)	0	0	0	1 (0.9%)

System Organ Class Preferred Term	De Novo N=54	Rollover			Total N=109
		CAM2038 N=24	Placebo N=31	Total N=55	
White blood cell count increased	1 (1.9%)	0	0	0	1 (0.9%)
Metabolism and nutrition disorders					
Hyponatraemia	1 (1.9%)	1 (4.2%)	1 (3.2%)	2 (3.6%)	3 (2.8%)
Hypercholesterolaemia	2 (3.7%)	0	0	0	2 (1.8%)
Hyperglycaemia	0	0	2 (6.5%)	2 (3.6%)	2 (1.8%)
Hypoglycaemia	1 (1.9%)	0	1 (3.2%)	1 (1.8%)	2 (1.8%)
Hypokalaemia	1 (1.9%)	0	1 (3.2%)	1 (1.8%)	2 (1.8%)
Hypochloraemia	0	0	1 (3.2%)	1 (1.8%)	1 (0.9%)
Hypertriglyceridaemia	1 (1.9%)	0	0	0	1 (0.9%)
Renal and urinary disorders					
Proteinuria	3 (5.6%)	0	0	0	3 (2.8%)
Glycosuria	1 (1.9%)	0	0	0	1 (0.9%)
Haematuria	1 (1.9%)	0	0	0	1 (0.9%)
Ketonuria	1 (1.9%)	0	0	0	1 (0.9%)
Nephrolithiasis	1 (1.9%)	0	0	0	1 (0.9%)

Two of the laboratory-related TEAEs were considered related to study drug, including a moderate TEAE of amylase increased in a Placebo rollover subject (3.2%) and a mild TEAE of liver function test abnormal in a de novo subject (1.9%).

The majority of laboratory-related TEAEs were mild or moderate in intensity; 1 de novo subject had a severe TEAE of blood creatine phosphokinase increased; however, this TEAE was not considered to be drug-related. There were no discontinuations due to these TEAEs.

Although there were differences in incidence, the patterns of laboratory-related TEAE results for other populations were similar to those of the Overall Safety Population, excluding Site 077.

12-Lead Electrocardiogram

QT prolongation is a known class effect of opioids. However, analyses of PK/pharmacodynamics relationships in the initial MAA showed that CAM2038 was not associated with significant QTc interval prolongation. The Fredericia corrected QTc (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.

For QTcB results, in the initial MAA. Further, the 12-lead electrocardiogram (ECG) results showed that no healthy volunteers had any QTcF observation ≥480 ms at any post-baseline visit or an increase in QTcF of ≥60 ms from baseline at any time point.

Across all trials in patients with OUD in the initial MAA, changes from baseline in each ECG parameter were minimal at end of trial and no clinically meaningful trends were observed.

Trial HS-16-555

During both periods of the double-blind phase in HS-16-555, a number of abnormalities were considered clinically significant and reported as TEAEs.

Two of the TEAEs reported during the titration period were assessed as treatment-related (ECG QT prolonged and ECG T wave inversion), while no TEAEs in the double-blind treatment period were treatment-related.

Open-Label Titration Period

Some subjects had QTcF values ≥450 to <480 msec at some visits, including baseline (Screening), while 1 to 3 subjects had QTcF values ≥480 to <500 msec at some visits, and no subjects had QTcF values ≥500 msec.

Three to 4 subjects had change from baseline in QTcF ≥60 msec before and after the Buprenex test dose and within 1 hour of the first CAM2038 dose, with 1 to 2 subjects with change from baseline in QTcF values ≥60 msec thereafter.

Double-Blind Treatment Period

No subjects in the CAM2038 treatment group had QTcF intervals ≥480 msec, while 1 or 2 subjects in the Placebo treatment group had occasional findings of QTcF interval ≥480 msec at some visits. One subject in the Placebo treatment group had QTcF interval ≥500 msec at Week 15.

A similar pattern was seen for change from baseline results, with a similar incidence of subjects with change from baseline in QTcF interval ≥30 msec across all post-baseline visits for CAM2038 and Placebo treatment groups (9.8% vs. 7.3%).

One subject (0.9%) in the CAM2038 treatment group and 2 subjects (1.8%) in the Placebo treatment group had a change from baseline in QTcF interval ≥60 msec.

No ECG-associated SAEs were reported during the double-blind phase.

Open-Label Titration Period

One to 3 de novo subjects had QTcF intervals ≥450 to <480 msec at some visits and 1 subject had a QTcF interval ≥480 to <500 msec prior to the Buprenex test dose, but no subjects had QTcF interval ≥500 msec.

Likewise, 1 to 5 subjects had change from baseline in QTcF ≥30 to <60 msec at some visits but no subjects had change in QTcF interval ≥60 msec.

Results were comparable in the Overall Safety Population, including Site 077; no additional subjects had QTcF ≥500 msec or change from baseline in QTcF ≥60 msec.

Open-Label Enrollment Period

One to 5 subjects overall (1.0% to 5.4%) had QTcF interval results ≥450 to <480 msec at some visits. At Week 47, 2 CAM2038 rollover subjects (9.5%) had QTcF interval ≥480 to <500 msec, and at end-of-treatment, 1 CAM2038 rollover subject (4.5%) had QTcF ≥480 to <500 msec; however, no subjects had QTcF ≥500 msec at any visit. One to 4 subjects (1.8% to 4.3%) overall had change from baseline in QTcF of ≥30 to <60 msec at some visits. At end-of-treatment, 1 CAM2038 rollover subject (4.5%) had a change from baseline in QTcF of ≥60 msec.

In the OLE phase of HS-16-555, 3 patients had an SAE of acute myocardial infarction, along with a patient with an SAE of bradycardia. None of the ECG-associated TEAEs, including the SAEs, were considered treatment-related.

Overall, aggregate data from HS-16-555 indicate that ECG results were within normal ranges and no marked group differences or changes over time were apparent.

Safety in special populations

Population Subgroups and Concomitant Medications

Population Subgroups

Across trials in patients with opioid dependence in the initial MAA, intrinsic factors had little impact on the overall TEAE profile, incidence of injection site TEAEs, or the most common TEAEs reported in patients with OUD, in the initial MAA.
After finalisation of the clinical trial report, a post hoc analysis was performed of AEs by age category in HS-16-555. This showed that the safety profile of CAM2038 was similar in patients aged <65 years and elderly patients aged ≥65 years.

Table 40***: Summary of adverse events by age category in HS-16-555***

Category	<65 years (n=442)	≥65 years (n=81)	≥65 years – 74 years (n=75)	≥75 years (n=6)	Total (n=523)
No. of patients (%) with any TEAE	272 (61.5%)	42 (51.9%)	38 (50.7%)	4 (66.7%)	314 (60.0%)
No. of patients (%) with TEAEs suspected to be drug-related	148 (33.5%)	25 (30.9%)	23 (30.7%)	2 (33.3%)	173 (33.1%)
No. of patients (%) with SAEs	19 (4.3%)	6 (7.4%)	5 (6.7%)	1 (16.7%)	25 (4.8%)
No. of patients (%) with fatal TEAEs	1 (0.2%)	0	0	0	1 (0.2%)
No. of patients (%) with TEAEs that led to withdrawal of trial drug	68 (15.4%)	12 (14.8%)	12 (16.0%)	0	80 (15.3%)
No. of patients (%) with TEAEs that led to trial discontinuation	68 (15.4%)	12 (14.8%)	12 (16.0%)	0	80 (15.3%)
No. of patients (%) with severe TEAEs	33 (7.5%)	5 (6.2%)	4 (5.3%)	1 (16.7%)	38 (7.3%)
No. of patients (%) with injection site TEAEs	17 (3.8%)	3 (3.7%)	5 (4.0%)	0	20 (3.8%)

SAE: serious adverse event; TEAE: treatment-emergent adverse event

Safety related to drug-drug interactions and other interactions

Concomitant Medications in Trial HS-16-555

During the titration period in both phases of HS-16-555 as well as during the double-blind treatment period and the OLE treatment period, rescue medication, consisting of 5 mg/325 mg hydrocodone/paracetamol every 4 to 6 hours, could be taken as needed up to 15 mg/975 mg/day for patients whose screening opioid dose was 40 to 79 mg/day MED or up to 30 mg/1,950 mg/day (6 tablets) for patients whose screening opioid dose was ≥80 mg/day MED. Consistent with prior medication use reported before entry into the titration period, the most common concomitant medications during the titration period of the double-blind phase in HS- 16-555 (≥20% of patients) included other centrally acting agents (30.2%), other analgesics and antipyretics (27.5%), HMG-CoA reductase inhibitors

(27.0%), other antidepressants (24.8%), benzodiazepine derivatives (20.3%), and proton pump inhibitors (20.3%). The most common individual drugs (≥10% of patients) were gabapentin (19.8%), lisinopril (14.4%), acetylsalicylic acid (14.4%), metformin (12.6%), and omeprazole (10.8%). The use of concomitant medications during the titration period was similar between the 2 treatment groups.

During the double-blind treatment period, the most common concomitant medications (≥20% of patients) were natural opium alkaloids (44.6%). As in the titration period, patients also used other centrally acting agents (29.3%), other analgesics and antipyretics (27.9%), HMG-CoA reductase inhibitors (27.0%), other antidepressants (25.7%), benzodiazepine derivatives (21.2%), and proton pump inhibitors (20.7%). The most common individual drugs (≥10% of patients) were gabapentin (20.3%), lisinopril (14.9%), acetylsalicylic acid (14.9%), metformin (13.1%), oxycodone/paracetamol (11.7%), and omeprazole (10.8%). The use of concomitant medications during the double-blind treatment period was generally similar between the treatment groups, however, more patients in the CAM2038 group than in the placebo group reported using natural opium alkaloids (48.2% versus 40.9%), other analgesics and antipyretics (33.0% versus 22.7%) and other antidepressants (30.4% versus 20.9%).

Although concomitant opium alkaloid use during the trial was prohibited by protocol unless approved by the Medical Monitor, several patients reported use during the follow-up period of the double-blind phase. However, it was neither anticipated that use of the opium alkaloids would have impacted the efficacy or safety results in the CAM2038 group, nor in the placebo group as described in the CTR.

Discontinuation due to adverse events

Trials Included in the Initial MAA
Across all trials included in the initial MAA, 12 subjects (1.6%) receiving CAM2038 had any TEAE resulting in withdrawal of the IMP. These were mainly injection site TEAEs and gastrointestinal events, in the initial MAA. No TEAEs led to withdrawal from the IMP in HS-15-549.

Trial HS-16-555

In the titration period of the double-blind phase in HS-16-555, 72 patients (15.4%) had TEAEs leading to withdrawal of the IMP and trial discontinuation. The most common TEAEs leading to withdrawal of the IMP were nausea (30 patients [6.4%]) and vomiting (17 patients [3.6%]).

Injection site TEAEs leading to withdrawal of the IMP included injection site pruritus (4 patients [0.9%]), injection site pain and injection site erythema (3 patients each [0.6%]), injection site induration and injection site swelling (2 patients each [0.4%]), and injection site discoloration (1 patient [0.2%]).
During the double-blind treatment period, 6 patients (2.7%) had TEAEs leading to withdrawal of the IMP and/or trial discontinuation; 4 in the CAM2038 group and 2 in the placebo group. TEAEs of weight decreased, decreased appetite and ageusia, and joint swelling were considered to be related to CAM2038. Two patients in the placebo group had treatment-related TEAEs leading to withdrawal of the IMP (1 patient with injection site pain and injection site swelling of moderate intensity and 1 patient with drug withdrawal syndrome of mild intensity).
During the titration period of the OLE phase, 5 patients (4.1%) had TEAEs that led to withdrawal of the IMP, of which nausea, vomiting, depressed level of consciousness, asthenia and tremor were considered treatment-related. During the OLE treatment period, 4 patients (3.7%) had TEAEs leading to withdrawal of the IMP, of which dizziness, sedation and peripheral oedema were considered treatment-related.

Overall, TEAEs leading to withdrawal of the IMP in HS-16-555 followed the same pattern as observed in the clinical trials included in the initial MAA, i.e., gastrointestinal TEAEs were the most common, followed by TEAEs of general disorders and administration site conditions.

Post marketing experience

The estimated cumulative patient exposure to Buvidal, based on marketing experience, was approximately 16,600 patient-years as per 30-Jul-2021.

2.5.1. Discussion on clinical safety

Background information and extent of exposure

The current clinical development programme with CAM2038 in patients with chronic pain consists of 2 clinical trials ; one Phase 2 trial (HS-15-549) in patients with OUD and moderate to severe chronic non-cancer pain and one Phase 3 trial (HS-16-555) in **opioid experienced patients with chronic pain**. Trial HS-15-549 was part of the initial MAA and has, hence, already been assessed during the initial review. In the initial MAA, 729 subjects were exposed to at least one injection of CAM2038 including 135 healthy volunteers and 594 patients with OUD, of whom 65 patients in HS-15-549 had moderate to severe chronic non-cancer pain, in the initial MAA. Since the approval, the estimated cumulative patient exposure to Buvidal, based on marketing experience, was approximately 16,600 patient-years as per 30-Jul-2021.

Trial HS-16-555 (conducted in patients with chronic pain and not included in the initial MAA) was a Phase 3, placebo-controlled, multi-centre, double-blind, EEW, randomised trial evaluating the efficacy and safety of CAM2038 in opioid-experienced patients with moderate to severe CLBP or other chronic pain conditions such as osteoarthritis, that required continuous, around the- clock treatment with opioids at a MED ≥40 mg/day. The safety data for Trial HS-16-555 were presented for each study period separately (i.e. Open-Label Titration Period, Double-Blind Treatment Period, Titration Period of the Open-Label Safety Extension Phase and Open-Label Enrollment Period) and also combined for the whole Double-Blind period.

The assessment of safety focuses on the HS-16-555 study and on the Primary Safety Population (Excluding Sites 068 and 077 due to GCP issues).

It is considered that the safety database for this new proposed indication (moderate to severe chronic pain in patients with opioid dependence) has a number of limitations:

- The number of patients enrolled to main study supporting this indication (HS-16-555) was small. Although 468 subjects entered the titration Period, (Excluding Sites 068 and 077 due to GCP issues) only 222 were randomized to either CAM2038 q1w (**17 subjects**), 95 CAM2038 q4w (**95 subjects**) and placebo (110 subjects). Excluding Site 077 only **132 subjects** were included in the Open-Label Safety Extension Phase.
- The number of elderly patients in particular those over 75 years of age who were exposed to CAM2038 for this indication was very small (i.e 6 patients over 75 years of age)
- The exposure to treatment in this study was short. The mean duration of exposure in the double-blind treatment period was 76.2 days in the CAM2038 group and 72.1 days in the placebo group. Only 58 patients were exposed to CAM2038 continuously for ≥52 weeks in trial HS-16-555.
- Many dose levels were investigated in the study (i.e 4mg. 8 mg, 12mg, 16 mg , 24 mg, 32 mg, 64mg, 96 mg and 128 mg) and the number of patients in each dose group was small. Therefore the safety of the particular dose in this proposed indication cannot be established.

Therefore, the applicant was asked discuss and justify the adequacy of the safety database to support the use of the product for the treatment of moderate to severe chronic pain in patients with opioid dependence taking into consideration differences in populations targeted by the product as compared to the original MAA.

Further, the applicant was asked to justify the safety of CAM2038 when used for long term.

In addition, the safety when used in elderly patients were requested to be justified.

In the response, the applicant highlighted that patient exposure to Buvidal is significant. As of 31-Jan-2022, the estimated patient exposure to Buvidal was 25,400 patient-years. Further, the applicant claims that the use of BPN is very well established for treatment of chronic pain and the populations of patients with opioid dependence with or without moderate to severe chronic pain are sufficiently similar from a safety perspective. However, these claims have not been sufficiently substantiated. There are differences between the population of patients investigated in studies supporting the opioid dependence indication as compared to the pivotal study (HS-16-555) provided as a part of this procedure and these differences may impact the safety profile of CAM2038 when used for chronic pain.

The potential impact of differences in patients characteristics on the safety profile of CAM2038 should be further discussed. As a part of this discussion, the applicant is asked to provide a head-to-head comparison of the frequency and exposure-adjusted incidence rate of TEAEs, treatment-related TEAEs, severe TEAEs, treatment-related severe TEAEs, serous TEAEs reported in studies in patients with opioid dependence as compared to patients with chronic pain. The frequency and exposure-adjusted incidence rate of TEAEs by PT and SOC for opioid use disorder and chronic pain disorder should be also compared.

In this response a particular attention should be made when CAM2038 is used in elderly patients.

Further, an extrapolation of the long term safety profile of CAM2038 when used for opioid dependence to patients with chronic pain could be insufficient. The applicant is requested to discuss. In addition , the applicant should consider adding the long term use for the treatment of chronic pain as a missing information in the RMP. In addition, the applicant should discuss on how further data on the use for the treatment of chronic pain could be generated in the post-marketing **(OC).**

Note:

The GCP inspection is proposed for the pivotal study provided as a part of this application. The final conclusion on the adequacy of the safety database can only be made once the outcome of this GCP inspection is available.

Common Adverse Events

64.1% of subjects who participated in the **Open-Label Titration Period** (Primary Safety Population) had at least 1 TEAE, with a total of 1157 TEAEs; 37.0% of subjects had TEAEs suspected to be related to CAM2038. Ten subjects (2.1%) had SAEs, including 1 SAE with a fatal outcome (0.2%).

Seventy-two (15.4%) subjects experienced TEAEs leading to withdrawal of study drug and study discontinuation. The majority of subjects had mild or moderate TEAEs. A total of 69 subjects (14.7%) had injection site TEAEs.

The frequency of TEAEs during the **Double-Blind Treatment Period** was smaller i.e. TEAEs were reported in **35.6%** of subjects in the Primary Safety Population. The incidence of subjects with TEAEs was higher in the CAM2038 treatment group (44 subjects [39.3%]) compared to the Placebo treatment group (35 subjects [31.8%]).

The incidence of subjects with TEAEs suspected to be drug-related was relatively low overall (19 subjects [8.6%]). 4 subjects (3.6%) in the CAM2038 treatment group experienced TEAEs resulting in withdrawal of study drug as well as study discontinuation. The majority of TEAEs were mild or moderate in intensity. Injection site TEAEs were experienced by 3 subjects (2.7%) in the CAM2038 treatment group and 4 subjects (3.6%) in the Placebo treatment group.

The higher proportions of patients with TEAEs during the titration periods than in the double-blind treatment could be explained by the fact that some events could be transient (i.e occur at the initiation of opioid therapy and then resolve with continued use of the drug). In addition, since treatment tolerability was a requirement for enrolment in the double-blind treatment, it is expected that fewer patients would experience TEAEs in this period.

During **the titration period** of the OLE phase, 56 of the 121 patients (**46.3%)** had at least 1 TEAE; 41 of 75 patients from the de novo group (initial titration), 6 of 21 patients from the CAM2038 rollover group and 9 of 25 patients from the placebo rollover group. Nearly half of de novo subjects (20 of 41 subjects [26.7% overall]) had drug-related TEAEs. The majority of Placebo rollover subjects had drug-related TEAEs (8 of 9 subjects [32.0% overall]), while only 1 CAM2038 rollover subject (4.8%) had a drug-related TEAE. There were no deaths in the Open-Label Titration Period, but 2 subjects (1.7%) experienced SAEs (1 de novo subject and 1 Placebo rollover subject).

During the **open-label enrollment period** of the OLE phase**,** 87 of the 109 patients **(79.8%)** experienced at least 1 TEAE. This high proportion of patients may reflect the extended period of time during which TEAEs were collected (up to 10 months for the 54 de novo patients and up to 7 months for the 55 rollover patients). Overall, 18.3% of patients had at least 1 treatment-related TEAE. There were no deaths, but 14 subjects (12.8%) overall experienced SAEs.

Most common individual TEAEs

The most common individual TEAEs observed during the Open-Label Titration Period were nausea and vomiting. Other commonly reported TEAEs were constipation, dizziness, headache, and injection site reactions, including injection site pruritus, injection site erythema, injection site pain, and injection site swelling. All these reactions are already listed in the SmPC.

The most common individual TEAEs during the double-blind treatment period in the CAM2038 treatment group were back pain, fall and oedema peripheral. Back pain and oedema peripheral are already listed in section 4.8 of the SmPC although the higher incidence of back pain in this study population could be reflection of insufficient efficacy of CAM2038.

During the double-blind treatment period fewer than 5% of subjects experienced injection site TEAEs overall, with a slightly higher incidence of subjects in the Placebo treatment group compared to the CAM2038 treatment group. Injection site reactions are listed in the SmPC.

Drug-related TEAEs reported by more than 1 subject in the CAM2038 treatment group were constipation (2 subjects) and injection site erythema (2 subjects). Other drug-related TEAEs were reported in single patients and included gastrooesophageal reflux disease, vomiting, fatigue, injection site erythema, pain and swelling, weight decreased, decreased appetite, joint swelling, ageusia, migraine, anxiety, euphoric mood and hyperhidrosis. Some of them are not currently listed in the SmPC such as gastrooesophageal reflux disease, fatigue, weight decreased, joint swelling, ageusia and hyperhidrosis.

During the open-label titration period of the open-label safety extension phase again the most commonly reported TEAEs overall were nausea, vomiting. Upper respiratory tract infection were reported in 7 subjects The most commonly reported injection site TEAEs in de novo subjects were injection site pruritus, injection site erythema, injection site pain and injection site swelling. These AEs with exceptions of upper respiratory tract infection are listed in the SmPC. In the open-label enrollment period of the open-label safety extension phase, the most common TEAEs (≥5% of patients) were urinary tract infection, arthralgia, nausea, vomiting, and increased blood glucose. Events such as nausea, vomiting and injection site reactions were assessed as related to CAM2038. Again these AEs are known to be associated with the CAM2038 treatment and they are listed in the SmPC.

Safety depending on the dose

There was also no clear dose-relationship between CAM2038 dose (weekly and monthly formulations) and the incidence of subjects with TEAEs. There was also no clear dose-relationship between the dose and the incidence of subjects with drug related AEs.
It needs to be noted however that the number of patients in each dose group (especially for monthly formulations) was small therefore these results needs to interpreted with caution.

Serious adverse event/deaths/other significant events

Deaths

One subject in the Placebo treatment group had an SAE of pancreatic carcinoma leading to death in the Double-Blind Treatment Period of this study (Primary Safety Population). One additional subject died during the Open-Label Titration Period prior to randomization to a treatment group and the cause of death could not be confirmed by the Investigator (initially suspected suicide that could not be confirmed by documentation). In addition, 1 subject died due to sepsis before the first dose of CAM2038 q1w. None of the deaths was considered to be related to study drug.
There were no deaths during the Open-Label Safety Extension Phase.

Serious adverse events

In the Open-Label Titration Period SAEs were reported in 10 subjects. There was no SAE which was reported in more than one subject.
Three subjects had SAEs that were considered by the Investigator to be related to study drug. One subject experienced nausea, intractable vomiting and asthenia (all of severe intensity). These AEs are already listed in section 4.8 of the SmPC.

One subject experienced acute **hepatic failure (severe)** and multiple organ dysfunction syndrome (severe) and was admitted to the hospital the day after the first dose of 8 mg CAM2038 q1w in the Open-Label Titration Period. It is noted that abnormal liver function tests, hepatic enzymes increased, alanine aminotransferase increased and aspartate aminotransferase increased are listed in the SmPC but acute hepatic failure is not listed. The Investigator considered the events of acute hepatic failure and multi-organ dysfunction syndrome as related to CAM2038.
Although there was a temporal relationship between onset of the SAEs and CAM2038 administration, the subject's rapid recovery supports the Sponsor's alternative explanation of rhabdomyolysis secondary to statin use, which can lead to transient hepatic and renal failure. The Sponsor's explanation is not fully supported. The applicant was asked to discuss cases of acute hepatic failure associated buprenorphine treatment and discuss whether the update to section 4.8 is necessary. The applicant clarified that In the Risk Management Plan (RMP) for Buvidal, severe hepatic impairment is defined as an important identified risk. Up to 31-Jan-2022, there was 1 patient in the post-marketing dataset who had a medical history of hepatic failure. One case of hepatic failure was reported in trial HS-16-55. Although there was a temporal relationship between the onset of this case of hepatic failure and CAM2038 administration in a non-elderly patient, the patient's rapid recovery supports the alternative explanation of rhabdomyolysis secondary to statin use. This clarification can be accepted. However it is concerned that cases of hepatic failure need to be monitored and if any reported these cases should be presented in the PSUR.

In the Double-Blind Treatment Period SAEs were reported only in 6 subjects. None of the SAEs during the Double-Blind Treatment Period were considered by the Investigator to be related to study drug. However, one SAE was assessed by the Sponsor as possibly related to study drug. An SAE of mental status changes (moderate intensity) occurred 1 day after the subject received the second dose of 128 mg CAM2038 q4w in the Double-Blind Treatment Period.

One subject experienced worsening of the schizoaffective disorder. The Investigator considered the event of worsening schizoaffective disorder to be related to study drug, suggesting that there may have been an interaction between the subject's concomitant medications and the study drug. However, the Sponsor believes that a more plausible explanation for the unexpected SAE is that the event was natural progression of the subject's underlying medical condition and is unrelated to study drug. Again, The Sponsor's explanation is not fully supported. The applicant was asked to discuss cases of worsening of psychiatric disorders associated with buprenorphine treatment and consider the relevant update to the SmPC. The applicant clarified that two patients had 'mental status changes' reported in trial HS-16-555. It can be agreed that with the applicant that based on these specific cases, both with complex medical history and multiple drug use, and the warnings already included in the SmPC, no further changes to the SmPC are considered needed.Nevertheless taking also into consideration that the Sponsor assessed

the event as possibly related to CAM2038, cases of "mental status changes' need to be monitored and presented in the PSUR.

Two subjects experienced SAEs during the open-label titration period; a de novo subject had SAEs of acute myocardial infarction and chronic obstructive pulmonary disease (worsening) and a Placebo rollover subject had an SAE of sleep apnoea syndrome. None of these SAEs were considered by the investigator to be related to study drug and did not lead to withdrawal of study drug.

14 subjects experienced SAEs during the Open-Label Enrollment Period; 7 de novo subjects (13.0%) and 7 rollover subjects (12.7%). Except for an event of dizziness in a de novo subject, the other SAEs were assessed by the Investigator as not related to study drug and did not lead to withdrawal of study drug.

The SAE of dizziness occurred 5 days after the subject had received the 4th dose of 96 mg CAM2038 q4w, the subject experienced dizziness, nausea, chills, weakness and persistent headache with photophobia. Dizziness is already listed in the SmPC. One SAE of accidental overdose was also reported. The applicant was asked background information and discuss reasons for overdose and whether similar cases could be prevented in the future. The applicant provided the requested discussion. The applicant highlighted that the potential risk of overdose may be even lower with the Buvidal formulation because 1) Buvidal is administered SC by HCPs only and 2) Buvidal has been shown to provide a rapid and sustained blockade of the effects of exogenously administered opioids. It is noted that overdose is included in the RMP as an important identified risk, hence, the benefit/risk balance in relation to overdose is planned monitored and addressed in the periodic safety update reports (PSURs) and through biannual signal detection.

Laboratory findings

In the study laboratory TEAEs were reported infrequently. Only bacteriuria, gamma-glutamyltransferase increased, blood glucose increased, aspartate aminotransferase increased, hyponatraemia and proteinuria were reported in more than 2 patients receiving CAM2038 in the study. Two of the laboratory-related TEAEs were considered related to study drug, including a moderate TEAE of amylase increased in a Placebo rollover subject (3.2%) and a mild TEAE of liver function test abnormal in a de novo subject (1.9%). In the SmPC abnormal liver function tests, alanine aminotransferase increased aspartate aminotransferase increased and hepatic enzymes increased are listed.

ECG and QT prolongation

QT prolongation is a known class effect of opioids. The following statement is included in the SmPC: *caution should be exercised when co-administering Buvidal with other medicinal products that prolong the QT interval and in patients with a history of long QT syndrome or other risk factors for QT prolongation*.

Safety in special population

It is noted that the population of patients enrolled to this study was older as compared to population of patients investigated in the original MAA. A post hoc analysis was performed of AEs by age category in HS-16-555 and based on this it is claimed that the safety profile of CAM2038 was similar in patients aged <65 years and elderly patients aged ≥65 years. However the number of patients in each age category was too small to make any firm conclusion.

The applicant proposed to update recommendations and changes the current wording "The efficacy and safety of buprenorphine in elderly patients > 65 years have not been established" and state instead that "No dosage adjustment is required in elderly patients ≥ 65 years of age." From safety perspective it needs to be highlighted in the SmPC that the number of elderly patients in particular those over 75 years of age who were exposed to CAM2038 was very small (i.e 6 patients over 75 years of age). The

applicant agreed to update the SmPC. The Applicant agrees to update the safety concerns in the RMP to include use in patients over 75 years of age as missing information

Concomitant medications

- Concomitant medications in patients suffering from chronic pain are likely to be different as compared to concomitant medications used for the treatment of opioid dependence. It is noted for example that benzodiazepines and gabapentinoids were used in a significant proportion of patients in HS-16-555 and this could be also observed in a clinical practice. As highlighted in the SmPC this combination (i.e Buprenorphine with benzodiazepines or gabapentinoids) is dangerous as it may result in death due to respiratory depression. Polypharmacy is likely to be more common in patients with chronic pain partially due to fact that these patients are older as compared to patients with opioid dependence. Further some medications prescribed in patients with chronic pain are less likely to be used in opioid dependence patients including simple analgesics such as acetaminophen, salicylates, and nonsteroidal anti-inflammatory drugs and adjuvant analgesics such as antidepressants, anticonvulsants, topical products, muscle relaxants, and sleeping agents.

Discontinuation due to adverse events

A significant proportion of patients discontinue due to adverse events in the titration period of the double-blind phase in HS-16-55 (i.e **72 patients (15.4%).** The most common TEAEs leading to withdrawal of the IMP were nausea (30 patients [6.4%]) vomiting (17 patients [3.6%]) and injection site TEAEs. Less patients discontinue in other study periods i.e , 6 patients (2.7%) in the during the double-blind treatment period, 5 patients (4.1%) during the titration period of the OLE phase and 4 patients (3.7%) in the OLE treatment period. TEAEs leading to withdrawal such as w**eight decreased**, decreased appetite, **ageusia**, **joint swelling**, nausea, vomiting, **depressed level of consciousness**, asthenia, tremor dizziness, injection site reations, **sedation and peripheral oedema were considered to be related to CAM2038.**

In general, it seems that the safety profile observed with CAM2038 in HS-16-555 study was consistent with the safety profile established during the original MAA. However, as already highlighted, the safety database in opioid dependent patients with moderate to severe chronic pain is small.

The applicant's claim on the similarities of safety profiles in opioid use disorder and chronic pain patients needs to be further substantiated. The potential impact of differences in patients characteristics on the safety profile of CAM2038 should be further discussed. In addition the applicant is asked to provide a head-to-head comparison of the overall safety (overall AE frequency, number and frequency of SAEs, frequency of related AEs and related SAEs, frequency of Grade 1-Grade 4 AEs) and the AE frequency by PT and SOC for opioid use disorder and chronic pain disorder populations of CAM2038 clinical studies.

There are differences between the population of patients investigated in studies supporting the opioid dependence indication as compared to the pivotal study (HS-16-555) provided as a part of this procedure. For this reason, an extrapolation of the long term safety profile of CAM2038 when used for opioid dependence to patients with chronic pain could be insufficient. The applicant is requested to discuss. Further the applicant should consider adding the long term use for the treatment of chronic pain as a missing information in the RMP. In addition, the applicant should discuss on how further data on the use for the treatment of chronic pain could be generated in the post-marketing

GCP issues affecting safety results.

30.6% of patients who were originally randomised to and completed the DB period was excluded from the efficacy and safety analyses.

The safety results from Sites 068 and 077 were not included in the Primary Safety Population as in these sites GCP issues associated with errors in safety reporting were noted.

The GCP inspection is proposed for the pivotal study provided as a part of this application. The final conclusion on the adequacy of the safety database can only be made once the outcome of this GCP inspection is available.

Additional expert consultations

N/a

Assessment of paediatric data on clinical safety

N/a

2.5.2. Conclusions on clinical safety

There are no major objections in relation to safety. However, the applicant's claim on the similarities of safety profiles in opioid use disorder and chronic pain patients needs to be further substantiated. There are differences between the population of patients investigated in studies supporting the opioid dependence indication as compared to the pivotal study (HS-16-555) provided as a part of this procedure. For this reason, an extrapolation of the long term safety profile of CAM2038 when used for opioid dependence to patients with chronic pain could be insufficient. The discussion is required. Further, the applicant should consider adding the long term use for the treatment of chronic pain as a missing information in the RMP. In addition, the applicant should discuss on how further data on the use for the treatment of chronic pain could be generated in the post-marketing.

2.5.3. PSUR cycle

To be decided.

2.5.4. Direct Healthcare Professional Communication

N/a

2.6. Significance <Non-Conformity> of paediatric studies

N/a

3. Risk management plan

The updated RMP version 2.1 has been submitted.

Summary of significant changes in this RMP:

Part I:

Addition of treatment of moderate to severe chronic pain in patients with opioid dependence

Part II.

Module SI - Epidemiology of the indication and target population

Module SIII - Clinical trial exposure

Module SV - Post-authorisation experience: this module has been updated with postauthorisation data for Buvidal

Module SVII.3 - Identified and potential risks: Editorial updates of sections characterisation of the risk

The Module SVIII - Summary of the safety concerns has been updated with patients over 75 years of age.

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; monoamine oxidase inhibitors [MAOI]; and serotonergic medicinal products) 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 Use in patients over 75 years of age

Assessor's comment:

The applicant should consider adding the long term use for the treatment of chronic pain as a missing information in the RMP
Further the applicant should discuss on how further data on the use for the treatment of chronic pain could be generated in the post-marketing. . Anyway, the MAH is invited to provide data in the upcoming PSURs about long-term safety.

Use in patients over 75 years of age has been added to the summary of safety concerns as missing information. Further, in accordance with the GVP module V, the applicant should discuss on how further data on the use in patients over 75 years of age could be generated in the post-marketing. Anyway, the MAH is invited to provide data in the upcoming PSURs regarding elderly.

3.1. Overall conclusion on the RMP

PRAC Rapporteur overall conclusion and recommendations:

At the current stage of the assessment of the dossier the RMP is acceptable provided that accurate and complete answers to the following questions are given:

- In the study HS-16-555, only 58 patients were exposed to CAM2038 continuously for ≥52 weeks. The applicant should discuss whether long term safety should be added as missing information and should propose appropriate additional measures accordingly in case of inclusion in the RMP safety concerns to further characterize long-term safety. Anyway, the MAH is invited to provide data in the upcoming PSURs about long-term safety.

- The number of elderly patients in particular those over 75 years of age who were exposed to CAM2038 for this indication was very small (i.e 6 patients over 75 years of age). Use in patients over 75 years of age has been added to the summary of safety concerns as missing information. The applicant should propose appropriate additional measures to further characterize this population.

Anyway, the MAH is invited to provide data in the upcoming PSURs regarding elderly.

☒The changes to the RMP <and the changes to the conditions and obligations of MA> could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information in section 5 are submitted.

4. Changes to the Product Information

As a result of this variation, section(s) **4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6** of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

4.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found unacceptable for the following reasons:

The bridging report needs to be provided.

4.1.2. Additional monitoring

N/a

4.1.3. Quick Response (QR) code

N/a

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

The most recent classifications define chronic pain as any somatic pain lasting longer than 3 months. Common types of chronic non-cancer pain include low back pain, osteoarthritis, headache, fibromyalgia and neuropathic pain. Chronic pain is very prevalent and affects over 20% of the European population, with increased presence in females and older individuals.

It is one of the most frequent reasons to seek medical care and a leading cause of disability and disease burden globally. Chronic pain management is one of the most difficult clinical challenges in medicine today with a high and unmet medical need. Treatment often requires a multimodal, interdisciplinary

approach, which might include pharmacotherapy, psychotherapy, integrative treatment and invasive procedures.

Opioids have been used for pain management for centuries and are regarded as effective in the management of pain. In chronic pain, opioid therapy can be a useful tool in achieving and maintaining an optimal level of pain control. However, long-term opioid therapy for chronic pain is associated with increased risks for side effects and misuse, diversion and opioid dependence. It has been estimated that, in individuals with chronic non-cancer pain, approximately 25% use any opioid analgesic and 10% use strong opioids. A recent systematic review found that more than one third of patients with non-cancer pain at speciality pain clinics had a problematic use of opioids, while the rate of addiction in studies specifically examining this in patients with chronic pain has been estimated to between 5% to 8% as the main risk factors for addiction. Increased prescription of opioids has in some European countries, such as the Netherlands, France and the United Kingdom, been accompanied by parallel increasing trends of misuse, such as opioid-related hospital admissions and mortality.

Among patients with diagnosed opioid dependence receiving pharmacological opioid agonist treatment for addiction, chronic pain is very common with reported prevalence rates in Europe of 33% to 55%. Chronic pain in patients with opioid dependence is often moderate to severe and associated with older age and psychiatric comorbidities, and the most frequently reported pain locations are the lower extremities and the back. Over 20% of patients with opioid dependence and chronic pain use illicit drugs for pain management, emphasising the need for new treatment options managing chronic pain in these patients.

5.1.2. Available therapies and unmet medical need

There is currently no medicinal product approved for treatment of both chronic pain and opioid dependence. The well-known drug substance buprenorphine (BPN) is, however, widely used both in the treatment of opioid dependence and in the treatment of pain. As a partial mu-opioid receptor (MOR) agonist, it has been shown to give dose-dependent analgesia with a ceiling effect on respiratory depression. Dose-dependent analgesia has been observed with intramuscular (IM) doses up to 10 mg. The effect of BPN on respiratory depression appears to be lower than that of full MOR agonists, due to a ceiling effect at higher doses. Furthermore, the slow dissociation of BPN from receptors results in a long effect duration and reduces withdrawal symptoms upon discontinuation. BPN has proven effective in patients with chronic cancer and non-cancer pain, with a reduced need for additional oral analgesics and improved quality of life. A large number of studies have also compared the efficacy of BPN with morphine for treatment of acute pain and a systematic review found BPN to be an equally efficacious analgesic agent. BPN is therefore an effective analgesic substance across a broad set of pain conditions. In addition, BPN presents with a lower abuse potential than most opioids indicated for chronic pain management. The US Drug Enforcement Administration (DEA) has classified BPN as a Schedule III substance, one that has a potential for abuse lower than substances in the Schedule I and II categories. Most other opioids indicated for chronic pain management, such as morphine, fentanyl, oxycodone, hydrocodone and hydromorphone, fall into the Schedule II category.

Several treatment goals have been proposed for improved patient therapy, many of which are based on World Health Organization (WHO) recommendations, including providing a stable plasma drug concentration to ensure long-lasting and effective pain relief and an improved quality of life. By using transdermal BPN formulations, such as BPN patches, the rate of drug delivery can be controlled and stable plasma concentrations achieved. However, transdermal administration of BPN results in slow onset and relatively low plasma BPN concentrations, which can result in suboptimal therapeutic effects, and is also associated with adverse skin reactions. Transdermal BPN formulations are not available in all EU countries, as these products have been approved through national and decentralised procedures. Thus, differences between countries regarding Marketing Authorisations of BPN products indicated for chronic pain or pain are not related to the efficacy of the active substance but related to operational and regulatory aspects. Finally, patches may be subject to abuse and diversion, as BPN may be extracted from the patches (including improperly disposed patches) and injected, snorted or otherwise misused.

5.1.3. Main clinical studies

The current clinical development programme with CAM2038 in patients with chronic pain consists of 2 clinical trials ; one Phase 2 open label trial (HS-15-549) in patients with OUD and moderate to severe chronic non-cancer pain and one Phase 3 trial (HS-16-555) in opioid experienced patients with chronic pain. Trial HS-15-549 was part of the initial MAA and has, hence, already been assessed during the initial review.

5.2. Favourable effects

In the primary analysis of Study HS-16--555 the change in weekly average of daily average pain intensity from baseline at randomisation at Week 12 was -0.9 in the CAM2038 arm and -1.9 in the placebo arm. The LS mean difference from placebo was 1.030 (95% CI: 0.493 to 1.568) with $p < 0.001$.

An additional MMRM sensitivity analysis using a combination of electronic and paper diaries produced similar results to the primary analysis, as did an analysis using data only from electronic diaries with at least 5 pain records per week. Similar results were also seen in a post hoc per protocol analysis. A sensitivity analysis using the Random Replacement Method in the mITT population with e-diary data only, showed an attenuation in effect size though the results remained statistically significant.

5.3. Uncertainties and limitations about favourable effects

Although the study appears to have met its primary endpoint and the sensitivity analyses supported the primary analysis there are a number of problems with the study which may undermine the validity of the study results. These include the GCP infringements that led to the exclusion of two sites, problems with use of electronic diaries with regard to recording pain scores and use of rescue medication. There was also greater use of other opioids and agents such as gabapentin and pregabalin in the CAM2038 compared to the placebo arm. All of these factors could have confounded the results of the primary endpoint. Thus the magnitude of the true effect size could be even smaller than 1 point on the 11-point NRS scale.

In addition the clinical relevance of the difference from baseline between CAM2038 and placebo of approximately 1 point on an 11-point scale is questioned. Throughout the 12 week randomised controlled treatment period pain scores in both treatment arms, though higher in the placebo arm, remained well below the screening phase/titration baseline values of 7 (see table 12) with the highest WAAPI in the placebo arm at 4.2 in Week 8 and the highest WAAPI in the CAM2038 arm at 3.5 at Week 12 in the CAM2038 arm, demonstrating a strong placebo effect.

It should also be borne in mind that approximately one-third of randomised patients were excluded from the study due to GCP infringements which hampers the validity of the clinical data from the pivotal study as a whole.

The presented clinical package is not in line with the Guideline on the clinical development of medicinal products intended for the treatment of pain (EMA/CHMP/970057/2011) as *efficacy and safety should be demonstrated in two studies in two different pain models.* However, only a single pivotal study was conducted in chronic lower back pain.

The Applicant is seeking a wider indication to include all patients with opioid dependence with moderate to severe chronic pain. Those with moderate to severe opioid dependence were not included in Study HS-16-555. The Applicant would appear to be substantiating the inclusion of this wider group based on the summary results included in the Clinical Overview addendum of the partially randomised open label HS-15-549 study that compared 3 weekly injections of 32mg CAM2038 or four 128mg monthly CAM2038 to daily doses of 24 mg SL BPN/NX given for 7 days. The primary objective of the study was to evaluate steady state pharmacokinetics with efficacy as an exploratory measure. Even if the true effect size was

agreed to be as presented and deemed to be clinically relevant the currently submitted data is insufficient to support the widening of the indication to all patients with chronic pain and opioid dependence.

5.4. Unfavourable effects

The assessment of safety was primary based on the results of HS-16-555 study.

64.1% of subjects who participated in the Open-Label Titration Period (Primary Safety Population) had at least 1 TEAE, with a total of 1157 TEAEs; 37.0% of subjects had TEAEs suspected to be related to CAM2038. Ten subjects (2.1%) had SAEs, including 1 SAE with a fatal outcome (0.2%). Seventy-two (15.4%) subjects experienced TEAEs leading to withdrawal of study drug and study discontinuation. The majority of subjects had mild or moderate TEAEs. A total of 69 subjects (14.7%) had injection site TEAEs.

The frequency of TEAEs during the Double-Blind Treatment Period was smaller i.e TEAEs were reported in 35.6% of subjects in the Primary Safety Population. The incidence of subjects with TEAEs was higher in the CAM2038 treatment group (44 subjects [39.3%]) compared to the Placebo treatment group (35 subjects [31.8%]). The incidence of subjects with TEAEs suspected to be drug-related was relatively low overall (19 subjects [8.6%]). 4 subjects (3.6%) in the CAM2038 treatment group experienced TEAEs resulting in withdrawal of study drug as well as study discontinuation. The majority of TEAEs were mild or moderate in intensity. Injection site TEAEs were experienced by 3 subjects (2.7%) in the CAM2038 treatment group and 4 subjects (3.6%) in the Placebo treatment group.

During the titration period of the OLE phase, 56 of the 121 patients (46.3%) had at least 1 TEAE; 41 of 75 patients from the de novo group (initial titration), 6 of 21 patients from the CAM2038 rollover group and 9 of 25 patients from the placebo rollover group. Nearly half of de novo subjects (20 of 41 subjects [26.7% overall]) had drug-related TEAEs. The majority of Placebo rollover subjects had drug-related TEAEs (8 of 9 subjects [32.0% overall]), while only 1 CAM2038 rollover subject (4.8%) had a drug-related TEAE. There were no deaths in the Open-Label Titration Period, but 2 subjects (1.7%) experienced SAEs (1 de novo subject and 1 Placebo rollover subject).

During the open-label enrollment period of the OLE phase, 87 of the 109 patients (79.8%) experienced at least 1 TEAE. This high proportion of patients may reflect the extended period of time during which TEAEs were collected (up to 10 months for the 54 de novo patients and up to 7 months for the 55 rollover patients). Overall, 18.3% of patients had at least 1 treatment-related TEAE. There were no deaths, but 14 subjects (12.8%) overall experienced SAEs.

The most common individual TEAEs observed during the Open-Label Titration Period were nausea and vomiting. Other commonly reported TEAEs were constipation, dizziness, headache, and injection site reactions, including injection site pruritus, injection site erythema, injection site pain, and injection site swelling.

The most common individual TEAEs during the double-blind treatment period in the CAM2038 treatment group were back pain, fall and oedema peripheral.

During the double-blind treatment period fewer than 5% of subjects experienced injection site TEAEs overall, with a slightly higher incidence of subjects in the Placebo treatment group compared to the CAM2038 treatment group.

Drug-related TEAEs reported by more than 1 subject in the CAM2038 treatment group were constipation (2 subjects) and injection site erythema (2 subjects). Other drug-related TEAEs were reported in single patients and included gastrooesophageal reflux disease, vomiting, fatigue, injection site erythema, pain and swelling, weight decreased, decreased appetite, joint swelling, ageusia, migraine, anxiety, euphoric mood and hyperhidrosis.

During the open-label titration period of the open-label safety extension phase again the most commonly reported TEAEs overall were nausea, vomiting. Upper respiratory tract infection were reported in 7 subjects The most commonly reported injection site TEAEs in de novo subjects were injection site pruritus, injection site erythema, injection site pain and injection site swelling.

In the open-label enrollment period of the open-label safety extension phase, the most common TEAEs (≥5% of patients) were urinary tract infection, arthralgia, nausea, vomiting, and increased blood glucose. Events such as nausea, vomiting and injection site reactions were assessed as related to CAM2038.

One subject in the Placebo treatment group had an SAE of pancreatic carcinoma leading to death in the Double-Blind Treatment Period of this study (Primary Safety Population). One additional subject died during the Open-Label Titration Period prior to randomization to a treatment group and the cause of death could not be confirmed by the Investigator (initially suspected suicide that could not be confirmed by documentation). In addition, 1 subject died due to sepsis before the first dose of CAM2038 q1w. None of the deaths was considered to be related to study drug. There were no deaths during the Open-Label Safety Extension Phase.

In the Open-Label Titration Period SAEs were reported in 10 subjects. There was no SAE which was reported in more than one subject.

Three subjects had SAEs that were considered by the Investigator to be related to study drug. One subject experienced nausea, intractable vomiting and asthenia (all of severe intensity).

One subject experienced acute hepatic failure (severe) and multiple organ dysfunction syndrome (severe) and was admitted to the hospital the day after the first dose of 8 mg CAM2038 q1w in the Open-Label Titration Period.

One subject experienced worsening of the schizoaffective disorder. The Investigator considered the event of worsening schizoaffective disorder to be related to study drug, suggesting that there may have been an interaction between the subject's concomitant medications and the study drug.

In the Double-Blind Treatment Period SAEs were reported only in 6 subjects. None of the SAEs during the Double-Blind Treatment Period were considered by the Investigator to be related to study drug.

Two subjects experienced SAEs during the open-label titration period; a de novo subject had SAEs of acute myocardial infarction and chronic obstructive pulmonary disease (worsening) and a Placebo rollover subject had an SAE of sleep apnoea syndrome. None of these SAEs were considered by the investigator to be related to study drug and did not lead to withdrawal of study drug.

14 subjects experienced SAEs during the Open-Label Enrollment Period; 7 de novo subjects (13.0%) and 7 rollover subjects (12.7%). Except for an event of dizziness in a de novo subject, the other SAEs were assessed by the Investigator as not related to study drug and did not lead to withdrawal of study drug.

The SAE of dizziness occurred 5 days after the subject had received the 4th dose of 96 mg CAM2038 q4w, the subject experienced dizziness, nausea, chills, weakness and persistent headache with photophobia. Dizziness is already listed in the SmPC. One SAE of accidental overdose was also reported.

5.5. Uncertainties and limitations about unfavourable effects

It seems that the safety profile observed with CAM2038 in HS-16-555 study was consistent with the safety profile established during the original MAA. However, the safety database in opioid dependent patients with moderate to severe chronic pain is small and exposure is short.

The applicant’s claim on the similarities of safety profiles in opioid use disorder and chronic pain patients needs to be further substantiated. The potential impact of differences in patients characteristics on the safety profile of CAM2038 should be further discussed. In addition the applicant is asked to provide a head-to-head comparison of the frequency and exposure-adjusted incidence rate of TEAEs, treatment-related TEAEs, severe TEAEs, treatment-related severe TEAEs, serous TEAEs reported in studies in patients with opioid dependence as compared to patients with chronic pain. The frequency and exposure-adjusted incidence rate of TEAEs by PT and SOC for opioid use disorder and chronic pain disorder should be also compared.

There are differences between the population of patients investigated in studies supporting the opioid dependence indication as compared to the pivotal study (HS-16-555) provided as a part of this procedure. For this reason, an extrapolation of the long term safety profile of CAM2038 when used for opioid dependence to patients with chronic pain could be insufficient. The applicant is requested to discuss. Further the applicant should consider adding the long term use for the treatment of chronic pain as a missing information in the RMP. In addition, the applicant should discuss on how further data on the use for the treatment of chronic pain could be generated in the post-marketing.

Additional ADRs have been reported in the HS-16-555 study and therefore the SmPC may need to be updated.

The safety results from Sites 068 and 077 were not included in the Primary Safety Population as in these sites **GCP issues** associated with errors in safety reporting were noted. The GCP inspection is proposed for the pivotal study provided as a part of this application. The final conclusion on the adequacy of the safety database can only be made once the outcome of this GCP inspection is available.

5.6. Effects Table

Table 41: ***Effects Table for Buvidal for Treatment of moderate to severe chronic pain in patients with opioid dependence***

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint	Mean (SD) Change from baseline at Week 12 in WAAPI score LS mean diff from placebo	11 point pain score	-0.9 (1.62) 1.030 (95% CI: 0.493, 1.568	-1.9 (1.97)	p ≤ 0.001	**Study HS-16-555**
Secondary endpoint	Mean Change from baseline at Week 12 in WAWPI score LS mean diff from placebo	11 point pain score	-1.1 (1.81) 1.108 (95% CI: 0.525, 1.691)	-2.2 (2.18)	p ≤ 0.001	**Study HS-16-555**
Secondary endpoint	The proportion of responders with a ≥30% in WAAPI score from baseline to Week 12 Proportional diff (95% CI)	%	60% 10.8% (-2.2%, 23.9%)	47%	p = 0.106	**Study HS-16-555**
Secondary endpoint	The proportion of responders with a ≥50% in WAAPI score from baseline to Week 12 Proportional diff (95% CI)	%	44% 10.2 % (-2.2%, 22.6%)	32%	p = 0.109	**Study HS-16-555**
Unfavourable Effects						
	Treatment-related TEAEs the percentage of patients with at least 1 TEAE	%	**Titration period of the double-blind phase:** **468 patients (64.1%)** **Double-blind treatment period:** **CAM2038: 39.3%** **Titration period of the OLE phase: 46.3%** **Open-Label Enrollment Period of the OLE phase: 79.8%**	**Double-blind treatment period:** **Placebo : 31.8%**		**HS-16-555 study**
	Serious Adverse Events		**Titration period of the double-blind phase:**			**HS-16-555 study**

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			10 patients (2.1%) **Double-blind treatment period:** **CAM2038:** **3 patients [2.7%]** **Titration period of the OLE phase:** **2 patients (1.7%)** **Open-Label Enrollment Period of the OLE phase:** **14 patients (12.8%)**	**Double-blind treatment period:** **Placebo :** **3 patients [2.7%]**		
	Treatment-Emergent Injection Site Adverse Events		**Titration period of the double-blind phase:** **69 (14.7%)** **Double-blind treatment period:** **CAM2038:** **3 (2.7%)** **Titration period of the OLE phase:** **13 subjects (10.7%)** **Open-Label Enrollment Period of the OLE phase:** **de novo subjects (11.1%)** **rollover subjects (9.1%**	**Double-blind treatment period:** **Placebo :** **4 (3.6%)**		**HS-16-555 study**

Abbreviations:

Notes:

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Though Study HS-16-555 met its primary efficacy endpoint and the sensitivity analyses supported the primary analysis there are a number of problems with the study which may undermine the validity of the study results e.g. problems with use of electronic diaries with regard to recording pain scores and use of rescue medication and imbalances in the use of other opioids and agents such as gabapentin and pregabalin in the CAM2038 compared to the placebo arm. All of these factors could have confounded the results of the primary endpoint. Thus the magnitude of the true effect size could be even smaller than 1.03 points on the 11-point NRS scale.

In addition the clinical relevance of the effect size of 1.03 points on the 11-point NRS scale is questioned.

The Applicant is seeking an indication in all opioid dependent patients with moderate to severe chronic pain in spite of only including those with mild opioid dependence in Study HS-16-555. The justification for widening the indication provided in the Clinical Overview Addendum and based on results from Study HS-15-549 is not considered sufficient.

Overall at this stage efficacy has not been adequately demonstrated.

In relation to safety, the applicant's claim on the similarities of safety profiles in opioid use disorder and chronic pain patients need to be further substantiated in particular in terms of long term use and when used in elderly patients. The potential impact of differences in patients characteristics on the safety profile of CAM2038 should be further discussed.

5.7.2. Balance of benefits and risks

Given that efficacy has not been demonstrated and the benefit risk balance for Buvidal in the sought indication is considered to be negative.

5.7.3. Additional considerations on the benefit-risk balance

N/a

5.8. Conclusions

The overall B/R of Buvidal is negative at present.